

Opportunities and challenges for junior investigators conducting pain clinical trials

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Abstract

Introduction: Clinical investigation serves a vital role to advance treatment and management strategies for patients with pain. For those new to clinical investigation, key advice for both the novice clinical investigator and the experienced researcher expanding to translational work may accelerate research efforts.

Objective: To review foundational material relevant to junior investigators focusing on pain clinical trials, with an emphasis on randomized controlled trials.

Methods: We reviewed recent publications and resources relevant to clinical investigators, with a particular emphasis on pain research.

Results: Understanding the approaches and barriers to clinical pain research is a first step to building a successful investigative portfolio. Key components of professional development include motivation, mentorship, and collaborative approaches to research. Many junior clinical investigators face challenges in pursuing research careers and sparking iterative progress toward success in clinical trials. Pain-specific research metrics and goals—including hypothesis development, study design considerations, and regulatory concerns—are also important considerations to junior investigators who pursue clinical trials. Approaches to build toward collaborative and independent funding are essential for investigators.

Conclusion: This work provides a foundation for understanding the clinical research process and helps inform the goals and plans of clinical investigators.

Keywords: Pain, Clinical trial, Pain measurement, Research design, Clinical protocol, Sample size

1. Introduction

Clinician-investigators address important scientific knowledge and clinical practice gaps, and this career path rewards many individuals who elect to pursue it. Building a successful career in pain clinical research depends on the combination of motivation, perseverance, and environment. Junior clinician-investigators who focus on pain clinical trials confront many potential challenges relative to some other specialties that incorporate research into a defined curriculum. Advanced clinical training

programs in medicine, nursing, and other fields may instruct trainees from diverse clinical training backgrounds and focus on clinical rather than research components. Due to time and funding constraints, many clinical programs do not routinely prepare trainees for clinical research. To navigate the growing number of national and local regulations that govern clinical research, all clinical researchers need training in the protection of human subjects and an appreciation for basic requirements about research. Clinical research, as defined by various regulatory bodies, involves a systematic investigation intended to contribute to generalizable knowledge by testing hypothesis or answering a question that applies to a larger population beyond that of the original study.³ As one type of clinical research, clinical trials investigate the effects of medicine, tests, or other products on human subjects.⁴³ Clinical research has evolved to include other subtypes, with treatment, prevention, and diagnostic research as examples of evolving disciplines. In contrast to clinical research, quality assessment and quality improvement work strives to improve performance of a process, program, or system.³⁷

While the focus of this article is on the clinician-investigator perspective, numerous overlapping health care disciplines face the same challenges in pursuing pain clinical research. Challenges can be grouped into logistical and conceptual challenges. Understanding and mitigating these 2 types of challenges is essential to successfully completing projects and achieving

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research goals. Human subject research involves layers of ethical, fiscal, and logistical procedures that can undermine even the most elegantly designed clinical trial. Understanding how local policies and procedures address ethical and regulatory training, as well as institutional review board (IRB) and fiscal regulations, will allow projects to move forward. Beyond the ethical and procedural obligations associated with clinical research, not proactively addressing these concerns in study planning and execution will jeopardize funding for or publishing the associated work product.

The decision to pursue research is based on personal values. Spanning a spectrum, it ranges from what others in the environment expect to a passion that is intrinsically motivating. For many clinical investigators, intellectual curiosity drives them forward. That drive can be put to the test with regulatory and logistical hurdles, and ultimately, one makes a decision about the value of this type of intellectual challenge and growth. The process is a series of iterative successes and failures, working toward a personal goal. Planning for and incorporating the expected hurdles, such as training, infrastructure, and logistics, buffer the iterative cycle of success and failure. Predictable pathways for success may disappear in a tight funding and regulatory climate, but the challenge and joy of pursuing a career as a clinical investigator exists for those who retains that spark of interest. In addition to internal motivation, additional incentives and rewards of a research career exist. Pain research confers a sense of “making a difference” through efforts that improve pain care and patient outcomes, as well as the personal and professional rewards of a career as a scholar, scientist, and thought leader that influence the field of pain management.

As a subset of pain researchers, aspiring clinical investigators also face unique obstacles to conducting clinical research, including financial challenges, personal mentoring, and scientific skills acquisition.³⁵ Clinicians have a front-line view of the clinical question, but many lack the research training, skills, and mentoring to overcome the hurdles to transition to clinical research. In the current health care environment that rewards the volume of care, junior clinicians typically have limited time devoted to the pursuit of research. Specifically, in the United States, clinicians, including those with research interests, are hired into clinical positions with contracts that reward clinical work but commonly do not incorporate research productivity. This model of hiring occurs regardless of private or academic practice environment. Therefore, practice incentives are not well aligned with research productivity, resulting in a financial disincentive to dedicate time to research. Personal fiscal incentives are also poorly aligned with the development of a clinical investigator career. Medical training may lead to significant debts, with average education-related debt rising to approximately \$160,000 for 2010 US medical graduates.³⁵ Adequate mentorship is another factor that junior clinical investigators frequently identify as a barrier.⁵ This speaks to the larger need for academic mentorship during the clinical training period. Finally, acquisition of research skills is lacking in most residency and fellowship training programs; therefore, the development of successful programs that teach research skills and build toward academic productivity is needed.¹

In the United States, pain medicine exists as a subspecialty, with commonly associated primary specialties including, but not limited to, anesthesiology, physical medicine and rehabilitation, neurology, and psychiatry. Focusing on one of the specialties, anesthesiology has relatively low research productivity,³⁰ which in part reflects the paradox of “fostering research and scholarship” and “maintaining revenue to support faculty” facing leaders of

academic departments and institutions.³⁹ In a survey of 1 academic anesthesiology institution, a majority of new faculty described their role as clinician-educators, with most (>70%) of their professional time and effort allocated to direct patient care and teaching.²⁹

As new investigators, junior clinical investigator often need mentorship and guidance in both overall career trajectories and concrete research development skills. The primary focus of this article is on approaches for primarily clinically trained researchers to better understand the components of the research process. Realizing that a fair number of aspiring clinical investigator do not have the training or experience to conduct pain-relevant research, we have written this review to provide junior clinicians in specialties across disciplines a basis for which they can start thinking about scientific inquiry and investigating a research question of interest. In subsequent sections, this article examines the essential considerations at the start regarding motivation, mentorship, and transitioning from ideas into reality. The importance of background literature searches sets up an exploration of study design in general and randomized controlled trials (RCTs) in particular. The focus then turns to components of an investigation, starting with key questions and aims, hypothesis generation, and determination of inclusion and exclusion criteria. Attention then shifts to outcome measures and pain-related research components that add value for the more experienced investigator considering translating their basic science work. Concluding sections highlight the important considerations for funding and resources available to pain researchers.

While this review is not a substitute for comprehensive training on research design through formal coursework and mentorship, we anticipate this review providing a framework and resources for junior clinical investigator in need of a jump start into the field of clinical trials. Understanding the process and collaborating on other researcher’s projects can provide valuable experience in the stages of bringing a research idea to successful implementation in a clinical trial. Today’s era of team science emphasizes the role of collaboration in fostering a successful research career. Work within an interdisciplinary team energizes the efforts of many researchers and provides an opportunity to foster motivation and social reward. Being a constructive team member or leader depends on understanding the process and components that initiate, sustain, and complete academic projects. Although not all efforts will be successful, building diverse clinical research portfolios will involve choosing projects that will ultimately fail or not be funded, and the true challenge is to move past these setbacks and continue forward.

2. Where to begin

Although ideally an important first step is to obtain some formal education and training in clinical investigation and research, we provide some general directions in where to begin in undertaking clinical research.

2.1. Motivation

In starting down the challenging path of academic research, it is worth reconnecting with the driving force and motivation behind your pursuit of clinical research. While some early career researchers have a bona fide passion for discovery and investigation, other junior investigators pursue research only to please external pressures from their superiors. Longevity and happiness in clinical research is related to how passionate you are about the topic you are researching because, if you are

successful, you will be lecturing on and communicating about this topic very frequently. Publishing only for the sake of promotion is unrewarding, and without a genuine interest, the pursuit of knowledge can be incredibly unsatisfying and therefore not likely to be successful in the long term. Pragmatically assessing your individual goals and working with different mentors to generate various ideas about what might work for you is an important part of career growth for researchers of any discipline.

Clinician educators can play a unique role in bringing topical clinical issues to research collaborations. The transition of the National Institutes of Health's (NIH's) biosketch format and publications on "team science" reflect the philosophical shift of many research foundations toward the value of collaboration. Funding shifts toward multicenter, large, collaborative clinical trials are driving the development of new research opportunities beyond the conventional role of principal investigator. Bringing clinical experience and shaping research protocols to reflect the key questions and pragmatic realities of clinical practice adds value to emerging research and can help a junior clinical investigator build the network and skills to advance toward independence.

2.2. Mentorship

One key consideration to address at the start is to find or choose a general career mentor who has the requisite time, experience, motivation, and genuine interest to provide meaningful mentorship for your clinical research. A mentor may be able to guide you through the process and be a sounding board for your ideas. An ideal mentor has a successful track record and experience in undertaking and publishing research and securing funding, places your interests first, and is genuinely interested in advancing your career. A mentor does not necessarily need to be a senior clinical investigator or someone with international or national name recognition, but instead someone who is accomplished and willing to spend time with you to explain each step of the process. Additionally, mentorship may be obtained by working with several types of researchers who are focused on different components of career development. Building a research career and academic portfolio is a different path for each investigator. Working with an overall mentor can be beneficial for discussing and strategizing long-term career goals. Focused mentoring for more short-term planning, such as specific projects, grant mechanisms, or career sponsorship, may be a beneficial complement.

Developing a mentorship team may support specific projects or ideas as your career develops. Many successful multidisciplinary projects may involve several senior clinical investigator, inside and outside your specialty. For example, scientific mentorship by a statistician, epidemiologist, or computer scientist may lead to enrichment of distinct yet important research skills. Developing a mix of short-term and long-term goals that are both achievable yet stretch your capabilities allows for the most robust professional growth. Mentors do not necessarily need to be in your department, campus, or institution, although physical proximity does facilitate meeting and communication and having the primary mentor within the researcher's specialty is ideal. Communication styles play an important part of any interpersonal dynamic. As the mentee, communicating effectively with your mentor is dependent on your ability to convey your interests, needs, strengths, and areas for growth. Another frequently unrecognized opportunity is peer mentoring. Finding other junior clinical investigators doing different scientific work at similar phases of their careers provides opportunities to learn about

resources and support. Many institutional, societal, and professional organizations have formal and informal programs (ie, AAMC faculty career development resources, <https://www.aamc.org/members/leadership/catalog/>).

2.3. Concept development

One of the most daunting initial tasks is to determine "What topic should I study?" and "What questions intrigue me and which I want to answer?" Most junior clinical investigators may not have extensive knowledge of the research literature in their specialty and may not appreciate some of the nuances and obstacles of possible lines of research within each area. As a result, the process of thinking of "What should I study?" can be overwhelming. Several approaches, which can be used simultaneously, can be adopted to address this central issue. Some of the best research answers simple questions that impact daily clinical care. Undertaking a systematic literature search (see "Background Literature Search" below) may serve as a useful first step to determine what has already been done and what potential gaps may exist in your area of interest. One can also consider the clinical relevance and importance of the potential area of research. The process of figuring out what to study comes well before the considerations of study design, but practical considerations may weigh in the development of the study idea.

2.4. Pragmatic execution: translating ideas to reality

A few practical points will improve the probability of success for your first clinical trial. The focus of this article is clinical trials and RCTs; however, other study types will be mentioned where there is concept overlap. Many junior investigators start with a vision of research based on articles of large-scale clinical trials. Although it is not impossible to start a large, multicenter, randomized trial or large (>1000 subjects), prospective, observational trial on your first attempt, your chances of long-term success will be greater and frustration will be potentially less if you begin with a more feasible and smaller-scale study. Conducting research via an existing database or a retrospective study on your population of interest may provide an efficient yet informative bridge to any future clinical trial. In particular, these lines of investigation may narrow the clinical question or generate additional hypotheses that merit further attention in prospective trials. Completing a "learning phase" or pilot clinical trial serves to generate preliminary data and allows you to gain experience with the research process. Pilot trials generally provide earlier tangible accomplishments (including abstracts and presentations at national meetings) compared to larger trials, with shorter time to study completion and publication of results. This momentum boosts the morale of the investigator, research team, and others in the department or company. Along the course of planning for the trial, you will need to recognize the study population available for recruitment and should probably only undertake studies for which you have access to the study population. In the increasingly competitive world of clinical research funding, many granting agencies focus on the impact of the idea, experience of the team, and likelihood that this idea can be successfully implemented. Assembling a team and obtaining the pilot data needed to move forward to grant submission is an educational process highly valued and even essential to funding agencies. Fortunately, numerous open source resources are available to support different stages of this process,

Table 1**Online resources for junior investigators conducting pain clinical trials.**

Topic	Resource URL
While helpful, these resources are not an adequate substitute for formal training in clinical research	
Background literature search	
PubMed tutorial	https://www.nlm.nih.gov/bsd/disted/pubmedtutorial/cover.html
EMBASE guides	http://help.elsevier.com/app/answers/list/p/9754/c/9540,9541
How to use the Cochrane Library	http://www.cochranelibrary.com/help/how-to-use-cochrane-library.html
General study design issues	
Coursera	https://www.coursera.org/
Equator Network	http://www.equator-network.org/
Developing a hypothesis	
NIH's Research Portfolio Online Reporting Tools (RePORT)	https://report.nih.gov/
Institute of Medicine's "Blueprint for Pain"	http://www.nationalacademies.org/hmd/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx
National Pain Strategy	https://iprcc.nih.gov/National-Pain-Strategy/Overview
Interagency Pain Research Coordinating Committee (IPRCC)	https://iprcc.nih.gov/
Outcomes	
Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)	http://www.immpact.org/
NIH Health Measures	http://www.healthmeasures.net/
Patient-Reported Outcomes Measurement Information System	http://www.healthmeasures.net/explore-measurement-systems/promis
Sample size calculation	
PS: Power and Sample Size Calculation	http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize
Informatics for Integrating Biology and the Bedside (i2b2)	https://www.i2b2.org/
Institutional Review Board and regulatory components	
Collaborative Institutional Training Initiative (CITI) Program	https://www.citiprogram.org/
Special consideration for studying pain	
NIH Interagency Committee's National Pain Strategy	https://iprcc.nih.gov/National-Pain-Strategy/Objectives-Updates
Canadian Institutes of Health Research Institute of Musculoskeletal Health and Arthritis	http://www.cihr-irsc.gc.ca/e/13217.html
Study protocol and national trial registration	
How to register your study at ClinicalTrials.gov	https://clinicaltrials.gov/ct2/manage-recs/how-register
International Clinical Trials Registry Platform	http://www.who.int/ictrp/
How to write a research project grant application	http://www.ninds.nih.gov/funding/write_grant_doc.htm
Funding	
Patient-Centered Outcomes Research Institute (PCORI)	http://www.pcori.org/
Agency for Healthcare Research and Quality	http://www.ahrq.gov/
Department of Defense (DOD)	http://cdmrp.army.mil/
Additional resources	
Pain Research Forum	http://www.painresearchforum.org
International Association for the Study of Pain's Pain Schools and Camps	https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=5115&navItemNumber=654
Association of American Medical Colleges (AAMC)	https://www.aamc.org/members/gfa/faculty_vitae/
NIH's Loan Repayment Program	https://www.lrp.nih.gov/

and you should leverage those that support your personal gaps in knowledge to help build your clinical research portfolio (Table 1). This can include several approaches to additional

training, including education in clinical research (certificate and degree programs), biostatistics and epidemiology courses, and online resources.

3. Background literature search

3.1. Is your idea novel?

Undertaking a systematic literature search is useful to ascertain the current state of research in your area of interest. A brief but focused literature search can help you determine the state of research in your area of investigation. If already covered, you can quickly move on to another topic. For investigations on treatment, consider first searching the Cochrane Database of Systematic Reviews.⁸ Learning how to undertake efficient and thorough literature searches is an essential tool for any clinical investigator, and the natural extension of the clinical skills of clinicians is well versed in chart reviews.

3.2. Methods for approaching background literature review

Building on existing work and understanding the strengths, limitations, and gaps of prior published literature is the key to successfully moving your science forward. You may have the best idea, but ultimately doing the work and disseminating the results through conferences and publications will lead to future work and academic success. Fortunately, this foundational step is available to most researchers with access to online library resources. One key to minimizing frustration is leveraging the resources available to you. Most academic institutions have library services that will support searches with minimal or no cost to academic faculty, and medical librarians are often available to assist. However, depending on the scope of your project, a full comprehensive search of the literature on multiple databases (eg, PubMed, Embase, Cochrane, CINAHL) utilizing the services of an informationist may not be initially necessary but can be of great help and save time. Using one database, such as PubMed, and typing in the key words of interest provides a quick overview of what has been published on the topic. It is advisable to try different combinations of related key words that may yield different results and articles. Save the results from key word searches including the exact terms, so that the search can be replicated at a later date. Once you start reviewing articles from your search, you will be able to retain and archive those articles relevant to your specific topic of interest. Review articles usually contain the highest yield overview of a topic and state of research in a field. Once you have read review articles, you should begin reading larger well-done trials, typically published in the higher impact journals. Focusing on the methods section and areas of limitation may inform your potential research approach or help generate additional lines of inquiry. Conducting a systematic review of a topic can in itself lead to a valuable manuscript, and the process is well described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (<http://www.prisma-statement.org>).

4. General study design issues

While the aims and hypothesis will drive your design, consideration of what resources are available to support your efforts institutionally can be very helpful in successfully completing a project. Many academic institutions and some industry groups have programs focused on increasing research training and supporting research infrastructure at a systems level. The NIH's National Center for Advancing Translational Science (<https://ncats.nih.gov/>) has funded Clinical and Translational Science Awards at many academic research centers. These Clinical and Translational Science Institutes have several mechanisms to support junior investigators including courses that survey the

research resources and training available at their institution. Academic centers often seek opportunities for collaboration with clinical investigators in private practice or private hospital-based practice. As a basic step, most academic centers require specific training in the responsible conduct of research prior to embarking on any IRB submission (<https://www.wirb.com/>). For those desiring additional training, many academic centers offer certificate programs and degree programs focused on enhancing research skills (<https://ncats.nih.gov/ctsa>). In addition, many open source courses have free or minimal fee online courses that have in-depth information about clinical trial design and interpretation (eg, <https://www.coursera.org/>) taught by leaders in the field.

The RCT is a prospective experimental study where the effect of an intervention is assessed by collecting data before and after an intervention has taken place.¹⁹ The key component of the RCT (and what distinguishes it from observational studies) is the process of randomization. This random assignment ideally creates comparable study groups in RCTs by eliminating factors that interfere with understanding the impact of the study intervention. On the other hand, observational studies typically follow a cohort of patients over time and assess the outcomes of interest within or between groups. The key difference is that, unlike the RCT, participants are not randomized and typically can "choose" or their provider can choose the patient's intervention. Observational studies can either be retrospective or prospective.

While existing guidelines and recommendations regarding how to conduct clinical trials may add significant burden to your workflow, their implementation strengthens your work (see "Checklist for the preparation and review of pain clinical trial publications"). Incorporate the appropriate reporting guideline prior to designing your study. For RCTs, the Consolidated Standards of Reporting Trials (CONSORT) (<http://www.consort-statement.org>) guideline is widely recognized. Similarly, the PRISMA (<http://www.prisma-statement.org>) for systematic reviews and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (<http://strobe-statement.org>) for observational studies are commonly accepted¹⁸ (see <http://www.equator-network.org> for further sites).

5. Some considerations for the randomized controlled trial

Clinical trial design is an entire field of study among biostatisticians, study coordinators, data managers, and epidemiologists.^{24,42} If possible, taking advantage of an academic center's consulting services will streamline this phase of your project. Research may or may not be the career focus of the junior clinical investigator, but involving people who are focused on helping successfully complete research projects with significant expertise can be important. Working with a team from study conception, including data managers, study coordinators, budget preparation experts, people experienced in drug supply, and people with regulatory or ethics expertise can streamline projects. Involve all of these components from the outset (study conception). Incorporating statisticians into your design and funding application can set your idea up for successful completion (see "Essential statistical aspects of clinical trials of pain treatments"). Early involvement with a statistician is far superior to waiting until after the data have been collected. For example, a statistician can help plan an adaptive clinical trial, which adapts part of the trial design in response to participant outcomes. The complexity of some types of adaptive clinical trials necessitates experienced statisticians and other clinical trial design experts, but it can limit cost and effort wasted for some hypotheses difficult to test with

a conventional RCT. Also, some adaptive designs may be simple enough to implement without statistical support. Prospectively designing your study to maximize scientific impact will facilitate both achieving your scientific aims and provide a solid foundation for publishing your results. The RCT is often considered the “gold standard” for trial design, as this study design allows one to determine a “cause-and-effect” relationship between an intervention and outcome of interest when properly conducted. The ability of a well-done RCT to make causal inferences allows this type of study to provide the strongest evidence of a treatment’s efficacy. Proper randomization promotes the comparability of baseline characteristics among the different treatment groups, facilitating causal inference between intervention and outcome. Another advantage of the RCT is that it can be tailored to answer a specific research question.³⁶

However, there are several drawbacks to an RCT as a starting project for a junior clinical investigator with limited experience, resources, and research infrastructure. Technical challenges include a need for identifying appropriate comparison group(s), the need to recruit a potentially large number of participants due in part to the possible high drop out of trial participants, especially when the intervention has undesirable side effects or little incentive exists to remain in the control arm.³⁶ Generally, RCTs take longer to conduct and are more expensive than a similarly sized observational study. Finally, ethical considerations may preclude using RCTs to answer certain research questions that are not suitable for randomization (eg, we would not randomize people to smoke or not to smoke to determine if smoking tobacco products can cause lung cancer). Comparative effectiveness trials, in which one active treatment is compared with another active treatment, may provide a reasonable study design when randomization to placebo is inappropriate and both treatments have very well-established efficacy. Proper randomization serves as a critical foundation to obtaining unbiased results, and experts in study design and methods ensure this vital step is appropriately conducted.

Blinding, or masking, is another important method to consider to reduce bias for RCTs. Different groups who participate in the trial may be blinded to the study arm assignment. In a single-blind study, participants or evaluators remain unaware of treatment to which they have been randomized. A double-blind study usually involves treating providers, study personnel, and outcome assessors remaining blinded to treatment assignment and even treatment hypotheses. While rarely performed, when a third-party conducts data analyses that are masked from the study hypotheses and treatment assignment, the trial may be described as triple-blinded. Regardless of the label used, trials with blinding should specify exactly which group(s) (eg, participants, providers, data collectors, data analysts) remain blinded and the methods used to achieve this result.

While not considered the gold standard, several other trial designs represent logistically simpler and less-expensive alternatives to RCTs. Examples include cohort, case-control, and cross-sectional studies. These designs may be the most scientifically reasonable, pragmatic, and realistic approaches to certain scientific questions. Additionally, the preliminary data provided by other types of studies can inform the design of future work to improve feasibility and funding support for the idea. Building iteratively toward funding and idea implementation can be a frustrating process, but this “sweat equity” provides a learning opportunity for junior clinical investigators and demonstrates the persistence and resilience required to pursue a research career.

6. Specifying a key question and aims

The first and principal decision to make at the outset of planning an investigation is to specify what key question the study will address. The key question lays out the issue of primary focus for the proposed investigation. This research question should reflect what the study will address in precise yet understandable terms. Clinical trials often progress through a series of defined stages in addressing key questions related to a novel compound, therapy, or treatment (**Table 2**). Among the different stages of clinical trials, junior investigators typically begin with questions that fall within the learning phase or phase 2. In this phase, one investigates issues that need to be resolved prior to proceeding to a confirmatory trial, such as dosage selection, proof of concept, biological activity, or target engagement. Identifying and clarifying a key question, and aims should precede any discussion of a hypothesis. After defining the key question and crystalizing the aims, decisions about what hypothesis to test and which research design and method to use may follow.

7. Developing a hypothesis

Hypothesis development can be inspired by several factors including direct experience with patients, conversations with colleagues, or broader views from conferences, published studies, and review articles. Ultimately, success of an idea and a related grant depend on the significance and innovation of the hypothesis. The process of selecting a general topic, focusing your area of investigation, and narrowing down possible research questions to a specific hypothesis challenges many early career investigators. Before settling on a line of inquiry, take time to understand what constitutes “good” research.⁴⁷ Two qualities are asking important questions (significance) and working on projects that may lead to seminal observations (novelty).³³ Identifying a question that fulfills the characteristics of good

Table 2
Phases of clinical trials.

Phase	Name	Purpose	Duration	Participants
I or 1	First-in-human	Evaluating preliminary safety and dosage range, drug metabolism, and bioavailability	Months	20–100 healthy volunteers or people with specific diagnosis
II or 2	Learning	Evaluating preliminary efficacy, longer-term safety, biological activity, target engagement, and most promising dosage(s)	Months to 2 years	Up to several hundred people with specific diagnosis
III or 3	Confirmatory	Confirming efficacy and evaluating long-term safety	1–4 years	300 to 3000 people with specific diagnosis
IV or 4	Surveillance or postmarketing studies	Safety and efficacy	Years	Several thousand people with specific diagnosis

Adapted from the US Food and Drug Administration. Drug development process. Clinical Research. Available at: <https://www.fda.gov/forpatients/approvals/drugs/ucm405622.htm>. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

research questions may be a “rate-limiting” issue but is a necessary investment of your time.^{22,33} Significance (importance) and innovation (novelty) are important criteria for review of grant proposals.

Aligning your research interests with national research priorities serves as one way to choose an area of investigation and garner support for your work. The Institute of Medicine’s “Blueprint for Pain” (<http://www.nationalacademies.org/hmd/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx>) and National Pain Strategy (<https://iprcc.nih.gov/National-Pain-Strategy/Overview>) have concrete recommendations relevant to the pain clinical research community. NIH task forces (<https://iprcc.nih.gov/>) exist for many pain conditions, and these working groups can provide guidance for research standards to include minimal data sets for your research proposal.¹² While your idea is most likely not going to completely unravel the mysteries of pain, your chances of success and funding rise when iteratively working toward a concrete goal that connects to a bigger picture. Committing time to research means time away from other areas in your life, which is another good reason to focus on why your work has impact. Early projects tend to be foundational work, but you should try to choose projects that have educational or scientific value. Educational value can translate to working on a review article or meta-analysis to understand a topic as you build a conceptual framework to develop and answer your own scientific questions.⁴⁰ Some junior clinical investigators work in environments with existing data available for analysis or have questions that would be answerable through a publicly available database. Building on these resources, prepare or occasionally discourage a clinical investigator from moving forward to the next step of transforming an idea to a funded proposal. In developing a hypothesis, your key question is “what important answer will this study provide that solves, or works toward solving, a problem?” To work toward funding, you need to develop the context to be the “right person, right place, and right time.” By focusing on these criteria, you will be able to highlight that you have the experience or experienced team members, the environment, and tools or pilot data to successfully investigate your impactful idea.

An additional approach to developing an idea is evaluating the pain-related research and resources within your research environment. Your idea may be an extension of work that is currently being investigated. Collaboration with others may foster both mentoring relationships and work toward funding. NIH’s Research Portfolio Online Reporting Tools (RePORT) (<https://report.nih.gov/>) provides valuable information about current researchers and projects at your institution related to pain as well as other projects similar to key words that you are interested in examining.⁴⁴ Working with an established team can provide some of the experience and mentoring to build toward identifying personal research goals and interests.

8. Inclusion and exclusion criteria

In shaping your idea, one important concept to consider is how the results will be useful once the project is successfully completed. The most concrete components of this during the study design phase are the inclusion and exclusion criteria. This has several practical ramifications. These criteria frame the external validity (generalizability) (validity) of your project. In designing and shaping your idea, focusing on the clinical impact of your study should drive a component of how you choose your patient population. For example, studies performed on veteran pain populations rarely include age, gender, and other

socioeconomic diversity that allows for broad implementation of findings. Some pain projects are focused on specific populations, such as obstetric or pediatric patients, that will provide very population-specific data that justify the associated ethical or research burden. Internal and external validity are a balancing point in any trial design, in that they are the compromises that have to be made inherent to the design of a trial. However, justification of this burden will be upon the clinical investigator to demonstrate and will result in additional regulatory and safety reviews justifying the need for research.

9. Outcomes

Determining the relevant outcomes for your clinical research is a critical decision to make after developing your hypothesis (see “Clinical Outcomes Assessment in Clinical Trials of Chronic Pain Treatments”). The field of pain research presents several challenges regarding outcomes that stem from the condition of pain itself. Difficulties in outcome measurement may occur due to the subjective nature of pain, the limited associations between objective findings, self-report, and behavioral responses, the common overlap of pain with other conditions, and pain’s multidimensional impact on sensory, emotional, cognitive, and behavioral dimensions. Due to these issues, as well as a lack of standardization in outcome assessment for pain clinical trials in the past, consensus guidelines regarding core outcomes for clinical trials of pain have been developed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).^{14–16} Other available guidelines include those for trials involving opioids,⁴⁸ pediatric participants,³⁸ and acute pain.⁹

Outcomes relevant to pain trials include those in 5 patient-reported outcome domains: pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, and symptoms and adverse event.⁴⁷ For example, a commonly measured outcome in the pain domain is pain intensity, which may be measured using a verbal rating scale, numeric rating scale, or a visual analog scale (VAS). Yet, past researchers note that pain intensity may not adequately capture the entire spectrum of the quality of pain or how pain impacts behavior and interferences with activities. As a result, methods exist to measure the separate but related entities of pain intensity, quality, behavior, and interference.¹⁴ In choosing an outcome for your clinical trial, you must consider what outcome aligns the best with your hypothesis of interest and what is feasible given available resources.

The research community demonstrates a growing interest in measuring patient-reported outcomes with valid and reliable instruments. Beside academic settings, patient-reported outcomes are assuming an increasing relevance to health care systems and private practice environments attempting to demonstrate meaningful outcomes with patients. To facilitate this, the NIH funded the development of the Patient-Reported Outcome Measurement Information System (PROMIS) (<http://www.healthmeasures.net/explore-measurement-systems/promis>), which provides access to standardized questionnaires for patient-reported outcomes at no charge and data collection tools for a small fee. PROMIS covers many pain-related domains with tools to measure pain, depression, anxiety, substance abuse, and sleep, among others. A consortium of academic institutions has adopted an electronic learning health system, Collaborative Health Outcomes Information Registry (CHOIR), for the collection of patient-reported outcomes, including PROMIS, and other measures integrated into the electronic health record.^{25,26} These data are being used in both retrospective registry analysis and prospective clinical trials.^{27,46}

Outcomes for pain, as well as other fields, require specification of 5 characteristics to communicate properly about your research, enhance your study method, and ensure reproducibility.⁴⁵ These include the *domain*, *measurement*, *metric*, *method of aggregation*, and *time point*. The *domain* describes the topic to be measured. For example, pain intensity, depression, and physical activity are examples of different domains relevant to pain clinical trials. *Measurement* specifies the instrument or tool used in the assessment of the outcome. For pain intensity, an example of measurement is VAS, while the Hamilton Anxiety Rating Scale is a measurement for anxiety. *Metric* specifies the method of characterizing the outcome. Your study could use a metric of change over time or the final value for VAS as the metric. With regard to analysis, *method of aggregation* defines how the data will be summarized. A method of aggregation of mean VAS, proportion with VAS decrease of $\geq 50\%$ or rate of pain resolution (as in pain trajectory analysis), could be used.⁴ Because each method of aggregation provides different information, statistical significance could differ based on which method you employ. Finally, *time point* demarcates the interval at which the outcome is measured.

Every clinical trial should have a single, clearly stated, and a priori defined primary outcome of interest that directly builds on the study hypothesis. Stating more than 1 primary outcome in your study introduces statistical issues with multiple comparisons that impact hypothesis testing. Having multiple primary outcome variables require specification of a method for statistical analysis that provides strong control of the familywise error rate or overall probability of a type I error. Failing to state, vaguely stating, or stating after the fact your primary outcome introduces the ability, either real or perceived, to cherry pick an outcome that demonstrates nominal statistical significance. This “fishing expedition” or “data dredging” introduces bias from the selective reporting of outcomes.

The primary outcome plays an important role in sample size calculations and ultimately the number of participants you will need to include in your trial to adequately test your hypothesis.²¹ Estimates of the number of participants needed for your trial depend on the anticipated characteristics of the outcome. In performing sample size calculations, recognize that your study may not have sufficient power (probability of a statistically significant result when there is a true effect of the treatment) to address secondary outcomes. While other outcomes may be of interest, you should consider the amount of time and cost involved to design your study to have adequate power for secondary outcomes. A power analysis in the planning stages of your study helps to inform the sample size needed to determine if an effect is present.

10. Sample size calculation

Determination of the sample size, calculated prior to study initiation or enrollment based on your hypothesis, primary outcome variable(s), and primary method for statistical analysis, represents a significant step in planning your research project.²⁰ This calculation provides an estimate regarding the number of participants you need to have adequate power to detect a treatment effect of a specified magnitude. Conducting a study with inadequate power to address the primary question creates at least 2 key problems for you. From a practical perspective, the probability of a type II error is increased (ie, a treatment may have a clinically meaningful effect that you may not have a high chance of detecting). From an ethical perspective, if the study is not adequately designed to address the primary question, the study

exposes participants to unacceptable risk or the burdens of research and needlessly expends valuable resources. Of course, not all hypotheses involve treatment group comparisons, particularly in early phase studies, so sample size is not always based on a power calculation. For example, it might be based on estimating a particular quantity (eg, adverse event rate) with a certain degree of accuracy.

Sample size estimates develop directly out of the hypothesis, primary outcome variable(s), and primary method for statistical analysis that you select for your study. Regardless of the trial, several key pieces of information are needed to perform sample size calculations.¹⁷ The first components are the power and significance level that you desire to use. By convention, researchers often specify power as 80% or 90% and significance as 5%. Other important elements include the primary method for statistical analysis, magnitude of the treatment effect that is of interest to detect, values of nuisance parameters (eg, SD), and anticipated dropout rate. Statisticians, accessible at many institutions and departments, serve as a resource to you for development, guidance, and execution of power and sample size calculations. Working with a statistician will help guide your design, but power calculations are generally informed by previous published or pilot work that helps shape scientific expectations. Important considerations include recruitment and retention. Modern statistical software packages such as Stata, SPSS, and SAS provide packages for these calculations, and PS (<http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize>) is an open source software developed at Vanderbilt that is also available for power and sample size calculations.^{13,49} An important consideration for this calculation is determining whether you have an available cohort for your study, that is, that the calculation yields a sample size that is feasible to recruit. Many institutions have clinical informatics groups that have adopted the i2b2 platform that allows for cohort discovery to determine the available patient population.³¹ This is more relevant and helpful with rare medical diagnoses or very specific pain populations and can be useful for grant proposals demonstrating that you have access to an appropriately sized population.

11. Institutional review board and regulatory components

Safety and regulatory components exist for all areas of research. The legacy of early medical research resulted in many discoveries that were conducted using methods the scientific community now considers ethically and morally questionable or unacceptable. Recognition of the need to protect the safety of research participants has resulted in many additional layers of oversight, and most institutions supervise research of human subjects in as streamlined a fashion as possible. Federal regulations require clinical trials involving human subjects to obtain either IRB approval or provide a letter of exemption for projects that qualify as non-human subjects research. Many funding bodies for pilot and other short-term grants also require this approval prior to release of funds. The critical elements for success involve paying attention to details required with applications and recognizing that; for most institutions, obtaining IRB and regulatory approval can be very lengthy processes. Some projects qualify for expedited review, but this is institutionally dependent. Many institutions have been held liable for unethical practices of individual researchers and have put together additional steps of review through Research Advisory Committees with additional training in patient information protection, experimental drug application information, financial management of grants, and

ethical training.⁶ Pursuing clinical research exposes patients to real and theoretical risks that need to be clearly identified and addressed in research protocols and proposals. Working with resources available within your environment when developing a project will refine your approach and minimize the risk of having a project rejected, suspended, or cited for deviating from ethical research standards.

12. Special consideration for studying pain

As with many complex chronic conditions, several national organizations and expert groups offer standard methods and approaches to investigating painful conditions. For example, reviewing the work of US-based multidisciplinary groups, such as Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials and the NIH Interagency Committee's National Pain Strategy, can help guide methods and measurements for different painful conditions.^{32,41} Additionally, some of these groups have recommended minimal data sets that can be important frameworks to build your study protocol and grant proposal. Discovering the options for expert-defined design considerations and outcome measures after study initiation will limit the potential of your work and potentially undermine your proposals and manuscripts when reviewed by topic experts. Specifically, the NIH PROMIS measures of pain and related domains include the highly relevant components of pain intensity, pain interference, and functional status, as well as depression and anxiety.²⁸

13. Study protocol and national trial registration

An important document relevant to clinical trials is the study protocol, which serves several purposes, including helping you organize and justify your research, helping the IRB ensure your research is performed in an ethical manner, and helping other researchers evaluate your work before, during, and after the research takes place. Many IRBs affiliated with academic centers have standardized templates for the protocol of a clinical trial, so taking the time to investigate the specific requirements of your particular IRB at the start of this process is well worth the time and energy. Regardless of the particular template, study protocols of any type share similarities regarding key elements that are necessary to describe when planning a clinical trial. Given these similarities, it can be very helpful to reach out to other researchers in your environment to determine whether there are any recent successful submissions they are willing to share for you to review.

Study protocols follow conventions of most manuscripts and writing. Making the reader work to understand your proposal potentially means loss of interest. A meaningful title should succinctly capture the purpose the research and state the study design. The summary of your idea and proposal will be requested in the form of an abstract or summary statement and is easiest to compose after the protocol is completed. Fundamentally, good scientific writing engages the reader, and it has an element of storytelling that is applicable to proposals, grant applications, and manuscripts. In the introduction, you demonstrate the background leading to the development of the idea, focusing on identifying the gap in knowledge. The introduction should clearly state the relevance of the proposed work and the impact that will follow completion of the study.

The introduction sets up a critical but concise portion of the study protocol: stating the study goal, key question(s) or objective(s), and aim(s). The goal of the study should be stated clearly and describe broadly what you hope to accomplish as a result by completing

the study. The key question or objective of the study is more specific and may be framed as seeking to answer the research question at the heart of the study protocol. Finally, if relevant, include your study aims and specific hypotheses to be tested. Aims detail how you will go about testing the hypothesis. Briefly summarize the relevant experimental approach and outcome or impact in a sentence or two.

13.1. Methods section and detailed approach

This section should bring forth your solution to the proposed gap and include specific details regarding the study that would allow replication of the results. Important components include the explicitly stated study design, study setting, study population, and recruitment plan. Important topics such as the source of participants, the methods used for recruitment, the time frame for study recruitment, and inclusion and exclusion criteria for participants must be detailed. Also describe your approach to the informed consent process, if relevant. Enumerating the number of patients that you will recruit involves calculating the sample size for your study. Assumptions used in sample size calculations should be described, including power, significance level (alpha), and how you will account for any anticipated attrition.

13.2. Data collection

Methods related to assessment and measurement of outcomes should include what data will be collected, how it will be collected, and the time frame of data collection. Data collection at baseline (such as demographics and other important variables), at follow-up (such as efficacy and safety data, biomarker data, compliance data, and adverse events), and at conclusion of the study should be described. Include the 5 characteristics of study outcomes important for study analysis (domain, measurement, metric, method of aggregation, and time point, as described above in Outcomes). Often, a time line of the study that details the schedule for outcome ascertainment may communicate this information in a more compact and understandable way compared to relying entirely on written descriptions. For some studies, this is a table that has the study visit in the columns and the evaluations in the rows, with X marking whether a particular evaluation is to be done at a particular visit.

13.3. Intervention

Details include the treatment, dosage, timing, route, safety considerations, and anticipated risks, as well as methods to promote blinding (eg, similar appearance, taste, etc.) if a placebo or alternative treatment is implemented. Trials involving randomization of participants should describe adequate methods for random sequence generation, including stratification and blocking if applicable, and allocation concealment to reduce selection bias.

13.4. Adverse event reporting

Similar to the description of outcome ascertainment, the method and frequency of assessing adverse outcomes should be listed. The capture of serious adverse events, which have a specific regulatory definition, is necessary. In the event of a serious adverse event, the plan for managing the situation and reporting to the IRB, data and safety monitoring board, or other

organizations should be detailed. If stopping the study due to adverse events is a possibility, the approach for this decision should contain a list of rules and procedures to enact should this take place.

13.5. Data management and safety

The IRB and granting organizations will examine your methods to address privacy and confidentiality concerns based on the study design, type of participants, and other study details. Methods used for deidentification of data should be described. Other concerns vary based on data format, include the storage of data (locked cabinet, encrypted server behind a firewall), access privileges (who has the key to locked paper records; read vs read/write access for digital data), and whether a publicly accessible data set will be released. Data management can be an afterthought for many junior clinical investigators, leading to insecure methods that are not compliant. Whenever possible, personnel with proper expertise in data management should be incorporated into the project. Important aspects of data management include timely data entry, periodic error checking of the data as the study progresses, error correction, and database locking. Institutional resources (eg, REDCap at many US institutions with a CTSI) can sometimes be utilized at minimal cost.

13.6. Statistical analysis

Statisticians should be involved in the design of the trial, and they can also ensure that you use appropriate language when crafting a statistical analysis plan. Important components include a description of the statistical methods to be used, how you will account for anticipated confounders, how you will deal with missing data, how you will address the issue of multiple comparisons (where applicable), what methods will be used for interim analyses and potential early stopping (where applicable), what software will be used for the analysis, and who will analyze the data. Methods used for analysis of the primary outcome should be emphasized, given the importance of your hypothesis a priori. Details regarding analysis of secondary outcomes and subgroup analyses are also important to consider because additional statistical testing proposed after obtaining study data falls into the domain of post hoc analysis and, if not prespecified, has limited credibility.

13.7. Ethical issues

Describe the ethical aspects of your study that are likely to raise concern. For members of the IRB who may have limited knowledge regarding pain research and proposed treatments, you should specify what aspects of the study represent standard of care or are performed in the course of routine patient care. This permits you to contrast elements that deviate from routine care, such as patients taking placebo treatment or delaying treatment for a period. Additionally, granting organizations, such as the NIH, require sections on the inclusion or exclusion of women, children, or minorities.

Research in special populations such as children (pre-2016 NIH definition actually included up to age 21 and now is limited to 18 and under), pregnant women, and other vulnerable groups may require additional justification for inclusion or exclusion. Additionally, ongoing pain literature has included work focusing on gender differences in pain.

13.8. Budget and budget justification for grants

This highly scrutinized section is not an afterthought to your proposal and may be a driving factor in some of your proposal design. Most granting organizations will require extensive descriptions of and justification of cost. Understanding the cost of what you need to complete the project is an important part of successful project completion. Many people underestimate the cost of infrastructure. Working with the grants and contracts team relevant to your environment should occur early and often. Most institutions have review deadlines that must be met prior to submission for institutional signoff, which can prevent timely submission of your proposal if not appropriately followed. Costs can include salary support for coinvestigators and study coordinators, statistical and data management support, treatment costs, publication expenses, as well as travel to relevant meetings. Training grants also generally include costs for parts of the educational plan that would require coursework to complete, which could be online, in person, or at short courses.

13.9. Presubmission review

Permitting the study protocol to undergo review by colleagues, mentors, and other select researchers is highly recommended. The goal of the review process is to improve study methodology and to ensure that the protocol is complete. Some investigators have access to formal review committees to ensure that the scientific question and methodology align and are appropriate to meaningfully test the proposed hypothesis. Given the cost in time, energy, and money in conducting clinical research, you would be wise to make use of these resources within your environment if available and not otherwise required. Involving other experts in reviewing your work will add significant additional time. Your last minute emergency is not necessarily their priority. After the study protocol has undergone review by these groups, including the IRB, the final document represents the approved plan for the clinical trial.

13.10. Postreview modifications

Changes to a study protocol may be needed in course of conducting a study but should not be undertaken lightly. In addition to their scientific basis, many investigators conduct pilot trials to solve problems with study protocols and methodology prior to conducting the larger study, which helps prevent unanticipated study protocol changes for large clinical trials. After obtaining approval from the IRB, changes to study protocols require resubmission, justification, and reapproval.

13.11. Clinical trial mandatory registration process

Upon approval of the study protocol, the clinical trial should be registered with a publicly accessible database to support scientific transparency. Clinical trials of drugs and study devices must be registered with ClinicalTrials.gov, per Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801).²³ For studies of any intervention, a clinical trial should be registered according to the policies of other prominent organizations, including the International Committee of Medical Journal Editors (ICMJE),^{10,11} the World Health Organization International Clinical Trials Registry Platform,⁵⁰ and American Association of Medical Colleges.³⁴ Registration of trials applies to prospective trials, both observational and randomized in design. Trial registration should take place at the time of or prior to enrollment of the first

participant, although some guidelines extend the deadline to no later than 21 days after the first participant enrolls. Accordingly, an increasing number of medical journals request the clinical trial registration number at the time of manuscript review, verify that data in the trial registry corresponds to that in the manuscript, and will not accept manuscripts for trials that fail to register prior to enrollment of the first patient.^{7,51} Some institutions have an organization account managed via a Protocol Registration and Results System administrator.

Continuing the process, updates to the registry regarding the clinical trial are recommended at periodic intervals, such as when patient recruitment begins, with conclusion of recruitment, with publication of study results, and with termination of the study. While reporting results of the trial on the site has become mandatory for many types of investigations, many researchers have not fully adopted the convention of publishing trial data despite convincing ethical, methodological, and scientific reasons.² Publishing the study protocol for a clinical trial in peer-reviewed literature represents another step to enhance transparency, obtain feedback in a formal manner, and reduce bias for a trial. However, given the time expenditure and cost associated with formally publishing a protocol, pursuing this step is likely to make sense with larger, confirmatory clinical trials.

14. Funding

14.1. Getting started

Similar to the business world, many major granting agencies require proof of concept, as well as the expertise of the investigator and strength of the environment to support the project. Recognizing this, many institutions have developed formal and informal processes to support junior investigators who start or continue down this pathway. To support your professional development, it is worth investigating what training your institution offers or what online open source curriculum would strengthen both your understanding and application. Institutional resources can range from research overview courses to research certificate or degree programs. Online (free) resources readily exist to support growth in the areas of statistics, clinical trial design, and ethical or regulatory information. Depending on the resources of your department or institutional research support, you may have an extensive application process to obtain this support. While a considerable amount of work, this application process can help identify gaps and flaws in your idea that might prevent successful completion of this process. Understanding that a grant proposal is your chance to highlight the strengths of your idea and demonstrate the value of your approach to problem solving will inform the tone of your application. Often researchers who are not experts in your fields will review your work, making it essential to clearly present your concept in a straightforward manner with minimal jargon.

14.2. Society or foundation

Moving beyond local resources, several societies and foundations support early career clinical investigators to develop professionally in pain medicine. Many have pilot funding or career development opportunities, including the International Association for the Study of Pain. These opportunities vary from country to country. Many national societies fund junior investigators. For example, in the United States, look to the American Academy of Pain Medicine, American Pain Society, American Society of Regional Anesthesia and Pain Medicine, and Foundation for

Anesthesiology Education and Research. The Canadian Pain Society supports early career investigators (<http://www.canadianpainsociety.ca/page/AwardsGrant>) and the European Pain Federation supports young scientists focusing on pain research (<https://www.europeanpainfederation.eu/eyap/e-g-g-research-grant/>). Additionally, opportunities for peer networking and development occur through the International Association for the Study of Pain's Pain Schools in Europe (<http://www.europeanpainschool.eu/>), North America (<http://northamericanpainschool.com/>), Latin America (<http://www.internationalpainschool.de/>), and other international and national societies. For junior investigators in the United States, at this stage of your career, if applicable, it is also worthwhile to consider applying to the NIH's Loan Repayment Program (<https://www.lrp.nih.gov/>), which will provide 2-year contracts for loan repayment if you meet their funding criteria and review.

14.3. Federal funding sources: US examples

Traditionally focused on the NIH, many institutions are recognizing the value of other federal granting sources such as PCORI (<http://www.pcori.org/>), Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>), and DOD (<http://cdmnp.army.mil/>). These granting bodies represent different scientific perspectives with specific foci. Reading about the missions and approaches will help direct your work to the best home. Understanding that granting organizations have specific portfolio needs is the first step to finding the best fit for your idea. Many of the federal agencies have career development grants (VHA, NIH, Agency for Healthcare Research and Quality), and these have defined program officers who help manage these grants. These program officers can have helpful advice about whether your idea fits within the scope of their group, and it is worth the effort to determine whether their agency will be interested in funding your idea. Even the highest scoring grant will not be funded if it does not align with the goals of the funding organization. Program officers can and will direct you to a better fit if they feel that this is appropriate and can also make suggestions to strengthen your application, so speak with them early and often if possible. The benefit of these grants is the protected time to focus on your research and career development.

While traditional career development grants lasting 2 to 5 years are a recognized pathway to future funding, there are alternative routes. For example, the NIH has pilot project granting mechanisms to support larger independently funded applications (R01 mechanisms) that can be worth applying for depending on the nature of your science and feedback of the program officer. These projects do not eliminate your eligibility for career development grants and provide further evidence of your future success. Ultimately, many researchers aspire to R01 funding, and there are multiple routes to achieve this goal.

15. Summary

Junior clinical investigators encounter many opportunities and challenges when first considering whether and how to conduct pain clinical trials in academia. The building blocks for such a journey begin with exploring the motivation, mentorship, and conceptual ideas unique to each early career researcher and his or her environment. This article has reviewed many of the steps that follow when conducting research projects leading up to and including a clinical trial. With time and focus, an appropriate and accessible research project can be crafted in response to any pain research question of interest. Whether starting a clinical trial

de novo, joining an on-going research project with an established pain research group, or reviewing the existing literature on a topic of interest, the work of junior clinical investigators is essential to ensuring the progress of clinical pain research.

Disclosures

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