Research Series

Session Outline

- Overview of K Awards
- Local resources
- Anatomy of a K Award
- Structure and writing tips

K Awards: NIH Goals

- The NIH has long believed that the development of independent investigators requires training.
- K Award program is designed to provide resources to develop independent senior investigators (from junior ones!)
- K Awards are as much (if not more) about the candidate as they are about the research:
  - They develop an individual.
  - They use a research project to accomplish that.

K Award Anatomy

- K Awards can be distinguished across several characteristics:
  - Made to an institution vs. an individual
  - Are directed to clinicians vs. PhD-trained investigators
  - Are directed toward a specific area (clinical research)
  - Are directed toward a specific investigator group
  - “Distance” from likely independence
- Which NIH Institutes sponsor the particular award type
- Important to match your position/level of training with the award

K Award Features

- 2 to 5 years in length
- Provide substantial salary support but limited research funding
- Contain both a training plan and a research plan
- Includes a team of mentors, co-mentors, advisors, etc.
- Goal: transition to independence
K Award Typical for Clinicians

- **K08 Mentored Clinical Scientist Research CDA**
  - Development of the independent clinical research scientist

- **K23 Mentored Patient-Oriented CDA**
  - Development of the independent research scientist in patient-oriented research (research conducted with human subjects in which an investigator directly interacts with subjects)

K Awards Typical for PhDs

- **K01 Mentored Research Scientist**
  - Intensive, supervised career development experience in the biomedical, behavioral, or clinical sciences leading to research

- **K25 Mentored Quantitative Research CDA**
  - 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

Institutional K Awards

- **K12 (KL2):** Typically to the institution, these are primarily focused on very early investigators (senior fellows, 1st-year faculty)

K Awards for More Senior PhDs

- **K02 Independent Scientist Award**
  - The K02 award provides three, four, or five years of salary support and protected time for newly independent scientists (later than most of you)

- **K24 Midcareer Patient-Oriented Research**

- **K26 Midcareer Investigator/Mouse Pathobiology**
K Awards for More Senior PhDs

- **K07 Academic Career Award**
  - Support for more senior investigators who have the expertise and leadership skills to enhance the aging and geriatric research capacity within their academic institution.

PhDs and Clinicians

- **K22 Career Transition Award**
- **K99/R00 Pathway to Independence**
Institutional Awards

- The University of Pittsburgh has many institutional K Awards.
  - ICRE KL2 Clinical Research Scholars Program
    - nearly 40 people funded through this mechanism
  - ICRE Patient Centered Outcomes Research (PCOR) Scholars
  - Multiple K12s

K Award Success Rates – 2018

- 2018: 3611 K Award applications → 1172 funded
  - Overall Ks 32.5%
  - K01 31.0%
  - K02 29.4%
  - K08 39.7%
  - K12 55.4%
  - K22 18.7%
  - K23 37.7%
  - K24 52.4%
  - K25 17.1%
  - K99/R00 26.2%

K Award Applications – 2009/2018

Overview of a K Application

- Career Development Award (K) Application
- Upload to PHS 398 Career Development Award Supplemental Form: Combined Candidate Information (Items 2-4: Candidate’s Background, Career Goals and Objectives, and Career Development/Training Activities During Award Period) and Research Strategy (Item 11)
- 12 pages (this is very little room!)

Information at ICRE Website

Be Careful!

- “Applicants are prohibited from using the Appendix to circumvent page limitations in any section of the application for which a page limit applies.”
- Pay attention to this……
Look at the Program Announcement!

Writing the K Award

- Plan ahead...way ahead...like **way, way ahead**
- Develop your team early and involve them in the project.

Read PHS Form SF424 (yes, actually read it)

K Awards have five sections about you and your plan:

- The Candidate (**that's you**)
- Career Goals and Objectives (**when you grow up**)
- Career Development (**the training plan**)
- Training in the Responsible Components of Research (**required of all K awards**)
- The Research Plan (**what you will do**)
- This can only be 12 pages long!

There are other required components.

- Mentoring plan (only required in some)
- Statements by mentors/collaborators
- Description of institutional environment (1 page)
- Institutional Commitment to candidate
  - This is **really important**.
  - Your institution needs to demonstrate that it is **enthusiastically** supporting your applications.
- Letter of Recommendation (some awards)
  - Request a letter of support from OACD
  Darlene F. Zellers, PhD, Director, zellersd@pitt.edu

Candidate Section

- The candidate background/career goals and objective sections have several purposes:
  - **Tell a story** about how you came to clinical research.
  - Describe what your **long-term goals** are.
    - How will this career award help you?
    - What will be your impact if your research is successful?
  - Provide evidence for your **potential**.
    - What have you already accomplished?
    - What has excited you about what you have done?
    - How do you plan to expand that into the future?
  - **Don't be shy**...your competition isn't.
The Training Plan

- **DO**: “I am developing a path to independence, and there are components of the proposed research that I cannot yet accomplish. The training plan will fill those gaps.”
- **DO NOT**: “I am doing this cool research, and by the way, I think I will get an MPH during the grant.”

Training Plan: Driven by the research project

- The best training plans are *tightly integrated* with the research plan.
- The research plan should *dictate the training plan*.
  - What skill do I need to complete the task?
  - How am I going to obtain those skills?
    - Can I obtain them before I need them?
    - Does my mentoring team have the appropriate expertise?
    - Do the skills make sense to have?
- Training plan should *develop independence* (and it should be clear how that happens)

Research plan determines training plan.

- The training plan should make sense *vis-à-vis* the skills and experiences that the trainee needs to develop in order to complete the research.

Training should make longitudinal sense.

- Make use of a wide variety of training opportunities:
  - Courses
  - Mentored, directed readings
  - National meetings (pre-courses)
  - One-on-one learning in the context of a project component (perhaps with a consultant)
- Not all training must come from a single source or mentor.

Remember the Goal of a K Award
Milestones should be related.

Year 1
- Set up
- Survey Development
- Training Plan

Year 2
- Patient Acquisition/Data
- Analysis

Year 3
- Write it up

Year 4

Year 5

Training Plan and Candidate = Research

- There is no specific formula, but K Awards are primarily for *individuals of high potential*, not research of high potential.
- The training plan and candidate section are *at least as important* as the research plan.
- The training plan must be *related* to the research plan.
- The goal should be *independence*.

Training in the responsible conduct of research.

- This is required.
- There are many mechanisms in the University through which to accomplish this:
  - CTSI RCR Training Center
    [http://www.ctsi.pitt.edu/RCR/index.shtml](http://www.ctsi.pitt.edu/RCR/index.shtml)
    Karen Schmidt, PhD can provide RCR text
    [kschmidt@pitt.edu](mailto:kschmidt@pitt.edu)
  - ICRE courses (CLRES 2050)
  - Health Science Portal online modules
  - GSPH course
  - National meeting courses

Research Programs:

- **DO**: “Examine and affiliate with an ongoing, existing project that can be expanded to include an independent component.”
- **DO NOT**: “Propose to accomplish a true, independent R0-1 5-year research project.”
- Remember: this is about *you* as much as the research… the research is a vehicle for you to grow.

Pros and Cons of True Independence

- A K Award only has *(at max)* $30,000 to do research.
  - Note: *this is not a lot of money*.
  - One can do little primary data collection or experiments with $25-30K.
- Attaching to an existing program provides structure and resources.
- To move to independence (an R Award), you *need* preliminary work (product from your K).
  - A completely independent project may take too long to develop results.

Pros and Cons of True Independence

- However, having your own project does demonstrate competence, potential for independence
- Research decisions are your own (but be careful….)
So, you want to do your own…..

• Strongly suggest you create a separate project attached to an existing one:
  – Pneumonia PORT: ~3500 observational study of outcomes in pneumonia (90-day mortality)
  • MD Junior faculty member extended to 1-year mortality
  – Optimal Timing of OLTX: large DES model of the US organ allocation system
  • PhD Junior faculty member developed a project to assess the impact of more flexible survival estimating methods
  – Lung cancer screening study: ~3000 high-risk patients screening with CT
    • PhD Junior faculty assessed QOL/anxiety/health utilization in sample of screened

Think about a realistic/productive timeline

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set up</td>
<td>Write it up</td>
<td>Publish</td>
<td>Set up</td>
<td>Write it up</td>
</tr>
</tbody>
</table>

Methods: The Most Important Section

• The methods section needs to clearly state:
  – What you are doing
  – How you are going to do it
  – How you will analyze the results
  – What you will do with unexpected finding/mishaps
• Mistakes in the methods section can be **FATAL.**
  – Analyze a set of data with an incorrect analysis plan.
  – Unrealistic power calculations, not based on data
  – Insufficient detail to allow the reader to assess the validity of the method

Caveat: there are new rules!

• Page limits are getting **much smaller.**
• Methods sections will have only a **few pages.**
• Appendices are **limited.**
• We have little experience with the new format, but:
  • Basic principles of clarity and organization may get even more important.

You have to be concise.

• “If I had more time, I would have written you a shorter letter.”
  - This is attributed to Jefferson, Hemingway, Pascal, Twain, and many others
  Doesn’t matter who said it – **take it to heart**
• This is **really important…** you don’t have space to ramble.

The Importance of Specific Aims

Many years ago (OK, it was many decades ago) I got some great grant writing advice that has stood me in good stead. A colleague told me the most important part of the whole proposal was the part that is usually less than a page long, the first section, Specific Aims. You should work hard on this page. Very hard. It tells the reviewer exactly what you are going to do, and if you are clever, it also tells him or her, why. Your goal is to get immediate buy-in that says, “Yes, this is interesting. I’d like to know the answer to these questions. I wonder what’s going to happen when (s)he does this.” Again, clarity is the key. The reviewer needs to understand exactly what you are going to do. If you can, you should tell them in the first paragraph why you are going to do it, but the elaboration of that comes next, Background and Significance.

David Ozonoff
Boston University

http://thepumphandle.wordpress.com/2006/11/16/writing-nih-grant-proposals/
Structure of a Specific Aims Page

- Background: set the stage for the problem.
- Convince the reader that the problem is important.
- Provide an overarching goal.
- Write clear, concise, specific aims that are active.

The paragraphs should be linked.

1st paragraph:
As the US population ages, patients under the care of physicians will present increasingly complex health problems that make clinical decision-making difficult. – More detail about this

2nd paragraph:
The use of health information technology (HIT) has long been viewed as a remedy for these problems, and the appropriate application of HIT for the physician or provider has shown to improve process and clinical outcomes in the care of many individual diseases. – More detail about this

The paragraphs should be linked, ctd.

3rd paragraph:
In this demonstration project, we will modify an existing electronic PHR to provide active and interactive alerts, feedback, disease-specific education, and patient self-management tools with the goal of improving multiple components of the ambulatory care of complex patients.

Set up the aims:
This demonstration will improve cardiovascular risk reduction in complex patients with comorbid illness through the following aims:

Specific Aims: Common Mistakes

- Poorly focused
- Underdeveloped
- Hypotheses not clearly articulated or not supported by literature
- Overly ambitious
- Impact overstated or not stated

New NIH Methods Format

- Research Strategy:
  – Significance
  – Innovation
  – Approach

Significance

(a) Significance

- Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses.
- Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.
- Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.
Innovation

(b) Innovation

• Explain how the application challenges current research or clinical practice paradigms.
• Describe any novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, and any advantage over existing methodologies, instrumentation, or interventions.

Approach

(c) Approach

• Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Unless addressed separately in Item 21 (Resource Sharing Plan), include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.
• Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.
• If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work.

Structure of the Methods Section

• Formatting is surprisingly important.
  – “This is an extremely well-written application by a new investigator…”
  – vs.
  – “The disorganization in this application makes it very difficult to evaluate. There are contradictions between sections…”
• This is not “style trumps content”; this is about making it clear (and easy to understand) exactly what you propose.
• Excellent form is a necessary but not sufficient condition for an excellent review….the science still has to be outstanding….and it is much harder in 12 pages.

Setting the Stage: Details of the Review Process

• The important fact is there is precious little time for review and comment:
  – Any time a reviewer has to spend time just figuring out what you are doing is wasted.
  – And it makes them angry……
• The structure and organization of the methods section allows for reviewers to concentrate on the science.

Pay attention to good writing practices.

- B.1: A clear subject heading
  Discuss in an introductory sentence what you are going to discuss this section. Put a sentence that takes about 7 words (B.1.1) and a very short description of each (B.1.2) and then a summary.
- B.1.1: Section heading
  Keep sections to detail a specific component of your work that is a standalone idea.
- B.1.2: Very clear subsection heading
  Make the subsections make sense in the order in which you present them.
- B. Summary:
  Develop a concise summary of what you said in each major section.

Boring…..

• Don’t have your application be 12 pages of solid text
Methods and Aims: A one-to-one correspondence is very helpful

AIM 1: \( kjsfj k ldlkkl sls \)

D. METHODS

D.1: Aim 1:

H1.1: \( kjsfj k ldlkkl sls \)

H1.2: \( kjsfj k ldlkkl sls \)

D.1.1. Hypothesis 1:

D.1.2. Hypothesis 2:

AIM 2:

H1.1: \( kjsfj k ldlkkl sls \)

H1.2: \( kjsfj k ldlkkl sls \)

Methods: Overview

• Start with a straightforward methodological overview:

“This study is a randomized, double blind, placebo controlled trial of the effect of the novel IL-7 inhibitor leukenblockin in the treatment of sepsis secondary to infection.”

“The proposed investigation will be conducted in two phases. In the first phase, a retrospective cohort study will be conducted using the institution’s extensive and detailed electronic medical record to determine the readmission rates after hip and knee replacement surgery secondary to thromboembolic complications. In phase two, a pre-post intervention design will be used to assess the impact of a post-surgical thrombosis prophylaxis program on baseline thromboembolic complication rates.”

Methods: A Structured, Clear Introduction

D. Research Design and Methods

The overall goal of this proposal is to evaluate whether mathematical models of embryo growth and development can be combined with statistical predictions of embryo transfer success and patient preferences for weights outcomes to produce a tool that could lead to more effective decisions concerning IVF. This work is divided into three aims:

Section D.1 describes the development of a model of the growth and development of embryos after harvest, Section D.2 presents how we will construct prediction models of embryo transfer success, including the classification of embryo quality, and Section D.3 illustrates the construction of the proof-of-concept MDP that will join the growth and development model with the statistical prediction model to evaluate the optimality of various transfer decisions. As we have done in previous modeling projects, we have assembled a Clinical Advisory Committee composed of individuals with expertise in IVF, general OB/GYN, and embryo growth and development. These individuals are listed in the budget pages, and their biographical sketches provided. All aspects of the modeling process will be conducted in conjunction with meetings and email exchanges with members of the oversight committee. The oversight committee will meet monthly, with the members from RBA joining by telephone.

Methods: Common Components

• There are often components of the research that are common to all (or many) of the Aims.

• Duplicating the description of the common components in each Aim is a poor use of space and repetitive (read “irritating”).

• Clearly describe the common components once and then reference this section (if necessary) in the sections on each Aim.

Methods: Common Components

• Study population
  – Describe the inclusion/exclusion criteria.
  – Recruitment criteria (refer to prior work if you have evidence you can attain the expected consent rates, etc.)
  – Ethnic mix and justification, if necessary

• The intervention
  – The description should be sufficiently detailed that you could replicate.
    • Doses, intervals, diagnostic tests with intervals
    • What the control group will experience (standard care vs. a particular protocol?)
  – The specific variables of interest that will be effected by the intervention

• Randomization method
  – How and when will the investigators assign treatment group
  – Rationale for block randomization or site-specific randomization schemes
  – Criteria required to break randomization

• Staff Training
  – Often required for chart reviewer, interviewers
  – Should describe a method of assessing competence, reliability
  – Should describe a method for error checking

• Data Management
  – Acquisition, codification, storage, manipulation
  – Data safety
Methods: Components in Each Aim

• Restate the **EXACT AIM** from the specific AIMS sections
  – Restate the individual hypotheses within each aim
• Useful (but not strictly required) to have similar structure across aims and hypotheses
• This is **VERY DIFFICULT** to do in 12 pages, and may not be possible

Methods: Caveats

• Very important to describe what can go wrong and what your back-up plan is
  – Recruitment issues
  – Ethnic makeup
  – Gender makeup
  – Unexpected outcome rates
    • Interim analysis plans
    • Analysis plan
    – Results of each aim: null vs. alternative
      • Although certain results are expected: they may not happen.
      • Have alternative strategies for important hypotheses.

Methods: Conclusion/Future Work

• Short section on the expected results of the overall research project
  – What it means for the disease process in general
  – How it can be used (either now or in the future)
• Future research
  – Describe a path regarding how these results will help structure future research.

Common Errors: Absent Methods

• Failing to provide a method for an AIM
  – Even in 12 pages, the reviewer still must be able to determine how you will accomplish EACH and EVERY aim.
  – Even if it is obvious to you, state what you will do.
    “The analysis plan for Hypothesis 3.3 is identical to that of 3.2. Please see section D.3.2.x for details of variable definitions and statistical analysis.”

Common Errors: Linked AIMS

• Failing to provide a backup plan in linked AIMS
• For example, examine the following series of aims:

  **AIM 1**: Determine if TNFα at presentation is associated with increases in severity of ARDS in patients with sepsis and pneumonia

  **AIM 2**: Develop an improved ICU mortality risk prediction equation including TNFα as a predictor

  **AIM 3**: Conduct an RCT of the improved risk prediction equation to improve ICU admission decision for patients in the ED with pneumonia

  • AIMS 2 and 3 **require** a successful and positive completion of AIM 1. They are irrelevant if AIM 1 finds no relationship
Linked Aims

- Aims by nature in a grant are related; that’s why they are in the same grant application!
- But there should be scientific value to EACH AIM independently
  - The AIMS or methods need to describe how each will be modified with all possible outcomes of the earlier aims.
  - This is especially true in hypothesis-driven research
- Explain consequences of null vs alternative hypothesis
  - “If the hypothesis is rejected, this implies...blah, blah, blah...” which will require the following modification to the analysis plan in Aim 2
  - Remember (in theory) you don’t actually know which way the research will go; that’s why it’s “research”

Common Errors: Unnecessary Detail

- There is a tendency to over-explain the methods that you will use if the method is “new” to you

Because the outcome variable of interest is dichotomous (takes on values of 0 and 1) standard linear regression is not an appropriate method of analysis. We will therefore use logistic regression, which is appropriate for this form of analysis. The impact of independent variable on the risk of death will be estimated through the following logistic function:

$$ P_i = \frac{1}{1 + e^{-(\alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + ... + \beta_j X_j)}} $$

Where the $X_i$'s represent the various independent variables and the $\beta$'s represent their coefficients.

Common Errors: Insufficient Detail

- The methods section must be sufficiently detailed that the reader could actually reproduce the work
- Statements like:
  - “The data will be analyzed.”
  - “Sensitivity analyses will be performed.”
  - “Quality of life will be measured.”
  - “Intervention and control will be compared.”
- Are totally inadequate descriptions

Insufficient Detail

- The data will be analyzed.
- Sensitivity analysis will be performed.
- The primary composite outcome will be compared between intervention and control, using an intention-to-treat analysis using a Chi-square test.
- Univariate sensitivity analyses will be performed for the variables (and ranges) listed in Table 4. Those variables found to have a significant effect on outcomes will be included in a probabilistic sensitivity analysis, using the distribution described in column 4 of Table 4.

Insufficient Detail

- Quality of Life will be measured.
- Intervention and control will be compared.
- The intervention and control group will be compared, using t-tests for continuous variable and Chi-squared tests for categorical variables.
- Subjects will be administered the SF-36 at baseline and at 6- and 12-month follow-up visits. In addition, the arthritis-specific quality-of-life tool (see appendix A3) will be administered at baseline and 12 months.
Common Errors: Power Calculations

- Power calculations should virtually always be based on the primary outcome.
  - Sample size determined by primary outcome may limit the ability to find significant results in secondary aims or outcomes.
  - ALREADY indicate the power for secondary aims or outcomes that are implied by the sample size powered for the primary aim.
- Completely unrealistic power calculations
  - Effect size too large and not based on data
  - Use of a non-standard type 1 or type 2 error

Common Errors: “Conceptual Models”

- For many types of grant applications, a “conceptual model” is often required to set the context of the intervention.
  - Very common in HSR-type applications
  - Replaced often with a mechanistic model in more basic science applications
- Describes the fundamental pathways by which the particular intervention, exposure, etc. is expected to have its effect.

Appropriate Conceptual Model

**B.3.2. Stages of Change as a guide to intervention content.**

The stages of change model, as outlined by Prochaska, describes the process of behavioral change that provides the foundation for the intervention proposed in this application. In this model, patients proceed through a series of stages toward behavior change (Figure 3).

- Patients are contemplative if they have not yet considered changing their behavior or are unaware of the potential dangers of their behavior.
- The contemplative stage indicates that the patient is aware of the dangers of their behavior and is considering changing them.
- If a patient is to change behavior, they first pass through a stage of determinate and preparation, after which they take action to change their behavior. Once changed, some patients maintain their new behavior, others relapse.
- The important concept is that an intervention directed for patients who are at one stage (pre-contemplation) may not be effective at the determination/preparation phase. For example, an intervention providing information about the behavior may induce people to become contemplative but is not expected to have an effect if patients are already at the determination/preparation phase.

In the proposed study, a previously validated assessment tool will be used to assess the study participant’s current stage, which will be used to assign one of the interventions consistent with the individual’s stage.

Conceptual Models: Ranking of Use

- Conceptual model that actually informs the research, components of which are directly tested in the conduct of the application
- Conceptual model that helps understand the implication of results or guides the intervention
- Conceptual model that justifies a type of intervention
- Conceptual model that is included for the sake of having one….and is not used directly

Common Errors: Planning Too Much

- AIMS that are too complex
  - Grant application with four aims and between six and 14 hypotheses per aim
- AIMS that exceed the ability of the data to answer
  - Application collected over 2800 variables on less than 40 patients and planned (literally) hundreds of analyses relating variables to outcomes
- AIMS that require inordinate follow-up

Peer Review: Overview

- Most institutes have study sections specifically for K Awards.
- Review 20-50 grants in one 2-day meeting.
- Composed of
  - Standing members
  - ad hoc members
  - Scientific Review Administrator (SRA) and Program Staff from the Institute
Strategies for Internal Review

- Early, but not “too often”
  - Have selected individuals read your grant a few times
  - You don’t want them to be fatigued about your work.
- Always have a methodologist/statistician read your methods section.
- Early on, if you can, make sure that the headings alone make sense.
- When near complete – the 10-minute read

Summary

- K Awards are an outstanding first grant – a lot of protected time, and they are (relatively) easy to obtain.
- **They are as much about you as about the research** – the reader should be excited about the career you want to create and the work you want to do.
- Prepare early.
  - Prepare early.
  - Prepare early.
  - Prepare early.