Clinical Research Careers: Reports from a NHLBI Pediatric Heart Network Clinical Research Skills Development Conference

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Background Wyman W. Lai, MD, MPH, and Victoria L. Vetter, MD, MPH.

The Pediatric Heart Network (PHN), funded under the U.S. National Institutes of Health–National Heart, Lung, and Blood Institute (NIH–NHLBI), includes two Clinical Research Skills Development (CRSD) Cores, which were awarded to The Children's Hospital of Philadelphia and to the Morgan Stanley Children's Hospital of New York–Presbyterian. To provide information on how to develop a clinical research career to a larger number of potential young investigators in pediatric cardiology, the directors of these two CRSD Cores jointly organized a one-day seminar for fellows and junior faculty from all of the PHN Core sites. The participants included faculty members from the PHN and the NHLBI. The day-long seminar was held on April 29, 2009, at the NHLBI site, immediately preceding the PHN Steering Committee meeting in Bethesda, MD.

Methods The goals of the seminar were 1) to provide fellows and early investigators with basic skills in clinical research 2) to provide a forum for discussion of important research career choices 3) to introduce attendees to each other and to established clinical researchers in pediatric cardiology, and 4) to publish a commentary on the future of clinical research in pediatric cardiology.

Results The following chapters are compilations of the talks given at the 2009 PHN Clinical Research Skills Development Seminar, published to share the information provided with a broader audience of those interested in learning how to develop a clinical research career in pediatric cardiology. The discussions of types of clinical research, research skills, career development strategies, funding, and career management are applicable to research careers in other areas of clinical medicine as well.

Conclusions The aim of this compilation is to stimulate those who might be interested in the research career options available to investigators. (Am Heart J 2011;161:13-67.)

PART 1: INTRODUCTION TO CLINICAL RESEARCH

The pathway to a Clinical research career is rarely straight or direct, but is a twisting, sometimes tortuous journey, full of hills and valleys, and unexpected detours; shortcuts are seldom present. It requires planning and preparation, repeated efforts, and guidance from those who have traveled the pathway before. For those who are contemplating this journey, the information provided here can serve as a roadmap.

The present compilation provides a glimpse of the variety of opportunities, from clinical observational studies to randomized clinical trials. The potential for collaboration with colleagues, the U.S. Food and Drug Administration (FDA), and a variety of industries is described.

Clinical research must be approached with the same rigor that is applied to any area of medically related scientific study. Many skills must be mastered, including an understanding of the subject and disciplines applicable to a particular research strategy. This requires an ability to develop focused research questions and hypotheses, to design a research study, to choose the appropriate measurements and outcomes, and to carefully collect

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and categorize and then accurately analyze data. This further requires the understanding and application of correct statistical methodologies, so that the results are not only statistically significant but also clinically significant. Additionally, knowledge of sampling and sample size, bias, confounding, correlations, associations, and relative risk and odds ratios is important, to prevent pitfalls that can limit effective research efforts.

Once research results have been interpreted, the dissemination of results is critically important, necessitating development of skills in the effective sharing of results by presentations, publications, and other means of communication. Researchers should also become familiar with the various sources and types of funding, support that will be required to move research efforts forward.

The successful clinical researcher will need internal fortitude, passion, and, very importantly, a good mentor. The mentor is someone who will support the young investigator's efforts and will share both disappointments and success. The support of a good mentor is critical in a successful research effort; it is worth investing the time needed to find the best match possible. Along the way, challenges in work-life balance inevitably arise; these are addressed here in a final chapter.

The future of clinical research in pediatric cardiology looks bright, mainly because of the talent, dedication, and passion of the individuals who are drawn to it. The authors of the chapters presented here, along with the Pediatric Heart Network of the NHLBI, wish the best of personal and professional success to all those who endeavor to move forward in a clinical research career.

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Table of Contents

TYPES OF CLINICAL RESEARCH

OVERVIEW OF GENERAL STUDY DESIGN

Marc Richmond, MD, and Wyman W. Lai, MD, MPH

When attempting to answer a clinical research question, it is important to choose the correct study design, one that will maximize the possibility of successfully answering the question. For some research questions, a limited retrospective observational study can adequately answer the question without imposing undue burdens on subjects or investigators. For others, only a randomized controlled trial can answer the question, and a more limited study may only use up resources without a beneficial purpose. A fundamental knowledge of all the available study designs is essential in choosing the most appropriate design and so maximizing the impact of the study findings while simultaneously minimizing the costs of the study.

Introduction

For a clinical investigator there are myriad study designs available to answer a research question. All study designs, however, can be classified into one of

two major categories: observational or experimental. The primary distinguishing factor between these categories is in how members of the study groups are assigned to the primary variable of interest (typically thought of as an exposure or treatment). In an observational study, subjects are allocated by outside factors, such as self-selection. This type of study requires fewer resources, but the nonrandom allocation of subjects makes observational studies more prone to biases and uncertainties, and therefore the conclusions drawn from them are limited. It is important to note that, although the language of observational studies is usually phrased in relation to epidemiologic studies, the same designs can be applied to examine nonrandomized therapeutic studies, where the exposure is a treatment and the outcome may be any measure of improvement in disease severity. In an experimental study, or clinical trial, the investigators actively place subjects into their assigned group, usually via a randomization algorithm. Although experimental studies are typically described in language consistent with therapeutic trials, the same study design may be used for a more epidemiologic research question.

Observational study designs

Case report or series

The simplest observational design is that of a case report. This is typically a communication that is solely descriptive in nature, the purpose of which is to publicize an intriguing presentation of disease or a novel treatment in a single patient. The natural extension of the case report is a case series, in which a group of patients are presented with some common thread connecting them. These cases may be linked by diagnosis, presentation, or treatment strategies. As with a case report, the goal of a case series is to alert the community at large to new or interesting presentations or treatments.

Cross-sectional study

A step up from a case series is the cross-sectional study. In this study design, all data are collected on the study population at a single moment in time. There is no longitudinal component to a cross-sectional study design, and both the exposure and the outcome are measured simultaneously. The advantages of this design are its simplicity in data collection and low resource requirements. Large, well-designed cross-sectional studies can often yield large volumes of important information. However, because temporal relationships cannot be reliably ascertained, analysis is limited to prevalence of outcomes and associations with exposures. Because of these limitations, there is limited ability to establish causation or to determine natural history and prognosis.

Cohort study

The gold standard of observational studies is the *prospective cohort study*. In this design, the investigator follows a defined population (typically divided into two groups, exposed and unexposed) for a finite period of time to evaluate an outcome, usually a disease. The patient populations and exposure variables are defined and measured before any outcomes have occurred or have been identified. The proportion of patients developing the outcome of interest in the exposed and unexposed groups is examined at the conclusion of the study. The prospective cohort study is an excellent method of determining disease etiology, and the prospective nature allows for high fidelity of data collection. However, following a prospective cohort in this way is often expensive and resource consuming, sometimes prohibitively so.

The *retrospective cohort study* design offers benefits similar to those of the prospective cohort study, but in a less resource-consuming way. The design for a retrospective cohort study is identical to the prospective design, in that the population is defined in the same way, the primary comparison is made between exposed and unexposed subject groups, and the development of the outcome of interest remains the primary objective. The difference is in the collection of data: all data, including the exposure variable, are collected retrospectively, after the outcomes have occurred. Although cost and resource requirements are decreased, the retrospective approach introduces information bias, limitations in recall, and recall bias. Furthermore, research questions are limited to those that can be answered with the available data.

Cohort studies have their limitations, especially for investigation of an infrequent outcome or disease. The rarer the outcome variable, the larger the cohort needed to ensure an adequate number of outcomes for statistical analysis.

Case–control study

A case–control study design can often meet many of the same goals as a cohort study, while requiring only a fraction of the sample size. The efficiency of the case–control design lies in the fact that the number of subjects with the outcome of interest (cases) is preordained. There is no need to recruit 100 subjects to witness one event with an incidence of 1%; the investigator can simply recruit that one subject. The control subjects are chosen from a similar cohort of patients who do not have the predefined outcome. The major limitation of a case–control study is that the ratio of subjects with the outcome (cases) to subjects without the outcome (controls) is fixed by the investigator. Thus, one cannot calculate the incidence of the outcome, or the risk of developing the outcome

Table I. Observational study designs

Observational study designs, key features, and examples
Case report or series — Descriptive case or cases
Example: The first documented case of single ventricle, first published in 1824, was reviewed with reinspection and photographs.[2]
Cross-sectional study — A group examined at one point in time
Example: The NHLBI-funded Pediatric Heart Network designed a cross-sectional study of children aged 6 to 18 years who had undergone a Fontan procedure. Health-related quality of life was measured by the Child Health Questionnaire and the Congenital Heart Adolescent and Teenager Questionnaire. Ventricular function was assessed by maximal exercise testing, echocardiography, cardiac magnetic resonance imaging, and B-type natriuretic peptide. The study was designed to detect a correlation of $R \geq 0.30$ between health status scores and measures of ventricular function and performance in a subcohort with all study measures completed.[3]
Cohort study — A group followed over time, prospectively or retrospectively
Prospective example: A multicenter, nonrandomized prospective study was performed in 13 pediatric cardiology centers from November 2004 to September 2007. The objective of this study was to determine the initial safety and results of unrestricted multi-institution routine community use of the Amplatzer septal occluder (ASO) for atrial septal defect (ASD) closure. Data were collected at the time of cardiac catheterization and 1 day postimplant. A total of 478 patients underwent cardiac catheterization for ASO device closure of an ASD.[4]
Retrospective example: To review the initial impact on mortality of infants with congenital heart disease of a new surgical technique, the mortality of 325 consecutive neonates with simple transposition of the great arteries admitted before, during, and after the preferred management changed from the Senning operation to the arterial switch (1978–1998) were compared with 100 consecutive neonates requiring a different neonatal open heart operation that did not change in that period.[5]
Case–control study — Two groups, based on the outcome
Example: To better define the risk factors of post-transplant lymphoproliferative disease (PTLD) in children, a case–control study was performed on all pediatric cardiac transplant recipients who developed PTLD. Nine patients who developed their first episodes of PTLD were matched by age (±1 yr) and time since transplant (±1 yr) with those who did not. Two controls, selected from a total of 95 transplant recipients, were matched to each case patient with PTLD.[6]

if exposed. Although risks cannot be determined in a case–control design, odds can be calculated, and an odds ratio is often the measure of interest in such a study. In case–control studies the odds ratio can have multiple interpretations and may estimate the traditional odds ratio, rate ratio, or risk ratio obtained from cohort studies, depending on the method used for case and control ascertainment.[1] Given these differences in interpretation, it is important to define the ratio of interest prior to study design and to plan the study accordingly. Of course case–control studies are subject to the same limitations of recall, data collection, information bias, and recall bias as all other retrospective studies; nonetheless, in many situations the efficiency of the case–control design will outweigh the limitations of a retrospective approach.

Experimental study designs

When trying to assess a causal relationship between either an exposure or treatment and an outcome, the best study design is an experimental study. A double-blinded randomized controlled trial is often considered the ultimate ideal in design, but is often difficult and costly to perform. This topic is discussed in greater detail in a later chapter (J.W. Newburger, *How to design a clinical trial*). Briefly, the common factor in all experimental study designs is that they are interventional in nature: that is, the intervention is actively applied to the study population by the investigator. The reason an experimental study can yield such strong conclusions is that the investigator is able to control for confounding factors, most commonly through the use of randomization. There are multiple types of randomization schema, all of which serve to minimize selection bias. Single-blind, double-blind, and triple-blind study designs are all used in randomized control trials. An open-label design may be appropriate in some situations; however, with this design there is no accounting for the placebo effect or therapeutic bias. A repeated-measures design (e.g., a cross-over design) uses each subject as his or her own control, and when designed correctly can yield reliable results while requiring the enrollment of fewer subjects than a standard randomized controlled trial.

Conclusion

There are a variety of study designs that can be applied to answering a specific research question (Table I). A good fundamental understanding of the advantages and limitations of each can allow for choosing the most appropriate study design, given the specific research question, study population, and resources available. Regardless of the study design, ethical considerations must always be taken into account, balancing subject safety and costs with the importance of the research and the potential benefits to the subjects and society as a whole.

For Suggested Readings see References 7-12.

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PEDIATRIC RESEARCH AND THE FDA

Jennifer S. Li, MD, MHS

Few of the approved products marketed in the United States have sufficient data to support pediatric labeling; recent legislative initiatives, particularly the Pediatric Exclusivity provision, have substantially improved drug labeling for children. These programs have raised several

important policy and study design questions. The U.S. Food and Drug Administration (FDA) has programs in place to develop future researchers in biostatistics, informatics, epidemiology, risk analysis, and other aspects of FDA regulatory science.

The U.S. Food and Drug Administration (FDA) is responsible for protecting the public health by assuring the safety, efficacy, and security of drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation. The FDA requires rigorously performed clinical trials as the basis for the labeling or package insert instructions that are provided with each product approved for use by adults. However, fewer than 25% of approved drugs marketed in the United States have sufficient pediatric data to support approval for labeling for dosing, safety, and efficacy in children. Inadequate dosing and safety information places children at risk for adverse events and denies them potential therapeutic benefits. Pediatricians must therefore prescribe agents to children for whom the dose, efficacy, and safety have not been studied. This practice, known as *off-label* use, may result in benefit, no effect, or harm. The lack of information has had a negative impact on pediatric therapeutics, including reliance on anecdotal practice patterns, adaptation of data from adult trials that may not be applicable to children, and the use of extemporaneous formulations that may be inconsistently bioavailable. A recent study by Pasquali et al[13] showed that in more than 30,000 children hospitalized with cardiovascular disease, 78% received more than one cardiovascular medication off-label, and 31% received more than three cardiovascular medications off-label.

The FDA Modernization Act of 1997 and the Best Pharmaceuticals for Children Act of 2002 authorized an incentive program known as *Pediatric Exclusivity* in the form of 6 additional months of marketing exclusivity for manufacturers who conducted pediatric clinical trials in response to a FDA written request. The Pediatric Research Equity Act (PREA) of 2003 codified the authority of the FDA to require pediatric studies of certain drugs and biological agents. (Text of these various Acts, with related resources, is available at the FDA website: (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.) As opposed to the Pediatric Exclusivity program, under PREA there is no financial incentive provided to perform studies. The studies under PREA are mandatory and typically include phase I and II pediatric studies, compared with Pediatric Exclusivity, which requires additional phase III efficacy studies. In addition, under PREA, a waiver can be granted if the drug or biologic does not have any applicability to children (e.g., conditions such as infertility or breast or prostate cancer) or if a deferral can be negotiated. Both Pediatric Exclusivity and PREA were reauthorized in the Food and Drug Administration Amendments Act of 2007 (available at the FDA website, as already cited). The European Medicines Agency has recently started to require drug studies in children and has begun to receive pediatric investigation plans for new molecular entities.

These legislative actions have resulted in substantial improvements in pediatric information in drug labeling. To date, there have been more than 350 labeling changes as a result of studies in pediatric patients.[14] Approximately half of the products studied for U.S. Pediatric Exclusivity have been found to have substantive differences in dosing, safety, or efficacy in children, compared with adult populations.[15]

Several industry-sponsored clinical trials have been performed in pediatric cardiovascular therapeutics under the Pediatric Exclusivity program. For example, many children with heart failure are treated with carvedilol, based on the beneficial effects demonstrated in multiple adult heart failure studies. In a randomized trial, however, carvedilol did not improve heart failure outcomes in children and adolescents with symptomatic heart failure.[16] In another study, the optimal dose of clopidogrel in children with a cardiac condition at risk for arterial thrombosis was only one-fifth of what would be given if extrapolating from adult data.[17] A pharmacokinetic study of sotalol showed that its clearance is linearly correlated with body surface area and creatinine clearance, with smaller children having greater drug exposure than larger children.[18] Multiple antihypertensive agents that clearly demonstrate a dose-effect in adults have failed to show such a dose-effect in children.[19]

These studies have been difficult to execute, because of the many barriers in conducting clinical trials in pediatric cardiovascular medicine: the relative rarity of disease, disease heterogeneity, lack of research infrastructure, ethical issues in pediatric research, and difficulty in identifying valid clinical end points. Moreover, many parents will hesitate to enroll their children in studies involving drugs when they are aware that these agents are readily available for adults. In addition, parents may have other concerns regarding conflict of interest in research between their physicians and pharmaceutical sponsors.

These programs have encouraged drug studies in children, but they have also engendered multiple criticisms. The criticisms include the financial windfall to the pharmaceutical industry, the resulting higher prices for drugs that are bought (at least for elderly persons) by Medicare dollars, the low incidence of publication of the pediatric trials, and the fact that the drugs under study typically do not reflect the therapeutic needs of children and instead follow utilization patterns in adults (e.g., studies of blockbuster lipid lowering agents).[20-22] In addition, this program is a substantial investment, children cannot give consent, and the trials are technically challenging. Given these issues, determining how to best transform these data into health policy

beyond modification of the existent labeling is vital to public health.

In addition, although children have benefited remarkably from these labeling changes, the long-term safety of such therapies in children is not well understood. The major tool for FDA post-market surveillance is an adverse event reporting system for collecting and analyzing information about adverse events. Voluntary reporting to the FDA began in 1973 and continues under MedWatch, a program created in 1993 to encourage all interested parties to voluntarily report adverse events (http://www.fda.gov/Safety/MedWatch/default.htm). MedWatch has several limitations: (1) it is a passive system, relying on healthcare professionals to report events; (2) reports are limited, because of missing case information and a lack of standard nomenclature (uncertain knowledge about the numerator); and (3) the system lacks information on the total number of drugs or devices in use (uncertain knowledge about the denominator). It is therefore quite difficult to determine the incidence or prevalence of drug-related and device-related events.[23]

Thus, several policy questions remain unanswered. In addition, many issues about pediatric study design need evaluation. Pediatric drug trials are often conducted after a product has been developed for adults, and information developed from previous adult trials is often used to design pediatric trials. However, because of the small number of pediatric patients with a given disease and the ethical mandate that children should not be exposed to additional risks without potential benefit, pediatric studies tend to be smaller in size. Nonetheless, well-powered safety and efficacy trials for therapeutics are a critical component of pediatric health.

To address these policy and study design issues, the FDA has several important programs in place to develop future researchers in the field of pharmacology and clinical trials. For young investigators, there is a new program called the Commissioner's Fellowship Program, a 2-year program that provides an opportunity for health professionals and scientists to receive training and experience at the FDA.[24] The Fellowship Program combines rigorous didactic coursework with the development of a regulatory science research project. Under the guidance of an FDA senior scientist–preceptor committed to mentoring, fellows will explore a specific aspect of FDA regulatory science. This experience can be in a biology, physics, or engineering laboratory, in a clinical review team, or in biostatistics, informatics, epidemiology, risk analysis, or other aspects of FDA science. The coursework is designed to provide an in-depth understanding of the science behind regulatory review, encompassing the activities of the FDA across foods, drugs, devices, biologics, and cosmetics. Coursework during the two years includes graduate level public policy, FDA law, epidemiology, clinical trials and design, and statistics. For more senior child health investigators, the FDA has additional opportunities for involvement. These activities include consulting as a Special Government Employee on advisory boards, as well as in certain capacities to perform meta-analytic research across studies in various therapeutic areas evaluating phase I, II, III, and IV clinical trials, pharmacokinetics and pharmacodynamics, and drug and device safety.

In addition, the FDA has programs in place to develop products for rare diseases and conditions; these include the Orphan Grant Program and the Pediatric Device Consortia Grant Program.[25] The Orphan Grant Program provides funding for research in orphan diseases (defined as those affecting <200,000 people in the United States). The Pediatric Device Consortia Grant Program solicits grant applications from institutions and organizations that propose to develop nonprofit consortia to facilitate pediatric medical device development. The FDA will provide grants to consortia whose business model and approach to device development will either result in, or substantially contribute to, market approval of medical devices designed specifically for use in children.

In summary, several legislative initiatives and existing programs are in place at the FDA aimed at bringing effective therapies to children. It is important for pediatricians and child health researchers to be aware of these drug and device development processes for children. Both future research into new therapies and continued scrutiny of existing therapies are vitally important for child health.

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RESEARCH INVOLVING DRUGS, DEVICES, AND INDUSTRY

J. Philip Saul, MD

Use of most drugs and devices in the pediatric population is not based on evidence gathered in children. Experience nonetheless indicates that clinical trials are feasible through groups of experienced investigators in all areas of pediatric cardiology, and a variety of available sponsors. Performing industry-sponsored research on drugs and devices versus research with alternative funding sources represents a balance. Industry funding can bring the freedom of adequate funding and support for a trial that has the potential to demonstrate the value of a new drug or device without the need and time for a grant application. However, funding from industry also generally comes with some strings attached, limiting flexibility in a variety of ways. The advantages and

disadvantages of industry-sponsored trials are discussed here, as well as the types of trials performed and a few details of the regulatory process.

Drug trials

Clinical trials involving new drugs are commonly classified into four phases, I–IV (and most recently also phase 0; see next section). Preclinical studies precede any of the four phases and involve animal- or cell-based experiments to obtain preliminary efficacy, safety, and pharmacokinetic (PK) information to determine whether studies in humans can or should proceed. Approval of a drug by the FDA typically comes after it has successfully passed phases I, II, and III. Post-approval studies are usually classified as phase IV, and most pediatric trials fall into this phase.

Trial phases: 0–IV

Phase 0 is a recent designation for exploratory trials designed to initially establish whether the drug or agent behaves in human subjects as was expected from preclinical studies. Typically, the studies involve the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the PK properties of the agent, how the body processes the drug, and the pharmacodynamics (PD) (i.e., how the drug works in the body).

Phase I trials are the first stage of testing in a small group of human subjects (20 to 100), typically healthy volunteers, to evaluate the safety, tolerability, and the PK and PD properties (either or both) of the drug. Trials are often conducted in an inpatient research unit, where the subjects can be observed by full-time staff. The trials include dose-ranging studies, to assess the appropriate dose for therapeutic use. Adult volunteers are usually paid for participation, but in general children would not be paid.

After initial safety has been confirmed, phase II trials are performed on somewhat larger groups of volunteers and subjects (20 to 300), to assess how well the drug works, as well as to continue safety assessments. Phase III studies are randomized controlled multicenter trials on large patient groups (from 300 up to many thousands) and are designed to be a definitive assessment of efficacy, in comparison with either a placebo or an active comparator (standard therapy). Phase III studies are typically used to gain approval by the FDA and to support indication claims for product labeling. The FDA and the equivalent European regulatory body (see further at http://www.fda.gov/InternationalPrograms/Agreements/ucm131179.htm) generally require either two successful phase III trials or a single highly successful phase III trial for approval.

Phase IV trials, also known as *Post Marketing Surveillance Trial*s, involve safety surveillance and additional efficacy evaluations of a drug after it has received permission to be sold. These studies may be required by the FDA or may be undertaken by the sponsoring company for other reasons, such as developing data for a new indication, or assessment of long-term adverse events in a larger population.

Most pediatric trials are phase IV studies. From 2000 to 2005, these trials were generally in response to an FDA Written Request asking for dosing, safety, and (if feasible) efficacy data in the pediatric population; the company is typically motivated by the promise of 6 months of additional Pediatric Exclusivity (as reviewed in the preceding chapter; see J.S. Li, *Pediatric research and the FDA*). In recent years, however, there have been a variety of other motivations for pediatric trials, including responses to other pediatric approval pathways and investigator-initiated trials. The officially designated pediatric age ranges are: neonate, birth to 30 days; infant, 1 month to 2 years; child, 2 to 12 years; and adolescent 13 to 16 (or 18) years. However, a Written Request often designates alternative age categories, most commonly as neonate, infant, 2–6 years, and 7–16 years.

Device trials

Devices undergo a different regulatory approval pathway than drugs.[26] The FDA uses a risk-based approach to determine whether a device can be marketed, by assigning each device into a regulatory class. *Class I* devices are simple low-risk devices, such as surgical instruments, and are generally considered exempt. *Class II* devices have moderate risk, such as a standard diagnostic catheter or bedside monitor, and can usually be approved by submission of a 510(k) marketing application, which requires demonstration of *substantial equivalence* to an already marketed and approved device. *Class III* devices are either high risk, such as many cardiac interventional devices (stents, internal defibrillators, ventricular assist devices) or new devices. Most Class III devices require a pre-market approval (PMA) process, which involves bench, animal, and clinical data to demonstrate safety and efficacy. The clinical trial is usually performed under an *Investigational Device Exemption (IDE)* protocol that includes at least midterm follow-up.

Another route often used for Class III devices in a pediatric population is the *Humanitarian Device Exemption (HDE),* intended for conditions that affect fewer than 4000 patients per year in the United States. An HDE allows for limited sales and marketing without the requirement of demonstrated efficacy, as long as there is reasonable evidence of safety and probable benefit. As an example, the pediatric ventricular assist device known as the *Berlin Heart* has been used under an HDE for a number of years because it is the only such device suitable for small children and has demonstrated

efficacy in Europe, but is not yet approved in the United States. Institutional Review Board (IRB) approval and informed consent (from the patient or family) at the local institution are required before the manufacturer can ship the device.

In 2007, Congress passed the Pediatric Medical Device Improvement and Safety Act,[27] which identified the pediatric need for improved access to new devices and post-marketing safety monitoring. Although the Act encourages sale of devices under an HDE for conditions affecting fewer than 4000 patients, which includes most pediatric conditions, to date there is no legislation or regulation equivalent to the 2002 Best Pharmaceuticals for Children Act to incentivize manufacturers to perform device trials in children.[21,28,29]

Advantages and disadvantages of industry sponsorship

Industry sponsorship offers a number of advantages in performing a clinical trial. The most important among these involve the potential to improve the care of pediatric patients through access to new drugs and devices, and establishment of dosing guidelines, safety data, and efficacy outcomes. Often a trial is the only mechanism that allows use of a new drug or device in the intended population prior to the official FDA approval. In addition, industry involvement usually provides adequate funding without the requirement for a prolonged grant application and funding process. Furthermore, because the company is motivated to get the trial done and publicized as quickly as possible, the funding generally provides support for a wide variety of necessary administrative functions, including IRB submission, consent design, data collection, patient follow-up, statistical support, and manuscript submission. For the individual investigators, participation in such trials also offers academic advantages, through the ability to be an early-stage user of new drugs or devices, mention in publications, opportunities for presentation of results, funding for research effort, and support of research infrastructure that can be useful for other trials as well. Finally, active participation in clinical trials with good recruitment leads to inclusion as an author on study publications, and builds a resume of experience for the investigator, which invariably reaps rewards through invitations to participate in, or even run, industry-sponsored and non-industry-sponsored trials in the future.

The primary disadvantage of an industry-sponsored trial is the shift in locus of control to the sponsor. In rare cases, the sponsor will provide an unrestricted educational grant to the trial proposers, which allows the investigators full control from design through publication, regardless of trial outcome. For most studies, however, the sponsor maintains final control over the study design, outcome variables, the body of data itself, analyses, and at least the timeline for approval of publications. Ideally, the interests of the investigators and of the company are enough aligned that significant conflicts do not arise, but if the results are not consistent with the company goals, then conflicts may arise. It is important, therefore, to structure contracts in advance, to allow for eventual publication after company review, regardless of the outcome. The best situation is to have access to and guaranteed use of the data. As with any funding source, another potential issue with industry-sponsored trials is inadequate funding. Typically, this issue arises more for investigator-initiated trials, with the trade-off being greater independence in all the other aspects of study performance, data analyses, and reporting.

Performance issues

Regardless of funding source, all drug and device trials in a pediatric population have a number of features and barriers in common. In this era, all investigators and personnel must have documented familiarity with a wide variety of IRB, regulatory, consent, and other issues related to trials and human subjects. In most cases this is accomplished through an online course, such as the Miami CITI course,[30] but generally each institution has its own guidelines. For any pediatric clinical trial, there is a specific overall threshold that there must be no potential for more than minimal harm (e.g., complications of a blood draw or intravenous administration), unless there is the potential for direct benefit to the subject. Study design is critical, with inclusion of equipoise, and well-thought-out goals addressing issues such as PK, PD, dosing, short-term and long-term safety, and efficacy. A critical feature is the adequacy of the patient population in the participating centers to allow complete recruitment and so to adequately power the trial. A trial that cannot reach conclusions for lack of significance is of minimal value to the investigators and the sponsor. Two important differences regarding recruitment in pediatric versus adult clinical trials is that, for the most part, only affected patients can be recruited as subjects in pediatric trials, and significant financial incentives cannot be used to induce children or their families to participate. Consequently, investigators must be creative in finding small rewards for participation, such as family expense reimbursement for travel, food, and lodging, and movie passes or perhaps a savings bond for the child. Most of these issues are addressed in detail in other chapters of this article.

One potentially important issue in trial participation is dealing with the rules specific to each institution's participation. Most academic centers have a wide variety of protective clauses built into their contracts, to ensure access to that institution's data and to protect intellectual property rights. Such rules may also serve as barriers to

participation and can dramatically slow down the contract process, limiting the investigator's ability to participate and to recruit patients, particularly in large multi-institutional studies. Ideally, the institution's legal office has a reasonable balance in its approach, allowing participation while still protecting the rights of the investigators and the institution.

How to develop trials

As a rough guide for the investigator interested in leading an industry-sponsored clinical trial, a few simple steps common to all trials can be identified. First and foremost, there has to be a need for the information that a proposed trial might generate. Second, it is important to develop preliminary end points, so that a power analysis can be performed to estimate the number of subjects and study centers necessary to complete the trial. The next step is to seek support for the study. Obtaining significant industry support will depend on the vendor identifying a financial gain for the company; a study in which the Pediatric Exclusivity rule might apply would be ideal. Other options include the NIH (for scientifically important questions), the FDA (for drugs currently approved in adults that qualify for an *orphan* designation), and even funding by a set of performing centers, if the trial costs can be minimized by the protocol being close to the standard of care. Finally, the investigator can provide tremendous value by knowing which centers and investigators are likely to participate and recruit subjects.

Summary

Pediatric clinical trials of drugs and devices are feasible through experienced groups of investigators in all areas of pediatric cardiology with available industry sponsors. Despite varied motivation on the part of sponsors, many trials have and can provide important benefits for the pediatric population, particularly when the investigators work together with the industry sponsor on the trial design. It is likely that Congress and the FDA will continue to find novel incentives to promote these pediatric clinical trials in the future.

Funding

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TRANSLATIONAL RESEARCH: CLINICIANS AND BASIC SCIENCE

Seema Mital, MD

There is a lack of growth in the numbers of clinician–scientists, at a time when the need for clinician–scientists is the greatest. Clinician–scientists are critical in translating major scientific breakthroughs and rapid advances in research technology to the bedside. Succeeding as a clinician–scientist requires considerable talents to excel in both clinical and research arenas. This chapter discusses the key role of clinician–scientists, with both opportunities and challenges, and points to guidelines for a successful career in translational research.

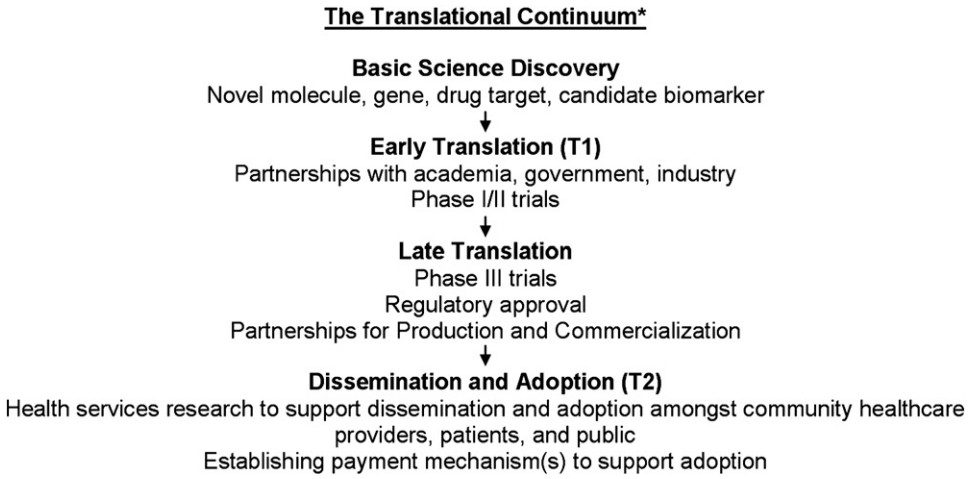
Defining translational research

The Translational Research Working Group of the NIH National Cancer Institute defines translational research as "research [that] transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce [disease] incidence, morbidity, and mortality" (http://www.cancer.gov/researchandfunding/trwg/TRWG-definition-and-TR-continuum). Such discoveries typically begin with basic or "bench" research and then progress to the clinic or patient's "bedside with bidirectional flow of knowledge. The Institute of Medicine's Clinical Research Roundtable (http://www.iom.edu/Activities/Research/ClinicalResRT.aspx) described two "translational blocks" in the clinical research enterprise, now labeled as T1 and T2. T1 refers to the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans. T2 refers to the translation of results from clinical studies into everyday clinical practice and health decision making. The flow chart in Figure 1 depicts the translational continuum that connects scientific discovery to clinical application.

The translation gap and the central role of clinicians in translational research

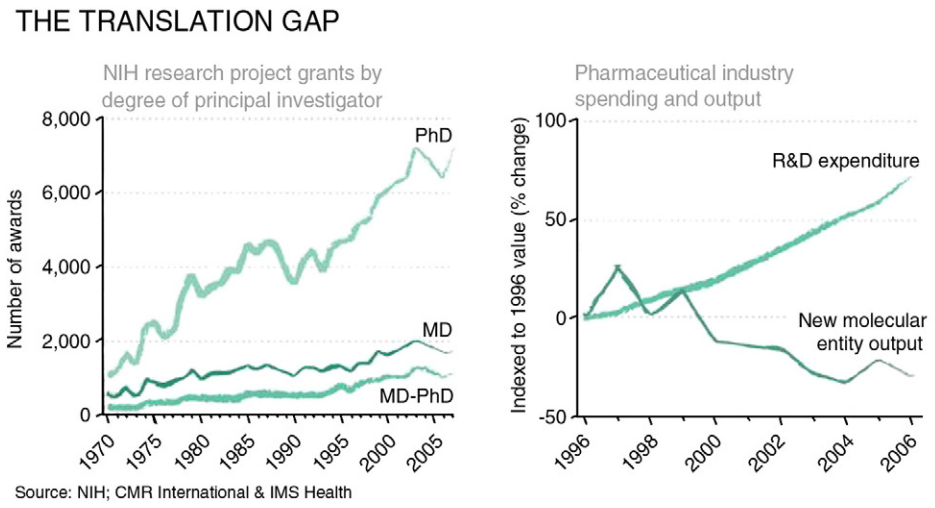
There has been growing concern that the enormous investment by the NIH and other funding agencies in biomedical research and understanding disease mechanisms has not translated proportionately into new diagnostics, treatments, and preventive measures for human disease. There appear to be multiple roadblocks in achieving scientific translation, relating both to insufficient manpower and to systems capacity. A review of the composition of the U.S. physician work force revealed a steady increase in the number of physicians engaged primarily in clinical care in the years from 1980 to 2003, without a concomitant increase in physicians engaged primarily in research or teaching. During the same time period, the average age at first R01 funding of investigators increased by 5–6 years. The translation gap depicted in Figure 2 reveals two divides, one between highly specialized PhD scientists (who perform the bulk of biomedical research) and MD-PhD clinician–scientists (a minority) and another between industry funding and output in terms of new molecular

Figure 1



The translation continuum, from basic science to dissemination and adoption. *Adapted from the President's Cancer Panel's 2004–2005 report Translating Research into Cancer Care: Delivering on the Promise.

Figure 2



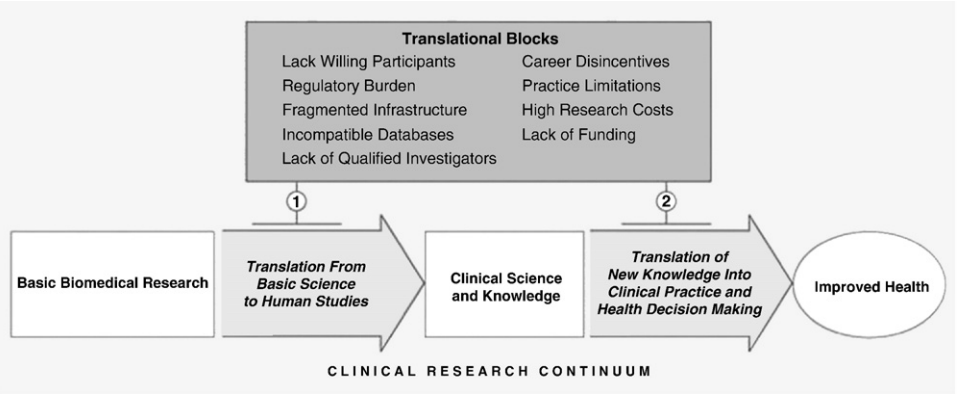
The Translation gap. The last 25 years have seen a surge in funded PhD scientists without an increase in clinician–scientists. Also, despite a growing investment by the private sector (i.e., pharmaceutical industry investment in research and development), the number of targets that have succeeded in the drug pipeline have not increased. Based on data from the U.S. National Institutes of Health (http://www.nih.gov), CMR International (http://www.cmr.org), and IMS Health (http://www.imshealth.com).

entities. This second gap represents the difficulty that private industry faces in pushing new targets identified through the burgeoning field of genomics, proteomics, and other high-throughput technologies through the drug discovery or diagnostics pipeline. An additional roadblock is in the dissemination and adoption of new diagnostics and therapeutics into medical practice (Figure 3).

The Clinical Research Round Table at the Institute of Medicine in June 2000 identified the challenges facing the national clinical research enterprise and formulated recommendations to address them. These areas include

1. Enhancing public participation in clinical research
2. Developing Information systems to support health-care research

Figure 3



Translation blocks in the clinical research continuum. Reproduced with permission from Sung et al.[31]

3. Developing an adequately trained workforce
4. Increasing funding for clinical and translational research

The NIH has invested in several efforts aimed at bridging the gap in translational research, enabling more research on human subjects and samples to generate findings relevant to humans, and not just animal models, and to facilitate the transformation of basic science breakthroughs into clinical applications. Clinicians and clinician–scientists play a central role in accelerating the translation of new knowledge from bench to bedside. The 21st century has seen major breakthroughs in biomedical research, including the unraveling of the sequence of the human genome, advances in sequencing technologies, proteomics and other "-omics" technologies, stem cell and reprogramming technologies, high-throughput drug and chemical screening for drug discovery, imaging technologies, and nanotechnologies—all of which can have direct clinical applications and can change the practice of medicine and usher in the era of personalized health care. The clinician–scientist stands at the crossroads of this translational continuum and possesses the unique skills necessary to harness discovery for patient and public benefit. Clinicians play a strategic role, not only in their close access and interaction with patients and a detailed understanding of the nature of human disease, but also in recognizing the gaps in knowledge of disease and in the application of advanced technologies and research findings toward newer diagnostic and therapeutic strategies for patient benefit.

Succeeding as a clinician–scientist

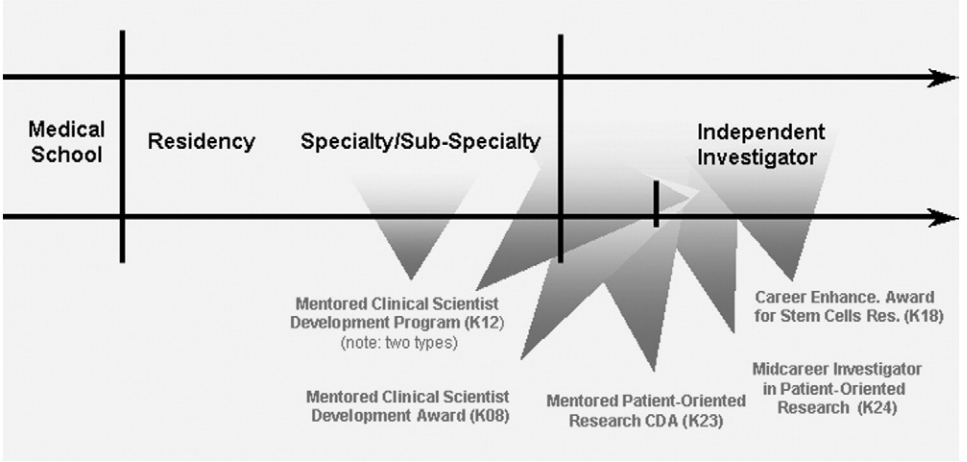
Success as a clinician–scientist requires expertise not only as scientist and as clinician, but also as a public health advocate who can engage both public and private sectors to invest in strategic research opportunities that can advance health care. The rapid advancements in science and technologies make it challenging for clinician–scientists to stay at the cutting edge of research and technologic advancements. Furthermore, the increasing complexity of research has generated the need for research teams with interdisciplinary collaborations that allow sharing of expertise across disciplines, to achieve research goals rapidly as well as to translate the findings quickly to the bedside. Most major advances in research, including genomics and stem cell research, have been the product of team efforts. The clinician–scientist is positioned to be an integral and critical member of such teams. The tools for success are described in greater detail in a later chapter (B.S. Marino and I.A. Williams, *Mapping a career development pathway in clinical research*).

Career development pathways in translational research

Training Opportunities

In 1998, the NIH responded to the need for expanding the pool of clinician–scientists by introducing new career development awards and, in 2002, the NIH began to offer competitive loan repayment programs offering at least two years of tax-free debt relief for clinical trainees committed to clinically oriented research training. The opportunities for training in basic and clinical research are described in detail in a later chapter of this article (J.D. Scott, *NIH early career research training opportunities for pediatricians*). These include NIH-funded fellowships and individual and institutional (i.e., T32) awards, as well as the NIH Pathway to Independence award (K99/R00) that supports a trainee's transition from a research fellowship to an early-career independent investigator. Other transition awards include predoctoral and postdoctoral fellowships and the

Figure 4



NIH career development awards (K series) for individuals with a health-professional doctorate. Adapted from the NIH K Kiosk website (http://grants1.nih.gov/training/careerdevelopmentawards.htm).

Fellow to Faculty Transition award offered by the American Heart Association.

Early career awards

The career development awards available to individuals with a health profession doctorate, typically after completion of clinical training and appointment to a faculty position, are diagrammed in Figure 4, and detailed descriptions are available in Table II. These include the Mentored Clinical Scientist Developmental Program Award (K12), the Mentored Clinical Scientist Award (K08) for those interested in basic research, the Mentored Patient-Oriented Research Career Development Award (K23) for those interested in clinical research, the Career Enhancement Award in Stem Cell Research (K18), the Mentored Quantitative Research Career Development Award (K25), and several others. Typically, a minimum 75% of full-time professional effort is required, with exceptions. Salary limits and research costs vary by Institute or Center. Additional information is available online at the NIH K Kiosk (http://grants.nih.gov/training/careerdevelopmentawards.htm).

Other early career and translational initiatives

Recognizing the importance of scientific collaboration in research advancement and training, the NIH launched the Clinical and Translational Science Awards (CTSA) consortium in October 2006 to assist institutions to forge interdisciplinary research teams consisting of basic, translational, and clinical investigators, community clinicians, clinical practices, networks, professional societies, and industry partners. The consortium began with 12 academic health centers in the United States and by 2009 had expanded to 46, with expansion to 60 institutions expected by 2012. The goal of the consortia is to provide opportunities for training and innovative research and to promote rapid application of research findings to clinical practice. These awards focus on advancing specific opportunities along a developmental pathway toward patient benefit, and they reward collaborative team science. Another effort by the NIH to promote bench-to-bedside translation is through a pilot program, the NIH Rapid Access to Interventional Development (RAID) program. When private sector capacity is limited or not available, especially for high-risk therapies, this pilot program provides, at no charge, critical resources for the development of new therapies accelerating the bench-to-bedside translation.

Overall, the doubling of the NIH budget between 1998 to 2003 led to an increase in the number of new R01 investigators but this increase was not sustained. To identify and attract new biomedical researchers, the NIH announced a policy in 2009 to identify Early Stage Investigators, defined as new investigators who are within 10 years of completing their terminal research degree or within 10 years of completing their medical residency at the time they apply for R01 grants and who have not previously competed successfully for a significant NIH independent research award. These applications are given special consideration during peer review and funding. Another new award is the NIH Director's New Innovator Award; as part of NIH's commitment to increasing opportunities for new scientists, this award supports exceptionally creative early-stage investigators who propose highly innovative projects that have the potential for unusually high impact.

Table II. NIH career development awards (K series)

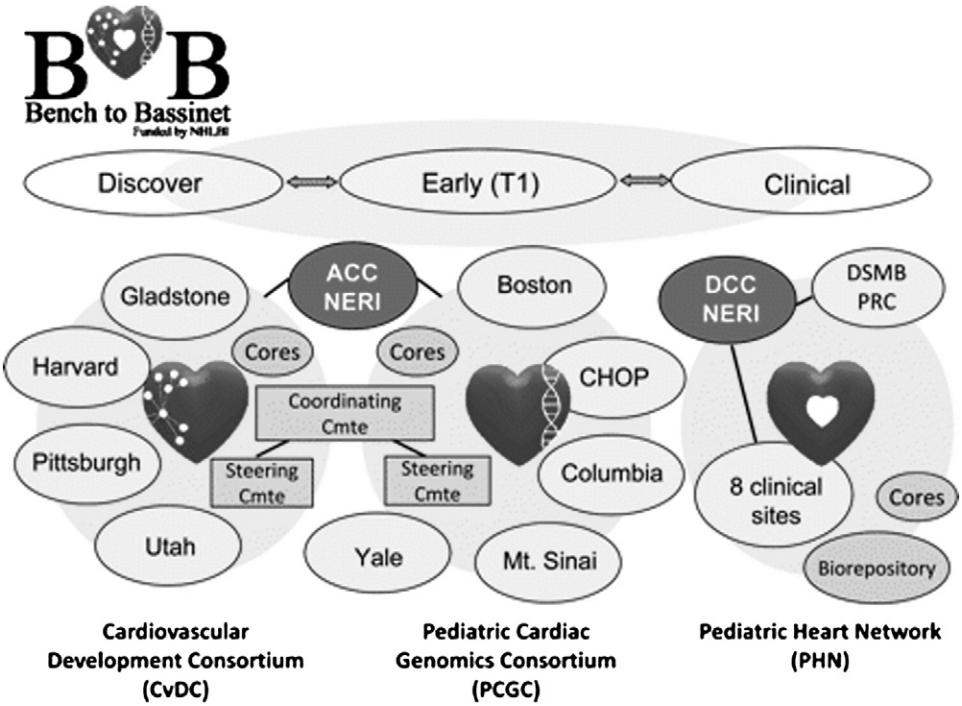
Type	Purpose	Duration
Mentored Research Scientist Development Award (K01)	This NIH-wide K01 program provides support and "protected time" for an intensive, supervised career development experience in the biomedical, behavioral, or clinical sciences leading to research independence. Some Institutes and Centers use the K01 to support individuals who propose to train in a new field; for individuals who have had a hiatus in their research career; or to increase research workforce diversity.	3–5 years
Mentored Clinical Scientist Research Career Development Award (K08)	The NIH-wide K08 program prepares qualified individuals for careers that have a significant impact on the health-related research needs of the Nation. This K08 provides support and "protected time" to individuals with a clinical doctoral degree for an intensive, supervised research career development experience in the fields of biomedical and behavioral research.	3–5 years
Mentored Clinical Scientist Development Program Award (K12)	The K12 program is supported by several Institutes and Centers. The K12 program provides support to an institution for the development of independent scientists. Most, but not all, K12 programs are focused on enhancing the careers of physician scientists.	Up to 5 years. Appointments of scholars are usually for 1–2 years
Career Transition Award (K22)	The K22 program is supported by a few Institutes and Centers. In general, the K22 program supports an individual postdoctoral fellow in transition to a faculty position. Applicants may be in an NIH Intramural Program. Some Institutes and Centers also accept applications from extramural scientists.	1–2 years (mentored) and up to 3 years (independent)
Mentored Patient-Oriented Research Career Development Award (K23)	The NIH-wide K23 program is designed to ensure a future cadre of well-trained scientists working in Patient-Oriented Research. The K23 is designed to encourage research-oriented clinicians to develop independent research skills and gain experience in advanced methods and experimental approaches needed to become an independent investigator conducting patient-oriented research.	3–5 years
Mentored Quantitative Research Career Development Award (K25)	The NIH-wide K25 program is designed to attract to NIH-relevant research those investigators whose quantitative science and engineering research has thus far not been focused primarily on questions of health and disease. The K25 is designed to support individuals with quantitative and engineering backgrounds to integrate their expertise with NIH-relevant research.	3–5 years
K30 Clinical Research Curriculum Award (CRCA)	The K30 Clinical Research Curriculum Award (CRCA) is designed to attract talented individuals to the challenges of clinical research and to provide them with the critical skills that are needed to translate basic discoveries into clinical treatments. It supports the development and/or improvement of core courses designed as in-depth instruction in the fundamental skills, methodologies, and theories necessary for the well-trained, independent, clinical researcher/	3 years. Appointments of scholars are usually for 1–2 years
NIH Pathway to Independence (PI) Award (K99/R00)	The NIH-wide K99/R00 program is designed to increase and maintain a strong cohort of new and talented NIH-supported independent investigators. The K99/R00 is designed to facilitate the transition from a mentored postdoctoral position to a stable faculty (or equivalent) position with independent NIH or other independent research support at an earlier stage than is currently the norm.	

See further at http://grants1.nih.gov/training/careerdevelopmentawards.htm.

Besides the NIH, the American Heart Association offers early-career funding in the form of Beginning Grant-in-aid (2 years) and Scientist Development Grant (3–4 years). These are offered at the national level, and some are offered by regional affiliates as well. In addition, new opportunities for participation in clinical and translational research continue to arise. Researchers need to stay abreast of emerging opportunities and take advantage of them as they arise.

An article by Lauer and Skarlatos[32] describes the translational research opportunities for cardiovascular diseases at the NHLBI. These include the Cardiac Translational Research Implementation Program (P20), NHLBI Pediatric Cardiac Genomics Consortium (U01), Pediatric Heart Network (U01), NHLBI Progenitor Cell Biology Consortium (U01), Cardiovascular Cell Therapy Research Network, Science Moving toward Research Translation and Therapy, NHLBI Centers for Cardiovascular Outcomes Research (U01), Cardiovascular Research Network (U01), among others. These research networks and consortia provide opportunities to young investigators to participate in network studies and in individual ancillary studies. The Pediatric Heart Network (http://www.pediatricheartnetwork.com) also supports

Figure 5



The NIH Pediatric Cardiovascular Translation Consortium is composed of four centers that comprise the Cardiac Development Consortium, five centers that comprise the Pediatric Cardiac Genomics Consortium, and eight clinical centers that comprise the Pediatric Heart Network. In addition, the network has steering committees, a data coordinating center (DCC), core laboratories and a central biorepository, a Protocol Review Committee (PRC), and a Data Safety and Monitoring Board (DSMB). This represents the continuum from discovery to early translation (T1) and late translation (T2). Reproduced with permission from Lauer and Skarlatos.[32] See also http://www.nhlbi.nih.gov/funding/inits/faq-ptc.htm.

two Clinical Research Skills Development Cores to train young fellows and faculty in research (http://www.nhlbi.nih.gov/funding/policies/ntwk_skill.htm). More recently, the NIH–NHLBI funded the Pediatric Cardiovascular Translation Consortium, which offers opportunities for research training and experience in areas of cardiac development, genomics, and clinical research, also known as the Bench to Bassinet program. Consisting of a Cardiac Development Consortium to facilitate gene discovery using basic science approaches and animal models and a Pediatric Cardiac Genomics Consortium that focuses on human genomics, the Consortium will interact with the Pediatric Heart Network to ensure rapid progression from the laboratory to human studies and clinical trials (Figure 5) (http://www.nhlbi.nih.gov/funding/inits/faq-ptc.htm).

The NIH's 2-year infusion of American Recovery and Reinvestment Act (ARRA) funds in 2009 were designed to empower the nation's best scientists to discover new cures, advance technology, and solve some of the greatest health challenges (http://recovery.nih.gov/). Although these funding opportunities were aimed at established investigators, the experience highlights the importance of being prepared and poised to capitalize on new funding opportunities that arise with changing emphasis on needs. Researchers also need to stay abreast of focused application opportunities offered through Requests for Applications (RFAs) or Program Announcements (PAs).

Finally, a clinician–scientist cannot stop at successful acquisition of independent research funding. In concert with research collaborators, the clinician–scientist needs to learn how to leverage research output to engage institutions, industry, funding agencies, government, health care policy makers, and the public and patient community, to ensure that research findings are not left sitting on shelves but are translated into advances in medicine that can benefit patients.

Summary

The clinician–scientist stands at the crossroads of the translational continuum and possesses the unique skills necessary to harness discovery for patient and public benefit. Success as a clinician–scientist requires expertise not only as a scientist and clinician, but also as a public health advocate, one who can engage both

public and private sectors to invest in strategic research opportunities that can advance health care. The need for clinician–scientists is greater today than it has ever been, if we are to achieve our goals of applying and translating basic research findings to the bedside. It is critical that we have a well-trained generation of clinician scientists to help achieve these goals and to continue the training of future generations of clinician scientists. Michael Brown, 1985 Nobel prize winner in medicine, said in his banquet speech, "*We are fortunate to live at a time when the methods of basic science are so powerful that they can be applied directly to clinical problems*". Now is the time to realize this goal.

For Suggested Readings see References 31-38.

Funding

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CLINICAL IMAGING LABORATORY RESEARCH

Steven D. Colan, MD

Because of the increasing sophistication of imaging and physiologic laboratories, it is not surprising that clinical imaging laboratory findings occupy an increasingly important role in clinical research. In addition to the importance of the clinical imaging laboratory for defining inclusion and exclusion criteria, the results of this testing may represent important study outcomes, or may be used as predictors of outcome. In this role, the laboratory functions as a research tool, and investigators with specific expertise in the laboratory techniques generally participate in a primary or important collaborative role. Multicenter studies often rely on centralized (core) laboratory analysis, which offers additional potential for investigations concerning the laboratory testing itself, beyond the use of the test results as a clinical finding. A variety of issues confront investigators who wish to participate in clinical imaging laboratory research.

The clinical research process involves many sources of data, including data generated in a variety of clinical laboratories. Some of these laboratories perform analyses that are standardized, commercialized processes. Generally, this work is performed on a fee-for-service basis and, although the results of these clinical tests may be used in the clinical research process, the method of analysis is not the purpose of the research. In contrast, a number of laboratories use techniques that are in evolution, are frequently highly observer-dependent, and generally are not commercially available. Examples of such work include many of the genetic analysis methods, histology analysis, and most clinical imaging, including ultrasound, angiography, and magnetic resonance imaging. For tests such as these, even though the results generated by the technique may be in common clinical and clinical research use, the methods themselves remain active research targets.

Echocardiography is an excellent example of the sort of techniques that occupy this overlap zone, of a clinical research tool that is at the same time a tool subject to ongoing research. For any specific research protocol, echocardiography may function in one or both of these roles. Data derived from echocardiograms are known to have much better intraobserver than interobserver variability, resulting in the common practice of relying on echocardiographic core laboratories for review and analysis of echocardiograms obtained in conjunction with multicenter studies. These three activities (i.e., research using echocardiograms, research on echocardiograms, and echocardiographic core laboratories) all offer opportunity for research participation by echocardiographers. These three types of research will be discussed with reference to echocardiography, but there is nothing unique about echocardiography in this regard. Other imaging modalities such as magnetic resonance imaging and cineangiography play similar roles in the research enterprise and have a large subjective and technique-dependent aspect that makes them not merely a tool in the research enterprise but also the focus of the research activity. Echocardiography was chosen as the focus of this discussion because it is a commonly used modality in cardiology research and is an exemplar of the research opportunities in clinical imaging laboratory research. The issues discussed below with regard to echocardiography are also applicable to other such imaging techniques. The discussion is not intended to be representative of the molecular, serologic, and genetic laboratories, however, as these involve an entirely different set of considerations.

Research using echocardiograms

As with most imaging modalities, the value of the data derived from echocardiograms is highly dependent on the skill of the individual observers. The echocardiographer therefore often plays an important role in study design with regard to selection of echocardiographic end points and methodology. Standardization of data acquisition is an effective means of reducing the random variance component of clinical testing and is of particular importance with a modality such as echocardiography, in which data acquisition is freehand. The echocardiographer plays a critical role in the effort to reduce this variance through ultrasonographer meetings and training sessions, as well as study design modifications that permit reliance on the fewest number of different personnel. Noncardiology studies often include cardiac end points in the study design, but do not always appreciate the

importance of having on-site cardiologist participation in quality control of data acquisition process. In addition, interpretation of echocardiographic findings is often complex, and participation of personnel with specific understanding of the significance and limitations of echocardiographic findings is essential.

Research on echocardiography

A high percentage of investigations into the physiologic meaning and diagnostic accuracy of echocardiographic findings are single-center studies with the primary aim of addressing these issues. These are the most common type of clinical imaging laboratory studies and the most accessible for junior investigators. Echocardiography as a field has benefited from a remarkable progression of technical advances, each of which has required in vitro and in vivo validation. Industry commonly works with interested centers in product development and testing. Advances such as Doppler, color Doppler, transesophageal probes, intracardiac probes, and three-dimensional imaging probes have each come to market through such cooperative ventures. These efforts often require a dedicated time commitment that exceeds the availability of senior personnel and thus frequently are ideal projects for junior staff.

Ultimately, single-center clinical studies invariably invite criticism concerning the generalizability of the findings, because of limited sample size, restricted race or age spectrum, restricted disease spectrum, and observer bias. For example, tissue Doppler findings have been reported to have a 100% sensitivity for preclinical diagnosis of subjects who carry a familial sarcomeric gene mutation–associated hypertrophic cardiomyopathy but do not manifest cardiac hypertrophy.[39] Subsequent studies indicated that diastolic abnormalities are often seen in such genotype-positive, phenotype-negative subjects, but the specificity and sensitivity of tissue Doppler were not as high as originally reported.[40] Both of these studies were conducted in relatively small cohorts that included multiple members of individual pedigrees. There are implications of these findings in terms of the pathophysiology of the disease and the potential diagnostic utility of the presence of abnormal diastolic indices; however, generalizability of these results requires confirmation in a larger, genetically diverse cohort, something best undertaken as a multicenter study.

The echocardiographic core laboratory

Many multicenter studies rely on echocardiographic core laboratory interpretations. Ultimately, this is often an economic decision. Usually, local interpretation of the echocardiogram is performed for purposes of patient care, and the center interpretation can also be used for study purposes. If additional analyses or measurements are required, the study may need to cover this expense. Alternatively, the images can be transferred to a central laboratory for analysis. Under these circumstances, the core laboratory results are typically used exclusively for research purposes and the entire expense of the analysis must be covered by the study. Because of this, the cost-per-echo is higher for core laboratory–based studies. However, interobserver variability is higher than intraobserver variability, and therefore fewer subjects are required to achieve study end points if the study is based on core laboratory analysis. The cost tradeoff for core laboratory–based studies is therefore the increase in per-subject echocardiographic costs versus the reduction in costs related to fewer subjects, a balance that generally tips in the favor of core laboratory analysis. In addition, for many studies, subject enrollment is the rate-limiting step, and reduction in total enrollment requirements can mean the difference between a successful versus an underpowered study, potentially justifying the increased price tag.

Operation of a core laboratory requires infrastructure such as image storage, workstations and specialized software, administrative and information technology support, and skilled personnel able to perform the echocardiographic analysis. Although there are some commercial echocardiographic core laboratories, many core laboratories are primarily academic operations, and the personnel are primarily motivated by the desire for participation in the specific research. The distinction should be clarified at the time of project design, to avoid conflicts concerning the level of participation of core laboratory personnel in the academic aspects of the research.

In addition to participation in the clinical research project itself, which generally falls under the category of research using echocardiograms, there is significant potential for ancillary projects that involve research on echocardiography. For example, the larger study sample size that is characteristic of multicenter studies enables more meaningful investigation of the specificity and sensitivity of echocardiographic findings, the interrelationship of derived variables, and (depending on the other data gathered in the course of the primary study) there may be potential for comparisons between imaging modalities or investigations into the physiologic mechanisms underlying specific echocardiographic findings.

There are excellent opportunities for fellow participation in clinical imaging laboratory research. Although it is difficult for the fellow to function completely independently, the role of the mentor is often restricted to advice and supervision, and in this setting the degree of independence often exceeds that in other projects. Fellow projects require completion in a restricted time frame, and therefore are generally best if they are based

on reanalysis of existing image data or very well-defined questions that involve concentrated but brief prospective data collections, such as exploration of new technology. Prospective clinical research studies using echocardiographic data as an end point (as opposed to research on echocardiography) are more challenging, because of the unpredictable nature of patient recruitment. An experienced mentor is of particular importance in this process, to help the fellow avoid the common mistake of undertaking a project that is too ambitious and then must be abandoned at the completion of the training period.

Beyond fellowship, those individuals who pursue clinical imaging laboratory research as a career activity generally spend a large percentage of their time in clinical imaging. Technological advances have formed the basis for most of the progress in clinical imaging and direct, hands-on experience is critical for the investigator who wishes to remain current with the relentless refinement of technology. Direct experience with the clinical application of newer measurement and display methods also provides invaluable information concerning their feasibility, practicability, and realized cost of implementation in the clinical setting. Direct contact with equipment manufacturers and software vendors, as well as cooperative agreements, are often advantageous and at times necessary to gain access to the information, raw data, and software revisions that may be required for particular investigations. There are exceptions to this model, with some clinical imaging investigators functioning exclusively in the research arena, and there are even imaging core laboratories that function as a fee-for-service enterprise without academic affiliation. These are the exceptions, however, and the majority of investigators who choose this career path will find their research and clinical activities deeply intertwined.

Funding

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IMPORTANT CLINICAL RESEARCH SKILLS

HOW TO DESIGN A CLINICAL TRIAL

Jane W. Newburger, MD, MPH

Clinical trials are human experiments in which the investigator controls the intervention and observes the outcome. Randomized clinical trials offer the strongest evidence for cause and effect and should be undertaken when other types of studies cannot answer the research question. This chapter briefly reviews aspects of designing randomized controlled trials, including entry criteria and subject recruitment, study end points, stratification, blinding, and data monitoring and analysis.

In determining the safety and efficacy of new medicines, devices, or surgical procedures, the randomized clinical trial provides the highest level of evidence about cause and effect. Comparisons of treatment groups in clinical trials may be designed to show superiority, equivalence or noninferiority, or dose–response relationships. Data from randomized clinical trials are highly prized when crafting evidence-based practice, and the field of pediatric cardiovascular disease has had increasing success in launching clinical trials that have impact on the field. Here we review basic aspects of designing randomized controlled trials as they apply to pediatric and congenital heart disease. Although in-depth description of clinical trial methodology is beyond the scope of the current review, excellent references related to clinical trial design are detailed in the Suggested Reading list at the end of this chapter.

Identification of a research problem

The first step in planning a randomized trial is to identify a research problem. Finding a research question amendable to a randomized trial is surprisingly difficult in pediatric and congenital heart disease. Ideally, this should be a high priority issue in the field, usually identified through clinical experience in conjunction with literature review. Clinical trials are expensive financially, and ethically, if patients are enrolled in a trial that is unlikely to improve clinical care. Thus, the proposed treatment should have a significant impact on morbidity or mortality. The research problem may be an area of controversy. Sometimes the window of opportunity in which randomization will still be acceptable in the field is narrow (i.e., the trial must be done “now or never”).

Scientific validity

Demonstration of the scientific validity of a proposed trial requires preliminary data and a research design that can answer the question. Feasibility is key; most patients and families must be willing to participate, and the cost must be acceptable. The best trials ask a clinically important question, have preliminary data, use a study design that answers the study question, are feasible, and do not entail risk without benefit. Clinical trials must have adequate power, defined as the probability of rejecting the null hypothesis when it is false. Simply put, statistical power is the probability of drawing a correct conclusion—for example, demonstrating a statistically significant difference or association when such a difference or association does exist.

Eligibility criteria

Next, design of eligibility criteria can be challenging. Eligibility criteria should include participants who have

the potential to benefit, in whom the benefit can be detected, and whose inclusion can be based on easily accessible information. Furthermore, these criteria should optimize the ease of recruitment, the likelihood of compliance with treatment and follow-up, and the generalizability of findings. Subjects should be excluded if they have an unacceptable risk of adverse reaction, if active treatment is unlikely to be effective, if they are unlikely to adhere to intervention, if they are unlikely to complete follow-up, or if they have practical problems in participating.

Entry criteria can be more or less restrictive. By limiting the variance between patients, more restrictive criteria allow a more precise comparison between treatment and control groups. Highly restrictive criteria, however, reduce the potential number of study subjects, and the results are less generalizable. For example, the Boston Circulatory Arrest Study enrolled only patients with simple d-transposition of the great artery (with intact ventricular septum or ventricular septal defect).[41] Because subjects were a highly homogeneous group, small effects of deep hypothermic circulatory arrest could be detected with a relatively limited sample size. However, the results may not be generalizable to other populations, particularly those with single ventricle who have many other more important risk factors for adverse neurologic outcome, including those preceding surgery (e.g., genetic abnormalities, fetal environment). Conversely, less restrictive criteria allow for easier recruitment of study subjects and greater generalizability, but may require a greater sample size for adequate power.

Patient recruitment

Patient recruitment is often the greatest challenge in clinical trials. It is especially important, therefore, to obtain realistic estimates of potential patient accrual using the exact study eligibility criteria that are planned prior to initiating the study. It is also important to organize a plan to capture as many potentially eligible patients as possible. One must enlist the support of colleagues and tailor the strategy of recruitment to each of the environments from which patients may be recruited (such as the emergency room, clinic, inpatient service, intensive care unit). The number of patients in the theoretical pool always exceeds those eligible, which again exceeds those who consent. For example, in the Pediatric Heart Network's trial of angiotensin converting enzyme inhibition in infants with single ventricle, 1245 subjects were screened, 533 (43%) were eligible, and only 230 (43% of eligible subjects) were enrolled.[42] Furthermore, for referral centers, if a trial requires return to the center, only those living close by can participate. These facts of life should be considered in sample size calculations.

Choice of study end points

The next challenge is that of defining appropriate study end points. The choice of study end points can be facilitated by reviewing the literature and identifying prior research with similar treatments or similar subject population. Ideally, the primary outcome is clinically relevant or important, easy to ascertain, has low measurement error, and can be observed independent of treatment assignment. The primary outcome is always chosen before the start of data collection. Ideally, one should have a single primary outcome. To choose the primary outcome, it is helpful to have some data regarding the magnitude of the expected treatment effect for the study proposal, the variability of the measure, and (if change over time is of interest) the correlation between measurements over time. In contrast, one can have multiple secondary outcomes. These are more often biologic, less precise, less objective, and possibly underpowered but important; when taken together, they contribute to the weight of evidence regarding a treatment effect. Brainstorming sessions are often needed to find primary end points that are both meaningful and for which sufficient data are available to perform reliable power calculations.

Ideally, primary end points for trials should reflect that subjects "feel better" or "live longer." Scales for assessing the quality of life in children with heart disease are now relatively well developed, but in children of young age, assessments of quality of life reflect parental assessment. Mortality rates are low in most pediatric cardiac conditions, and rare and diverse disorders create limited sample sizes, which are obstacles to achievement of adequate power.

Surrogate and composite outcome variables

Because mortality is generally rare and measurement of some outcomes might take decades, the use of surrogate outcomes is particularly attractive in pediatric cardiology research. A *surrogate end point* is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. Under some circumstances, the FDA may grant approval of a drug or device based on an effect on a surrogate end point that is reasonably likely to predict clinical benefit based upon such evidence. Use of a surrogate outcome variable can reduce study duration if the surrogate outcome occurs before the primary outcome. However, there are numerous examples of trials using surrogate outcomes in adult cardiovascular disease that ultimately did not predict the outcome of interest.[43]

Another method of enhancing statistical power in face of rare outcomes is to construct a *composite end point*. This can be a composite event, one that is considered to have occurred if any one of several different outcomes are observed. The components of a composite end point

should generally be expected to move in the same direction; for example, one would not combine bleeding and clotting end points in a composite outcome for a trial of an antithrombotic agent in neonates with systemic-to-pulmonary artery shunts. In drug trials, the components of a composite outcome should all be related to its believed mechanism. Within pediatric cardiology, an excellent example of a composite outcome came from the PRIMACORP trial.[44] This trial had the study objective of determining the efficacy and safety of prophylactic use of milrinone versus placebo in pediatric patients at high risk of developing low cardiac output syndrome following cardiac surgery. The primary end point was the composite of mortality or a clinical diagnosis of low cardiac output syndrome, which required initiation of additional inotropic support, escalation of existing pharmacologic support (at least 100% over baseline), or mechanical support (extracorporeal membrane oxygenation, ventricular assist device, intra-aortic balloon pump).

Randomization

Randomization is important in removing conscious or unconscious bias in allocation to the treatment or control group and ensures comparability between treatment groups. In some studies, randomization has proved to be very difficult, because participants have such strong preferences. For example, in the early days of device closure of atrial septal defects, it proved to be infeasible to randomize children to surgical versus transcatheter closure.

Stratification

Stratification reduces or eliminates variation in outcomes by ensuring the same distribution of a known predictor in both treatment groups. It enhances the power of a small trial by reducing variation in outcome due to chance disproportion of important baseline variables. For example, in the Pediatric Heart Network's single ventricle reconstruction trial,[45] treatment assignment to the Blalock–Taussig shunt versus the right ventricular-to-pulmonary artery shunt was stratified by the presence or absence of aortic atresia and obstructed pulmonary venous return, both of which are known risk factors for mortality that might not have been equally distributed between the treatment groups by chance. Stratification ensured that children with these risk factors would be equally represented in both treatment groups. In general, the number of strata should be small (usually no more than three or four), to minimize the likelihood of imbalances between treatment groups due to incomplete filling of blocks.

Blinding

Blinding removes conscious or unconscious bias in a patient's report of symptoms and in an investigator's report of outcomes. In a double-blind study, neither the participant nor the investigator knows whether the participant is in the intervention or control group. In a single-blind study, either the patient or the physician is unaware of the treatment assignment. In an unblinded or open study, both the patient and physician are aware of the treatment assignment. Blinding can present some logistic difficulties. For example, it can be challenging to match the treatment drug and placebo in appearance and in taste. Some trials cannot be blinded (e.g., cardiac catheterization versus surgical management). All blinded studies require a procedure to unblind clinicians in emergency situations.

Statistical consultation

Sample size estimation requires knowledge of the expected mean difference or δ between treatments of interest, as well as an estimate of variability in the study population of interest, obtained either from pilot data or from published manuscripts. Clinical trials must have sufficient statistical power to detect meaningful differences between groups. The size of that difference is determined by what is clinically important, rather than by what is statistically feasible. Adequate sample size and statistical power are particularly difficult to achieve in trials involving populations with rare congenital heart defects. For example, when testing the effect of a method of intraoperative vital organ support on Psychomotor Development score of the Bayley Scales, the sample size required to detect a difference between mean scores of 7.5 points (e.g., 0.5 SD) with 90% power using a two-sided .05-level test is 84 subjects per group, a sample size that is easily achievable for most forms of congenital heart disease in a multi-center study. However, to detect a difference of 3 points (0.2 SD) would require more than 500 subjects per group! Achieving adequate power for detection of differences in dichotomous outcomes is even more challenging. For example, to demonstrate that transplant-free survival improved from 90% to 95% with 90% power would require almost 600 patients per treatment group. Thus, to avoid the heartbreak of discovering that one does not have adequate sample size to answer the study question, it is essential to consult a statistician at the earliest stages of designing a randomized clinical trial.

Study visits

Clinical trials often entail three types of visits. The *screening visit* ascertains whether a patient is eligible for the study. At the *baseline visit*, which occurs before treatment starts, one determines the comparability of treatment groups with respect to important baseline variables. *Follow-up visits* occur after initiation of the

intervention or control treatments; study outcomes are measured at these visits. A chart of the study tests according to day or time of visit is a helpful resource while the trial is ongoing.

Data forms

The design of data forms is one of the most challenging tasks in trial design. Data collection should be parsimonious, to keep the study efficient and to minimize the time needed for data entry, editing, quality control, system design and data cleaning, and data analysis. However, the collected data must be sufficient to allow the study hypothesis to be answered and properly analyzed.

Biostatistical analysis

In data analysis of trials, the patient is always analyzed according to treatment group assignment ("once randomized, analyzed"). Analysis in the group to which one was assigned is called the "intention to treat" principle. Secondary analyses can investigate outcomes according to the treatment that was actually received, but frequent cross-overs from one strategy to the other can undermine the analysis plan. "Per protocol" analyses exclude those patients who did not adhere to the randomized management strategy or to other aspects of the protocol (e.g., outcome assessment). The analysis is thus restricted to ideal patients, creating bias when nonadherence is related to prognosis. The analysis plan is always prespecified.

Multicenter trials

Especially for rare diseases, multicenter trials can be the only means of accruing a sufficient sample size in a reasonable time frame. They provide the best basis for generalization of findings, because patients are recruited from a wide population and treatment is administered in a broader range of clinical settings. However, these are much more complex to administer, and virtually always require a professional data center and core laboratories. Quality assurance is essential. Multicenter trials require central training, central interpretation of key data, central monitoring of safety with a medical monitor, site visits, and report cards.

Data and Safety Monitoring Board

All clinical trials, whether single-center or multicenter, require a Data and Safety Monitoring Board (DSMB). The DSMB personnel must be independent of the protocol and of patient enrollment. Ideally, members of the DSMB should be drawn from an institution other than the participating institution or institutions, and they should be knowledgeable in the relevant specialties represented in the trials. Most DSMBs include a statistician and an ethicist. There should be a preplanned evaluation of study outcomes while the study is being conducted. Interim analyses are necessary, to make sure that the study is safe. In some circumstances, if there is a very dramatic benefit, the study may be stopped early (using "stopping rules"). For example, the first U.S. multicenter trial on intravenous γ-globulin versus aspirin was terminated early by its DSMB because it was felt to be unethical to withhold intravenous γ-globulin from children with Kawasaki disease.[46]

Adverse events

Adverse events should be defined in the study protocol. They are classified according to severity, relationship to the study protocol, and expectedness. A challenge in all pediatric studies is that of adverse events particular to children. In addition to the usual adverse events, one needs to consider effects on somatic growth, cognitive ability, and academic achievement and behavior, as well as effects evident only with very long-term follow-up.

Children may not be allowed to take risks without the possibility of benefit. Because they are often small, the amount of blood drawn must be limited. Children hate having blood tests, so a requirement for frequent blood tests that would otherwise not be performed is a good recipe for study withdrawal and noncompliance. Finally, school-age children and their parents are unlikely to participate in a protocol that requires them to miss many school days because of research visits.

Finally, clinical trials are a team sport. They cannot be done without an enthusiastic roster of medical colleagues, nurses, and research personnel, including study coordinators, data entry clerks, and of course statisticians. The tipping point for many patients in giving consent to a trial comes when the bedside personnel in the intensive care unit are knowledgeable and positive about a research study.

In summary, the randomized clinical trial provides the strongest evidence for cause and effect and is sometimes the only design that can answer clinical questions. Although "they don't call them trials for nothing," when successful, the randomized clinical trial can be a crowning accomplishment for a multicenter group of investigators and one of the most exciting opportunities to improve clinical practice.

For Suggested Readings see References 8 and 47-55.

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KEY STATISTICAL CONCEPTS AND STATISTICAL COLLABORATION: APPROACHES FOR SUCCESFUL CLINICAL RESEARCH

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In this chapter we describe how to develop statistical skills, provide an overview of key statistical concepts, and illustrate how collaboration with a statistician can help a clinical investigator conduct successful research. An understanding of statistical concepts promotes appropriate study design, data collection, data analysis, and interpretation of findings. Statistical topics covered include probability distributions, research hypotheses, factors impacting required sample size, statistical versus clinical significance, and optimal approaches for reporting study results. Familiarity with statistical concepts will both facilitate the working relationship between clinician and statistician and help to achieve a rigorously designed study, one that will produce high-quality results from which valid conclusions can be made.

A research study has many components, including design, execution, analysis, and interpretation of findings. Effective collaboration between a clinical investigator and a statistician will increase the likelihood of success in all of these areas, as well as minimizing pitfalls. Here, we first describe how to develop statistical skills. An understanding of statistical concepts, in conjunction with early collaboration with a statistician, will promote appropriate study design, data collection, data analysis, and interpretation of findings. An overview of key statistical concepts is provided. Familiarity with these concepts will facilitate the working relationship between clinician and statistician, and will also help to achieve a rigorously designed study, yielding high-quality results from which valid inferences and conclusions can be made.

Statistical education and resources

The appropriate application of statistical principles to a research study can be accomplished in two ways: by developing a working knowledge of statistics and by collaborating with a statistician. Although formal coursework in statistics is not required, one or two biostatistics courses, completed in isolation or as part of a program in clinical effectiveness or public health, will greatly facilitate a career in academic clinical medicine. Knowledge of key statistical concepts will allow a clinical investigator to critically consider design elements for the proposed research and enhance communication with a statistician. In an academic medicine setting, there may be one or more statisticians who work directly in a clinical department or in the medical research institution's Clinical Translational Research Center, if one exists. Alternatively, a dedicated department of biostatistics located in a school of public health or medical school may be affiliated with the medical research institution and may have statisticians available for collaboration as a consultant or as a biostatistical investigator for the proposed research. Meeting with a statistician at the design phase of a study can prove efficient in the long run.

Initial collaboration

At an initial meeting with a statistician, it is important to relay information about the study that will allow the statistician to understand the motivation for the research. The research question will drive decisions about the target patient population and will help formulate the formal research hypothesis for the study. A statistician can construct the sampling plan for the proposed study, to ensure that the study captures the target population and that results are generalizable to the population of interest. Other key information to relay to the statistician includes the outcome measures, the types of data intended for collection and the rationale for their collection, and the underlying mechanism of action of any treatment to be investigated. An understanding of this information will allow the statistician to suggest the most appropriate design, data collection requirements, and analytic approach to answer the research question.

Often, investigators involve a statistician only at the end of the study, to analyze data already collected. However, sound statistical principles should be applied at the time of study design and monitoring, so that the research question can be answered in the most efficient manner. Monitoring study data as they accrue is important for quality assurance purposes; a periodic review of the study data will allow identification of problems in measurement or collection, so that these can be addressed in a timely fashion. A continuing collaboration with a statistician from start to end helps ensure that the research data on which analyses will be conducted is both high quality and relevant. An appreciation for the origins of data will enhance the investigator's skill in making inferences from study results later.

Statistical principles

Testing for differences

All data arise from an underlying probability distribution. The shape of the distribution is characterized by a measure of central tendency (e.g., the mean) and a measure of variation. Data that are collected in an experiment, observational study, or trial are ideally randomly selected from a population with a particular underlying distribution. The variability in the data can arise from multiple sources. The primary goal of statistics is to determine whether differences that we observe

between groups arise from natural variation, or from some other source, such as an intervention or treatment.

In a randomized trial of an investigational versus a standard treatment, data from the two groups will result in two estimates of the mean of the distribution from whence it arose. With statistics, we can determine quantitatively whether the two distributions are from the same source (in which case any differences between the two means are attributable to natural variation due to sampling) or whether the mean of the investigational treatment group is so far away from that of the standard treatment that one must conclude that it came from a different distribution altogether. These two scenarios are typically characterized in research by the statement of a null hypothesis (H_0) and an alternative hypothesis (H_A) for the study. In the setting of a two-group comparison, a null hypothesis typically describes a situation of no difference between groups—or, in other words, that collected data do not differ from what is expected if the difference between groups is attributable only to random variation. An alternative hypothesis typically describes the scenario of a difference between groups that is attributable to the treatment under study. For example, in a recent randomized trial of enalapril in infants of single ventricle, the null hypothesis was

H_0:. There is no difference in the mean weight-for-age *z*-scores at 14 months for patients assigned to enalapril vs. placebo.

The alternative hypothesis was

H_A:. There is a difference in the mean weight-for-age *z*-scores at 14 months for patients assigned to enalapril vs. placebo.

Using statistics, we can conduct a test of whether there is sufficient evidence to reject the null hypothesis, in favor of the alternative hypothesis, which may or may not indicate the specific direction (two-sided hypothesis) of the expected treatment effect. The test statistic has an associated *p* value. The *p* value is the probability that the observed test statistic or ones more extreme could have occurred by chance if the null hypothesis is true. When the *p* value is small, it means that the difference observed is so large that it is very unlikely that the treatment difference in outcome is due to natural variation alone; in other words, the difference observed (if in the absence of confounders) is due to some additional factor, namely, the treatment itself. It should be noted that a *p* value may be misleading if there are flaws in the study design or analysis. Understanding probability distributions will help a clinical investigator to make appropriate study conclusions.

Sample size

One of the most common questions that a researcher has for a statistician is, "How many patients/animals/specimens do I need?" There are four factors that determine the required sample size for a study: (1) the desired power, (2) the significance level, (3) the variance, or spread, of the outcome measure, and (4) the minimum clinically significant difference (MCSD). Many textbooks and software (such as NCSS/PASS [Kaysville, UT] and Stata [College Station, TX]) provide sample size formulas for a variety of study designs. We will review here only the factors noted above that influence required sample size.

To help understand the determination of the sample size, one must first consider the possible outcomes of a study. For example, if we study two treatments to determine if they are different, we find one of four results: (1) we conclude that responses to the two treatments are not different when, in reality, they are not different (correct decision); (2) we conclude that responses to the two treatments are not different when, in reality, they are different (type II error, or β); (3) we conclude that treatment responses are different when, in reality, they are not different (type I error, or α); or (4) we conclude that treatment responses are different when, in reality, they are different (correct decision).

The values α and β are usually selected by the statistician based on the null and alternative study hypotheses H_0 and H_A specified by the clinical investigator. The type I error rate α is the probability that the null hypothesis is rejected when the null hypothesis is true, or finding significance when there is no true difference ("false positive"). This error rate is typically selected to be .05, but a smaller value may be preferable when (1) a false positive result has serious or expensive consequences; (2) a monitoring plan for potential early stopping is also in place (which alters the study-wise type I error rate, because it requires comparison of treatment groups at multiple time points instead of only at trial end); and (3) there are a large number of correlated outcomes and it is desirable to minimize a false positive finding that might arise from multiple testing.

The type II error rate β is the probability that the null hypothesis is not rejected when the null hypothesis is indeed false; that is, declaring a 'negative' result when there is a true underlying difference. Choosing a design and sample size that maximize the statistical power (designated as $1 - \beta$) of the study (rejecting H_0 when it is indeed false) is desirable, within constraints of budget and research conditions. Typically, 80% is considered minimum acceptable power for a clinical study, and studies requiring a large amount of resources and of a nonpilot nature are usually designed to have 85% or 90% power.

It is important for the clinical investigator to appreciate that while the two factors just discussed (power and significance level) are statistical, the third (variance) is a hybrid, and the last (MCSD) is a clinical concern, to which we will return shortly. The variance is a component of the

sample size calculation over which the clinical investigator does have some control. Continuous outcome measures (e.g., continuous weight-for-age *z*-score) will have a smaller variance than a categorical variable based on the same measure (e.g., growth failure, defined as weight-for-age *z*-score < -2). Despite their higher variance, certain categorical outcomes or measures with a well-known threshold or cutoff have greater clinical relevance and are sometimes easier to interpret, and therefore may be preferable study end points.

Once the specific outcome measure is chosen, other considerations that affect its variance are (1) the heterogeneity of the target population, which can be altered by eligibility criteria (more heterogeneity induces higher variance); (2) measurement error (e.g., use of available versus standardized equipment); and (3) in a multicenter study, central versus local measurement (many measures will have lower variance when measured centrally by one or two observers trained in a standard manner, than when measured by different observers at each center). All of these factors should be considered at the design phase of the study. The cost of having additional subjects in the study can be weighed against the costs of implementing standardized equipment or centralized readings (or both) for the primary outcome measure.

The final component, MCSD, is often mistakenly assumed to be a statistical decision. It is, rather, the one factor that investigators determine based on their clinical judgment. In a two-group study design, the MCSD should be the smallest difference that a clinician would be disappointed to miss, that is, to result in a non–statistically significant comparison. For example, if a surgical mortality rate is 15%, and an absolute MCSD of 3% is chosen, then a 12% mortality rate or less is considered a clinically significant improvement. Any difference smaller than 3% (a relative reduction in mortality of 20%) is not clinically important and would not be sufficiently large to alter clinical practice. Of note, an MCSD is not necessarily the same as a difference that has been observed in a prior or pilot study. The larger the specified MCSD, the smaller the required sample size, because the difference due to a systematic change such as a treatment will be easier to detect when large, even in the presence of random variation. The size of a MCSD may vary according to the type of outcome measure, the disease or discipline under study, and the risk/benefit ratio for the treatment being tested.

There are other factors that the clinical investigator and statistician can consider as design parameters that will affect the required sample size. They fall roughly into two categories: factors that are *statistical* or related to the length of the study, and factors that are *clinical* or related to the target patient population. Statistical factors include (1) the use of repeated measurements (that is, the same measurement collected at multiple time points for each patient, such as blood pressures or ventricular size over time); (2) statistical adjustment for other factors that are related to the study outcome, which will remove unexplained variation and increase precision of the treatment effect; (3) increasing the length of follow-up time in a study that has a time-to-event primary outcome (such as time to transplant); and (4) allowance for a specified dropout proportion d, where the revised sample size $n^* = n/(1 - d)$.

A clinical factor that affects sample size is how the target patient population is defined. Specifically, eligibility criteria can affect sample size, as mentioned earlier. The exclusion of patients who are less likely to benefit from treatment will increase the observed treatment difference and possibly decrease variance. Note, however, that modification of the eligibility criteria in this manner results in a tradeoff between generalizability of results and maximizing the chances of observing a significant treatment effect. For example, in a pharmacologic trial for Marfan syndrome, restricting the study to a target population with moderately severe disease progression (defined as those with aortic root size at least three standard deviations above normal) identifies patients who may be most likely to respond to treatment. Any conclusions about the effectiveness of the drug being tested can be applied only to those with similar disease severity. The study result cannot be generalized to patients with less severe disease.

Significance of the findings

While a significant treatment effect is desirable, it should be noted that not all such differences are clinically important. Conversely, some differences are clinically important and real, but are not statistically significant when the study is underpowered (that is, when the type II error rate is too high). This topic should be discussed between the clinical investigator and the statistician. If the sample size is sufficiently large, almost any difference can be shown to be statistically significant. For example, in a study of functional health status and laboratory measures in 546 children, the correlation of health status score and brain natriuretic peptide had a p value of .009, but the correlation was -0.12. This may be a real association, but its magnitude is very small. It is up to the clinical investigator when summarizing results to consider whether the findings, regardless of statistical significance, will alter management or serve as useful study end points.

Reporting study findings

When a research study is at its conclusion, the analysis and interpretation phase is ideally a close collaboration between the statistician and the clinical investigator. Some cautions to keep in mind include avoiding the isolated use of a p value to report results. Preferably, the

mean treatment difference between groups or other effect size estimate in conjunction with the *p* value will be used. Knowledge of the effect size will allow one to appreciate whether a nonsignificant result is due to low power. The most informative report will provide not only the *p* value and the effect size estimate, but also a confidence interval, which indicates the range in which the underlying true difference may reside.

The final step of the collaboration between statistician and clinician is in the formulation of conclusions from the completed research study. Tell a story with the data and demonstrate important similarities in the study groups, as well as differences. Report differences in both directions when formulating conclusions, not just those that favor the hypothesis. Be judicious when reporting results that have 'marginal' significance, typically defined as a *p* value greater than .05 but less than .10. Pocock and Ware, (2009) suggest that the word 'trend' is "best avoided because it implies special pleading when the evidence is slim".[56] Finally, always state the limitations of the study, and be conservative in stating positive results unless the evidence is overwhelming; allow others to objectively assess the findings. If an effective statistical–clinical collaboration has ensued, then a rigorous study design, careful monitoring, appropriate analysis, and clear and judicious presentation of findings will stand on their own collective merits for assessment by other investigators, and then may lead to changes in practice and improvements in patient outcomes.

For Suggested Readings see References 56-58.

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DATA MANAGEMENT AND THE ANALYSIS PLAN

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Data analysis is an important component of a research study, whereby data are used to answer the study's questions and achieve its aims. Data analysis entails much more than just a compendium of statistical tests; rather, it is based on a detailed plan of how variables will be used and relationships explored to address the study's aims, and early consultation with a statistician is encouraged. The variables and the plan must therefore be clearly specified in advance of any data collection, to ensure that the correct measurements are being made in a valid and reliable manner and are captured and coded in the proper format with an up-to-date data manual. Before analysis, data must be checked to discover any data entry errors and extreme or inappropriate values, assess the amount of missing data, and to determine frequencies and distributions of values for variables. Statistical testing is used to discover the relationships of interest between variables, including confounding and interaction, and to determine the level of confidence in the results. Effective communication with a statistician regarding analysis must include a properly formatted data set and manual, along with a detailed analysis plan linked to the study aims.

Research studies generate data, which are then used to answer questions and create new knowledge. The collection and management of data must be keyed to the purposes of the research, including aims, questions, and hypotheses. The nature and the quality of the data collected are major determinants of the validity and reliability of the answers that the data will eventually provide.

A careful plan for data management and analysis is, therefore, a key component of a protocol. Data management entails decisions about what data are to be collected and in what form, what quality control measures and data checks will be in place and monitored, and how the data will be stored and prepared for analysis.

Data analysis entails decisions about what relationships within the data are to be explored to address the research question. These are necessary steps before statistical analyses can be applied, which specifies the nature of relationships and an estimation of their reliability or freedom from random error. A detailed data management strategy and analysis plan are necessary for effective communication with a statistician, and statisticians can be helpful in developing as well as implementing these strategies and plans. Many investigators mistakenly assume that an analysis plan is strictly a compendium of statistical tests to be used, when in fact an analysis plan must include description of all components of the study and data collection that justify and support the statistical testing strategy. The analysis plan must be keyed to the study aims, questions, and hypotheses. The purpose of this chapter is to provide a practical guide for the steps and decisions leading to an informed analysis plan.

Aims, questions and hypotheses

The most important first step when embarking on a research study is to be able to clearly state the overall purpose or aim. This broadly defines the area of interest or controversy to be explored by the investigation. More importantly, underlying the aim should be some questions. It is necessary to explicitly state these questions with as much specificity as possible and to clearly pose them in the form of a question. For each question, there should be a hypothesis (which can be thought of as an informed guess) as a proposed answer to the question. A well-defined and specific question and hypothesis will inform what key variables and relationships are being pursued, and will suggest an appropriate study

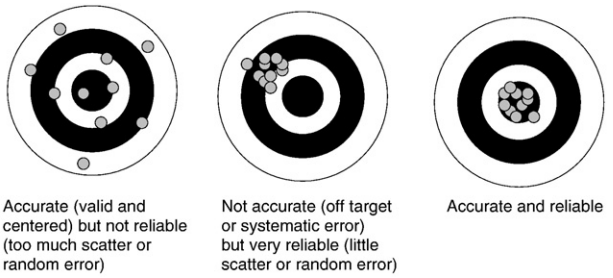
Table III. A worked example from study aim to analysis plan for a simple study

Element	Example
Aim	To determine the impact of self-report vs. proxy-report on the assessment of functional health status in children with congenital heart disease.
Specific research question	For children and adolescents after the Fontan procedure, do parents report lower functional health status for their children than the patients report for themselves, and is this influenced by the presence or absence of healthy normal siblings?
Hypothesis	Parent-report scores will be lower than self-report scores for functional health status, particularly for physical functioning domains, but the differences will be less if the patient has a healthy normal sibling.
Primary outcome measure, or dependent variable	Domain scores as assessed by a generic, standardized and validated functional health status questionnaire. Level of measurement: continuous variable with normal distribution.
Primary associated factor, or independent variable	Whether the questionnaire was completed by the parent or the patient. Level of measurement: nominal variable with two levels.
Interaction factor	Presence of a healthy normal sibling. Level of measurement: nominal variables with two categories.
Data analysis plan	
1.	Describe the patient and parent characteristics, the domains scores as reported separately for the parent and the patient, and the differences in domain scores for parent–patient pairs. Describe differences in parent-patient domain scores separately for those patients with vs. without a sibling.
2.	Test for statistical significance of differences between matched pairs using a paired *t* test.
3.	Test for statistical significance of any interaction regarding presence (or absence) of a sibling with parent-patient differences in domain scores using an unpaired *t* test.

population and study design. An optimal analysis plan will eventually be keyed to each of these questions and hypotheses. An example is given in Table III.

Of note, the processes of stating aims and hypotheses, deciding what information to collect, and the specification of the analysis plan should not be thought of as three independent tasks. Practically speaking, however, they are nonetheless specified sequentially—although there should be a constant looking back to make sure that the data analysis plan consistently relates to the aims, and that the data collected are sufficient to achieve the analysis plan.

Figure 6



Pictorial analogy of the measurement properties of validity (accuracy) and reliability (error).

Data management: from information to measurements to variables

Decisions regarding what information is needed are usually driven by the study questions, with an important contribution coming from a thorough literature review. Information to be gathered can be grouped into broad categories. First, information is required to completely characterize the study subjects, particularly regarding prespecified inclusion and exclusion criteria. Second, information is required to indicate the spectrum and magnitude of outcomes or responses. This information will become the dependent variables in the analysis plan. Third, information is required regarding factors that are of interest in terms of their potential association with the dependent variables. This information can include study subject characteristics, and will become independent variables in the analysis plan. It is a challenge and a balancing act to include enough detailed information and to be broad in data collection while also being parsimonious and maintaining feasibility.

Once a decision has been made regarding what information to collect, the next step is to *operationalize* the information (i.e., to define the practical aspects of selecting and recording measurements pertinent to the information that is required). This entails consideration of definitions and standardization, and determination of measurement properties. Measurement properties include *validity*, which is the degree to which the method of measurement provides a true reflection of the concept you are aiming to measure (Figure 6). An example might be the degree to which left ventricular volumes are a valid measure of the degree of aortic valve regurgitation. Ideally, the assessment of validity is best achieved if there is a criterion standard or gold standard of the concept, for comparison.

Another measurement property is *accuracy* or *reliability*, which is the degree of measurement variation. Usually, the greater the degree of subjectivity to a measurement, the lower the accuracy or reliability.

Variability, or the deviation from truth, can be systematic or random. Data quality procedures can be incorporated that serve to increase the accuracy with which a measurement is made and reported, such as *adjudication* (measurement or assessment by a panel of objective and, often, independent experts) and *centralization* (minimizing observer bias and increasing standardization). *Responsiveness* is another measurement property; it represents the degree to which a measurement changes in response to influencing factors.

An important consideration for each data element, and a key step in the movement from measurements to variables, is *level of measurement*. This refers to the nature of the measurement: categorical, ordinal, ratio, or continuous. For example, aortic regurgitation can be measured as present versus absent (categorical), subjectively graded from absent to severe (ordinal), measured as the ratio of the diameter of the regurgitant jet versus the aortic annulus (ratio), or indicated by left ventricular end-diastolic and end-systolic volumes (continuous). The level of measurement has important implications for statistical power and selection of statistical procedures. In addition, new variables can be created through recoding, collapsing data, or using existing variables to calculate new variables. Note, however, that measurement errors may be compounded when variables are combined. The data collection process details how the measurements are to be captured from the data source or sources. Data can be recorded onto paper forms, directly entered into computerized databases, or downloaded from existing electronic data sources. Although many platforms exist for data management, the use of commonly available software packages, such as Microsoft Access (a relational database program) or Excel (a spreadsheet application), facilitates eventual import into nearly all available statistical analysis programs.

Creating and maintaining a coding manual or data dictionary is an important component of a protocol and an essential tool when approaching data analysis. It is the key to the database, and ensures that anyone using the database will know what all the variables mean and how they are coded. For each data element, information in a coding manual or data dictionary includes (1) a short variable name, (2) a variable description and definition, (3) coding with description and definition for each, (4) level of measurement, (5) measurement units, and (6) format. The manual should include descriptions as to how missing data are to be handled, and may include descriptive statistics and further created variables. The manual should be continuously updated.

Between collection and analysis: data cleaning and description

Once data collection and entry are complete, the next step is to take a preliminary look at the data. The purpose of this is to identify the characteristics of the data that might influence or limit the data analysis. For each variable, the amount of missing data must be determined. Data may be missing because it was not available or was not measured, or because it was not applicable for that particular subject. Some variables will be conditional on another variable, such as the variable 'duration of circulatory arrest,' which would be conditional on the variable specifying 'use of circulatory arrest.' Data entry errors need to be corrected, and subjects with extreme values (outliers) need to be re-explored. Some errors require a more complex look at the data set; for example, one might note that, based on the dates entered, a subject had died before the date of surgery.

Calculation of descriptive statistics for each variable is important for detecting some errors and for determining the method of data presentation and analysis. Categorical and ordinal level data should be reported as frequencies. The description of ratio or continuous variables begins with examination of the distribution of values, which is most evident from frequency plots. Measures of the center of the distribution and the nature of the variation around that center are explored. For variables with a bell-shaped distribution, mean and standard deviation are reported. For variables with a skewed distribution, median, maximum and minimum values, and percentile or quartile values are reported. It is important to keep the presentation appropriate, particularly by keeping the use and number of decimal places to the minimum supported by the data. Some common errors in data presentation often seen in publications include use of decimal places on percentages (rarely necessary), use of the standard error of the mean instead of the standard deviation, and use of mean and standard deviation when the distribution is highly skewed (usually evident when the value of the standard deviation is 50% or more of the value of the mean, if there are important differences between the median and the mean, or if there are important differences between the median and the upper versus the lower quartile, percentile or maximum and minimum values).

Data analysis plan: defining relationships between variables

All studies except case reports should determine associations, and a study should rarely be purely descriptive in scope. An analysis plan allows you to define the associations between variables to help answer your question and, as a result, should be keyed directly to the study questions and hypotheses. The analysis plan begins with a description of the characteristics of the study subjects, the proposed independent variables, and outcomes or dependent variables. The goal of the analysis plan is then to define relationships between the outcomes and the proposed independent variables, which may include subject characteristics.

The relationship between an outcome and a factor may be simple versus complex, or direct versus indirect. These types of relationships can be causal or confounded, or can represent an interaction.

Causal relationships between risk factors and outcomes are relationships that (1) are considered to be biologically plausible, (2) exhibit a correct temporal relationship, (3) are strong, specific, and consistent, (4) show a dose–response nature, (5) are free of known and potential confounders; and (6) are free of systematic and random measurement errors. Randomized controlled trials give the best evidence in terms of defining a causal relationship with an intervention. *Confounded* or biased relationships occur when the relationship between a factor and an outcome is mediated by their relationship with a third (often unmeasured) factor. Observational studies generally test hypotheses about associations and are often subject to both known and unknown degrees of confounding. For example, a nonrandomized comparison from observational data showed that mortality was greater for surgical versus balloon valvotomy for neonates with critical aortic stenosis; however, left heart hypoplasia and ventricular dysfunction was noted to be more prevalent before valvotomy for the surgical patients, and were significantly related to mortality. After statistical adjustment for these confounding factors, there appeared to be no difference in mortality for surgical versus balloon valvotomy. In observational studies, multivariable statistical methods are often required to detect and adjust for potential confounding. The analysis plan should specify what factors might be explored as potential confounders.

Interaction represents a specific type of relationship. Interaction exists when the nature of the association between a factor and an outcome is influenced by some other characteristic, such that the association is not consistent. For example, consider a hypothetical outcomes study of surgical versus balloon valvotomy for neonates with critical aortic stenosis. Suppose that the results show that aortic regurgitation is significantly worse for the balloon valvotomy than the surgical valvotomy patients, but only for those balloon valvotomy patients who had unicuspid aortic valve morphology. Valve morphology interacts with type of valvotomy in determining severity of post-valvotomy aortic regurgitation. The analysis plan should specify what factors might be explored as potential interaction terms.

How to communicate with a statistician

Effective communication with a statistician has two main components. The first component entails what the statistician needs to know about the study. A statistician may not be an expert in the content area of the study and thus may need some background information. Most of this should be detailed in the protocol, which should be provided to the statistician. A statistician should be involved early for advice. The aims, questions, and hypotheses for the study should be clearly communicated to the statistician. The data set should be in proper format and cleaned, and accompanied with an informative coding manual or data dictionary. It is important to discuss which new variables are to be created. The data analysis plan should be discussed, including its rationale. When results are available, they should be discussed with the statistician to clearly and accurately interpret and communicate their meaning, and to discuss and specify further steps. The statistician should also advise regarding appropriate presentation of the results.

The second component entails what skills the investigator needs to understand what the statistician is saying, and to have basic fluency with statistical concepts and terminology. It is important for the investigator to have a working knowledge and understanding of data description, the nature of relationships between variables, and what analytic methods are available for discovering simple and complex relationships. The investigator should also be able to interpret the results of a statistical analysis. Minimal training for investigators should include introductory courses in epidemiology, study design, and statistical analysis. A more advanced fluency would entail having knowledge of probability theory and mathematics, and an understanding of the limitations and assumptions underlying statistical testing. For investigators planning a career focus in clinical research and for those who wish to perform their own analyses or perform studies with complex statistical analysis techniques, completion of an advanced degree in one of these related fields is recommended.

For Suggested Readings see References 8 and 59.

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DATABASING: DEVELOPING AND WORKING WITH A DATABASE

Steven D. Colan, MD

Electronic data repositories are essential to all but the simplest of research endeavors. The software solutions vary enormously in terms of cost, ease of use, resource demands, and utility. Deciding whether to use an electronic spreadsheet or a true relational database management system (RDMS), either desktop or enterprise, should be made on the basis of issues such as the complexity of the data model and single versus multicenter data. The data repository decision is best made during study design, because conversion from one system to another incurs additional expense and recovers only a subset of the benefits. Although most young investigators

choose an electronic spreadsheet, the additional learning curve, start-up time, and expense of creating a relational database will generally be recovered during the course of the project because of the improved data integrity and more powerful data analysis features of a RDMS. The retention period for the data is another decision that should be made at inception, and serious consideration should be given to whether the data captured in the course of the research project have sufficient long-term clinical or research value to justify incorporating these data into the electronic medical record.

The accumulation of data in electronic format for statistic analysis is a critical aspect of the research enterprise, one for which numerous tools are available. Deciding which of these tools to use is driven by many considerations, including availability, expense, ease of use, required expertise, and acceptability to the various members of the research team, including the statistician. Although the ability to transfer data between software packages has improved enormously, thereby enabling an initial decision to be reconsidered over the course of a project, the database may require extensive and time-consuming reorganization during any such data transfer process. Therefore, insofar as possible, selection of the tool best suited to the task should be made at study inception. Although there is overlap between the software categories, the available tools can be loosely categorized as spreadsheets, desktop databases, and enterprise databases.

Electronic spreadsheets

The electronic spreadsheet (ES) is the computerized version of the classic accounting tool, consisting of a row–column tabular organization for data entry. The power of the ES derives from the features that are enabled by the electronic format (such as complex calculations, macro-enabled extensibility, and integrated charting capabilities). Although access to these features requires experience, use of the ES for data storage requires virtually no training. A sufficient number of statistical analysis features are standard features of these software packages that, for many projects, the investigator can capture, analyze, and graph the data within a single ES program. The software is inexpensive, is widely available, and supports transfer among many other software packages including virtually all of the microcomputer-based statistic packages. Even though it is probably the research data repository most commonly used, the ES has a number of very important liabilities. The properties of the rows and columns are not enforced, permitting mixed format data entry (dates, numbers, text) within any variable. No range checking or other protection against data entry error is provided. Certain features such as sorting can irretrievably destroy the data integrity if incorrectly performed. Basically, the software provides enormous flexibility, but by doing so provides no data protection.

Perhaps most importantly, the ES is not a database. A database is a collection of data organized for ease and speed of search and retrieval, whereas the ES is designed for ease and speed of data capture. The point at which most investigators first encounter the limitations of the ES is when dealing with multidimensional data, such as multiple types of data samples (e.g., echocardiograms and cardiac catheterizations) or multiple instances of the same type of sample, as is characteristic of most longitudinal datasets. The ES is intrinsically a two-dimensional space. Although many of the packages now support linkage of multiple row–column tables within the same workspace, the software does not enforce the referential integrity of this linkage. A true database is a collection of two-dimensional tables with a structure that is defined by the relationships between the tables and is capable of supporting *n*-dimensional data structures.

Relational database management system

An internal data organization is the essence of a true database and accounts for the term *relational database management system* (RDMS). The RDMS provides the structural protections that are absent from the ES. Each variable has an enforced type (character, numeric, date, and the like). Range checking is provided (useful for preventing inadvertent mixed entry of the same variable in, for example, centimeters and millimeters). Blank and null values have distinct storage. However, the real power of the RDMS is the ability to rapidly extract records with matching criteria, to retrieve related data across tables based on the defined inter-table relationships, and to update or modify data in bulk. For example, if data are being periodically extracted from another database, such as an electronic medical record (EMR), the RDMS permits automatic matching and insertion of the new or updated observations to the correct person or event.

A simple example of the power of a RDMS is useful for demonstrating the difference from an ES. If a database is organized with three related tables—with the primary table containing subject data such as a unique identifier, date of birth, sex, race, and other characteristics to be recorded, the secondary table containing a potentially unlimited number of echocardiographic events (date, time, type) linked to each subject, and a tertiary table containing tissue Doppler timing intervals from multiple anatomic locations linked to each of the echocardiograms—it is possible to rapidly identify all subjects who have ever had intraventricular dyssynchrony, defined as a difference of more than 50 ms for isovolumic activation time. Such analysis would be far more labor-intensive and time-consuming using an ES. The

downside of a RDMS is that it does require more up-front time and knowledge to set up the database in the first place. For anything but the simplest of projects, this time will be more than recouped at the time of data analysis. The ability to define and conduct queries of this sort is useful not merely for final data analysis, but also to generate periodic reports during the course of the project, to detect and verify outliers, and to generate deidentified datasets for data sharing.

Relational database management systems are generally categorized as desktop versus enterprise. The desktop versions are less expensive, highly portable, and require less expertise to develop and manage. The enterprise database systems are far more expensive, because (1) the software is more costly, (2) the database must usually be housed on dedicated servers, and (3) far greater information technology expertise is required for maintenance and optimization. The decision as to which of these platforms to use is usually based on consideration of (1) whether support is needed for multiple concurrent users, (2) whether full-time network connectivity can be ensured, (3) the total size of the dataset, and (4) the overall speed performance that is required.

Selection of a research data repository

To summarize, the selection of the correct platform requires consideration of the size and scope of the project, the computer skills of the investigator, and the available support, both in terms of money and personnel. The ES can be used by virtually anyone, has the least cost, and is ideal for simple two-dimensional datasets on short-term projects. Use of a relational database is preferable for more complex data collections, particularly if longitudinal data collection is intended. It is not uncommon for a project to evolve over time from simple to complex, and if such a transition is at all likely, then there is a net saving through the use of a RDMS from the start. The portability and ease of modification of a desktop database system, coupled with the capacity for multidimensional datasets, generally makes this ideal for a single-center project that involves a limited number of users. Most multicenter projects will benefit from the features provided by the enterprise RDMS, including (1) support for complex datasets with multiple simultaneous users, (2) greater security requirements, (3) support for electronic feeds, and (4) Internet-based data entry and retrieval.

Transcending the research data repository

Clinical research is generally conducted by establishing a data repository to which data from numerous and disparate sources can be fed. This legacy process evolved naturally from the need to gather data from sources that were generally paper-based, such as the hard-copy medical record (clinical data), in conjunction with capture of research data not generally recorded as part of the clinical process. The transition from paper to electronic storage has made some structured clinical data, such as laboratory results, directly retrievable in an analyzable format through electronic queries. Nonetheless, the vast majority of clinical information is stored as text (e.g., progress reports, operative reports, and discharge summaries). Regardless of whether the data are electronic or hard-copy, these unstructured clinical data have to be encoded in some fashion before they can be analyzed. This process of information extraction and encoding, and thereby transforming unstructured to structured data, remains one of the most labor-intensive aspects of the clinical research enterprise.

Research data (i.e., data captured exclusively for purposes of research) may also exist in structured and unstructured forms. Insofar as possible, the research data are generally captured in structured formats, although at least at the time of project inception some unstructured data are usually accommodated when the range of categories that will be encountered during data collection are not yet fully understood.

Because the data are being collected from disparate data sources, subject identifiers must be retained, to match the data to the correct subject. The retention of patient identifiers has led to the requirement by Institutional Review Boards that research databases be destroyed or anonymized at study completion, to avoid inadvertent loss of confidentiality. Unfortunately, this data management paradigm results in net data loss over time. There are vast pools of data that have been painstakingly gathered, frequently at great expense, and then are either destroyed or abandoned over time. Often, these data retain value to future researchers, and possibly also to clinical care. An example from personal experience is informative.[60] We performed a retrospective analysis of the relationship between coronary artery anatomy and surgical outcome in children who had an arterial switch operation performed for transposition of the great arteries. This involved extraction of descriptions of the coronary pattern from surgical notes, echocardiographic reports, cardiac catheterization reports, and direct review of the original echocardiograms and angiograms to group them into the seven anatomic patterns that we encountered. This study was designed to examine short-term outcomes, but it is reasonable to hypothesize that coronary artery pattern may also represent a risk factor for ischemia later in life for these patients. Unfortunately, destruction of this research dataset would have made this long-term evaluation difficult if not impossible. The obvious solution was to incorporate these data into the EMR as structured, analyzable data, and that is what we eventually accomplished.

The advances in electronic data capture and storage justify abandoning the existing research data processing model and to consider a completely different approach to capture of both clinical and research data. The primary weaknesses in the current model are the unstructured nature of most clinical data and the failure to permanently associate data acquired in the course of clinical research with the clinical record of the subject. The solution to the first problem is to develop systems for EMR capture of clinical classification or coding of diagnoses, procedures, complications, and outcomes and to introduce these systems to the work stream of the clinical encounter. This is a large undertaking, but has the greatest long-term potential yield when the classification systems are standardized and in wide use.[61,62] There are a number of efforts to facilitate such development, spearheaded generally by subspecialty organizations.

The solution to the second problem is to enable capture of data acquired in the course of research to the EMR or an associated data warehouse. Effectively, the desire is to merge the research database with the EMR. There are a number of serious obstacles to development of a consolidated data repository, but there are also huge potential benefits. Perhaps the largest obstacle is the common philosophy that research data are a personal possession of the researcher. This sense of ownership is based on the effort or funding from which the data derive (either or both), and is not an issue that can or should be ignored. Restrictions on use and provision of proper credit can be provided through a planned infrastructure that tracks information concerning the source of the data, the responsible investigators, methodologies, patient characteristics, and other relevant detail. Clearly, the original investigators would derive greater academic benefit from data reuse than from data sequestration or destruction. Some data would need to be sequestered, such as genetic results from laboratories not approved under the Clinical Laboratory Improvement Amendments (CLIA). Any informed consent limitations on data use would need to be respected (although renewed consent for alternative data use might be possible), but such a data model would almost certainly result in greater planning on the part of investigators as to eventual data use. A data repository such as this would also enable post hoc analyses using deidentified data, thereby avoiding the need for additional informed consent.

What is a nascent clinical investigator to do?

Fellows and junior faculty are generally in need of very specific information technology skills that will allow them to accomplish a specific research-support task. In contrast, most books and courses on database development target the broader subject matter and do not focus on specific use. For those with little experience in computer programming or database design, learning the language and general principles of these fields can be intimidating and time-consuming. There are usually support personnel who can help with database development, and one option for the investigator is to request that these personnel provide guidance with the specific tools available within the institution. For the desk-top database applications, no harm results from the trial-and-error approach to self education using one of the many user manuals that are widely available, particularly when there are personnel available who can help overcome specific obstacles that may be encountered. Most investigators are not interested in a career change into information technology, but there is no question that data capture and storage are such critical aspects of the research enterprise that a general understanding of database design and query is useful.

It can be particularly challenging for the fellow or junior faculty member to become involved in the design of institutional capture of clinical data. Even for individuals who are experienced in computer programming and database design there are generally significant institutional barriers to participation in this process. This often drives creative individuals into independent data capture development projects that may parallel existing institutional efforts. Under the best of circumstances it is usually expensive and time-consuming to merge these efforts. The best option, therefore, is to work with the hospital information technology personnel to either create a usable linkage at the time of project inception or, at a minimum, to design a verifiable data structure that can be transparently imported into the institutional data structure.

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HOW TO WRITE A RESEARCH APPLICATION

Jane W. Newburger, MD, MPH

The writing of one's first research application is a rite of passage for fellows and junior faculty who are interested in pursuing academic careers in pediatric cardiovascular disease. This brief review covers basic principles in writing a research application. It is important to target proposals to funding sources geared to trainees and junior faculty. Successful applications generally ask important questions, use methods that allow the research questions to be answered, include pilot data demonstrating feasibility, and discuss potential pitfalls and solutions. Common reasons for failure include lack of clarity in the specific aims and scientific rationale, absence of pilot data, inadequate sample size or power, end points that

cannot be measured precisely or that have uncertain longer-term importance, and other evidence of lack of feasibility of the project. When the agony of grant preparation is followed by the ecstasy of successful funding, the ensuing benefits of protected time and added financial resources facilitate innovation and discovery for the early career investigator.

Research funding is critical to investigation. Extramurally funded research is as cherished as publication in the best journal and confers legitimacy on a researcher. Fellows and junior faculty should concentrate their applications on resources that are targeted to them.

In writing a research application, pilot data are critical to demonstrating the commitment of the applicant and the feasibility of the project. Initial grants are often written in the second or third year of fellowship. Applications are judged by pilot data, prior publications, and mentorship, but most fellow applicants have relatively few prior peer-reviewed publications. Excellent funding sources include the National Institutes of Health, foundations, and societies such as the American Heart Association or the American Academy of Pediatrics. Fellows at many institutions are also eligible for intramural grants, such as those that are supplied by the NIH Clinical and Translational Research Awards.

What are the determinants of a successful application? For fellows, an outstanding mentor or mentorship team is vital. Most fellows have not had an opportunity to write many publications. In contrast, for junior faculty, the record of personal productivity becomes more important. New or original ideas in a well-prepared proposal create a sense of excitement in reviewers. A grant application should be meticulous in its description of specific aims, preliminary results, methods, and potential pitfalls and their solutions. Sloppiness in English usage or typing errors, and lack of clarity about the aims or methods of the study, suggest to the reviewer that the conduct of the research may likewise be sloppy or ill-conceived.

To familiarize oneself with the funder, it is helpful to examine grants written by other individuals who were successfully funded by that organization. It is also important to be sure that the funder or sponsor has funded the type of project that one is considering (for example, “clinical research” for some sponsors pertains to laboratory work done on human samples). To assess whether one's application is appropriately targeted to a particular funding source, it is helpful to review the research interests of the members of the study section or review committee. Finally, if uncertainty remains about the suitability of an application for a particular foundation or sponsor, one should directly inquire of the sponsor organization.

It is helpful to begin planning for a grant application with a two- to three-page outline that includes specific aims and research hypotheses. First, one should be able to justify why the aim of the study is important. The outline should include each of the elements that will be necessary in designing a statistically sound trial, including the aims, ascertainment of subjects, data obtained, statistical conduct, and risk/benefit ratio.

Even the seasoned researcher finds critical review by colleagues to be invaluable. Fellows and junior faculty should discuss their applications not only with their mentors but with any other interested faculty.

There are many reasons that a grant can fail to be funded. The specific aims may lack clarity and focus. The scientific rationale may not be compelling. If relevant published work is not cited, the applicant will appear to be unworthy. Lack of pilot data will make the reviewers wonder whether the grant is feasible. Primary outcome variables that are difficult to ascertain or measure, or that do not have importance for the well-being of the patient, are reasons for failure. A sloppy application will lead reviewers to suspect that the applicant may fail because of lack of attention to detail. It is particularly important to recognize potential problems and to propose solutions in the application. Finally, if the proposal does not seem important or if it is incremental to well-established data and methods, funding is unlikely. Reviewers expect that one will devote an adequate percent effort to complete the protocol. Similarly, the protocol and budget should include personnel and laboratory research sources that are sufficient to execute the protocol. It is vital that one demonstrate the feasibility of recruitment of a sufficient number of study subjects. This is best demonstrated by applying the study entry criteria to the experience at one's institution over the preceding 3–5 years.

Finally, perhaps one of the most common reasons for failure is procrastination. It takes at least one month of relatively protected time to write one's first grant application. Therefore, it is important to make a schedule for the one or two months before the grant deadline. Fellows and junior faculty should determine internal deadlines for their offices of sponsored programs and for sign-off by the department chair. They should also consider the other obligations and availability of their mentors or coinvestigators. When one is depending on the input of others with busy schedules, it is especially unwise to leave the writing of grants to the last minute.

What happens when one's grant is funded? After the initial moments of joy and exaltation, there is plenty of hard work ahead. Nonetheless, extramural funding provides the adequate resources for exploration and discovery of innovations that have potential to affect the lives of children and their families.

For Suggested Readings see References 8 and 63-68.

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PRESENTING DATA: ABSTRACT, POSTER, MANUSCRIPT

L. LuAnn Minich, MD

Although individual styles for presenting data vary widely, guidelines have been established to facilitate the process and to improve the acceptance rate for an abstract or publication. This chapter provides suggestions for preparing and presenting data in abstract, poster, and manuscript formats.

Similar to the practice of medicine, the presentation of data has established guidelines with wide variation in individual styles. By attending research sessions and reading scientific literature, the novice author can observe the techniques of successful presenters and adapt them to create an individualized approach to the presentation of data. Experienced presenters may continue to refine their style, using the same opportunities in a process of lifelong learning. This chapter focuses on guidelines for preparing and presenting data in an abstract, poster, and manuscript.

Preparing the abstract

Author selection

The process of presenting data actually begins with choosing a research topic and assembling a qualified team to design and complete the project. The contributions of each team member should be used to determine authorship, according to published guidelines as recommended by most journals. Typically, the first author listed has the primary responsibility for the dissemination of data, including insuring accuracy, compiling all revisions, reworking the drafts from the coauthors, and gaining consensus from all authors regarding the final submission. The last author is considered the senior author and usually has established expertise in the area of the research being presented. This author should supervise and guide the coauthors through the research process, data analysis and interpretation, and manuscript production. All other authors should participate fully in the preparation and critique of the manuscript, as well as in verification of the authenticity of the data. These individuals are listed in order of contribution or, if all have equal contribution, in alphabetical order. The first and senior author should resolve conflicts by a frank discussion of individual merit and adherence to published guidelines. Agreement of authorship early in the presentation process may avoid later conflicts that can delay manuscript publication.

Meeting selection

Data are often presented first as an abstract. This allows the research findings to be quickly assembled and scrutinized at a scientific forum. The abstract should be written only after the research question has been asked, investigated, and answered. Once these steps are complete, the authors should agree on a meeting for abstract submission, based on the audience's interest in their field of research, the relationship of the abstract data to the emphasis of the meeting, and the ability to meet the deadline for submission (available on the organization's website). To develop a realistic timeline, the inexperienced submitter should estimate the time it will take for completion of data collection, organization and analysis of results, preparation of the abstract, and critique by all coauthors and mentors—and then double it. It is useful to include time for drafting the manuscript as part of the abstract timeline because, regardless of the success of the abstract submission, the research findings will not be validated until a manuscript is published. The manuscript draft allows the authors to build on the abstract and to be more organized, both in presenting and defending their data and in seeking feedback from others at the meeting. This feedback will be invaluable, and should lead to improvements as the manuscript is revised in preparation for publication.

Title selection

The organization's website will provide the guidelines for submission (e.g., word limitations, font size, fees), and these should be followed carefully. The title is your first consideration. You and your coauthors should spend time on it. The title is the most frequently read part of the abstract. Ideally, it should be catchy, informative, clear, concise, and reflect the meeting emphasis. A good title is one that makes the reader want to hear more, and a good abstract delivers all that the title implies. Some have suggested that a good abstract or poster title might include a statement of the question being asked or the answer to that question; that is different from the manuscript title, which typically describes the research project in a more general manner (although more journals are encouraging declarative titles that state the findings).

Data selection and preparation

Because of the restriction on number of words or characters, the writer must strike a balance between clarity and comprehensiveness. Data should be carefully selected and focused on supporting the conclusions in a logical manner that can be easily followed by the reviewer. Data presented in tables should be simple and should not be repeated in the text. Reviewers are often sorting through large numbers of prospective research abstracts, looking for important contributions. The abstract should be constructed to make it easy for the reviewer to understand the contribution of the results to the specific meeting and to the field in general. Although the authors have time to review the related literature and become comfortable with complex

ideas, these ideas need to be expressed simply for the reviewer, who has less time for any one abstract and will not have reviewed recent publications to the same extent. Long sentences and overuse of jargon or unfamiliar abbreviations often frustrate the reviewer and can compromise the final abstract score. Similarly, errors in grammar and spelling may be interpreted as carelessness and (fairly or not) considered synonymous with carelessness in research.

Components of the abstract

Abstract formats vary by meeting, but most include five sections: background, objectives, methods, results, and conclusions. (Occasionally, a few key references are allowed or required.) The Background section (1–2 sentences) explains how the idea for the research came about. The Objectives section (maximum of 3 objectives) ideally includes a hypothesis and explains why the study was done (1 sentence). The Methods section requires a clear and precise description of how the research was done and includes such aspects as study design, study population, inclusion–exclusion criteria, techniques, and other relevant features (1–3 sentences). The Results section reports the findings and is written in the past tense. This section is the longest (3–4 sentences). The presentation of results is enhanced by a clear, consistent format for presenting the data. The format should change (for example, from table to graph) only if the type of data included is different. It is especially important to proofread this section and make sure that all numbers add up and that the findings are internally consistent. The Conclusions section (1–2 sentences) states what was learned from the project. Because the data presented in the abstract should persuade the audience, it is important to provide at least one take-home message here, emphasizing how practice should be changed or how the field will be advanced. Be sure that the results support the conclusion. Some authors will include speculations at the end of the abstract. If this is done, the speculations must be clearly differentiated from the conclusions and constructed to avoid unwarranted controversy or distraction from the data.

Preparing and presenting the poster

Poster preparation

The acceptance package provides information regarding the format of the poster presentation. Details such as poster size, computer use, and author availability times are available in the acceptance letter or on the organization's website. The key to a successful poster presentation is allowing adequate time for its preparation. A realistic timeline should be made for completion of the poster, including review by all authors, as well as by interested colleagues. The presenter will need to be the expert and therefore should be facile with all aspects of the research project and data analysis, as well as the existing knowledge in the area. The order of putting together the components of the abstract into poster form is highly individualized. Some experienced investigators prefer to start with the conclusions, using reverse organization to ensure that the data are included and organized to clearly support them.

The best beginning for poster preparation is a well-organized, logical abstract. All data from the abstract should be included, and more can be added. It has been estimated that the average person scans a poster for 10 seconds from 10 feet away. Thus, the poster must be eye-catching, with high-resolution figures big enough to be seen. A catchy, informative, clear, and concise title is particularly important for poster presentations. Mistakes in grammar, spelling, and numbers should be avoided, as they may be taken as evidence of sloppy research. At least one person who is unfamiliar with the research project should be asked to proofread the poster, to avoid reading past errors.

Poster presentation

Considering all formats, poster sessions allow presentation of the most data. Viewers can take all the time they want to read and analyze your work. Most presenters find this format to be less stressful and more focused than the oral abstract. Because the viewer drives the focus of the interaction, the challenge for the poster presentation is to adapt the research discussion for all levels of audience expertise, from general to very specialized. The presenter should be available for the entire designated time to answer questions and interact with the audience. No representation is unacceptable. If the presenter has a conflict with other meeting responsibilities, arrangements should be made for a coauthor to be available. Enthusiasm and confidence in the work should be evident. This is an opportunity for the authors not only to explain and defend their work, but also to obtain feedback from experts in the field. If the poster is carefully prepared and executed, much of the work of manuscript preparation is completed.

Preparing and submitting the manuscript

Manuscript style

The manuscript should be drafted concomitant with the preparation of the abstract and poster. As this process progresses, there is no substitute for thoroughly reading the related literature. Cutting corners in this area will compromise the authors' opportunity to persuade the reader and may lead to delays or even failure to get the research published. It is often useful to review examples of similar published articles to select the best

journal for potential publication of the research. Once the journal is selected, the instructions for authors (available on the website) for manuscript style should be carefully reviewed and followed explicitly, including such elements as format, word count, reference style, and preparation of figures and tables. In particular, the structure and length of each section will vary and must be constructed to adhere to the specifications of the targeted journal. As with all aspects of presenting data, it is important to start early, create a timeline, and stick to it. Regardless of how well the abstract was prepared for the poster, it typically needs to be revised to meet the journal specifications.

Caveats for manuscript preparation and submission

Many experts in successful manuscript publication recommend focusing on the title, abstract, and tables and figures, because these are the most widely read parts of the manuscript. The manuscript is usually divided into the same five sections as described for the standalone abstract, but adds a Discussion section and includes references. Subheadings may be useful to improve clarity of the various comparisons made in the data analysis. It is important to stay within the specified section—for example, research results should not be in the section describing the methods used to obtain them, and vice versa. The methods should have enough detail so the findings can be replicated by another research team. Tables should be clear and supplement rather than duplicate information in the text. Figures should be simple, high quality, and explained by clear, concise legends.

Feedback from the poster session or platform presentation, especially if it resulted in a lively interaction, can contribute to development of the Discussion section. The discussion should address the main question first, and should clearly state what is new in this study and how the findings contribute or expand the knowledge in the field. The results should be compared and contrasted with other published results, but an exhaustive literature review should be avoided. If the results differ from previous reports by other investigators, offering possible explanations may strengthen the manuscript. The limitations of the study should be listed at the end of the discussion section, along with the effect they may have on the data presented in the manuscript. The manuscript should end with conclusions that avoid overstating the findings. As for to the abstract, conclusions should be supported by the data presented in the results section. References should be given for previously published information. The authors are responsible for ensuring that the information is accurate and that the sources are current and listings are complete. Commercially available reference management software packages are useful for streamlining this process.

Resubmissions

Despite conscientious attempts at perfecting the manuscript prior to submission, inevitably some are rejected. The authors should set aside time to carefully consider the original reviewers' critiques and respond to those that strengthen the manuscript; the revision should incorporate these changes. The manuscript will also need to be reformatted according to the style of the new journal selected for resubmission, including reference style (here again, reference management software can save much time and effort). If the priority score is low, submission to a journal with a lower impact factor may lead to publication.

In conclusion, motivated mentors are important for assisting the novice researcher throughout the process of preparing the manuscript. The initial draft is rarely close to the finished product and requires all coauthors to provide frequent input and edit multiple revisions. Writing is a learned process, and improvement occurs with each abstract, presentation, and manuscript. It is a talent worth cultivating, because research success is validated by successful publication.

For Suggested Readings see References 69-75.

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PART II: CLINICAL RESEARCH CAREER DEVELOPMENT

A CAREER IN CLINICAL RESEARCH

HOW TO GET STARTED ON A RESEARCH CAREER

Elizabeth Goldmuntz, MD

Getting started on a research career can be a daunting task for the person in training when a pathway is not clearly defined. At the outset, it is helpful for a trainee to talk to as many people as possible to define a desirable career path and research role. With a career goal in mind, proactively arranging a schedule that accommodates research training is critical, and may require defining significant periods of time for advanced course work or laboratory-based research. Choosing a mentor is the most important decision moving forward; indeed, it is more important than the initial specific project undertaken. Of course, the specific project is also critical; it should address a significant question that can be answered in the time and with the resources allotted. The initial project should serve as a training ground and an opportunity to start a series of investigations, rather than serving only to answer an isolated question. The trainee must remember that good research training requires (1) training and

mentorship, (2) dedicated time and effort, (3) resources and support, and (4) persistence. Far from abandoning clinical practice, research can serve to augment clinical knowledge and analytical skills. Though daunting at first, getting starting on a research career can be exciting and rewarding. Success must be measured in small steps, and with the hard work comes tremendous gratification, knowledge, and the opportunity to contribute to the advancement of patient care.

Introduction

Getting started can sometimes be the most difficult thing to do in any situation, particularly when there is no clearly defined path to follow. Throughout medical training, students and trainees are given a set of classes to attend, material to learn, clinical schedules to follow, list of patients to see, and are even assigned time to take vacations. At this stage, most time is scheduled and ordered, with little self-determination permitted. For those trainees who lack significant research experience, figuring out how to get started on an open-ended research career can be a daunting task. Add to this uncertainty the apparent change in pace from rapid-fire clinical demands to the more deliberate, sometimes laborious nature of research, and some in training may choose to walk away. Those who persist will find unique opportunities, lessons, and benefits to engaging in research. Listed below are some helpful points for the trainee to consider as he or she gets started.

Research role

First, trainees should consider the research role that they might want to assume in the future. Numerous career pathways with varying degrees of engagement in research and clinical activities are available, including

1. the clinician who helps identify eligible subjects for research protocols;
2. the clinician who provides services to on-going research protocols, such as interpreting clinical tests; and
3. the collaborator or coinvestigator who works more extensively on existing clinical or translational protocols. This person may assist in study design, provide services, and assist with data interpretation and manuscript preparation in a limited fashion. Such an individual may be listed as a collaborator or coinvestigator on a grant, and may or may not draw salary support from these activities. In addition, there is
4. the principal investigator (or "PI") who directs the research overall, whether it be clinical, translational or basic science oriented. This person oversees all aspects of the research including the design and execution of the project, the writing of grants or garnering of resources to support the program, and the writing of manuscripts for publication. The PI usually garners a significant portion of salary support from the research activities. Of course, one may serve as PI for one protocol, and a collaborator or coinvestigator on another.

Such pathways are often defined by the percent effort an attending physician devotes to clinical, research or administrative endeavors. Those devoting most of their time to clinical activities might be assigned a so-called 80–20 split, with ~80% of their time spent providing direct clinical care and ~20% directed toward research activities. In contrast, those devoting most of their time to research endeavors (including securing outside funding) may apportion their time in the opposite 80–20 split, spending 80% of their time in research. Clearly, attending physicians apportion their time for different activities according to many different formulae, and for many different reasons.

Some trainees know exactly what they want to do from the outset. Others will better define their level of interest and career goals by engaging in research activities. Many people clarify their goals with time, adjusting their level of engagement in research over the span of their entire career.

Preparation

Second, trainees must prepare for the research role that they want to assume. This point may sound like a statement of the obvious, but quite often fellows and junior faculty come to the end of their assigned research time recognizing what they might have done, but did not plan to do and therefore did not accomplish. For example, the trainee who aspires to work in a basic science laboratory or enroll in a Master's-level educational program must arrange clinical commitments to accommodate long stretches of dedicated research or educational time. Those who envision applying to the National Institutes of Health (NIH) or to foundations for research training support need to plan many months, if not years, ahead to identify appropriate mentorship, acquire preliminary data, and prepare the application.

Time and training

Third, trainees must remember that good research requires dedicated time and training. Most recognize the need for supervision, training, and practice to become a doctor or specialist. However, some may not fully appreciate that research is a skill to be mentored, learned, and practiced in much the same way as clinical medicine. Becoming an independent investigator requires training and practice, supervision, and mentorship, with gradual steps toward independence. Particularly in the current era, invaluable skills and preparation are gained from enrolling in Master's-level education in

clinical research, including courses on research design and methods, database development, epidemiology, statistics, and scientific writing. Basic science training will require years of dedicated experimentation and education to develop a sufficient publication record with which to compete for extramural funding. In addition to training, research takes time. Unfortunately, the fellow and junior attending have multiple competing interests for their attention, and research may not be made a priority. Many are told that research is for "week nights and weekends," but little happens without dedicated time and effort. Overall, becoming an independent investigator is a gradual process involving a series of small steps, starting with mentored projects and evolving into independent research.

Focused research

Fourth, trainees should avoid the trap of picking a haphazard set of projects and instead develop a focused line of research. There are always interesting projects to do, but it is important to ask, Do these projects tell a focused, cohesive story? Do they provide preliminary data for future studies? Is there a question to be asked following this first one? Too often trainees are prime targets for assignments derived from questions raised in a conference. The projects sound easy, until numerous charts need review, a database needs to be built, data must be analyzed, and a manuscript has to be written. In some cases, it is helpful to engage in a variety of projects, thus exploring different fields that one might want to pursue long term. The trainee should beware of committing to too many disconnected projects associated with multiple mentors that fail to build his or her own personal research direction. Ideally, a set of inter-related research projects create the potential for well-focused, long-term investigations.

Clinical skills

Fifth, trainees must dispel the myth that they cannot be a great clinician if they conduct research. Though trainees all need to focus their clinical activities, a trainee is not abandoning clinical medicine just by engaging in research. Given that research takes time, it may take longer for the fellow or junior attending who dedicates significant periods of time to research training to become a practiced and confident clinician. Clinical skills mature over time, and that insecurity will abate, if not disappear. In fact, research may augment clinical skills and analytical abilities, and often defines areas of particular clinical expertise.

Research success

How should trainees get started? It is critical that trainees speak to many people early in their training to identify a desirable career path, an area of interest to explore, or a skill to master and apply to their specialty. A trainee must not be afraid to get started, to fail or falter, or to be different. Many people adjust their career and research directions, expectations, and goals over their life time. A good research project is rarely designed in a single meeting, and projects rarely work out on the first try.

What does a trainee need to be successful in training for a research career? Mentorship is the single most important determinant of successful research training and career development. A person with experience and energy who is willing to provide training and guidance is far more important to one's success than the topic of the project. At first the research project is a means to an end; it is a training ground. Although the trainee may have many collaborators or even several mentors, it is critical that each trainee identify one particular mentor who clearly identifies the trainee as their particular mentee, and invests in his or her success. In return, the trainee must invest in the research to make it worth both of their time.

Other critical components to success include

1. Persistence and stamina
2. Support with provision of dedicated research time and resources
3. A well-designed project.

The project should be of interest, provide a training opportunity, develop preliminary data, and answer a worthwhile question. Most importantly, the project must be of appropriate size and scope, and readily doable. It is critical to be realistic about what a trainee can accomplish in the time and with the resources provided. It is unrealistic to think that one person can train in both basic and clinical research.

Conclusion

In conclusion, the trainee should not wait for his or her research months to begin before considering research directions, but should instead be proactive in initiating and pursuing a research career. Training opportunities and subspecialty fellowships vary in format and in the time allotted for research activities. For example, fellows in pediatric cardiology are usually allotted no more than 1 year of research time during a 3-year fellowship. Thus, it is common in this setting for trainees dedicated to an academic career to seek at least a fourth year of training. Other programs provide 2 years of dedicated research time, allowing for the development of more in-depth educational and research endeavors. Regardless of the time allotted, the trainee must speak to numerous investigators to assess opportunities at the outset of their fellowship. It is optimal to pick a research mentor in the middle of the first year, so that training options can be explored and research protocols developed. For example, if coursework is under consideration,

applications to enroll in Master's-level programs must be completed in the first year, to allow matriculation in the summer or fall of the second year of fellowship. Likewise a prospective research protocol can take months to develop and then go through Institutional Review Board approval. Such preparatory steps may best be taken before actual the research months begin, if that is possible. Those trainees interested in applying for a mentored research training grant should ideally use their first year of research to acquire preliminary data that can be used in an application for funding submitted in the subsequent year (most likely the beginning of their third or fourth year of training). Ideally, manuscripts should be written in the third year of fellowship (or continuing into the fourth year), to qualify to sit for the subspecialty boards, to establish productivity in job and grant applications, and to complete work before changing institutions. Unless enrolled in a Master's thesis program, at least two manuscripts should result from work accomplished during fellowship training. As very general guidelines, these suggestions must be adapted to each trainee's situation and opportunities, but they do highlight the necessity of planning in advance.

Although it may be daunting at first, getting starting on a research career can be exciting and rewarding. Success must be measured in small steps, and with all of the hard work comes tremendous gratification, knowledge, and the opportunity to contribute to the advancement of patient care.

For Suggested Readings see References 76 and 77.

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HOW TO CHOOSE A RESEARCH MENTOR

Wyman W. Lai, MD, MPH

The choice of a mentor is a very important step for a young researcher. It is essential to explore your options for mentorship along multiple research and career pathways. Select someone with whom you are compatible. At different stages in your career, you may benefit from switching mentors; you may also benefit from having multiple mentors at one time. This chapter addresses the characteristics of a good research mentor, one who possesses the proper scientific and personal mentoring credentials, along with techniques for gathering information on potential mentors. Lastly, common pitfalls are examined, and a list of questions for prospective mentors is provided.

Introduction

It is widely accepted that the choice of a mentor is one of the most important decisions that a young researcher must make. In Greek mythology, Mentor was a trusted friend whom Odysseus left in charge of his son, Telemachus, and of his palace as he went off to fight in the Trojan War. As defined in the current entry of Wikipedia, a mentor is "a trusted friend, counselor or teacher, usually a more experienced person." Mentors provide their expertise to less experienced individuals to help them advance their careers, enhance their education, and build their networks.

Before embarking on a search for a mentor, you must first think carefully about your career goals. Do not fall into the trap of defining success by what others might expect of you. Knowledge of your own strengths and limitations, both academic and social, will allow you to choose a path that will have the greatest likelihood of success. Your mentor should be able to help point you in the right direction, but the final decisions are your responsibility. There are no substitutes for enthusiasm and hard work. Mentors will likely gravitate toward those who are willing to put in the effort necessary to become a successful investigator.

Scientific and personal mentoring credentials

To enhance your education and provide you with a supportive network, a research mentor must possess the proper scientific and personal mentoring credentials. The necessary scientific mentoring credentials include the following:

1. *Expertise in, and commitment to, an area of research that interests you*. Early in your career, it is helpful to choose a research project in which your mentor is very interested. You will have a better chance of success if the completion of your research project is of significant consequence to your mentor. That is, look for a mentor with expertise that matches your interests, and then be guided in your interests by that expertise.
2. *History of publication*. You must find a research mentor who has a record of successful publication. Good writing skills will be essential in your career, and these skills can be learned by example. A good research mentor should be able to help you define a question that, when appropriately answered, will lead to a publication.
3. *History of grant funding*. A history of grant funding helps identify individuals who have effectively answered a question and then moved on to other important questions.
4. *Availability of collaborators and educational opportunities*. Look for situations where there is a critical mass of research going on. Having collaborators to work with will increase your research

productivity and improve your chances for a productive research career. Formal research training and educational opportunities are also often associated with a busy research program.

Because networking is a crucial component of career advancement, a research mentor should possess the following personal mentoring credentials.

1. *History of mentoring success*. This trait is easy to define but hard to find. A good mentor should be interested in the success of others. You should look into the mentor's history of job placement for trainees.
2. *Willingness and ability to commit time and resources*. In addition to providing you with the necessary resources (such as space, equipment, materials, and statistical support), a good mentor is someone who can commit the time necessary to mentor you.
3. *A leader in the field*. A leader in the field will have more opportunities to introduce you to others who can help you in your research. Networking will lead to potential job opportunities.
4. *A role model*. You will likely adopt some of the character traits of your mentor, so choose a good role model.

Mentoring options

Most of us follow a stringent career timetable, so starting early is important. It is essential to explore your options for mentorship along multiple research and career pathways. Look for mentors both within and outside of your division, department, or institution. Some institutions and professional organizations have organized mentoring programs for early investigators.

In academic mentorship, the best predictor of future performance is past performance. Mentors have a variety of styles and personalities. Select someone with whom you are compatible, but realize that this is not necessarily a life-long choice. Early in the relationship, the roles of the mentee and mentor should be clearly defined. These roles and expectations should be re-evaluated at regular intervals.

A mentee is not limited to only one mentor. With professional advancement, your mentoring needs may change. At different stages in your career, you might benefit from switching to a new mentor (a "rolling mentoring" approach). An alternative approach is to have multiple mentors available to you at any given time (a "layered mentoring" approach). For example, you can choose a mentor for research questions only, another mentor for academic advancement questions, and yet another mentor for help in balancing family and career. Some of these mentoring relationships may be more formal than others.

Researching a research mentor

Resources are available to aid you in the search process for a research mentor. Prior to meeting with a potential mentor, the publication record of that investigator may be found using PubMed (http://www.ncbi.nlm.nih.gov/PubMed). In addition to learning about the breadth and depth of research that a potential mentor has been involved with, you will discover the potential mentor's history of collaboration. The NIH RePORTER (http://projectreporter.nih.gov/reporter.cfm) is a good resource for gathering information on the history of NIH funding and related publications for a particular investigator, and for finding investigators who have NIH funding on a particular topic. A description of each of the funded projects, whether active or completed, is available.

In addition to database searches, you should seek information from individuals who know or who have worked with a potential research mentor. Former and current trainees are likely your best source of information. In addition to the ones currently at your institution, former trainees are often junior investigators listed on publications featuring your potential mentor as the senior author. Some of these former trainees may be open to talking about their experiences; their publication records and current contact information are easily accessible (e.g., through PubMed). Senior faculty members in your institution or from another institution are frequently good resources for information on potential mentors. These individuals have had the opportunity to witness the growth of the potential mentor and his or her former trainees.

Common pitfalls

The questions below are designed, in part, to help you to avoid some of the common mistakes made in the mentor selection process. First, be sure that your potential mentor has a track record for research, preferably funded, in an area that is of substantial interest to you. When you are looking for a long-term commitment with a research mentor, try to avoid projects that are of only secondary interest to that mentor. Second, avoid choosing a very junior faculty member as your primary mentor, one who does not have the time or experience to mentor an even more junior mentee. Although well-intentioned, very junior investigators will necessarily need to devote most of their time establishing themselves in their field. Finally, avoid choosing a busy investigator who will not be able to devote a portion of his or her time to mentoring you. Find a person with whom you are compatible, and who will commit the necessary time toward helping you build a research career.

Questions to ask

There is little practical advice available for those in search of a research mentor. This list of questions to ask a prospective mentor may help to fill that gap.

- What areas of research are you most interested in? Are you planning any changes in the direction of your research?
- How is your research supported? What grant-funded research do you have?
- Are formal research training programs available through your laboratory, division, or department? Is there adequate institutional support for you and your trainees?
- Do you have a research project or position for someone with my background and interests? If not, do you know of someone who might?
- What type of collaborations have you developed with others in your institution? Or with others locally, regionally, or nationally?
- Do you have the time to mentor an additional person? How frequently do you meet with your mentees? Do you prefer formal mentor–mentee arrangements?
- What are your plans for the future? Are you planning to move soon?

A final piece of advice that will help in the selection process for a research mentor is, "Don't be afraid to ask." That is, during this process you will benefit from speaking to many individuals, including successful individuals in other careers. Ask other fellows and junior attendings about how they made their research mentor choices. Speak to both junior and senior researchers within and outside your institution for guidance.

For Suggested Readings see References 78-82.

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HOW TO CHOOSE A RESEARCH QUESTION

Victoria L. Vetter, MD, MPH

A research project must start with a research question that defines exactly what is to be investigated. The process of choosing a research question should follow a logical progression. It requires personal insight and understanding, in addition to an inquisitiveness and willingness to explore broad areas. After expanding one's horizons, the choice of a good research question requires a narrowing or focus on a small, important answerable inquiry. Development of a research question follows the principles of the acronym FINER; that is, it should be feasible, important, novel, ethical, and relevant. Additionally, a good research question is clear, specific, focused, answerable, and practical, but still significant and innovative. It has the potential to provide important results and relates to a problem or issues of interest to the researcher and to the scientific community. It should have the potential to have an impact on the field. Lastly, the choice of research question should spark personal interest and excitement and confirm the choice of an individual career pathway, serving as the first of many questions to come.

Introduction

Life is full of questions and decisions. A pediatric cardiologist or pediatric cardiology fellow has decided where to go to college and medical school, what type of doctor to be, and where to obtain residency and fellowship training. But that is just the beginning of a clinical research career. All pediatric cardiology fellowship training programs provide some type of training and have some level of research expectation. For those planning a clinical career, a clear understanding of the scope and limitations of research is important as is the ability to critically analyze and apply new information from clinical research studies. Those aspiring to a clinical research career are faced with exciting new questions. If the answer is *Yes* to the question, "Do I want to participate in clinical research?" it is time to start on the pathway to an exciting career.

The next steps include choosing a mentor, reading and talking with others involved in clinical research, and considering a variety of interesting topics. However, the answer to "What is my research question?" can be determined only by the individual doing the research. Certainly, the mentor or others in the training or academic program can provide opportunities to work on their research project or question, but to be successful and satisfied, the individual planning a research career will need to develop a specific and personal area of interest. The guiding principle is to find an area that stimulates intense interest, and even passion; additionally, it should always be an area that is important to both to the researcher and to the field. Although that area may change over time, following a somewhat connected pathway is what moves clinical researchers and their research efforts forward.

What is a research question?

A research question is different from a topic, which is broad. Instead, it is what the researcher wants to know about the topic. A research question precisely defines the area to be investigated. It is specific and limited in nature. The research question is the most important part of the research proposal or project, and should be hypothesis-based, to be formulated and tested. It is the organizing principle of the research study. Putting the question into words will allow focus on specific investigation to determine what is known in the field about the question. Identifying the research question and hypothesis will determine the specific data that are needed to provide answers, and how these data should be collected and analyzed.

Where do research questions originate?

Research questions are derived from research goals and interests—that is, from topics that stimulate interest, excitement, and passion. Research questions can result from careful and insightful reading of the literature to examine existing knowledge and to identify knowledge gaps. They may be inspired from attendance at scientific meetings or continuing medical education courses. Often, they begin with clinical questions (observations or problems) that do not seem to have complete or fully developed answers or accepted management patterns. Questions often are raised in conferences and other brainstorming sessions with colleagues and mentors. The clinical researcher should be alert in all of these settings and jot down these questions, to return to them later and more fully examine the possibilities they raise.

How do you develop your research question?

Early in a clinical career, individuals are interested in all of the new areas that are encountered, each providing interesting questions at every turn. That is great for a clinician, and one must indeed explore and learn about all of those areas. However, a successful clinical researcher must *focus* and choose one of these areas that is of greatest interest, and then develop a specific question, to start on the path to an exciting research career.

Throughout the literature on research questions, one finds the acronym FINER offered as a guide to developing a specific research question. FINER stands for feasible, interesting, novel, ethical, and relevant.

Feasible

To be feasible, a question should lead to a research project that is narrow enough in scope to be manageable. How narrow should be defined in part by the allotted time frame and by the support available. Is the project expected to be completed in a year, or is there a 3- to 5-year grant or time interval? One must remember to leave enough time not only to collect data, but to analyze the data, formulate conclusions from the results, and write an abstract and manuscript to disseminate the findings, as well as time to develop a grant application to continue the research effort. Additionally, a feasible project is one for which adequate support with regard to personnel, technology, and funding is available. Feasibility also depends on having an adequate number of subjects available; thus, a first-order step in the research process is a rough determination of the likelihood of identifying or recruiting (depending on the study design) the necessary number of subjects. A statistical determination of the number of subjects needed to obtain adequate power to answer the research question should be made early in the research process.

Interesting

The only way to sustain a research effort is to work on a topic and question about which the researcher is passionate. Unfortunately, if only one person (or research team) in the world is interested in the topic, it may be very difficult to find funding and to get the work published. This does not mean that it has to be a common problem, or one in which everyone is interested, but it should be important to the field and others should be interested, as well. Remember, many of the most important scientific discoveries have been found in obscure, low-prevalence conditions. A creative person may be able to spark interest in others where little initially exists. Indicating possible broader applications of the research or pointing out the dependence of other research on the specific research question being investigated can be a useful approach to raising the interest of others.

Novel

Novelty is often considered the most difficult objective to achieve, but that is simply because new researchers often try to reach too far at once. The first research question is not expected to win the Nobel Prize. It is only necessary to add some measure of new knowledge to the field and the literature. The question can be novel or unique if it is a new topic that is embedded in an existing body of knowledge, but one not completely explored. It can help explain the difference between existing knowledge and new knowledge. It can clarify an area that is not well understood by the larger scientific community. Furthermore, it can identify gaps and misunderstanding in knowledge or literature, and focus on these gaps to clear confusion or provide more complete understanding. It can provide new information or a new view on controversial areas. The research question may simply address an area that has been neglected. Innovation has become one of the key components evaluated to obtain NIH funding. Critically exploring how the research question can be innovative will not only increase the interest of others, but will help to focus the question and enhance the likelihood of funding support.

Ethical

All clinical researchers should be familiar with the premises of the Belmont Report (available online at http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm) and understand the meaning of *respect for persons*, *beneficence*, and *justice.* With that background, often reinforced by required educational components from institutions before research can be initiated, the new clinical researcher needs to become familiar with all of the regulatory principles and procedures that lead to Institutional Review Board (IRB) submission and approval. Thus, a research question must follow the ethical principles of research.

Relevant

The principle of relevance is akin to the need for the research question to be interesting to others, but requires more substance. The question should be original and worth asking. This is not to say that research that seeks to confirm prior research is not relevant. Questions to ask include, "What contribution will my research make?" And "Who will benefit from this information?" In the end, the question should pass the "So What?" test.

One should think about the multidisciplinary aspects of the question. How might this research relate to other fields outside the specific area of interest in pediatric cardiology? Many areas of research within pediatric cardiology cross into other disciplines, making a research question more relevant and likely to result in exponential increases of knowledge as others expand the initial research. A question may be relevant in a variety of different areas, including scientific knowledge and future research, clinical care, health policy, or public health.

A good research question

A good research question is clear, specific, focused, answerable, practical, and relevant. It has the potential to provide important results and relates to a problem or issues of interest to both the researcher and the scientific community. It should have the potential to have an impact on the field. A focused question is the key to success. Thus, the research question should be a single primary question about which a protocol can be developed. Secondary questions can be related to the primary question or to other related hypotheses. Work should focus on one question at a time—or two to three at the most, if the questions are clearly related in some fashion, and if asking related questions is efficient and likely to result in successful output. The question should link constructs and suggest associations or relationships. Good research questions serve as the basis for the next question, or will stimulate others to ask the next appropriate questions.

A poor research question

A poor research question is one that is not testable with empiric evidence. New investigators often mistake choosing a topic with choosing a question associated with the topic. Choosing a topic precedes choosing a question, but is only the beginning of the process; a specific question must be developed from the topic. Poor questions are often vague, ambiguous, or nonspecific. They may include several good questions, but be too broad to be answered with a single research protocol; these need to be broken down into manageable and answerable questions. Poor research questions lead to poor research, which leads to failure get results published or obtain funding support.

Summary

At this point, the reader should stop reading and write down three research questions that are of personal interest at this point. Take some time to think about what areas are exciting. Narrow the focus and get ready for an exciting career in clinical research. All research involves a lot of hard work and a bit of luck, as well.

So, good luck with your research. Follow your passion and you will have a successful and rewarding career in clinical research.

For Suggested Readings see References 83-95.

Funding

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MAPPING A CAREER DEVELOPMENT PATHWAY IN CLINICAL RESEARCH

Bradley S. Marino, MD, MPP, MSCE, and Ismee A. Williams, MD, MS

To be successful in academic medicine, where both grant funding and job opportunities are becoming increasingly competitive, advanced training in research methodology is essential. Pediatric cardiologists who wish to succeed as independent clinical investigators need to start planning early for such a career, ideally during fellowship. Young trainees and junior faculty are in a unique position to take advantage of training and funding opportunities that are not available to more senior faculty members. This chapter suggests ways to map a career trajectory and addresses training and funding opportunities that will enable the fellow trainee or junior faculty member to become a successful clinician–scientist.

Mapping your academic career

In the past, pediatric cardiologists were trained primarily to be excellent clinicians and to develop a broad range of skill sets. As a result, most pediatric cardiologists participated minimally in research. Those pediatric cardiologists who became leading researchers often developed their research skills through their own special interest and efforts, a particularly influential mentor, or the availability of training and support at a few leading academic programs. Today, fellow trainees and junior faculty have the opportunity to map out their careers to enable them to develop into successful clinician–scientists in pediatric cardiology. Fellow trainees and junior faculty often spend an extra year or more training in a particular clinical subspecialty within pediatric cardiology and seek specific training

to develop research expertise. In the new era, the pursuit of well-defined clinical and research training plans, in combination, will properly prepare fellow trainees and junior faculty for an academic career in clinical research.

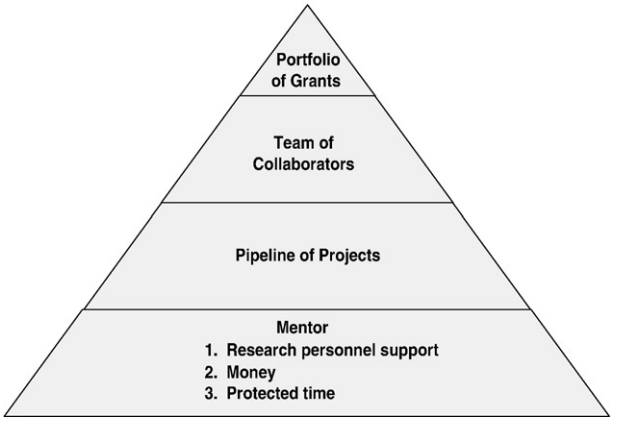
Basic scientists complete postdoctoral training in the laboratory of a successful principal investigator to obtain domain knowledge, gain experience with important techniques, and receive mentorship as they launch their scientific careers. The methodological, training, and experiential requirements of the clinical researcher are no different. To become a viable clinical scientist, the fellow trainee or junior faculty member must pursue appropriate research mentorship and advanced education in clinical research methodology. Advanced research training during fellowship or during the first several years of the junior faculty member's initial academic position may include (1) a local certificate program, (2) a summer program at regional or national research center of excellence, or (3) pursuit of a formal Master's degree in one or more relevant fields (e.g., clinical or translational research, public health, clinical epidemiology, or biostatistics).

Fellow trainees must choose their first academic position carefully. Focused clinical duties and work expectations should be clearly described, along with a research education and mentorship plan. Protected time for research activities with an identified mentor, and clear commitments for infrastructure support (personnel, bioinformatics, and statistics), space, and start-up funds for supplies for a clearly defined period of time should be described. Although the balance between the clinical and research components of an individual faculty member's total effort will vary, it is critical to agree on a balance of responsibilities with your division chief and with the clinical and research mentors who will foster the success of an academic research career. It is important to note that total clinical and research effort may vary between investigators, and will likely vary during the career of any single investigator.

The research mentor, developmental plan, and clinician–scientist pyramid for success

To become a successful clinician–scientist, the fellow trainee or junior faculty member must have a good working relationship with a committed mentor. The most important job of any research mentor is to advocate for the mentee, to guarantee protected research time, and to provide resources, opportunities, and advice. The mentor should assist the mentee with a *gap analysis*, which is the systematic review of existing knowledge in a particular research area to determine new opportunities for investigation.

Figure 7



The clinician-scientist pyramid for success.

After the mentee performs a gap analysis in the chosen research area, several short-term cross-sectional or retrospective projects may be developed and pursued over the first 2 years, to generate pilot data for future local and regional grant applications. During the first 12 to 18 months of the research plan, longer term 3-year and 5-year prospective projects may be developed to generate pilot data for potential national foundation and National Institutes of Health (NIH) funding applications. A well-articulated development plan allows for progressive growth of the fellow trainee or junior faculty member and provides the best chance to transition to a funded faculty position or to serve as a vital scientific collaborator.

The mentee, with the help of the mentor, should develop and review a set of *periodic priority lists*, which includes four distinct lists:

List 1: Things that the mentee is doing but wants to quit.
List 2: Things that the mentee is not doing but wants to start.
List 3: Things that the mentee wants to keep doing.
List 4: How the mentee plans to shorten list 1 and lengthen list 2 over the next 6 months.[96]

The mentee should review the periodic priority list at least every 6 months with the mentor. With the assistance of a good mentor, the fellow trainee or junior faculty member should create realistic 1-year, 3-year, and 5-year career developmental plans for clinical and scientific growth and academic success.

It is critical to have a research plan that will allow the fellow trainee or junior faculty member to build a personal *clinician–scientist pyramid* (Figure 7). The foundation of the pyramid is grounded in the mentorship the trainee is receiving, the protected time allotted to

pursue research, money for supplies, personnel support, and space as required. Without these basic elements, fellow trainees or junior faculty members will find it difficult to develop their own research program. Once a foundation is established, the 5-year research plan will allow the fellow trainee or junior faculty member to create a *project pipeline* that will provide pilot data required for additional funding. Furthermore, the project pipeline will over time yield a team of collaborators that will enrich and support the work of the junior investigator, who will in turn support the research of the collaborators. These research relationships will ultimately result in the highest quality research and a portfolio of grants for the mid-level faculty member, allowing for the transition from research trainee to funded investigator.

Qualities of a successful clinician–scientist

As fellow trainees or junior faculty members mature, they must acquire the qualities that allow for success as a clinician–scientist. The successful clinician–scientist is committed, determined, and focused on intertwining both the clinical work and the research area of interest. The "fire in the belly" found in the best clinician–scientists helps them remain on their specific research path. In addition, successful independent investigators must be resilient, unafraid to question dogma, and able to learn from their failures, which become opportunities for future growth and success. Even the best scientists have an equal number of successes and failures relative to outcomes from specific research and manuscript and grant submissions. All successful clinicians and scientists have superior time-management skills, but this is even more important for the clinician–scientist, who needs to balance both clinical and scientific commitments. Excellent time-management skills will extract the most out of the time available (at its best, it seems like creating time), which is critical to the clinician–scientist meeting his or her specific obligations.

Training and funding opportunities

A list of training and funding opportunities for the junior investigator follows here. This chapter by no means provides an exhaustive list, and fellow trainees and junior faculty are advised to discuss training and funding opportunities with their mentor or division chief, or to contact their institution's research foundation or office of sponsored programs for more information. In addition, direct contact with officials at the National Institutes of Health or the external foundations offering funding opportunities may be very helpful for determining the most appropriate funding options based on your research interests, level of training, or faculty rank.

Funding for junior investigators

Among the various funding opportunities available for clinical researchers, many specifically target the junior investigator. Sources range from local institutional or university-sponsored grants to national and international awards. Given that all awards are competitive and that the clinical research funding environment is limited, all investigators should prepare to submit multiple applications in anticipation of receiving multiple rejections. The rejection of multiple grant applications is expected, especially early in the investigator's research career, and does not predict the ultimate future success of the junior investigator. Many awards will have similar objectives; therefore, it is possible that you will be able to submit the same proposal to multiple sources. Our advice is to start early, and to be prolific with grant applications. Unfortunately, there is no national clearing house for all research related to pediatric cardiovascular disease that can give the investigator a complete list of local institutional, national foundation, or NIH funding opportunities. Finding appropriate funding options and gathering the required information for submission requires both personal initiative and guidance from the junior investigator's mentor.

Local institutional funding

Typically, local sources of funding are likely to be less competitive than national and international grant mechanisms, because the applicant pool is smaller, but this is not always the case. Often specific schools, departments, or divisions will have funds designated for research funding, many for junior investigators. The junior investigator should contact the local institutional research foundation or grants office to inquire about opportunities specific to the area of interest. Many centers publicize funding opportunities in a centralized manner, either via websites or via e-mail server lists with periodic announcements of upcoming deadlines. A junior investigator needs to subscribe to such e-mail lists, or get access to communication from other centralized mechanisms. For those institutions with a Clinical Translational Science Award (CTSA), the CTSA will often have funding available for pilot initiatives or junior investigators. Junior investigators who work at an institution with a CTSA are advised to contact the administrators of their CTSA to inquire about potential funding opportunities.

Private foundation funding

Private foundations offer another opportunity for grant funding. For example, the junior investigator pursuing research on pediatric cardiomyopathy may submit grant applications to the American Academy of Pediatrics' Research Fellowship Award, the American College of Cardiology's Young Investigators Award Competition, the Myocarditis Foundation Research Fellowship Grant, or

the Children's Cardiomyopathy Foundation and American Heart Association's Pediatric Cardiomyopathy Joint Research Award. The American Academy of Pediatrics' Research Fellowship Award and American College of Cardiology's Young Investigators Award competitions support all types of pediatric cardiovascular research, The American Heart Association has a large number of potential awards for the junior investigator, including the Fellow-to-Faculty Transition Award, the National Clinical Research Program for early career investigators, the National Scientist Development Grant for beginning scientists, and Regional AHA Affiliate Awards (Scientist Development Grant, Clinical Research Program, and Beginning Grant-In-Aid Program). Information about the purpose, eligibility, duration of support, and budget for specific national and regional AHA awards may be found online (http://www.americanheart.org/presenter.jhtml?identifier=9713). Other foundation grants that may be appropriate for pediatric cardiovascular research include the Burroughs Wellcome Fund Career Awards for Medical Scientists, the Children's Heart Foundation, the Doris Duke Clinical Scientist Development Award, the Pew Scholars Program in the Biomedical Sciences, the Robert Wood Johnson Foundation, and the Thrasher Research Fund. Specific information about the purpose, eligibility, duration of support, and budget for these foundation grants may be obtained from the specific granting agencies and at their websites.

For awards that target the junior investigator, application requirements may stipulate that the principal investigator be only 2–4 years out from completion of training. Awards vary in both duration as well as amount of funding, and some provide funding that is greater than that available through the NIH. Foundation grants are open to submission nationally, and often internationally, and therefore tend to be highly competitive. On the other hand, many foundation grants are not well publicized, and therefore it pays to be knowledgeable about specific foundation grant options.

NIH funding

The NIH is, collectively, one of the most competitive and highly regarded sources of research funding in the United States. There are five basic types of awards available, denoted by different letters:

Research grants (R series)
Career development awards (K series)
Research training and fellowships (T and F series)
Program project and center grants (P series)
Cooperative grants (U series)

For more detailed information, see the chapter on NIH opportunities (J.D. Scott, *NIH early career research training opportunities for pediatricians*) later in this article.

Clinical and Translational Science Awards

Clinical and Translational Science Awards (CTSA) are awarded to institutions across the United States by the National Center for Research Resources (NCRR), one of the 27 centers and institutes at the NIH.[97] In addition, CTSA-funded institutions offer a variety of scholarship-based training programs for young investigators that include both Master's degree programs in biostatistics or public health as well as early career development grants. The KL2 Scholars Mentored Career Development program (not to be confused with the K12 Mentored Clinical Scientist Development Program) is an example of such a program that serves as a bridge by which junior faculty can achieve research independence. The main purpose of the KL2 program is for the applicant to gain the knowledge and skills necessary to function effectively on interdisciplinary research teams; an applicant must have a professorial appointment (clinical or tenure track) at the time of the award and must be able to devote a minimum of 2 years toward the training program. The program includes rigorous training that introduces the applicant to a wide range of clinical and translational research methods through both classroom and laboratory instruction. The KL2 award includes varied research rotations, a mentored research project, participation in multidisciplinary seminars and colloquia on clinical and translational research, and at some sites access to a research Master's degree program in clinical or translational research, public health, clinical epidemiology, and biostatistics. Different institutions have different offerings and applicant requirements, and qualified candidates are urged to contact their local CTSA representative early, to inquire about application processes and deadlines. (For more information, see J.D. Scott, *NIH early career research training opportunities for pediatricians*, later in this article.)

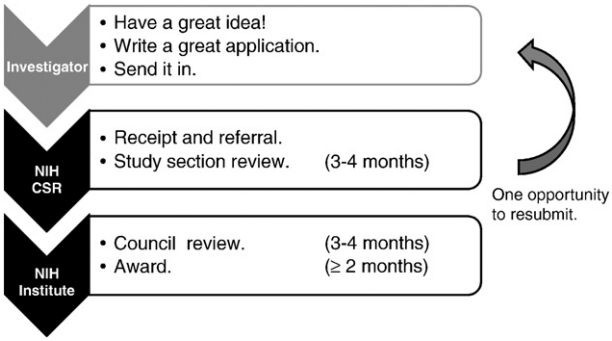
Conclusion

To succeed as an independent clinical or translational researcher, it is essential for a fellow trainee or a junior faculty member to obtain training in research methodology. Furthermore, it is important to choose an initial academic position with focused clinical duties, protected time, and appropriate clinical and research mentorship and support. It is critical to have a research plan that will allow one to build a clinician–scientist pyramid. Thereafter, the junior investigator should strive to emulate the qualities of other successful clinician–scientists and begin to build a funding history as a principal investigator or a vital collaborator.

Funding

This work was supported by a grant from the National Heart, Lung, and Blood Institute (U01 HL68271).

Figure 8



Overview of the NIH grant process. CSR, Center for Scientific Review.

FUNDING IN THE CURRENT ENVIRONMENT

ORIENTATION TO NIH AND SCIENTIFIC REVIEW: NIH FOR BEGINNERS

Gail D. Pearson, MD, ScD, and Frank Evans, PhD

More than 80% of research funded by the U.S. National Institutes of Health (NIH) supports extramural research conducted by independent researchers at more than 3000 universities, medical centers, and other institutions. Extramural program staff, who have advanced degrees and research experience, provide the interface between NIH and the extramural research community. The National Heart, Lung, and Blood Institute (NHLBI) is a major source of funding for pediatric cardiovascular research. Most of the NHLBI's extramural grant funding (82% in 2008) supports unsolicited or investigator-initiated research. This chapter summarizes electronic resources and offers practical tips based on the authors' nearly two decades of collective experience advising grant applicants.

Introduction

The National Heart, Lung, and Blood Institute (NHLBI) is a major source of funding for pediatric cardiovascular research and has funded research in congenital heart disease since 1949. Well-known studies that have been funded by NHLBI include the two Natural History studies of aortic stenosis, pulmonary stenosis, and ventricular septal defects; the trials of high-dose aspirin and intravenous γ-globulin in Kawasaki disease, and the Baltimore–Washington Infant Study. NHLBI currently funds a large portfolio of pediatric cardiovascular research, ranging from cardiac development to clinical trials, and supports a wide range of investigators, from fellows to senior researchers. The purpose of this chapter is to provide resources for those who wish to become one of these funded researchers.

The technical aspects of applying for an NIH grant are covered well at a number of websites, and a great deal has been written on posing a research question and writing a compelling scientific plan, and a recent excellent overview of the NIH grant application process has been published (see Suggested Readings at the end of this chapter). Here, we will focus on practical tips and on common questions that we have been asked in our nearly two decades of collective experience advising grant applicants (Figure 8).

Program staff: We're here to help

The NIH consists of 27 semi-autonomous institutes and centers. Most of these, such as the NHLBI, have a specific research agenda and fund both intramural ("within the walls") and extramural ("outside the walls") research. Intramural research is conducted by NIH employees and fellows within NIH facilities. Extramural research, which accounts for more than 80% of NIH's research funding, is conducted by independent researchers at more than 3000 universities, medical centers, and other non-NIH research institutions.

Extramural program staff, who have advanced degrees and research experience, provide the interface between their institutes and the extramural research community. Program staff oversee scientific aspects of extramural grants and contracts, provide scientific leadership in their areas of expertise, and help shape overall research policy for their institute and the NIH. Program staff provide guidance on the grant application process, rather than detailed scientific advice on a given research proposal, and they are not involved in the peer review of applications.

The program staff are happy to answer questions and help you navigate the NIH grant process.

Is NHLBI interested in my research?

This is a frequently asked question. The short answer is *yes*, if the proposed research pertains to NHLBI's specific research agenda: heart, lung, blood, or sleep.

Most of NHLBI's extramural grant funding (82% in 2008) supports unsolicited or investigator-initiated research. In this scenario, the investigator proposes a research topic and applies for funding using one of the standard NIH grant mechanisms. NHBLI funds investigator-initiated grants on the basis of their peer review score and the available funds.

Some of NHLBI's extramural research funding supports solicited or NHLBI-initiated research. In this scenario, NHLBI proposes a broad research topic, but the investigator is usually free to propose a detailed topic and approach. NHLBI funds solicited grants on the basis of their peer review score, their adherence to the solicited topic, and available funds. Examples of NHLBI-

initiated research include the Framingham Heart Study and collaborative research networks, such as the Pediatric Heart Network. NHLBI solicits applications when there is a gap in science or resources that is not likely to be addressed otherwise. The topics, which are reviewed extensively within NHLBI, come from the expertise of the extramural program staff and interactions with the extramural research community.

The application process

The NIH has many types of research grant mechanisms. Among the most well-known are the R01 (research project grant), R21 (exploratory/developmental research grant), and the P01 (program project grant) series. The research grant mechanisms vary by duration, budget, preliminary data, and the nature of the research institution. For example, R01s are usually limited to 5 years, whereas R21s are usually limited to 2 years. Research grant mechanisms typically do not require a specific minimum level of effort by the principal investigator, although training and career development grant mechanisms, such as K08 or K23, often do. The area of training and career development grant mechanisms is covered in the next chapter of this article (J.D. Scott, *NIH early career research training opportunities for pediatricians*).

The details and limitations of each mechanism are given in the corresponding funding opportunity announcement. Investigator-initiated applications are submitted in response to a parent announcement for the given grant mechanism; these are available on the NIH Office of Extramural Research website (http://grants.nih.gov). There are three receipt dates per year for investigator-initiated applications.

NHLBI-initiated grant applications are submitted in response to a Program Announcement (PA) or a Request for Applications (RFA); these are available in the NIH Guide or on the NHLBI website. NHLBI-initiated contract applications are submitted in response to a Request for Proposals (RFP), available on the NHLBI website. The PAs usually have multiple receipt dates, but RFAs and RFPs often have only a single receipt date.

Grants and contracts differ in several ways, but chiefly in terms of the monitoring of funding and the degree to which the NHLBI is involved in the research. Grants are considered an "assistance mechanism," and NHLBI typically leaves the aims and approach to the discretion of the investigator. By contrast, contracts are used to procure specific products or services and the research aims and approach may be specified in detail in the RFP.

Most NIH grant applications are submitted electronically through http://www.grants.gov. Research institutions must be registered with Grants.gov. Investigators must be registered with NIH's eRA Commons (Electronic Research Administration; http://era.nih.gov/), which allows the investigator to follow the progress of the application and receive a summary of the review (known commonly as the "summary statement") and other communications. Your grants office or equivalent business office can create an investigator eRA Commons account for you, but you should allow 2–4 weeks before the application receipt date. Figure 7 summarizes the application and review process.

The review process

Grant applications are received by the NIH Center for Scientific Review (CSR), a separate component of NIH responsible for all aspects of the peer review process. The CSR assigns the application to an Institute for funding consideration and to a Scientific Review Group (SRG, colloquially called a *study section*) for review based on the scientific content of the application. Applicants can request specific assignments or specific scientific expertise that may be needed for review in a cover letter. The CSR honors these requests if possible.

The SRGs are organized by a Scientific Review Officer (SRO)—that is, by a CSR staff member who corresponds to the funding institute's program staff. The SROs have advanced degrees and research experience, but they rarely are in a position to offer detailed scientific advice on a given research proposal, and they are not involved in funding decisions. The SRO is your primary contact between submitting a grant application and completion of review.

Members of SRGs are experienced extramural researchers who volunteer their time and effort to review grant applications for NIH. They evaluate applications using five core criteria: significance, investigators, innovation, approach, and research environment. The reviewers are free to weigh these criteria as they see fit. They often give significance the most weight, and an application does not necessarily have to be strong in all five criteria to be successful. The reviewers are also asked to consider human subjects protection and animal welfare, if applicable.

All applications, whether discussed or not, receive a summary statement of the reviewers' comments posted within 30 days of the SRG meeting. Applications that are discussed receive a priority score ranging from 10 (best) to 90 (worst). Priority scores are normalized for most research grant applications to produce a percentile score ranging from 1 (best) to 99 (worst). Institute program staff can help you understand the score and summary statement and the potential for funding.

The Advisory Council of the funding Institute, which meets 1–3 months after the SRG, serves as a second tier of review. The Council may examine a given application in

detail or, more commonly, simply accepts the SRG's recommendation. Based on available funds, the peer review scores, and advice from Council and Institute staff, the Institute director establishes a pay line (i.e., the highest fundable score) for each grant mechanism.

Applications that are not funded remain active for two additional Council rounds, and will be paid if the pay line improves during this period. The Council meets three times per year to consider grant applications, corresponding to the three receipt dates for investigator-initiated applications. Applicants are usually advised to revise and resubmit the application, however, because there is no guarantee that the pay line will increase. An application can be revised and resubmitted for review one time only. The decision of whether to revise and resubmit is up to the investigator, although the Institute program staff can help you weigh the options.

Major recent changes

Application

Applications have been shortened considerably, with new page limits. The research section has been cut from 25 to 12 pages, which puts a premium on clear, concise writing and an ability to convey key concepts rather than minute experimental details. Applicants are permitted to revise and resubmit their application only once, in contrast to having up to two opportunities for re-review.

Investigator

It has always been an NIH priority to encourage new investigators through various programs. NIH defines a New Investigator (NI) as one who has not competed successfully as Principal Investigator for a significant NIH independent research award. An Early Stage Investigator (ESI) is a NI within 10 years of completing the terminal research degree or medical residency. Applications from NIs and ESIs are grouped together in the SRG meeting, and reviewers are instructed to give less emphasis to preliminary data and publication history. Currently, NHLBI offers a preferential pay line for R01 applications from ESIs (but not other NIs). As always, the NHLBI website (http://www.nhlbi.nih.gov) should be consulted for updates.

Review

NIH has recently undertaken a major effort to enhance peer review. The goals were to retain the best reviewers, to improve the quality and transparency of review, and to ensure balanced and fair reviews. As a result, applications have been shortened and restructured to align with the core review criteria. Similarly, the summary statement has been restructured, and a new 9-point scoring system is used for individual review criteria and the overall score. Greater emphasis is placed on significance and investigator than on details of the approach.

Top 10 recommendations to applicants

Over the years, we have developed several themes for advising grant applicants. They are summarized here. There is also an Insider's Guide to Peer Review for Applicants with similar types of information (see Suggested Readings at the end of this chapter):

- **Tell a story.** Especially now with shorter page limits, grant applications need to have a cogent and compelling rationale. Reviewers are experienced scientists but are not necessarily expert in the details of your particular area, so you need to be able to convince them why your work is important.
- **Follow the rules.** The average SRG reviews 100 applications per meeting, a large burden for reviewers, who are performing a valuable community service to the biomedical research community. If you do not follow the rules for margin width, font size, page limits, and the like, it will be much easier for reviewers to put your grant at the bottom of the scoring pile. This also applies to eliminating typing errors and following correct English grammar, spelling, and usage rules.
- **Ask for help.** NIH Program staff can provide a lot of help in navigating the system. You should also seek out colleagues who have received NIH funding, and get to know your grants or business office. Also, ask a friend who is not in your field to read your application to see if it follows the "tell a story" rule well.
- **Plan ahead.** Work on a well-written, well-thought-out grant application will start several months before the due date. Time should be allowed for review by collaborators and mentors and for the business office to complete the budget and get internal sign-off. In addition, you will need time to incorporate feedback and to edit your initial drafts.
- **Be informed.** Information on NIH-funded grants is available through the NIH RePORTER (http://projectreporter.nih.gov/reporter.cfm). This website offers reports, data, and analyses of NIH research activities, which may be helpful as you plan your research.
- **Take the plunge.** Your idea is as good as anyone's, and you will get useful feedback through the peer review process, even if you are not successful the first time.
- **Be persistent.** Many grants do not get funded the first time, so you will often need to revise and resubmit.
- **Don't panic.** If your grant did not get a fundable score the first time, take a deep breath. Read the summary statement a couple of times, take another deep breath, and then put it down for a week. After you come back to it, contact the assigned program staff member (the name will be on the summary statement), and ask to set up a time to talk about your options. The program staff member

Table IV. Selected offices and resources at the U.S. National Institutes of Health (NIH)

Offices and resources (URL)	Remarks
Office of Extramural Research (http://grants.nih.gov/grants/oer.htm.)	Provides current information on all aspects of grants and funding, including grant application basics, grants process overview, types of grant programs, how to apply, the peer review process, award management, foreign grants information, electronic grants, and NIH financial operations
CSR Insider's Guide to Peer Review for Applicants (http://cms.csr.nih.gov/ResourcesforApplicants/Advice.htm.)	Advice on writing a grant application from reviewers, themselves, and the NIH Center for Scientific Review
NIH, NHLBI. Children and Clinical Studies (http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php.)	A multimedia bilingual resource for families and researchers about the importance and conduct of pediatric research
NHLBI Fact Book (http://www.nhlbi.nih.gov/about/factpdf.htm.)	Annual compilation of Institute activities containing administrative information on grants, contracts, clinical trials, and research training and career development programs
NHLBI Clinical Research Guide (http://www.nhlbi.nih.gov/crg/index.php.)	Guide to preparing, submitting, and managing clinical research applications
Organization (http://www.nih.gov/about/organization.htm.)	Brief overview of the NIH organization
Budget (http://www.nih.gov/about/budget.htm.)	Brief overview of the NIH budget

may have attended the SRG meeting and, although they cannot give you insider information or tell you who the reviewers were, they can help interpret the sometimes cryptic comments in the summary statement.

- **Tell another story.** When you revise and resubmit, the reviewers want to know that you considered and responded to all of their comments, and they also want to be able to see where you made changes in the grant application in response to them. This does not mean that you have to agree with all of their comments, but your response should explain why you may be taking another approach if that is the case.
- **Know the literature.** Be familiar with the literature on your subject and with relevant literature from other fields. Avoid proposing something that has already been established in the literature. Address literature that contradicts your hypothesis and explain how your research will resolve the contradiction.

An annotated summary of some of the most relevant online resources at the NIH is presented in Table IV.

Disclaimer

The views expressed here are those of the authors and do not necessarily reflect the official position of the NIH or the NHLBI.

For Suggested Readings see Reference 98.

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No extramural funding was used to support this work.

NIH EARLY CAREER RESEARCH TRAINING OPPORTUNITIES FOR PEDIATRICIANS

Jane D. Scott, ScD, MSN

The U.S. National Institutes of Health (NIH) fund many research programs to train young MD and PhD scientists. Early career clinicians, contemplating research careers, frequently have difficulty knowing *where* to look for research training resources, and as well as *when* to start planning for research training. The purpose of this chapter is to provide a brief overview of NIH research training mechanisms and to provide helpful hints in looking for research training opportunities.

Ask early, ask often

If you are interested in pursuing a career in pediatric research, and have not completed a research degree (PhD, MS), the time to start seriously considering your options is early in your residency, so that you can pursue research training in conjunction with your fellowship, or as a separate fellowship. A first step is to talk with faculty mentors with research interests similar to yours. Also, identify research fellows in your department or institution and ask how they found a training program. Start attending research conferences and seminars, to see what issues and topics are of particular interest to you. In addition, begin to explore the NIH extramural research training website (http://grants.nih.gov/training/extramural.htm) for a better understanding of the types of training programs that are available.

Special pediatric research opportunities

Medical school debt frequently deters highly skilled individuals from pursuing research training. In response to this problem, the NIH sponsors five Loan Repayment Programs (LRPs) in an effort to recruit and retain highly qualified health professionals as research investigators (http://www.lrp.nih.gov). One of these programs is specifically aimed at encouraging pediatric research. For individuals agreeing to engage in research training at least 50% effort for 2 years, the program may provide loan repayments of as much as $35,000 annually for up to 2 years. The LRP program requires an application, and faculty support, and not all who apply are accepted. For those who do qualify, however, the program is an

enormous help by reducing medical school debt and reducing hurdles to research training.

Institutional postdoctoral training programs

National Research Service Award (NRSA) Institutional Training (T32) Programs provide postdoctoral research fellowships for clinicians wishing to pursue research. These programs are 2–3 years in length, and are sometimes aligned with fellowship programs. T32 Program Directors are senior scientists who provide oversight of the training program, research activities, and trainees. T32 programs are awarded to universities, and trainee selection by program faculty is competitive. The NIH currently funds approximately 2400 T32 programs, including several focused on pediatric cardiovascular research. A comprehensive list of all Institutional Training awards can be found at (http://grants.nih.gov/training/outcomes.htm).

The T32 programs and descriptions can be obtained through the NIH RePORTER, a powerful search engine just released by NIH. To search for T32 programs, go to http://projectreporter.nih.gov/reporter.cfm. Select "Funding Mechanism" and request "Training, Institutional." Next, request an NIH Institute that you believe aligns with your research interests (or choose All), and hit Enter. RePORTER then provides the program name, the principal investigator's name, institution, and contact information. In addition, peer-reviewed articles generated by each program are available under the results section. The NIH RePORTER provides detailed information about programs, and is enormously useful in comparing training opportunities.

Individual postdoctoral research training awards

There are two commonly used awards that generally follow T32 training. The F32 NRSA individual postdoctoral fellowship (http://grants1.nih.gov/grants/guide/pa-files/PA-09-210.html) provides an opportunity to strengthen the applicant's understanding of the health-related sciences, within the broad scope of biomedical, behavioral, or clinical research or other specific disciplines relevant to the research mission of the NIH. Applicants with a health professional doctoral degree may use the proposed postdoctoral training to satisfy a portion of the degree requirements for a Master's degree, a research doctoral degree, or any other advanced research degree program. Additional fellowship programs may be found online at the NIH F kiosk (http://grants.nih.gov/training/F_files_nrsa.htm).

The NIH Pathway to Independence Award (K99/R00) (http://grants2.nih.gov/grants/guide/pa-files/pa-10-063.html) is designed to facilitate a timely transition from a mentored postdoctoral research position to a stable independent research position with independent NIH or other research support at an earlier stage than is currently the norm. The K99 offers up to 2 years of mentored postdoctoral training, and followed by up to three 3 of R00 support, after the applicant has successfully transitioned to an assistant professor position. The R00 provides independent research monies and salary support to protect the young investigator's time during the early independent phase of the career. This is the only NIH research training award that does not require citizenship or a permanent resident's "green card" for eligibility.

Institutional early career development awards

Since 2006, the NIH's National Center for Research Resources (NCRR) has sponsored the Clinical and Translational Science Awards (CTSA) programs, a national consortium of medical research institutions working together to improve the way biomedical research is conducted nationwide. As of 2009, there were 47 funded programs, and many programs have training components to train clinical and translational researchers. For more information on the NCRR CTSA program, funded sites, and clinical training activities see the Web pages at http://www.ctsaweb.org/ or http://www.ncrr.nih.gov/. Each site provides information regarding the CTSA program, its website, and contact information.

Individual early career development awards

The next level of research training is the Mentored Research Career Development Awards, also known as individual K awards. These are frequently awarded late in fellowship, or to new faculty. These awards provide support for salary, research, career development and tuition support, and travel. Awards range from 3 to 5 years. The two most popular awards are the K08 Mentored Clinical Scientist Research Career Development and the K23 Mentored Patient-Oriented Research Career Development Award. The K08 Mentored Award provides support and "protected time" to individuals with a clinical doctoral degree for an intensive, supervised research career development experience in the fields of biomedical and behavioral research, including translational research. The K23 Mentored Award provides comparable career development and training for individuals who have made a commitment to patient-oriented research.

Career development awardees are generally required to commit 75% effort to research training under these awards. Three years ago, the NHLBI created an exemption to the "percent effort requirement" for cardiothoracic surgeons, vascular surgeons, and interventional cardiologists, whereby these clinicians may pursue research training at 50% effort.

To effectively determine program availability, check the K Kiosk at the NIH website (http://grants.nih.gov/training/careerdevelopmentawards.htm), and also check with the institute to which you wish to apply. Program

availability and institute-specific requirements are also found through links to the individual NIH Institute and Center websites at http://www.nih.gov/icd/index.html.

Final suggestions

Research training opportunities are provided by all NIH Institutes and Centers, and there are Program Staff at each institute who are available to answer questions regarding research training opportunities and current Institute interests, and to provide guidance as to what training mechanism would be most appropriate to pursue. Program staff can be very helpful in providing feedback regarding the proposed application and on whether the research topic falls within the scope of interest of a particular institute.

Ultimately, your success depends on your willingness to pursue what frequently seems like a convoluted obstacle course. Start inquiry about research training early in your residency, and find clinician–scientists who are willing to provide you with research training guidance and advice. Persistence is key, and there are many paths to success.

Disclaimer

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CAREER MANAGEMENT

BALANCING WORK AND LIFE

Meryl S. Cohen, MD

No one person can claim expertise on how to develop equilibrium between work and home life; in fact, no one formula fits every person. Moreover, work and life balance changes over the span of one's career. Commitment to one's profession and dedication to one's family provides an opportunity to develop a balance that works. Although this is a difficult challenge for anyone, it is achievable. Integration of the personal and professional aspects of life often differ for men and women. Although it is not universally the case, women typically face the challenges of advancing their career and achieving academic promotion while usually assuming the primary responsibility for home life and childcare. Men face similar obstacles, and have the added burden of the stereotypes associated with their gender. Academic institutions need to recognize the importance of flexibility in the workplace, and must ensure that advancement of career is not achieved at the expense of family life. Mentors play a large role in academic success, but to foster a successful relationship it is also important that the mentor has similar views on work–life balance as the mentee. In achieving balance, it remains important to demonstrate hard work, productivity, and commitment to one's profession. Flexibility, organization, and appropriate prioritization are keys to success both at work and in the home.

Introduction

A career in academic pediatric cardiology requires dedication, fortitude, and long hours; often the commitment and workload do not cease at the end of the typical workday. In addition to the clinical challenges and teaching requirements, there is the expectation that there will be productivity in the realm of research activities, including presentation of research studies at national meetings, grant writing to obtain funding, and publication in peer-reviewed journals. Often, there is not enough time in the day to accomplish these tasks because of clinical, teaching, and administrative duties. As a result, work life spills into home life, and personal time dwindles.

There are no experts on how to develop equilibrium between work and home life, and no one formula fits every person. Moreover, work and life balance changes over the span of one's career. Commitment to one's profession and dedication to one's family provide an opportunity to develop a balance that works. Although this is a difficult challenge for anyone, it is achievable.

Integration of the personal and professional aspects of life can be daunting, and may differ for men and women. Although this is not universal, women typically face the challenges of advancing their career and achieving academic promotion while also usually assuming the primary responsibility for home life and childcare. In fact, women report that 90% of their time away from work is spent on childcare. The limited time period for reproductive success often coincides with the time that women faculty are asked to be the most academically productive, as promotion deadlines fast approach. In addition, many academic institutions in the United States are archaic with regard to family-friendly policies that are available in other workplace environments and are commonplace in other countries. Women also perceive less institutional support for family life than men do. Despite these challenges, 84% of women are satisfied with their career choices (although 31% would choose a different career path if given the choice again).

Men are not left out of this equation by any means. They face similar obstacles, and have the added burden of the stereotypes associated with their gender. A “less academic” track or part-time work is more acceptable in the academic environment for woman than for men. Even though childcare is now generally shared between

parents, paternity leave is either very short-lived or nonexistent at many institutions. Furthermore, men often perceive that it is their duty to be the primary income provider for a household. Men overall express 76% satisfaction with a career in academic medicine; the most common predictors of burnout for men include control over work hours and number of hours worked. This highlights the importance of family time in the setting of active careers.

Both sexes face challenges of work–life balance, but there is no doubt that women continue to be at a disadvantage with regard to achieving academic success. Many studies assessing academic promotion report that female faculty in academic tracks take longer to achieve promotion and are less likely to be promoted than their male peers. In the academic setting, women continue to be paid on average 11% less than men when adjusted for rank, track, specialty, years, and administrative positions. Moreover, women physicians who choose to have children have fewer peer-reviewed publications than do their male counterparts with families. It is well recognized that the first and last authorship positions on manuscripts carry the most weight for promotion; a recent study assessing authorship from six prominent medical journals published over the last four decades reported that the number of women authors in these important authorship positions were overwhelmingly in the minority. The situation was not completely bleak. Women authors became more prevalent over the latter part of the study period, with the greatest impact in the fields of pediatrics and obstetrics and gynecology.

Despite the inherent obstacles, women are more likely than men to pursue an academic medical career; this remains true even though advancement to associate or full professor rank is significantly lower than expected. The field of pediatric cardiology is not immune to gender disparity in relation to academic promotion. The proportion of women in the ranks of instructor and assistant professor is higher than that of men at five of the largest pediatric cardiology centers in the United States (including The Children's Hospital of Philadelphia, Children's Hospital Boston, Columbia Presbyterian, University of Michigan, and Texas Children's Hospital, Houston). At these same centers, men overwhelmingly predominate at the rank of associate or full professor. There are of course, caveats to these findings (e.g., women faculty tend to be younger), but these do not entirely account for the disparity.

Certainly, challenges exist to successful work–life balance, but there are many measures that can help assure success at both the professional and personal level. Academic institutions need to recognize the importance of flexibility in the workplace and must ensure that advancement of careers is not achieved at the expense of family life. There are areas within the academic setting where improvements can be made to allow for more personal time, including departmental mentoring for career development, administrative secretarial support, the potential for sabbatical time from clinical and administrative duties, strong family leave policies, and on-site child-care.

One of the overall themes to success is the fundamental role of the mentor. Studies suggest that junior faculty desire mentors whom they perceive as having themselves achieved work–life balance. In addition to guidance on research projects and clinical acumen, mentees appreciate advice on how to choose an appropriate academic track, knowledge about maternity and paternity leave options, and the development of organizational skills. As important as it is for the mentor to provide opportunities for professional exposure such as research projects and invited presentations, it is as imperative to help protect mentees from spending time on inappropriate research projects, overcommitment to committee participation or administrative roles, and taking on too much clinical work. It is important for mentees to learn when it is appropriate to say “no.”

Regarding one's own decisions regarding academic work life, there are several options that may help an individual achieve work–life balance. If one has a family or is interested in starting one, it may be beneficial to delay starting an academic track with its promotion clock, and even to consider part-time work. Policies exist at many academic institutions for flexible work hours. Knowledge of these by-laws at one's institution is beneficial. Over the last decade, physicians who work part-time have become a significant portion of the workforce. For some, this is temporary; for others, it is a more permanent option. Almost 90% of part-time physicians are women who change course primarily for childcare; however, many men choose to work part-time as well.

Part-time work has many potential advantages. The promotion clock can often be delayed, or its pace altered, with additional time added prior to promotion. Men and women who work part-time are able to maintain their skills yet still have personal or family time during the work week. Of course, part-time work also carries some disadvantages. The slower pathway to promotion will inevitably result in full-time colleagues passing part-time peers by in advancement and opportunity. Moreover, one must overcome the perception that a part-time worker is not as committed as someone who has a full-time position. Ironically, part-time work often results in significantly less pay for the amount of time spent working, because issues do not go away on one's day off. These are some of the sacrifices of such a decision. Despite such potential drawbacks, part-time work can help physicians through particularly vulnerable periods, such as the early infancy of their children, or caring for an ailing spouse or parent.

Alternative academic tracks have become standard at many universities, providing flexible options to faculty.

These tracks typically emphasize clinical performance and teaching, with fewer requirements for research and peer-reviewed publications. Often, this type of track is more conducive to part-time work, and more feasible for physicians who cannot find the time to perform research or obtain grant funding. These tracks are a very viable option for physicians with active family lives, and may reduce some of the stress associated with demands for research productivity.

Work–life balance requires organization and prioritization. One of the most challenging situations for a professional is when one's partner has an equally time-consuming occupation. In family life, difficult decisions have to be made. Often, one parent has to step back while the other pursues career goals. Once this happens, it is challenging to halt momentum, but with perseverance these roles can change over time and the other partner can take a turn dedicating more time to home life.

Many of us have learned from our mentors some methods that can make home life a bit less frenetic. Here are some suggestions to consider to help achieve work–life balance.

1. Hire out household chores such as house cleaning, laundry, garden work, and food shopping (as far as practical), so that time at home is not taken up by these tasks.
2. Find a comfortable and reliable situation for child-care, so that there is less anxiety associated with absence from the home.
3. Make time for the important family events such as children's sports events, concerts and plays, school visits, and bedtime rituals.
4. Use every vacation day given, and try to avoid doing work during that time.
5. Make dinnertime sacred, with no interruptions by television, phones, or computers. This is one of the best opportunities to be kept up to date on children's activities and daily school life. For couples without children at home, dinnertime is equally an opportunity to stay connected.
6. Make alliances or networks with stay-at-home or other working parents.
7. Try to batch patient phone calls and e-mails to a particular time each day so, that this activity does not impinge on family time.

Although work travel for invited lectures is important for career building, one should consider that each opportunity to speak at a meeting means less time at home with family. One should try to prioritize the importance of these opportunities and occasionally choose not to accept the invitation. An alternative strategy is to take family along to meetings (although that can have its own stresses). Sometimes, not all the professional work can be done during normal work hours. In that case, the hours after children's bedtime or the early hours before school may prove to be productive. Working from home can be effective in some situations, particularly when it comes to manuscript or grant writing; there are often fewer distractions, and much can be accomplished during the time one would be traveling to and from work. Personal time for exercise, hobbies, and time with friends should not be excluded. Time can be made available for all aspects of life, if the working environment is family-friendly and supportive.

The opportunity for flexibility in the workplace must be offset by success. It remains important to demonstrate hard work, productivity, and commitment to one's profession. There is a fine line between being perceived as feeling “entitled” and being able to spend a fulfilling amount of time at home. It is important to recognize that work–life balance will change over the course of one's life and career. There will be times when dedication to work efforts will be essential to development of clinical skills and research activities (notably, grant deadlines, abstract presentations). In contrast, there will be times when home life will have increased demands (such as the birth of a child, care of a sick relative). Through flexibility, organization, and appropriate choices, one can achieve meaningful balance between personal needs, commitments to others including family and friends, and professional responsibilities.

For Suggested Readings see References 99-107.

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