CHAPTER 7

SPECIFIC AIMS SECTION: CONCEPTUAL OVERVIEW & CREATING A BULLET OUTLINE

CONCEPTUAL OVERVIEW

TIP: Strategically, the Specific Aims section should be written to create a ‘partnership’ with the assigned reviewers who will represent you at the review-panel meeting. You will provide the conceptual framework on which they will orally hang the details of what will be done.

The Specific Aims section is critical to writing a first-class NIH grant application. It is the most important section related to the development of your proposal, in our opinion, because as noted earlier, it becomes the template or master plan for the rest of your Research Plan; if this section works well, everything else will fall naturally into place.

The Specific Aims section has an equally important role in the review of your proposal: recruiting reviewers to vote a fundable priority score for it. The majority of reviewers – those who were not assigned your application – in all probability will not have read your proposal before it comes up for evaluation at the review-panel meeting. Regardless, these reviewers have an equal vote in establishing your proposal’s priority score. You need to appreciate that they will want to make an informed vote, not a directed one. Therefore, at the meeting, while your assigned reviewers are presenting your proposal to other members of the panel the vast majority of the others will be playing catch up – reading parts of your proposal to determine whether or not they agree with what they are hearing. In other words – and this is what you must understand – they will be doing two things at the same time: listening to your spokespersons – the primary, secondary and tertiary reviewers – while, at the same time, they will be reading parts of your proposal – the title, the Project Summary/Abstract, the Specific Aims section and the Significance and Innovation subsections of the Research Strategy section. If you have ever tried to read and comprehend something that is filled with detail at the same time that someone is talking to you, you know that it is impossible; either comprehension of what you are reading or of what you are hearing suffers. This fact is what informs our approach to writing the Specific Aims section.

The Specific Aims section must include everything about your application that is important and exciting – but without a lot of detail. It must provide a conceptual framework on which your assigned reviewers can orally hang the details of what is proposed. Thus, in this section you are ‘partnering’ with your assigned reviewers at the review-panel meeting. The flow of logic has to be even more compelling than it is elsewhere in the proposal – so compelling that reviewers can follow it at the meeting while someone is talking to them at the same time. Together with the Significance and Innovation subsections, it is one of the most important parts of the application in terms of capturing the affirmative vote of the majority of reviewers.
TIP: The secret to creating a compelling flow of logic in this section is to appropriately link its components, one to another, which requires in-depth understanding of what each component is meant to convey.

Just as each grant mechanism exists for a purpose, and just as each section of the application has a purpose, each component of each section exists for a reason. The reason is to contribute something important to understanding of what is proposed. To optimize their ability to create a flow of logic, components need to relate to each other in very specific ways, i.e., they need to be linked one to another. Such linkages are best established, in our opinion, by starting this section, not by writing everything out in full, but by creating a bullet outline.

CREATE A BULLET OUTLINE

TIP: Outlining is your key to developing linkage and to avoiding unnecessary detail!

One of the most important tips that we can give you regarding development of this section is to begin by creating a bullet outline. When extra verbiage is removed and you are dealing only with brief bullets you can see better how the various components relate to each other and can recognize and eliminate extraneous detail. Without the interfering clutter of unnecessary words, the outline approach also allows you to see whether or not the logic and the concepts flow, as they must in a competitive application. To help you create your bullet outline, in this chapter we will ask you to make a series of responses in a set order. An interactive template is available on our Web site (www.grantcentral.com/downloads.html) in which you can make your responses. Those responses will become the bullets in your outline. Once you are satisfied with the bullets you have written and how they link to each other, we will help you to expand them into sentences that will collectively become the first draft of your Specific Aims section. You can then modify, amplify, re-write and otherwise refine your first draft to produce the version that will become the template for writing the rest of your application (chapter 8).

The explanations that follow will give you a strong working knowledge of the purpose of each component, as well as how it must be linked to other components. When you create your bullets we recommend that you do so in four, distinct paragraphs. The first three are meant to gradually ratchet up detail the deeper into the section the reviewer reads, while the last is included to tell reviewers what they will get for their investment if they decide to invest in your proposal.

**Introductory Paragraph**

**Opening Sentence.** Begin with an interest-grabbing sentence that immediately establishes the relevance of your proposal to human health. You want to convey that, by supporting your proposal, the reviewers will be helping NIH accomplish its goals, which are to improve the control of disease, enhance human health, and advance understanding of biological systems. For example, were you writing an application about a biochemical defect you suspect is the cause of manic-depressive illness, what you write here should not focus on fundamental biochemistry. Instead, you should create one that makes clear how important manic depression is in this country, both from the standpoint of numbers of people affected and the cost of caring for such persons. Be careful not to open with something that the audience you are targeting would obviously know. Now, write a bullet that conveys the medical importance of your area of interest.
Current Knowledge. This component has two purposes. The first of these is to help the less expert members of the review panel get up to speed with respect to what is currently known about the topic of your proposal. A few cleverly written sentences are needed that bring reviewers from the most important, older knowledge to the edge of the field as it exists today. Only key citations should be provided using the reviewer-friendly ‘author/year’ approach that is described in chapter 11, i.e., not numerals. The current-knowledge component has the additional purpose of setting up presentation of the gap in the knowledge base or unmet need that your application will address. Write bullets that flow logically, one into the next, in such a way that they will lead the reviewer to the ‘jumping-off point’ for your application, i.e., what needs to be done next.

Gap in the Knowledge Base / Unmet Need. This component is one of the most important in creating the Specific Aims section, because all of the logic downstream flows from it. It should be simple and direct. It should very specifically identify either the gap in the knowledge base or the need that will drive your application. Furthermore, it must link back to the ‘current knowledge’ component as the next logical step that is required to advance the field.

Gap in the Knowledge Base to be Addressed: Now that your reviewers have an appreciation for what is known, you need to introduce them to what is missing and, therefore, holding back the field. The gap in the knowledge base that you highlight should be the one that you will address with this research proposal. Write a bullet that clearly defines the gap that you want to fill.

Statement of Need and Objective Evidence for Its Existence: If you are writing an application that will be driven either purely by need or one that will be a ‘hybrid’ – a proposal that offers both a statement of need and, later, a central hypothesis – you should write a single bullet that denotes the need. We want to emphasize that, even though most kinds of applications to NIH should not be driven purely by a statement of need, there are some that must be. For example, a proposal to renovate space (a construction grant) would have to be driven by a statement of need for the renovation. An application to purchase a piece of equipment (equipment grant) would, likewise, have to be driven by need for the equipment. If you are going to use a statement of need to drive a research-grant proposal, in most cases you should take the hybrid approach, i.e., provide focus for the application with a subsequent central hypothesis (see below).

Follow the bullet for the statement of need with one or more bullets that provide objective evidence for existence of the need (e.g., your own assessment of need and/or the publications of others that corroborate existence of the need).

At the conclusion of the first paragraph, the reviewers should understand that the research area is medically relevant, they should be up to speed with respect to current knowledge in the field, and they should understand that there is a gap in the knowledge base that constitutes an important problem.

‘What, Why, Who’ Paragraph

The first three components in this paragraph must create a focusing progression that takes the reviewer from the broadest to the narrowest focus that is relevant to this application.
Long-Term Goal. The purpose of this component is to project the continuum of research that you will pursue over the course of multiple periods of grant support. In other words, this component should tell reviewers what the ‘big picture’ of your research program is. It must be relevant to public health, i.e., to NIH’s mission and must be broad enough to encompass the gap or unmet need that you delineated in the first paragraph. It should reflect the niche area that you intend to systematically develop as your own – the area in which you will become the acknowledged expert, if you are not that person already. Also, it must be realistic, i.e., something that is clearly achievable over a finite period of time. For example, if you were a cancer researcher, it would not be credible to write that your long-term goal is to cure cancer. Now, write a single bullet that denotes what your long-term goal is.

Objective of this Application. This component defines the purpose of your grant application, i.e., what it seeks to accomplish, which must be either to fill the gap or meet the need that you delineated in the first paragraph. Thus, this component must link back to the gap/need. It also must link to your long-term goal as the next logical step along the continuum of research that was projected by that component. Be certain that your objective emphasizes the product of the research, not the process that produced it. For example, “to study” something would not be an appropriate goal; what you want is what the study will produce. In addition, “to study” is temporally indeterminate; how would you know when you had studied enough? Write a single bullet that projects your objective for this application.

Central Hypothesis and How Formulated.

The central hypothesis must link to the objective, because the objective will be accomplished by objectively testing the central hypothesis. The purpose of the hypothesis is to provide focus for your research project and, therefore, your grant application. Thus, your hypothesis must be ‘directional,’ i.e., it is what gives direction – focus – to the research. In other words, it must be your ‘best bet’ as to how to attain the objective, which must be to either fill the gap or meet the need (the latter for a ‘hybrid’ application). A good hypothesis must be objectively testable and cannot project a predetermined conclusion. And, very importantly, it should be crafted to have readily identifiable ‘parts’ that set up the specific aims, which will test those parts. Now, write a single bullet that conveys what your central hypothesis is.

How formulated. Write additional bullets that tell your reviewers how the central hypothesis was formulated – how you focused on this starting point from among all others as your ‘best bet.’ Your own preliminary data are the most important basis for formulating the hypothesis. That bullet should be first, therefore. Published work of others, if any, that guided formulation should be highlighted in additional bullets.

Rationale. The purpose of this component is to convey to reviewers why you want to undertake the proposed research. In most cases, you want to because doing so will yield new knowledge that will advance the field. Thus, your rationale should tell reviewers what will become possible after the research is completed that is not possible now. It must pass the litmus test! The gap / unmet need delineated in the first paragraph represents a problem because its continued existence blocks the next step in the field from being taken. Once the proposed research has been completed you will be able to take the blocked step – that is why you want to do the research. You get few opportunities in a grant application to excite reviewers. This is one of them. Crevly written, the rationale – why you want to do the research – can truly be exciting because it conveys that the expected outcomes will clearly advance the field vertically. Now, write a bullet that delivers that message.
At the conclusion of the second paragraph, the reviewers should understand: 1) what the continuum of research is that you are following; 2) what the next step along that continuum is; 3) why you want to take that next step; and 4) what your 'best bet' is regarding how to take that next step.

**Specific Aims 'Paragraph'**

As the name implies, this component conveys specifics about the research. The approach to creating the aims differs for hypothesis- and need-driven proposals.

*Hypothesis-Driven Applications.* Although there are disciplinary exceptions, as noted above, most reviewers of NIH grant proposals demand hypothesis-driven research. The aims are probably the most difficult components of the section to write. They must clearly grow out of your central hypothesis because their purpose is to objectively test its parts. Thus, with respect to linkage, there must be complete concordance between the aims and the parts of your central hypothesis. The aims need to be brief, informative, attention-getting 'headlines' that will attract a reviewer's attention and whet his/her interest. Each aim should convey why that part of the research is being proposed, not what will be done. Under no circumstance in a hypothesis-driven application should your aims be descriptive, i.e., project what is best referred to as 'look-to-see' research (I will do something, look to see what happens, and then describe whatever that outcome is – the antithesis of hypothesis-driven research.). For this reason you should avoid using words in your aims that connotate a descriptive approach, such as (but not limited to) compare, correlate, describe, catalog, or investigate. Neither should they be statements regarding 'what' will be done, i.e., the process that will be involved should not be emphasized. What you want them to project is 'why' — conceptually, why is this part of the research necessary? They should deliberately be broad and open-ended, but then focused by a working hypothesis.

The aim must be written globally to ensure that it encompasses any alternative to which you might have to turn in the unlikely event that the primary hypothesis tests invalid. 'Identify the mechanism that is responsible for macrophage activation.' is an example of an aim that is written at a broad, open-ended level. If the purpose of the aim is to "identify the mechanism," then the working hypothesis must be the 'best bet' as to what the mechanism is. It might read something like, 'The working hypothesis for this aim is that the mechanism entails binding of IFN-γ to its receptor, which activates STAT-1α and then, in concert with other transcription factors, up-regulates the expression of genes that result in activation. It is based on preliminary data that will be presented later (see Preliminary Studies under Aim #1, Research Strategy-Approach).'

By narrowing the focus to a specific entity with the working hypothesis, the applicant avoids criticism that the aim is unfocused and open-ended. Later in the application, under Potential Problems and Alternative Strategies (Research Strategy-Approach), the fall-back position — a viable alternative to which the applicant would turn in the event of hypothesis invalidity — will be offered. That assures the reviewers that, regardless of how the primary hypothesis tests, the applicant will still land on his/her feet and attain the application's overall objective. The trap of writing an aim like, 'Determine whether STAT-1α initiates macrophage activation.' is avoided. With such an aim, if it is STAT-1α, there's no problem. However, if it's not — and the aim really should be interpreted to read 'Determine whether or not STAT-1α initiates macrophage activation.,' the applicant (and the reviewer) is left with nothing other than a negative outcome, which is rarely enough to satisfy NIH reviewers.
The example below will illustrate further how to avoid the trap of writing descriptive aims. It should clarify why well written aims in hypothesis-driven proposals are most often an answer to the question, "Why am I proposing this part of the research?"

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**CONVERSION OF DESCRIPTIVE SPECIFIC AIMS (‘WHAT’ WILL BE DONE) TO ONES THAT ARE CONCEPTUAL (‘WHY’ THE WORK IS PROPOSED)**

1. **Determine the genotypic allele frequencies of the AAA and BBB genes in a closed, unselected, drug-naïve population.**

2. **Determine the genotypic allele frequencies of the AAA and BBB genes in a population that has been highly selected by frequent long-term drug treatment.**

3. **Select for alleles that convey resistance by comparing gene expression in the naïve population with the frequently treated population.**

Note that each of the above is a detailed description of ‘what’ will be done. The first two set up different populations – untreated and treated. The third aim seeks to determine what the difference is by comparing the two populations. Were we to ask the investigator why s/he wants to make the comparison, s/he would respond without hesitation, ‘To identify the alleles that most likely cause resistance.’ Thus, all three of the aims, above, could better be combined into a single, ‘why’ aim, such as:

1. **Identify candidate resistance alleles.**

That aim, if left uncomplemented, would be criticized as unfocused and open ended. Thus, a working hypothesis is required to bring focus – your ‘best bet,’ based on preliminary studies to date, as to what the resistance alleles are most likely to be. This is one reason why preliminary studies are so important at the R01 level: the data generated allow formulation of a focusing hypothesis for each aim. It isn’t necessary that the research proposed be already completed, as some would contend. However, enough has to have been done to allow the applicant to formulate a strong working hypothesis that provides direction – focus – for the proposed studies. The research design presented later would be structured to test that working hypothesis and would offer an alternative to which the applicant would turn in the unlikely event that the working hypothesis tests invalid. We want to re-emphasize again here that the combination of the broad aim, focused by a working hypothesis, which is then complemented later by an ‘escape-hatch’ alternative, is a powerful way of assuring reviewers that, regardless of how the original working hypothesis tests, the objective of the aim will be attained.

The aims you present must test all of the parts of your central hypothesis, nothing more and nothing less. Ideally, the reviewer should be able to see easily that each aim links to a specific part of your central hypothesis. If an aim isn’t clearly related to testing some aspect of the central hypothesis, it is likely to be rejected by reviewers as superfluous.

No more than three-to-four aims should be offered; the page limitation on the Research Strategy section precludes developing any more aims than four substantively. Each aim should be of
approximately equal weight, i.e., equal in importance to the other aims and projects a similar amount of work. The first aim must flow logically into the second, and so on; however, none of them can be absolutely dependent on an expected outcome of an earlier aim. Why? Because, should the critical aim either not be achieved or yield an unexpected outcome the subsequent, dependent aim(s) could not be pursued as proposed. For example, consider an application on gene regulation that has as its first specific aim, 'Clone the promoter [regulator] for gene X.' Examination of the subsequent aims reveals that all of them are dependent on availability of the promoter. Such an application would be fundamentally and fatally flawed because, if the promoter couldn’t be cloned, the rest of the work couldn’t be done. The applicant should have realized that fact and cloned the promoter as part of his/her preliminary studies. Alternatively, an R21 could have been written to accomplish that part of the study, which would remove the risk that the promoter couldn’t be cloned. In other words, it would be a stepping stone to a later R01 that would support the aims that are dependent on having the cloned promoter.

Using these tips, write bullets that summarize your aims. Follow each with another bullet that projects the working hypothesis for that aim. Make sure that the number of aims is concordant with the number of parts that are found in your central hypothesis.

Need-Driven Applications. The aims in a pure need-driven application are 180° different, compared to those in a hypothesis-driven proposal. In other words, they will be – and it is OK for them to be – descriptive. The aims here are the tasks that must be undertaken, in the order that they must be undertaken, to attain the objective. Thus, in contrast to a hypothesis-driven application, it is acceptable in a need-driven proposal for the aims to describe what will be done. The paragraph that is subordinate to a need-driven aim should summarize the approach that will be used to accomplish that particular task.

‘Payoff’ Paragraph

TIP: The purpose of this last paragraph is to inform reviewers what they can expect for a return if they vote to recommend funding of your application. This paragraph is particularly important in helping to develop advocacy for your proposal among the majority of reviewers who will not, in all likelihood, have read your complete application. It is a paragraph in which a great deal of effort should be invested, therefore.

Expected Outcomes. These are the expected products of the research. In other words, these represent the ‘payoff’ that reviewers can expect to realize if they vote to recommend funding of your application. We want you to include them here, together, rather than individually under the related aims, because reviewers can more easily see that the outcomes collectively attain the overall objective of the proposal. There should be at least one important expected outcome for each of your aims. There must be clear linkage back to the specific aims that produced them.

Now, write bullets that tell your reviewers what they can expect from your research as outcomes. As noted earlier, you need at least one important outcome for each aim.

Generality Regarding Positive Impact. This final part of the Specific Aims section must summarize the general impact of the expected outcomes. We recommend that you deliberately write a bullet that is a generality that segues into details that will be presented in the next, Significance and Innovation subsections of the Research Strategy section. In most cases, your
positive-impact bullet should make clear that, collectively, the outcomes will advance your field vertically, as well as contribute to the mission of the NIH Institute/Center that you are targeting.

After completing your bullet outline, print it and consider carefully how all of the elements relate to each other. Do they relate and link to each other logically and well? Remember that we called attention earlier to how important the phrasing of the gap in the knowledge base is, because that statement sets up everything downstream with respect to the flow of logic. As is shown in the figure, below, if you are proposing hypothesis-driven research, how you present the gap automatically sets up the objective, because the objective must be to fill the gap. When you write your objective, you set up your central hypothesis, because that is what must be objectively tested in order to attain the objective. When you write your central hypothesis, it ordains what the aims will be, because they are the means that will be used to test each part of your central hypothesis. The aims, in turn, dictate what the expected outcomes will be, and those, in turn must collectively result in attainment of the objective, thereby filling the gap. If you

**LINEAR PROGRESSION OF LOGIC FOR A STRONG SPECIFIC AIMS SECTION**

![Diagram of Logic Progression]

are proposing a project that is driven purely by a statement of need, the only differences in the figure, above, would be that “GAP” would become “NEED” and the CENTRAL HYPOTHESIS would be eliminated. Otherwise, the progression of logic would be the same. Also, make sure that your long-term goal encompasses the gap in the knowledge base that you plan to fill. Check to be sure that the rationale passes the test of telling the reviewer what will become possible after the project is completed that is not possible now. In other words, it should make clear that, once the research has been done, it will be possible to take the vertical step in the field that is now blocked.

Spend as much time as you need to refine and perfect your bullets, making sure that they are as well crafted as they can be. The better that these work in creating the all-important flow of logic, the easier it will be to write this section, which is the subject of the next chapter.
DEVELOPMENTAL STEPS FOR CHAPTER SEVEN:

1. Appreciate that there are two audiences for whom you are writing: the minority audience (primary, secondary and tertiary reviewers) and the majority audience (those reviewers who, in all likelihood, will not have read your application prior to the time that it comes up for consideration at the review-panel meeting).

2. Realize that this section of the application is written for the second, majority audience.

3. Understand the strategy that underlies this section, which is to provide a conceptual framework that will allow your representatives at the meeting (the primary, secondary and tertiary reviewers) to hang details on it, thereby helping reviewers who are relatively ignorant of your application to reach a point where they can cast an informed vote.

4. Understand the purpose of each component that makes up the Specific Aims section and how each must be written to meet its purpose.

5. Appreciate how the components must be linked to one another in order to create a linear progression of logic.

6. Download the interactive template from our Web site (www.grantcentral.com/downloads.html) that will facilitate development of your bullet outline.

7. Create a bullet outline that includes each of the ten components that comprise the Specific Aims section.

8. After leaving the outline alone for a day or so, return to it to determine whether it can be improved. Continue to do so until you, as the PI, cannot make it any better.

9. Seek constructive criticism of the bullet outline from the Key Persons and Other Significant Contributors who are on your research team.

10. Continue to work on the outline until each component meets its purpose, each is linked to the others in the way(s) that it should be, and the progression of logic is linear. When you reach that point, you are ready to proceed to chapter 8.
CHAPTER 8

WRITING THE SPECIFIC AIDS SECTION

Instructions for PHS 398 Research Plan Component / Specific Aims Section:
"State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved. List succinctly the specific objectives of the research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology." You are limited to one page.

In the previous chapter, we introduced you to the purpose of each of the ten components of the Specific Aims section and showed you how to create a bullet outline using them. In this chapter, we will guide you through the process of expanding your bullets, which is the initial step in formulating the first draft of this section. As can be seen from the instructions in the text box, above, this section is limited to one page. Succinct writing will be required, therefore, if you expect to get everything needed into the allowed space. Only the most important, 'linchpin' references should be cited here. Set up the page using some of the same space-saving approaches that are described in chapter 5 for the one-page Introduction: use Georgia, Arial or Helvetica as your typeface at 11 points, auto-hyphenate (do not hyphenate manually), use full justification and single space after each sentence. We recommend that you start with one-inch margins, because that is a more reviewer-friendly approach than using the minimum of 0.5 inch. For the same reason, open a line after each paragraph. If clever editing of the first draft still leaves you over the one-page limit, then and only then, go to 0.5-inch margins. The last thing that you should give up, in our opinion, is the open line after paragraphs. You don't want your application to look like pages from a telephone directory! The formatting for this page should be what is used for the other documents that will collectively constitute your Research Plan.

In terms of writing the Research Plan, we recommend that nothing be left to the interpretation of reviewers. If you allow them to interpret what you have written, they may not make the desired interpretation or – worse – they may make the wrong interpretation. To avoid this problem we recommend that you help reviewers make the connections that you want them to make. The approach we have developed allows you to ‘tell’ reviewers exactly why information has been included without running the risk of being seen as pedantic or condescending while doing so. The approach entails ‘labeling’ of the components that make up the section in such a way that there can be no question as to why you have included the information. Labeling of key sentences also helps to lead reviewers through what you have written. (A well-written proposal leads reviewers without them knowing that they are being led.) The approach makes comprehension effortless, because no work is needed to appreciate why material has been included. As you expand your bullets we will recommend where and how to use such 'labels.'

We also recommend that you increase reviewer friendliness by highlighting key words that identify components you know reviewers will need to find in order to review your proposal. We will tell you which words to highlight later in this chapter. Judicious use of subtle highlighting – we
recommend italics – is the key; overuse causes such highlighting to lose its effect and can even become an aggravation to reviewers. Of the four allowed typefaces, italicized *single* words or *several* words aren’t that noticeable with either Arial (which is the typeface for this *Workbook*) or Helvetica. We recommend, therefore, that you also underline with these typefaces to make *single* words or *several* words stand out, as is illustrated in this sentence. More than several words, i.e., phrases or entire sentences, are sufficiently prominent in italics that you don’t have to underline. To do so would be overuse of highlighting – to the point that it would be an aggravating distraction. If you are using Georgia, which is what this typeface is, italicized *single* or *several* words stand out adequately and underlining is not needed. The same is true for *Palatino Linotype*, which is what this typeface is. We do not recommend the latter typeface because of the extra room it requires as a result of wider line spacing (evident here) – unless, of course, you change the default setting for line spacing.

**EXPANSION OF YOUR BULLET OUTLINE INTO SENTENCES**

Once you are satisfied with your outline, the next step is to expand it into your first draft of the *Specific Aims* section.

*Introductory Paragraph*

**Opening Sentence.** Expand the bullet that you wrote for your opening sentence. Make sure that it reads well and flows easily into the presentation of what is currently known. Make sure that the sentence is arresting and, as such, will immediately attract the reviewer’s interest and attention.

**Current Knowledge.** Working from the bullets that reflect current knowledge, write two-to-four complete sentences that convey what is known about your subject area. The first sentence should be labeled to signal this component’s purpose. For example, “It is well known that ...” or “It has long been appreciated that ...”. The series of two-to-four sentences should narrow reviewers’ focus from the most important older current knowledge to the edge of the field as it exists today. Cite only the most important references in doing so.

**Gap in the Knowledge Base/Unmet Need.** Next, expand the bullet that you wrote to delineate the gap in the knowledge base or the unmet need that will drive the application. Label this sentence by beginning with something like, ‘What is not known is ...’ or ‘Thus there is an *urgent [or critical] need* for ...’. Note that *urgent need* is highlighted in italics. If you are offering a statement of need, next, expand the bullets that provide objective evidence for existence of the need. If publications of other investigators are used to support existence of the need, cite that work.

*What, Why, Who Paragraph*

TIP: The first 3 components in this paragraph create a focusing progression, which the reviewer must perceive. To help ensure that s/he makes that connection, the long-term goal, objective and central hypothesis should be presented without interposed explanatory information. These three components should be juxtaposed, so that there is a seamless flow of logic from the broadest (the long-term goal) to the narrowest focus (the central hypothesis).
**Long-Term Goal.** Expand the bullet for your long-term research goal. It should clearly encompass the gap or unmet need that was delineated in the first paragraph. Do so by completing the following: 'Our [My] long-term goal is to ....' Note that the words 'long-term goal' have been italicized and underlined to make them easier for reviewers to find. Note, also, that there is a hyphen between "long" and "term." It is required because those two words created a compound adjective that modifies "goal."

**Overall Objective.** Now, expand the bullet you wrote for the overall objective into a single sentence that conveys what you want to produce with this research project. Make sure that what you write here links back to the gap in the knowledge base or unmet need that you presented in the first paragraph; the objective of any grant application must be to either fill that gap or meet that need. Label this sentence by beginning it with something like, 'The overall objective of this application, which is the next step toward attainment of our long-term goal, is to .......' Note use of the phrase, "which is the next step toward attainment of our long-term goal." Including something like it assures that reviewers will recognize that this application represents the next step along the continuum of research that is projected by your long-term goal. The words "long-term goal" should not be underlined and italicized when they are used the second time. When you have completed this sentence, make certain that it links back to the gap/unmet need component and that it relates clearly to your long-term goal.

**Central Hypothesis and How Formulated.** This component will not be included if your proposal is purely need driven. It will be included if you are writing either a hypothesis-driven application or a 'hybrid' — one that is driven both by a statement of need and by a central hypothesis. The expanded bullet should convey your 'best bet' as to how the objective can be attained. Ideally, it should have readily identifiable parts that will be used to set up the aims. Make sure that you label this component so that it can be found easily by reviewers. For example, 'Our central hypothesis is that ....' Be certain that what you have proposed is objectively testable.

Now, expand the bullet(s) that you wrote to describe how your hypothesis was formulated, i.e., why it has been chosen as your 'best bet.' If the work of others is used in addition to your own preliminary data to support formulation of your central hypothesis, the relevant publications should be cited.

**Rationale.** Next, expand the bullet that summarizes your rationale. 'Label' this component so that it is readily recognizable, e.g., 'The rationale that underlies the proposed research is that ....' Remember that the litmus test is to ask yourself, 'Does this tell the reviewer what will become possible after I have completed the research that is, not possible now?' It should convey that you will be able to take the next vertical step in the field that is currently blocked by existence of the gap/need.

**Specific Aims ‘Paragraph’**

Begin paragraph three with a sentence something like, 'We plan to objectively test our central hypothesis and, thereby, attain the objective of this application by pursuing the following specific aims: ' Next, expand the bullets for your specific aims and the working hypothesis for each. After doing so, make certain that each clearly links back to a part of your central hypothesis. If you find that doesn't link back, either eliminate it or create a part in the hypothesis that will support its inclusion.

Because the aims are so important, we recommend that you set each off as a separate 'headline,' and that it and its subordinate paragraph be indented one tab. For the same reason, we
recommend that you present them in bolded italics. Nothing in the subordinate paragraphs should be bolded or otherwise highlighted, except for 'working hypothesis.'

**Payoff Paragraph**

**Expected Outcomes.** Continue by expanding the bullets that present your expected outcomes. Label the opening sentence with something like, 'It is anticipated that these aims will yield the following expected outcomes. First, ___________. Second, ___________.' Continue to develop this component using the same approach for each expected outcome.

**Generality Regarding Positive Impact.** Conclude the fourth paragraph and your Specific Aims section by expanding the bullet that you wrote to generalize about positive impact. Make sure that what you write sets up an easy transition into the next section, Research Strategy, which will begin with the Significance and Innovation subsections. In those two subsections, you will provide specific detail that validates the general statement about positive impact that you write here. This sentence should also be used to segue into the next section. To accomplish these things, we recommend that you begin and end the sentence with something like, 'These outcomes are expected to have an important positive impact because ___________, as will now be detailed in the next section.'

**FINALIZING YOUR SPECIFIC AIMS SECTION**

As the next step, revise and refine the sentences that you have written until they flow well. Add material, if needed, to link the sentences appropriately and blend them into readable prose. Edit until you have no more than a single page. Convert to a PDF file for upload into the PHS 398 Research Plan component at the site indicated, below.
EXAMPLE OF A HYPOTHESIS-DRIVEN SPECIFIC AIMS SECTION

Interferon gamma (IFN-γ) is central to the maintenance of homeostasis, as well as to host defense against a variety of pathogenic microorganisms and tumor cells. In addition, it can have an active role in the pathogenesis of a number of diseases. IFN-γ mediates all of these effects through a single binding protein (the α subunit of the IFN-γ-receptor complex), which is present on the surfaces of all normal nucleated cell types (Granger & Coe, 1994). While it is known that the binding protein initiates signal transduction (Yu, 2000), and it is understood mechanistically how it does so (Griffin et al., 2004; Campbell, 2008), what is not clear is how this critically important protein is produced. Lack of such knowledge is an important problem, because, without it, acquiring the ability to modulate the number of receptors on cells pharmacologically is highly unlikely.

Our long-term goal is to understand how the receptor for IFN-γ can be manipulated for preventive and therapeutic purposes. The objective here, which is our next step in pursuit of that goal, is to determine how production of the receptor’s α subunit is regulated transcriptionally. Our central hypothesis is that both constitutive and stimulated regulation are required through different sets of cis-acting response elements in the gene's promoter. Our hypothesis has been formulated on the basis of our own preliminary data produced using the promoter that we recently cloned (Galaway et al., 2008; see Justification and Feasibility sub-subsection under Research Strategy-Approach). In addition, the work of Adams & Seagram (2008) is supportive of the hypothesis. The rationale for the proposed research is that, once it is known how transcription of the α chain's gene is regulated, production of the subunit can likely be manipulated either up or down pharmacologically, resulting in new and innovative approaches to the prevention and treatment of a variety of diseases.

We plan to test our central hypothesis and, thereby, accomplish the objective of this application by pursuing the following two specific aims:

1. Identify the DNA response elements that regulate constitutive transcription of the subunit's gene.
   Based on the preliminary data referred to above, our working hypothesis is that one or more Sp1 sites are critical to the regulation of constitutive transcription.

2. Determine how stimulated transcription is up-regulated by different stimuli.
   We postulate, again on the basis of our preliminary data, that cyclic AMP response elements (e.g., CRE and AP-2) regulate stimulated transcription of the subunit's gene, regardless of how stimulated transcription is activated.

With respect to expected outcomes, the work proposed in aims 1 and 2 is expected to identify the full complement of response elements and the cognate transcription factors that are responsible for constitutive and stimulated transcription of the α subunit's gene. Such results are expected to have an important positive impact, because the identified components are highly likely to provide new targets for preventive and therapeutic interventions in addition to fundamentally advancing the fields of receptor biology and immunotherapy, as will now be detailed in the next section.

The 'hybrid' approach would be similar, except that the first paragraph would contain a statement of need and a summary of objective evidence in support of its existence. The central hypothesis would be the applicant's best bet as to how to meet the need. Research proposals driven purely by need rarely succeed at NIH, which is why we do not recommend them for that purpose. Need-driven proposals to NIH are usually for things like equipment.
DEVELOPMENTAL STEPS FOR CHAPTER EIGHT:

1. Set up the page for the Specific Aims section to maximize space, with two exceptions: (i) open a line after each paragraph and use 1-inch margins, left and right, if at all possible.
2. Expand the bullets for your Specific Aims section into complete sentences.
3. ‘Label’ them in such a way that reviewers will know precisely why the related information has been included.
4. Cite only key references in this section.
5. Highlight key words using either underlined italics (Arial or Helvetica typefaces) or italics alone (Georgia).
6. Avoid the use of Palatino Linotype because of the extra space it requires.
7. Present the ten components that make up the Specific Aims section in four separate paragraphs.
8. Make your specific aims and the related subordinate paragraphs stand out by indenting them 1 tab and presenting the aims, themselves, in bolded italics.
9. Edit and refine the section until it reads well and occupies no more than 1 page.
10. Convert the Specific Aims section into a PDF file.
11. Upload the Specific Aims section into the PHS 398 Research Plan component.