

# The Jewel in the Crown: Specific Aims Section of Investigator-Initiated Grant Proposals

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The specific aims section of National Institutes of Health and other grants is the most important component, as it summarizes the scientific premise, gap in current knowledge, hypotheses, methods, and expected results of the project proposed. The reviewer usually reads this section first and forms an immediate opinion, usually confirmed on reading the entire grant. This treatise reviews the philosophical background underlying generation of hypotheses, emphasizes the important characteristics of the specific aims section, and offers a point-by-point roadmap for writing. This perspective arose out of a new Endocrine Society initiative in which senior investigators review the specific aims of next-generation members.

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**Freeform/Key Words:** gaps in knowledge, grantsmanship, grant writing, specific aims, scientific premises

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The Trainee and Career Development Core Committee of the Endocrine Society introduced a new program in 2017 aimed at educating trainees and early-career investigators in the art of grant writing. Trainees were encouraged to submit a specific aims page that would be reviewed one-on-one by experienced, successful senior Endocrine Society members. In the course of this process, we realized that few publications had been devoted to the specific aims component of grants previously and that a treatise on this topic would be beneficial for those new to grant writing [1–12]. A well-written specific aims section of a grant proposal is critical for obtaining highly competitive funding. This process involves identifying critical knowledge gaps and devising methods to close those gaps [1, 4, 6–8, 10, 13, 14]. Integral to this process are the scientific premises and resulting hypotheses incorporated into the specific aims.

## 1. Historical Background

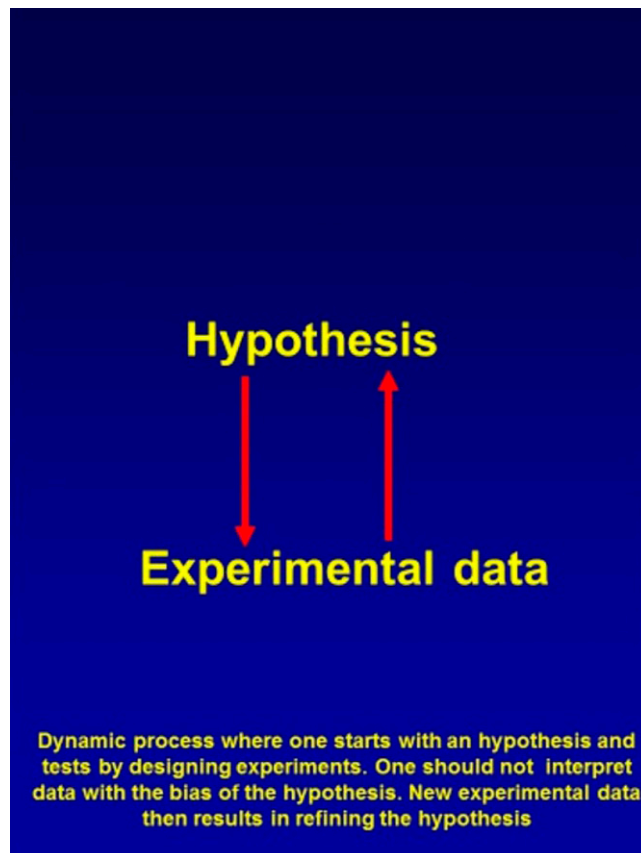
The key concepts behind framing and testing hypotheses were not clearly articulated until the mid-1800s. Prior to that time, biomedical research was not considered a scientific discipline with rigorous intellectual demands underlying the process. Claude Bernard, considered the “Father of Experimental Medicine,” was perhaps the first to clearly articulate that biomedical research is a rigorous scientific discipline with stature equal to that of other scientific fields. He termed this discipline “Experimental Medicine” in his key treatise called *An Introduction to the Study of Experimental Medicine* written in 1865 and translated into English in 1927 [15]. The key principles raised in this treatise are as pertinent today as when written and should be considered key to successful grant writing.

Bernard changed the perception of biomedical research by his clear articulation of the approach and methods to be used in obtaining biomedical information. He highlighted the idea that “scientific medicine, like the other sciences, can be established only by experimental

means, that is, a direct and rigorous examination and melding of reason and facts.” He emphasized that “the experimenter must clearly understand the scientific principles which guide the reasoning process. You cannot separate two things: the obtaining of facts and the mind and its reasoning process.” He further explained the concept of experimental methodology as a “dynamic process where one starts with a hypothesis and tests by designing experiments.” Interestingly he cautioned that “one should not interpret data with the bias of the original hypothesis” but should be viewed objectively based on the data. He noted that “new experimental data then result in refining the hypothesis” (Fig. 1). He also emphasized the importance of new and emerging technology: “Every time that a new technique or instrument comes along, we invariably see scientific progress and questions to which this means of analysis can be applied.” More recent advice about interpreting hypotheses comes from the cult book *Zen and the Art of Motorcycle Maintenance* by Robert M. Pirsig, which focuses on experiments that do not provide the yes/no answers desired [16]. He used the term “mu experiment” to characterize the type of data obtained. The result of such experiments forces one to raise a hypothesis that was not thought of prior to the experiment. Science often advances more rapidly with the mu experiment than it does when one asks questions based on hypotheses that have been suggested by other data.

## 2. Emerging Concepts Relating to Philosophy of Science

More recent thinking places emphasis on the concept of the scientific premise. This requires a firm understanding of the literature underlying the development of a premise and then a hypothesis. Taken together, this information provides the basis for plausibility, which is the



**Figure 1.** Diagrammatic representation of the concepts of Claude Bernard with respect to conducting experiments based on testing hypotheses and interpreting the results so as to generate new hypotheses or modifying existing ones.

bedrock of scientific research. Junior investigators should understand that new technology has made possible the concept of “hypothesis generating research.” For example, genome-wide association studies that are designed to identify single nucleotide polymorphisms of possible biomedical importance represent one aspect of this “new approach” to scientific endeavors [17, 18]. Once a highly statistically significant single nucleotide polymorphism is identified, the next step is to generate a hypothesis regarding its function and subsequently to design experiments to test this hypothesis. This “hypothesis-generating” approach usually requires very large databases and multiple investigators. Accordingly, the more junior investigator should understand that “hypothesis-driven” rather than “hypothesis-generating” research is the avenue critical to the success of their grant writing.

### 3. Review of Literature Discussing the Specific Aims Section

Multiple articles have provided recommendations for successful grant writing but few focus on the specific aims section. For example, Wisdom *et al.* [13] reviewed 1130 abstracts on grant writing and ultimately selected 53 for closer scrutiny. Only two sentences in this treatise discuss specific aims indicating 1) “include 2 to 4 aims or objectives and these should be clear, concise and realistic given the time and resources proposed” and 2) “the research questions and study aims should drive the methods proposed.” On further review, we found online documents that provided additional insight into the preparation of this section from personal perspectives [4, 6, 8–10].

### 4. Impact of the Specific Aims Page

This is the most important component of any grant proposal. The reviewer usually reads this page first and gains a general impression of the work to be accomplished and the means of approaching the questions proposed. If the reviewer is highly interested in and excited by the project after reading it, he/she will be less critical of the details in the approach section of the grant. Specific aims should be written in such a way as to generate interest, enthusiasm, and excitement. A highly polished specific aims section will influence how the reviewer will judge the entirety of the grant. For these reasons, the specific aims section serves as more than a roadmap for describing what will be done. Described in a wider context, the specific aims section is analogous to what a salesman does, as illustrated in Fig. 2.

### 5. Importance of the Approach

Generating hypotheses and testing them experimentally are the capstones of the grant writing process. Emphasis on the scientific approach as “hypothesis driven” requires explicit

#### **Writer of specific aims is analogous to a salesperson with an innovative idea**

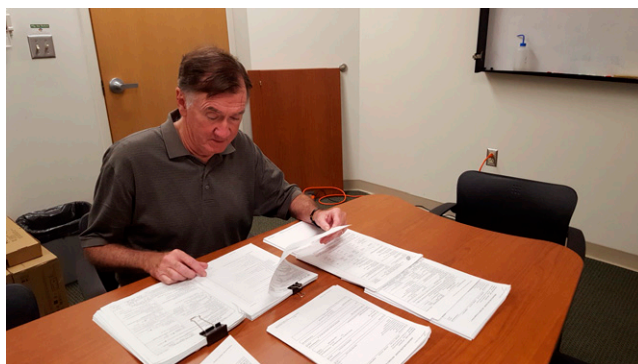
- 1. Is well prepared**
- 2. Is credible**
- 3. Makes a good first impression**
- 4. Provides supporting documentation**
- 5. Has something special to offer**
- 6. Presents logical, well thought out plan**
- 7. Inspires**
- 8. Conveys confidence in the approach**
- 9. Knows the background of the idea**

**Figure 2.** The analogy of a salesman selling his products and the concepts needed to get the interest of customers is relevant to grant writing, as described in the text.

language. The key concepts to be conveyed are the clear identification of gaps in knowledge and the importance of the information needed to fill those gaps. Hypotheses are then formulated that suggest potential mechanisms that need to be understood to fill these gaps. A hypothesis has to be plausible based both on known underlying knowledge but also on the likelihood that a hypothesis might be correct. It should reflect significance and novelty, two important criteria for grant application assessment. The key word, “scientific premise,” encompasses both of these two components of plausibility. Key terms emphasized by the National Institutes of Health and other granting agencies to capture these ideas are scientific premise and hypothesis. It is also critical to highlight the importance of filling the gap in knowledge and the means to accomplish this goal. Key words here are novel, innovative, groundbreaking, and high impact, to name a few. On the other hand, certain words convey non-hypothesis-driven research and can raise red flags as to the approaches taken. These include the terms describe, explore, investigate, correlate, and estimate, as examples. When the reviewer judges that the work is merely the obtaining of facts without clear hypotheses to be tested, the comment is often made by the reviewer that this is a “fishing expedition,” a phrase that usually assigns the grant to the least favorable categories.

Another red flag is the term “overly ambitious.” This is not such a problem for a senior investigator who has demonstrated the ability to be highly productive. For an unproven junior investigator, the extent of the work proposed has to be considered to be within the realm of what can be accomplished. As this term is highly subject to interpretation, prereview of the specific aims by senior investigators early in the process of writing and designing the proposal can provide guidance to avoid the “overly ambitious” critique. The critique words descriptive and correlative may also signify non-hypothesis-driven specific aims.

The writing on the specific aims page should be written in a positive fashion with the strategy that the pitfalls and critique of the grant, which inherently exist, can be overcome (as detailed in a later section of the grant) (Fig. 2). Citing the analogy of the brief description used in selling ideas or products [1, 3], it is not prudent to initially point out the flaws but important to emphasize the positive. It is also important to write in a nondense, clear fashion using simple language so that the reviewer need not reread the grant several times to understand. The reviewer usually is assigned several grants to read and does not have time to reread a grant several times to understand the intent (Fig. 3). It is also important to recognize that the reviewer may not always be an expert in the specific area of the proposed work. One should be cognizant of the fact that it is an acquired talent to learn to write in such a way as to describe complex ideas in a simple and clearly understandable fashion. Having expert grant writers critique your writing is an effective way to learn this skill. Another key concept is that explicit language is important in conveying your ideas. For example, although it would appear obvious, it is difficult to convey the important gap in knowledge that you are trying to fill and this should be explicitly stated. Finally, the reviewer needs to be convinced of the importance



**Figure 3.** Reviewers are extremely busy and do not have the time or energy to reread a grant several times. For this reason, grants must be clear, nondense, and written in an easily readable and understandable fashion.

of filling that gap. One may articulate clearly a scientific premise, but the importance of the issues underlying that premise represent a key component of successful grant writing.

The principles described by Bernard [15] and others [4] in the paragraphs above are clear and easily understood. However, the challenge is to convey each of these in a one-page component of the grant, the specific aims page. It requires substantial mentoring for a junior investigator to successfully accomplish these goals, indeed a major challenge. Recognition of the goals by reviewing checklists and comparing these goals with the written document is a useful task for the grant writer (Table 1). Asking successful senior investigators to comment on and critique the specific aims provides another important component of the process. This was the intent of why the Trainee and Career Development Core Committee is asking senior investigators to specifically review the specific aims component of the grant proposals of trainees.

Regarding advice for investigators whose first language is not English, clear, concise, idiomatically correct language is essential to gain the respect and enthusiasm of the reviewer. Although not impossible, this is a difficulty when the principal investigator is not writing in his/her first language. Important advice is to ask a colleague with excellent English language skills to critique your grant.

**Table 1. Checklist for Preparation of Specific Aims**

General Characteristic	Does Not Meet		Reviewer's Critiques	This Critique Not Applicable		Comments
	Meets	Comments		Applicable	Comments	
Hypothesis driven			Overly ambitious			
Novel			Fishing expedition			
Innovative			Descriptive			
High impact			Correlative			
High significance			Leap of logic			
Exciting			Unsupported hypothesis			
Gaps in knowledge explicitly stated			Dense			
PI knowledgeable about literature			Mundane			
Scientifically plausible			Scientifically not plausible			
Each specific aim not dependent on other aim			No clear endpoints			
Methods validated or feasible			Expectations not credible			
Expected outcomes delineated			Work already done by another investigator			
PI's team well positioned to do this project			New methodology will take inordinate time to validate			
Rational plausible			Trivial or ultimate impact minimal			
Components are logical						
Two to four aims included						
Transformative						
Language easily understandable						
PI can critically evaluate literature						

Abbreviation: PI, principal investigator.

## 6. General Principles in Writing Components of the Specific Aims Page

This is the most important component of the application and is a template or master plan for the entire application [4, 6–10]. This section includes everything about the application that is important but without the specific details. It is important to know that, in general, the specific aims page will be used by the program officer to select and recruit reviewers for the grant. Most members of a review panel, not specifically assigned as a primary or secondary reviewer, will likely only read the specific aims section. Writing a grant involves creating a partnership with the reviewer, and this section should be written with that in mind.

There are several key principles that should be taken into account when writing the specific aims page. The purpose of the specific aims section is not just to provide a roadmap of the work to be done, but to present the new idea(s), key preliminary study results that render the proposed work feasible, the rationale for the studies proposed, the expected outcomes, and the reasons why one should be enthusiastic about the grant. Several key points in the presentation are pertinent:

1. Explicitly state the gaps in knowledge that exist and write in such a way as to gain the confidence of the reviewer that a critical review of the literature has been undertaken.
2. Clearly put forward the hypotheses to be tested. The specific aims page should provide an overarching hypothesis for the project as well as individual hypotheses as each specific aim.
3. Dispel the notion that the study is merely to explore facts to generate a hypothesis based on those facts (*i.e.*, fishing expedition).
4. Establish scientific plausibility of the hypothesis based on existing literature.
5. Summarize the pilot/preliminary data that support the hypothesis.
6. Convey the fact that testing the hypothesis will contribute important information (*i.e.*, significance and novelty) either for science in general (intellectual content) or for the ultimate benefit of patients (translational or clinical research). Although recent emphasis has been on the practical, translational application of research findings, new information for its own sake can have importance well beyond the original perception of its importance. Who knew that understanding of the structure of DNA in the double helix would have such profound implications? The key is to inspire confidence that the studies proposed will advance important knowledge in the area of study and fill the identified gaps.
7. Write in such a way as to convey the fact that the investigator:
  - a. is knowledgeable about the literature;
  - b. can critically evaluate existing data; and
  - c. knows the limits about what can be accomplished (*i.e.*, inspires confidence that the project is not overly ambitious).
8. Briefly describe the novel methods in such a way that the reviewer can get a sense of innovation (another important criterion of assessing the proposed grant application) in the proposed work and how it can be effectively used to address the aims proposed. Recognize what Bernard said about the value of new and innovative methods in addressing specific questions.
9. Provide a general conclusion statement reflecting the gains from doing the proposed work and giving the impression of the totality of the project.
10. The characteristics of the specific aims include the following:
  - a. Each aim should be hypothesis driven.
  - b. No specific aim should be completely dependent upon another (*e.g.*, if specific aim 1 is not supported by data, then the subsequent aims become irrelevant).
  - c. Specific aims should be related to each other in a complementary fashion.

- d. Provide subheadings that clarify as specifically as possible what is to be done.
- e. As much as is possible, identify the expected outcomes of each aim.
- f. Covey the concept that the methods are feasible.

## *A. Specific Structural Components of Specific Aims Page*

### **A-1. Introductory paragraph**

The overall goal of the introductory paragraph is to introduce your research subject and quickly capture the reviewer's attention. The first sentence serves as a "hook" to gain the reviewer's interest. This should briefly describe what research is about and convey a sense of the importance or urgency of the research. In addition, this sentence should be interest-grabbing and immediately establish the relevance of the proposal to human health. The three to five following sentences review what is known about the current state of knowledge. One then outlines the current gap(s) in knowledge (what is not known) and states these gaps directly and succinctly. The grant writer then indicates the critical need to fill that gap and indicates that filling that gap is the driving force for the proposal.

### **A-2. What, why, who paragraph**

This section should convince the reviewers that you and your team have the solution to the problem. The long-range goal is then articulated. This projects the continuum of research that you will pursue over the course of multiple periods of grant support. Several components are then articulated: 1) a description of the "big picture," including the narrow purpose of the project, which is described to match the critical need; 2) an identification of a clearly defined endpoint linking back to the gap(s) in knowledge and central hypothesis; 3) a broad rationale defining what will become possible after the project is finished and the reason for pursuing the project; and 4) an outline of the collective basis upon which this grant should have a competitive advantage, namely why you or your group are the best to accomplish the aims based on qualifications, preliminary data, unique skills, technologies, and past successes.

### **A-3. Specific aims paragraph**

This provides a logical, step-by-step development of key hypotheses and activities by which you will fulfill the objective to address the critical need. Each aim should flow logically into the next and collectively address objectives. The ideas should be conceptual, not descriptive if possible; avoid one aim being completely dependent on another aim. This section should be brief and informative, and use headlines that will attract the reviewer's attention. Each aim should convey why that part of the research is being performed, not what will be done. Avoid descriptive terms such as compare, correlate, describe, and investigate. Well-written grants present two to four specific aims. Avoid having less than two (not enough work) or more than four (too much work) specific aims. Each specific aim should be a brief, focused idea statement. It's best to present it as a subsidiary hypothesis that is related to the overarching hypothesis. Include subtext with more details, including measurements and comparisons that tie into specific hypothesis.

### **A-4. Payoff paragraph**

This paragraph develops advocacy for your proposal among the majority of reviewers who will not, in all likelihood, have read the complete application. The writing should convince the reviewer of the:

1. Significance/innovation/transformation nature of the grant: A statement should directly follow the aims/goal/objectives and build advocacy for the grant.

2. Expectations of the grant: This statement must be specific and credible. This component articulates the expected products of the research and details the payoff that the reviewers can expect to realize if they vote to recommend funding of this application.
3. Impact of the grant: How will these outcomes fill the identified need? The positive impact statement should make clear that collectively, the outcomes will advance the field substantially.
4. Inspirational nature of the grant: How will this change current knowledge?

#### *B. Common Critiques of Grants That Can Be Dispelled by Well-Written Specific Aims*

1. Overly ambitious
2. Not hypothesis driven
3. Fishing expedition
4. Idea and hypothesis not plausible
5. Correlative
6. Descriptive
7. Methods to test the hypothesis are not feasible, not available, or will take an inordinate amount of time to develop and sufficiently validate.
8. Lack of understanding of underlying literature
9. Work already done by another investigator but the investigators writing the grant do not know the literature.
10. The work proposed is trivial in importance and ultimate impact.
11. The work is not innovative.

#### *C. Strategy in Preparing Specific Aims*

1. Put yourself in the position of a reviewer and what he/she will use as criteria for judging the specific aims as excellent.
2. Have as many individuals as possible read and critique.
3. After writing, put off for a few days and reread.
4. Try to reread as an objective reviewer would read.
5. Recognize that the specific aims for a training grant may differ from a nontraining grant.
6. Take a look at a few successful grant proposals to use as a template.
7. Look at the guidelines provided by the funding agency (*i.e.*, National Institutes of Health).

## **7. Conclusions**

The specific aims page is the most critical and difficult component of a grant to write effectively. If the reviewer is not excited about the grant after reading this page, it will be difficult to win him/her over in the more detailed part of the grant. For this reason, the writer is well advised to ask several objective and experienced investigators to review this page early on in the grant writing process. Most experienced investigators advise that a junior investigator should plan a minimum of six months to write a competitive grant. This takes into account the time available for review of the specific aims and then later, the entire grant by other more senior investigators. The suggestion is to have the specific aims page reviewed first. It should be recognized that the reviewers deciding whether the grant should be funded may not be experts in the highly specific area covered by the proposal. For this reason, the grant writer should ask a senior investigator outside of the field to review and critique the page. Finally, the grant writer is “selling ideas and approaches” and should be cognizant of the best means to gain the confidence and to inspire the reviewer.



## Acknowledgments

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Disclosure Summary: The authors have nothing to disclose.

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