OVERVIEW: PART TWO

THE TEMPLATE OR MASTER PLAN FOR YOUR PROPOSAL

Once you have completed all of the activities that are summarized in Part One, you will be positioned well to begin development of the grant application, itself. The process should begin with development of the all-important Specific Aims section (section A of the Research Plan) and the significance subsection of the Background and Significance section (section B). These parts will introduce reviewers to everything that is important and exciting about your proposal.

Chapter seven, "Specific Aims Section: Conceptual Overview & Creating a Bullet Outline," addresses the conceptual approach that underlies formulation of the Specific Aims section, provides the specific purpose for each of the thirteen components that collectively comprise this section, and will help you to develop the bullet outline that will be the foundation from which this section is developed.

Chapter eight, "Writing the Specific Aims Section, will take you, step-by-step, through the development of a first draft of your Specific Aims section. This will begin with expansion of the bullet outline, which will then be refined to provide an integrated overview of everything that is important about your proposal.

Chapter nine, "Significance Subsection of the Background and Significance Section," will focus on development of the paragraph that is arguably the most important one in the entire grant application. You will be guided through a three-part approach to writing this part of your proposal.

These are the parts of your application that will provide the 'blueprint' – the template or master plan – for development of the rest of your Research Plan. If these sections are written well, the rest of the Research Plan becomes relatively easy to write. Thus, we encourage you to make the investment in them that will maximize the positive impact that they can have on both the preparation and review of your application.
CHAPTER 7

SPECIFIC AIMS SECTION: CONCEPTUAL OVERVIEW & CREATING A BULLET OUTLINE

TIP: Strategically, the Specific Aims section should be written to create a 'partnership' with the reviewers who will represent you at the review-panel meeting. You provide a conceptual framework on which they can 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 that is 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 additional role: leading the majority of reviewers decide to vote a fundable priority score for your proposal. This group of reviewers — those who were not assigned your application — 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 be doing two things at the same time: listening to your spokespersons — the primary, secondary and tertiary reviewers — as they state your case while, at the same time, they will be reading parts of your proposal — the Specific Aims section and the Project Summary/Abstract (i.e., Description) — as a means of either corroborating or refuting what they are hearing. If you have tried to read and comprehend something that is replete with detail at the same time that someone is talking to you, you know that it is impossible; either understanding of what you are reading or what you are hearing suffers. This fact informs our approach to writing the Specific Aims section. It must be written to help the majority of reviewers 'catch up' so that they can cast an informed vote at the end of your 15-to-20 minute window of opportunity at the review-panel meeting.

TIP: The secret to optimizing the impact of this section is writing each component to meet its purpose, which requires in-depth understanding of what each is meant to accomplish.

In addition to each component having a specific purpose, each has to be linked to others it relates to in such a way that a linear progression of logic is created. The flow of logic must be compelling — so compelling that it leads reviewers to a position of advocacy without them knowing that they are being led. An additional aid in leading reviewers is 'labeling' of each component in such a way that there can be no question in the reviewer's mind as to why the information has been included (see chapter 8). The latter strategy increases the reviewer friendliness of your proposal by reducing the amount of work that reviewers have to do as they read what you have written.
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. In our opinion, outlining is the key to writing a powerful Specific Aims section. 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. We will help you to create your bullet outline by asking you to make a series of responses in a set order. Your responses will become the bullets in your outline, which you should create in a separate computer file. Once you are satisfied with the bullets you have written and how they link to each other, we will ask 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.

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 the others when you create your bullets. We recommend that they be presented in four paragraphs:

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 to 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, your bullet for this component should not focus on the 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 that this opening sentence does not state information that would be intrinsically obvious to the review group that you are targeting. Now, write a bullet that conveys the medical importance of your area of interest.

Current Knowledge. Your assigned reviewers will likely be the members of the panel who are most qualified to review the topic you are presenting. If not experts, they will be close to having that level of expertise. The remainder of the panel will be less knowledgeable. This component has the purpose of getting everyone at the review-panel table up to speed with respect to what is currently known about the topic of your proposal. It is not meant to be a comprehensive overview. Rather, it should consist of a few cleverly written sentences that are designed to bring reviewers from the most important, older knowledge to the edge of the field as it exists today. This component has the additional purpose of setting the scene for 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 unmet need that will drive your application. This component must be a clear and logical extension of the ‘current knowledge’ component by reflecting 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 essential information that is missing and, therefore, holding back your 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 of 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 substitute this component for the gap in the knowledge base described in the paragraph, above. Write a single bullet that denotes the need. For example, it might reflect the need for renovation of space (the kind of statement that would drive a construction grant) or purchase of an expensive piece of equipment (equipment grant). Follow 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).

**The Gap / Unmet Need as a Problem.** The purpose of this component is to convey that the gap / unmet need represents an important problem. It is a problem because its existence blocks vertical advancement of the field. Write a bullet that conveys what the vertical step is that is being blocked.

> 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**

**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. Create a bullet that is broad enough to encompass the gap or unmet need that you have delineated in the first paragraph. Also, it must be realistic, i.e., something that is clearly achievable over a 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.

**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. It must be clear that your objective is the next logical step along the continuum of research that is projected by your long-term goal – that linkage must exist between the two. Write a single bullet that describes your objective. Be certain that your objective has a defined end point, i.e., that it is not indeterminate in focus. For example, “to study”
something would not be an appropriate goal; how would you know when you had “studied” it enough? In addition, such an objective puts too much emphasis on process and not enough on the product of the research.

**Central Hypothesis and How Formulated.**

*The central hypothesis* must link to the objective, because the latter will be accomplished by testing the former. The purpose of the hypothesis is to provide focus for your grant application. Thus, your hypothesis must be ‘directional,’ i.e., it must give direction to the research. It must be your ‘best bet’ as to how to accomplish your objective. Write a single bullet that conveys what your central hypothesis is. A good hypothesis must be objectively testable and cannot project a predetermined conclusion. It should also have ‘parts’ that serve to set up the specific aims, which will be the means of testing it.

*How formulated.* Write additional bullets that tell your reviewers how the central hypothesis was formulated – how you focused on this starting point from among others as your ‘best bet.’ Your own preliminary data are the strongest basis for formulating the hypothesis. That bullet should be the first of these. Published work of others, if any, should be highlighted in additional bullets and presented as complementary to your own preliminary results.

**Rationale.** The purpose of this component is to convey to reviewers why you want to undertake the proposed research. In most cases, research is performed because it 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 that litmus test! This component must link back to the problem that you framed at the end of the first paragraph. There, you posed the gap / unmet need as 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. Cleverly 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, without setting up redundancy with the ‘gap as a problem’ component, i.e., without using the exact same words, write a bullet that delivers that message.

**Well-Prepared.** As you know, two of the five mandatory criteria used to evaluate NIH grant applications are “Investigators” and the research “Environment.” You should end the second paragraph by conveying why you, your colleagues, and your research environment distinguish your application from one that could be written by investigators elsewhere who are equally qualified on the basis of expertise alone. Thus, the purpose of this component is to tell reviewers why the research team you have assembled is better prepared to perform the proposed research. First and foremost among the things that distinguish your research team are your preliminary data, which both allow you to formulate a focusing central hypothesis and support the feasibility of your aims. Your competitors, though they may be equally qualified on the basis of expertise, cannot bring such direction to the research. Begin this series of bullets, therefore, with one that summarizes why your preliminary data are supportive of the project. Continue with additional, complementary bullets, e.g., such things as the combined expertise of your research team (e.g., basic and clinical researchers working together to provide the entire spectrum of expertise necessary to obtain a definitive outcome) or extensive experience with a demanding model. Conclude with a bullet or two about your research environment and why it is particularly supportive of the kinds of research that will be performed. This may be because of essential core facilities, provision of skilled technical support by the institution, or because you
are surrounded by colleagues who have complementary research interests (i.e., other investigators with whom to discuss and evaluate your data). Be specific with all of your bullets here! Avoid the temptation of indulging in clichés (e.g., state-of-the-art equipment) and empty generalities (e.g., Dr. X is an outstanding molecular biologist). Write as many bullets as you can, but make certain that they reflect things that are truly distinguishing.

At the conclusion of the second paragraph, the reviewers should understand:
1) in general, what you plan to do; 2) that what you are proposing will fill the gap in the knowledge base that you have delineated; 3) that your group is well prepared to undertake the proposed work, compared to others; and 4) that the work will be done in an environment that is conducive to its success.

**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, 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 in a hypothesis-driven proposal is to test all aspects of the hypothesis. Thus, with respect to linkage, there must be complete concordance between the aims and the parts of your central hypothesis. They 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 connote 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 do I want to do this part of the research? They should deliberately be broad and open-ended, but then focused by a working hypothesis. ‘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, based on preliminary data that will be presented later (see Preliminary Studies), 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.’ By narrowing the focus to a specific entity with the working hypothesis, the applicant avoids criticism that the aim is unfocused and open-ended. The trap of writing an aim like, ‘Determine whether STAT-1α initiates macrophage activation.’ has also been avoided. With such an aim, if it is STAT-1α, the applicant has accomplished something important; however, if it’s not, the applicant (and the reviewer) is left with nothing other than a negative outcome, which is
rarely enough to satisfy NIH reviewers. This approach will minimize the likelihood that your aims will be seen either as descriptive or as an ‘unfocused fishing expedition.’

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.”

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

‘WHAT’ (will be done?):

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

2. **Determine genotypic allele frequencies of the AAA and BBB genes in a population of helminths that have been highly selected by frequent long-term treatment with avermectin / milbemycin.**

3. **In parallel with research objective #2, select for alleles that convey resistance by frequent treatment of a naïve population of helminths with avermectin/milbemycin.**

4. **Determine the genetic basis for resistance to avermectin / milbemycin in helminths.**

Note that each of the above is a detailed description of ‘what’ will be done. The first three set up different populations of helminths. When we ask ‘why’ the investigator wants to create these populations the answer is that the outcomes of subsequent comparisons are expected to allow him/her to identify alleles that are candidates for conferring resistance. The more appropriate aim, which combines the first three from above, is the conceptual, ‘why’ aim that is presented below as #1. The same approach can be used to correct aim #4, above: **why** does the investigator want to do that? Because s/he wants to identify which of the candidate alleles is causally responsible for the development of resistance. Writing aim #2 that way much more clearly conveys ‘why’ the research is proposed.

‘WHY’ (is it being done?):

1. **Identify candidate resistance alleles.**

2. **Establish which candidate alleles are causally responsible for avermectin / milbemycin resistance.**

While these are good examples of conceptual, ‘why’ aims, as noted above, they would be fundamentally flawed if left to stand alone. **Why?** Because they are open-ended and completely lacking in focus. Thus, each aim should be focused by its own working hypothesis, which the applicant would present in a paragraph that is subordinate to the related aim. 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 complete already, 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. Thus, for the first 'why' aim, above, the applicant would have had to have done enough preliminary work to narrow the focus from all genes to a select few. A brief sentence (or two) that describes how the hypothesis will be tested should also be included. For example:

1. **Identify candidate resistance alleles.**

The working hypothesis for this aim, based on data that will be presented under Preliminary Studies, is that specific alleles of the AAA and BBB genes explain the development of resistance. The approach used to test this hypothesis will be comparison of genotypic allele frequencies in AM-naïve and AM-resistant helminths.

Note that the broad aim 'headline' states unequivocally that candidate resistance alleles will be identified, and that the subordinate paragraph focuses the search on a specific pair of genes, based on the investigator's own preliminary data. Later, when studies under the aim are detailed in the Research Design and Methods section, the investigator would present alternatives to which s/he would turn in the unlikely event that the working hypothesis would prove to be invalid. In the example above, investigation of alternative genes would be proposed, along with a brief explanation as to why they are the next most likely possibilities. The combination of the broad aim, focused by a working hypothesis, which is then complemented later by 'escape-hatch' alternatives, is a powerful way of assuring reviewers that, regardless of how the original working hypothesis test, the objective of the aim will be accomplished.

As noted in the paragraph that preceded the example, the aims you present must fully test your central hypothesis, nothing more and nothing less. Ideally, each aim should be seen as testing 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 the reviewers as superfluous.

Two-to-five aims are needed (we recommend two or three as ideal). The page limitation for the Research Plan precludes developing any more aims than five substantively. Each aim should be of approximately equal weight, i.e., equal in importance to the other aims and projects an approximately equal amount of work. The first aim must flow logically into the second, and so on; however, no one 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 isn't cloned, the rest of the work can't be done. The applicant should have realized that fact and cloned the promoter as part of his/her preliminary studies. Alternatively, an R03 could have been written to accomplish that part of the study as a stepping stone to a later R01 that would definitively develop the aims that are dependent on having cloned the promoter.

Using these tips, write bullets that summarize your aims. Follow each with another bullet that summarizes 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 need-driven application set forth tasks that must be undertaken, in the order that they must be undertaken, to accomplish the objective. Thus, in contrast to a hypothesis-driven application, it is acceptable in a need-driven proposal to
offer tasks that 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 among the majority of reviewers who have not read your complete application. It is a paragraph in which a great deal of effort should be invested, therefore.

**Innovation.** The purpose of the first component in the fourth paragraph is to tell reviewers why the proposed research is innovative. “Innovation” is one of the five mandatory NIH review criteria. It is the most subjective of the five. Because of this, reviewers appreciate knowing why the applicant thinks that the proposed research is innovative. Usually, it is because the proposed approach differs from that which has been taken by others. You may have created a new technology, for example, that will allow you to address problems that have thwarted others. You may be challenging dogma of your field or proposing something that will make — not in a cliché sense — a real paradigm shift. It is important to appreciate, however, that your project does not have to be innovative to be fundable; not all scientifically meritorious research is inherently innovative. Thus, this component is optional. If you are proposing valuable, must-be-done-to-take-the-next-step kind of research — but it is not inherently innovative, you will damage your credibility if you contrive something related to this mandatory review criterion. In such a case you should not try to punch this ‘button,’ realizing that you don’t have to because it is an optional criterion.

Write bullets here, providing that you can do so credibly, that convey one or more reasons why your research/approach is innovative.

**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 they collectively validate your central hypothesis (that is what you expect) and, by doing so, 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 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 paragraph. 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 or 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**

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GAP
↓↓↑
OBJECTIVE ←
CENTRAL HYPOTHESIS ↓
SPECIFIC AIMS ↓
EXPECTED OUTCOMES
```

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 description of the gap as a problem, at the end of the first paragraph, links well with the rationale. The former should describe the gap as preventing an important step in the field from being taken, and the rationale should make clear that, once the research has been done, it will become possible to take that step. 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. If these work, the writing of this section, which is the subject of the next chapter, then becomes relatively easy.

**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 have not read your application prior to the time that it comes up for review 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 (primary, secondary and tertiary reviewers) to hang details on it, thereby helping reviewers who are relatively ignorant of your application 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 it must be written to meet its purpose.

5. Appreciate how the components must be linked to each other to create a linear progression of logic.

6. Create a bullet outline that includes each of the thirteen components that comprise the Specific Aims section.

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

8. Seek constructive criticism of the bullet outline from the members of your research team.

9. 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 this 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: “List the broad, long-term objectives and the goal of the specific 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. One page is recommended.”

In the previous chapter, we introduced you to the purpose of each of the thirteen 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 quoted instructions in the box, above, the recommended length for this section is one page. Appreciate that it is only a recommendation, not an absolute restriction like the page limitation for the Research Plan. We recommend that your deliberately write more than one page – about 1.25 pages. There are two reasons why. First, we want you to include more in this section than NIH wants you to. It is very difficult to get all that we want you to include on a single page without it coming across as choppy. Second, the significance paragraph, which begins the next Background and Significance section, begins on the second page of the Research Plan. If your application is reviewed late in the meeting, reviewers may be too burned out to turn the page if they see that the Specific Aims section ends at the bottom of the first page. Thus, they would miss finding the significance paragraph, which in our opinion is the most important paragraph in your grant application. By deliberately running the Specific Aims section onto the second page you force them to turn the first page, thereby guaranteeing that they will see the significance paragraph. If they have the time they will read it, because every reviewer recognizes the importance of this part of the application.

As a philosophical approach to writing grant applications 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 comprehend what is being presented in this section. The approach we have developed informs reviewers, especially those – the majority – who will not have seen your application before it comes up for consideration at the review-panel meeting, of exactly why information has been included. It minimizes the risk of being pedantic or condescending while doing so. The approach entails ‘labeling’ certain of the components in such a way that there can be no question as to why you have included the related information. Labeling of key sentences also helps to lead reviewers seamlessly through what you have written. The approach makes comprehension easy for reviewers, because there is absolutely no effort involved in understanding why material has been included. As you expand your bullets we will make suggestions as to where and how to create these informative ‘labels.’
There is a second approach that we recommend that you use: italicize key words to make them easy for reviewers to find. As you proceed through this Workbook, you will find that we recommend italicizing key words, phrases and even sentences. *Judicious use* of highlighting to call attention to things that you know members of the review panel will need is reviewer friendly and, therefore, good grantmanship. We suggest the use of italics as the least obtrusive way to do so. If you are using either Arial or Helvetica as your typeface single words or several words don't stand out that clearly when only italics are used. We recommend, therefore, that you also underline single words or several words to make them stand out. Phrases or entire sentences in these two typefaces stand out, so you should not underline them. To do so is overuse of highlighting – to the point that it can be an aggravating distraction. If you are using Georgia, *which is what this typeface is*, italics alone stand out adequately and underlining is not needed, even for single words. The same is true for Palatino Linotype, *which is what this typeface is*. As you expand certain of your bullets we will call you attention to words that we recommend you italicize in the Specific Aims section.

Finally, we recommend that you include few, if any, citations in this section. This part of the application is being written for the majority of reviewers who will not have seen your application before it comes up for review at the meeting. They will not have time at the meeting to look up references, even if you would provide them, and most of them will not be close enough to your subject that they will recognize specific references, even if you give them author / year. Thus, with the exceptions that we will call attention to, we recommend that you *not* cite the literature in this 'overview' section.

**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 you write 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 convincingly convey what is known about your subject area. The first sentence should be labeled to signal what 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 that which is contemporary, i.e., to the edge of the field as it exists today.

**Gap in the Knowledge Base / Unmet Need.** Next, expand the bullet that you wrote to delineate the gap in the knowledge base or unmet need that will be the subject of this 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, now expand the bullets that provide objective evidence for existence of the need. If the publications of other investigators are used as one means of supporting existence of need, cite their work.
Gap / Unmet Need as an Important Problem. Now, write a sentence that expands your bullets regarding why the gap in the knowledge base / unmet need is an important problem. This will be the concluding sentence of the introductory paragraph. It should be 'labeled' in such a way that reviewers are certain to understand that the gap / unmet need is a problem. For example, you might begin it with something like, 'Lack of such knowledge represents an important problem because, until the knowledge becomes available, ...' or 'Continued existence of this need represents an important problem because, until it is met, ...' The sentence would be completed by describing the vertical step in the field that is being blocked by continued existence of the gap / unmet need.

What, Why, Who Paragraph

TIP: An important tip that will help to better link your long-term goal, objective and central hypothesis is to avoid the temptation to interpose explanatory information – extraneous details – between them. These three components should ideally be immediately juxtaposed, so that there is a seamless flow of logic from the 'forest' (the long-term goal) to the 'tree' that will be the subject of this application (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. Write a comparable sentence 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.

Overall Objective. Now, expand the bullet you wrote into a single sentence that conveys what the objective of this application is – what you expect to accomplish. 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 either be to 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 the phrase "which is the next step toward attainment of our long-term goal." Including something like this in the statement of your objective helps reviewers connect to the fact that there is linkage between this component and the continuum of research that is reflected by your long-term goal. The words "long-term goal" should not be underlined and italicized in this second use of them. When you have completed this sentence, make certain that it links back to the gap / unmet need component and that its relationship to your long-term goal is clear.

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. Expand the bullet that you wrote previously to convey your 'best bet' as to how the objective can best be attained. 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 truly 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 you use the work of others as support for 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?’ Assure that this sentence links back to how the gap / unmet need was described as a problem at the end of the first paragraph. Be aware of the fact that the potential exists for setting up horrible redundancy if you don’t paraphrase cleverly. Look at the words that you used at the end of the first paragraph to convey that the gap / unmet need is a problem because it blocks the next vertical step and make certain that the same ones aren’t used here to indicate that, once the research has been completed, you will be able to take the blocked step. You must make the rationale seem fresh and exciting.

Well Prepared. Next, expand the bullets into sentences that summarize why you and your colleagues have the competitive edge in this area of research. In most cases, you will want to call attention to the full range of your research team’s strong points, because no one feature is likely to be that distinguishing; it is usually the constellation of strengths that prepares you well to undertake the proposed studies. As noted in the preceding chapter, your preliminary data are the most important things that distinguish you from equally qualified investigators elsewhere. If you invoked your preliminary data earlier as one basis for formulating your central hypothesis, you can call attention to them again here without being redundant. Simply begin the ‘well prepared’ component with something like, ‘In addition to our supportive preliminary data, we are well prepared to undertake the proposed research because ….’ Continue with the other things that summarize why you and your colleagues are the ones who should do what is propose. The operational word in the preceding sentence is “summarize.” In other words, there should not be a lot of detail included here. For example, instead of giving specifics about each participant’s expertise, the point that you want to make is that you have the scope and breadth of expertise necessary to conduct the research successfully. Thus, the related sentence might read something like, ‘In addition, we have assembled a research team with the scope and breadth of expertise (molecular genetics, bioinformatics and pathology) needed to complete all phases of the research successfully (see Biographical Sketches).’ Similarly, if you have physical or intellectual resources that distinguish you and your colleagues from your competitors, summarize those with something like, ‘Also, all members of the team are full members of the Center for Molecular Pathogenesis, which gives us access to important investigative resources, as well as other funded investigators who are pursuing research that is complementary to that what is proposed here (see Resources section).’

Specific Aims ‘Paragraph’

Begin paragraph three with a sentence something like, ‘We plan to test our central hypothesis and accomplish the overall objective of this application by pursuing the following specific aims.’ Continue by expanding the bullets for your specific aims and the working hypothesis for each. Because the aims – the ‘headlines’ – are so important, we recommend that you set each off as a separate paragraph indented one tab and that you present them in bolded italics. Nothing in the subordinate paragraphs should be bolded or otherwise highlighted, except for ‘working hypothesis,’ which should be italicized.

Payoff Paragraph

Innovation. If you have written a bullet that describes why your research/approach is innovative, expand it into a sentence that will open paragraph four. Don’t be shy. If you have a claim to innovation, be direct about it: ‘The proposed research is innovative, because ….’
**Expected Outcomes.** Continue by expanding the bullets that present your expected outcomes and why they are important. If you have used an 'innovation' sentence to open this paragraph, you might begin this component with something like, 'This innovative approach is projected to yield the following expected outcomes. First, ____________ , which is important, because __________.' Alternatively, if you did not open the paragraph with a statement about innovation, begin with a sentence something like: 'At the completion of these studies, we anticipate the following expected outcomes.' Continue to develop this component in the same way that you would if innovation had been used to open the paragraph (see earlier in this paragraph).

**Generality Regarding Positive Impact.** Conclude the fourth paragraph and your Specific Aims section by expanding the bullets that you wrote to generalize about the positive impact that your expected outcomes will have. Make sure that what you write sets up an easy transition into the next section, Background and Significance, which will begin with the ‘significance’ subsection. In that paragraph, you will detail and substantiate with specifics the general statement about positive impact that you write here. Thus, this concluding sentence for the Specific Aims section might read something like, 'The outcomes are expected to have important positive impact because the vertical step in the field they will enable resolves a persistent and pervasive health problem, as will now be detailed in the next paragraph.'

**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. If the compelling flow of logic that you need isn't there, you may have to completely rewrite the components that don't work. It may even be necessary to go back to the bullet outline stage. Whatever it takes, invest the effort until it works. When you are done, you should have approximately 1.25 pages. If you have more than that, prune what you have written until you meet that mark. Switching to a font smaller than 11 point (more than 15 characters and spaces per linear inch), narrowing the margins, or taking out the open lines between paragraphs to reach the goal of 1.25 pages should not be considered because making such changes compromises reviewer friendliness.

**EXAMPLES OF SPECIFIC AIMS SECTIONS**

Prior to discussing how the Specific Aims section is uploaded for electronic submission we want to offer you two well-written examples, one hypothesis driven and the other driven by a statement of need.
EXAMPLE OF A HYPOTHESIS-DRIVEN SPECIFIC AIMS SECTION

SPECIFIC AIMS

Interferon gamma (IFN-γ) has been referred to as a 'master cytokine,' because of its many effects, both direct and indirect, on cellular components of the inflammatory and immune responses. It 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. In recent years, considerable progress has been made in showing that the α subunit must work with a species-specific accessory factor (referred to as the β subunit) to transduce signals that are initiated by the binding of ligand. While it is evident that the binding protein of the receptor complex initiates signal transduction, it is still entirely unclear how this critical 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 production of the receptor for IFN-γ can be modulated on cell surfaces for preventive and therapeutic purposes. The objective of this application, which is the next step in pursuit of that goal, is to determine how production of the receptor's α subunit is regulated transcriptionally. The central hypothesis of the application is that there are both constitutive and stimulated regulation of transcription, and that such control is mediated through different sets of cis-acting response elements in the promoter of the gene that encodes the chain. Our hypothesis has been formulated on the basis of strong preliminary data produced in our laboratory, having recently cloned and characterized the promoter for the gene that encodes the human α subunit (Galaway et al., in press; see Preliminary Studies). The rationale for the proposed research is that, once it is known how transcription of the α chain's gene is regulated, its production can be either up- or down-regulated pharmacologically in new and innovative approaches to the prevention and treatment of a variety of diseases. In addition to our supportive preliminary data, we are particularly well prepared to undertake the proposed research, because a multidisciplinary research team that has been assembled that has the scope and breadth of expertise and experience needed to obtain definitive outcomes (see Biographical Sketches). In addition, the work will be conducted in a research environment that is conducive to its successful completion. For example, it contains numerous funded investigators and shared resources that are dedicated to complementary structure/function studies of cellular receptors (see Resources section).

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

1. **Identify the DNA response elements and transcription factors that regulate constitutive transcription of the α subunit's gene.**
   Based on work that will be presented under Preliminary Studies, the working hypothesis here is that one or more Sp1 sites are critical to the regulation of constitutive transcription.

2. **Determine how stimulated transcription is up-regulated by two widely differing stimuli.**
   We postulate, again on the basis of preliminary data, that cyclic AMP response elements (e.g., CRE and AP-2) are essential to regulating stimulated transcription of the gene, and that the same elements will be involved, regardless of how stimulated transcription is activated.
The proposed work is innovative, because it capitalizes on a new means of identifying active response elements, which was developed by our group. In addition, it takes advantage of the cloned promoter for the subunit's gene, which to our knowledge is available in no other laboratory. With respect to expected outcomes, the combination of work proposed in aims 1 and 2 is collectively expected to identify the full complement of response elements and the cognate transcription factors that are responsible for constitutive and stimulated transcription of the subunit's gene. Such results will have an important positive impact, because the identified components are expected to provide new targets for preventive and therapeutic interventions that will aid the growing numbers of persons in this country who have either acquired or age-related immunodeficiency. In addition, it is expected that the results will fundamentally advance the fields of receptor biology and immunotherapy, as will now be detailed in the next section.

EXAMPLE OF A NEED-BASED SPECIFIC AIMS SECTION

A. SPECIFIC AIMS:

While cigarette smoking has decreased significantly in the U.S. general public during the past decade, evidence suggests that smoking has actually increased among women of child-bearing age, a fact that places these women and their unborn/newly born children at significant risk of both short- and long-term adverse health effects. The problem is particularly acute for low-income women and those who are members of ethnic minorities. With respect to adverse health effects on the new-born child, these include premature birth and the problems attendant to it; chronic pulmonary disease leading to increased risk of development of asthma; and increased susceptibility to infections. Of particular importance are recent studies indicating that almost 50% of mothers who quit smoking during pregnancy resume smoking by the time the infants are only three-months old. Of mothers who resume smoking, evidence suggests that cigarette usage actually increases relative to pre-pregnancy smoking levels. The primary reason often cited for resumption of cigarette smoking among new mothers is stress associated with caring for the new child, although this issue has not been extensively studied. Given the multiple adverse consequences of secondary cigarette smoke on newborn infants, there is a critical need to better understand the factors that impact the decision of new mothers to resume smoking. Objective evidence for existence of this need derives from our own assessment (see Preliminary Studies section) and independent recognition of it by Conway and her colleagues (2003). Its continued existence represents an important problem because, until the need is met, development of effective strategies to help these mothers avoid resumption of this health-destroying habit will likely remain problematic. In the absence of new and effective interventions, tens of thousands of newborns will continue to be placed at unnecessary health risk.

Our long-term goal is to improve the health of at-risk newborn children, especially those who are born to low-income and minority families with histories of smoking. The objective of this application is to identify the risk factors that will predict postpartum smoking relapse and, based on this information, design an intervention that will reduce recidivism among low-income, recently postpartum mothers who quit smoking during their pregnancies. Study subjects will be recruited from a community-based clinical setting for low-income women (see Facilities & Other Resources section). The intervention that we will develop will involve an integrated approach using principles derived from the Relapse Prevention Model, first described by Marlatt (1985), and the Child Health Model published by Barnard and Eyers (1979). Our rationale for this project is that its successful completion is expected to provide a strong, conceptual, evidence-based intervention that will effectively reduce recurrence of smoking postpartum. Both formative and summa-
tive evaluation will be used to corroborate / refute this expectation. In addition to our supportive preliminary data, we are well prepared to pursue this project because the Principal Investigator (J. Smith) has highly relevant experience, having investigated factors that contribute to substance abuse by pregnant, low-income mothers for her Ph.D. dissertation (see Biographical Sketch). In addition, the research team will have ready access to strong statistical support through our nursing Clinical-Research Center (see Facilities & Other Resources section for details).

We expect to achieve our objective by pursuit of the following two specific aims:

Specific aim #1: Identify factors that will predict relapse of smoking among postpartum mothers. Our preliminary data (see Preliminary Studies section) strongly implicate perceived self image of the mother as a predictive factor and suggest equally strongly that others also exist. These include, but may not be limited to, perceived infant irritability, perceived parenting stress and peer pressure as factors that are also predictive of smoking relapse after childbirth.

Specific aim #2: Develop an intervention that will reduce recurrence of smoking postpartum. We will establish an evidence-based strategy for development of an intervention that will target factors that contribute to smoking, thereby assisting new mothers to resist the urge to resume smoking.

This project is innovative because the approach to creating the intervention uniquely targets factors that will predict smoking recurrence and, thus, mothers who are at greatest risk. It is anticipated that this innovative approach will yield the following expected outcomes: First, we will have identified specific factors that will predict relapse of smoking among mothers of newborns. Second, we expect to be able to use these predictors to develop an effective intervention that will target members of a large, at-risk group. We further expect that the intervention will be applicable to implementation in a comprehensive, community-based clinical setting. The proposed plan for rigorous evaluation is expected to allow us to confirm the efficacy of the new intervention. As a result, in addition to contributing vertically to the field of smoking intervention, the results of this study are expected to have an important positive impact, not only on the health of at-risk newborn children, but also on that of their mothers, as will now be detailed in the next section.
After you have completed your Specific Aims section it must be uploaded into the SF 424 application kit. You do so using the PHS 398 Research Plan Component, which is reproduced below.

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application
   (for RESUBMISSION or REVISION only)
2. Specific Aims
3. Background and Significance
4. Preliminary Studies / Progress Report
5. Research Design and Methods

Once you have the final version of your Specific Aims section convert it into a PDF file. Don’t worry if there is a lot of ‘white space’ on the second page of your Specific Aims section. It won’t eat up space because it will be eliminated after your application has been received and assembled by NIH. (You will have two business days after assembly to view and check the application to ensure that such deletions have been made.) Using the “Add Attachment” button on the right of line 2, section 2, upload the file. Once you have done so the other two buttons on the line will be activated, allowing you to view and/or delete the file. If later revisions must be made, delete the uploaded file and load the revision in its place using the “Add Attachment” button, as you did originally.

DEVELOPMENTAL STEPS FOR CHAPTER EIGHT:

1. Expand the bullets for your Specific Aims section into complete sentences.
2. ‘Label’ them in such a way that reviewers will know precisely what they are included to convey.
3. Highlight key words using either underlined italics (Arial or Helvetica typefaces) or italics alone (Georgia and Palatino Linotype typefaces).
4. Present the components in four separate paragraphs.
5. Use one-inch margins all around.
6. Open a line between paragraphs and between each aim and the subordinate paragraph of the preceding aim.
7. Make your specific aims stand out by presenting them in bolded italics.
8. Deliberately make the Specific Aims section extend onto page 2 of the Research Plan. Edit and refine the section until it reads well and occupies no more than 1.25-1.5 pages.
9. Convert the Specific Aims section into a PDF file.
10. Upload the Specific Aims section into the PHS 398 Research Plan.
CHAPTER 9

SIGNIFICANCE SUBSECTION OF THE BACKGROUND AND SIGNIFICANCE SECTION

GENERAL CONSIDERATIONS

Instructions for Significance Subsection of the PHS 398 Research Plan Component / Background and Significance Section: "State concisely the importance and health relevance of the research described in this application by relating the specific aims to the broad, long-term objectives. If the aims of the application are achieved, state how scientific knowledge or clinical practice will be advanced. Describe the effect of these studies on the concepts, methods, technologies, treatments, services or preventative interventions that drive this field."

An important part of our proposal-writing strategy is to gradually ratchet up detail as the reviewer reads further into the application. The idea is to get the reader 'hooked' on the conceptual, exciting parts of your proposal to the extent that s/he will want to read the details that are presented later. The second, Background and Significance section is where you begin to increase the level of detail that is included. It is meant to provide detail and citations that will extend and validate key parts of your Specific Aims section.

**TIP:** The purpose of the significance subsection is to help justify the need for the research that will be proposed. The 'spin' that you put on what is written here should be consistent with that purpose. Many applicants make the mistake of inadequately emphasizing significance, which seriously undercuts the fundability of their application.

The significance paragraph is a brief one (no more than 1/3-to-1/2 page) that is located at the beginning of the Background and Significance section (Section B). It is arguably the most important paragraph in your entire application, because the review criterion "SIGNIFICANCE" is so important. It should have a bolded, italicized title, Significance or Significance of the proposed research, so that the reviewer will immediately recognize that this is the part of your proposal that addresses significance. What makes research significant? It is because benefits of some kind will accrue to application of the new knowledge. It is a difficult paragraph to write because of the potential for creating obvious redundancy with the preceding Specific Aims section. You can do so by ensuring that the content of the significance paragraph is written with appropriate paraphrasing and expansion of detail.

Because of its relative importance, this paragraph will be read by most, if not all, of the reviewers at the panel meeting – even those who haven’t read your proposal prior to that time. It is
strategically important, therefore, to ensure that it is on the second page of the Research Plan, immediately after the final paragraph of the Specific Aims section, where all reviewers – even those who are seeing your application for the first time at the review-panel meeting – will be guaranteed to find it.

Unlike the preceding Specific Aims section, it is essential that you begin to cite relevant references from the primary literature here. You should avoid citing reviews, for the most part, because they tell the reviewer nothing about your command of the field’s primary literature. We recommend that you cite references using author/year (e.g., Young, 1998; or Abelson and Rafferty, 2003; or Zaharias et al., 2000). Your primary, secondary and tertiary reviewers will be close enough to being experts on the subject you are offering that they will be able to recognize most of the citations if they are presented as author/year. This prevents them from having to flip to the Literature Cited section. No matter how intimately familiar a reviewer is with your subject area, s/he will not be able to recognize references that are cited by number (e.g., 24, 36, and 92). Asking reviewers to flip back and forth in the application to appreciate which citations you have chosen to justify the need to do what you are proposing is not reviewer friendly. If you are a New Investigator and first author of most of your papers, another reason for using this approach is that it is a clever way to impress on reviewers that you have done the work that is being cited – something that is impossible to do if numerals are used.

CREATION OF THE FIRST DRAFT OF YOUR SIGNIFICANCE SUBSECTION

We recommend that you write this paragraph to have three readily identifiable parts:

Part 1 should detail and expand upon the fact that a gap in the knowledge base or unmet need exists and that its continued existence is an important problem. It should conclude with a sentence that explicitly describes the contribution that you expect to make with the proposed research. The contribution sentence should link back to what you wrote for your objective in the Specific Aims section, because your contribution will be the result of attaining your objective.

Part 2 is the statement of significance. It should appear approximately in the middle of the paragraph and should be a simple, direct statement regarding why the expected contribution is important – why it is significant. This sentence is arguably the most important one that you will write in the application. We recommend, therefore, that it be highlighted by putting it entirely in italics. Even if you are using Arial or Helvetica as your typeface, do not also underline because italics alone for an entire sentence will stand well enough and will not be obtrusive, as would be the case if you also underlined.

Part 3 should validate your assertion of significance. Because significance derives from benefits that could be expected to accrue to application of the new knowledge, this third part should consist of a list of such benefits. In most cases, the benefits will relate to advancement of the field in which the research is based. Any ‘fringe benefits’ that might accrue to the research should also be claimed. By fringe benefits, we mean outcomes that would be beneficial when extrapolated to other venues and/or fields, such as animal health.

If you follow this three-part format, you will write a strong, compelling significance subsection. Use the suggestions provided below to trigger your own ideas. Once you have a general feel
for what you want to write, get it down on paper. *The major goal here is to produce a first draft, i.e., something that can be revised and embellished later.* The most efficient approach will likely come from the developmental sequence that you used with your *Specific Aims* section: bullet outline, followed by expanding the bullets into sentences, after which the paragraph is created by integrating and linking the sentences appropriately.

**Part 1:**

*Opening sentences.* You want to use these sentences to expand and underscore the human health relevance of the problem that you have chosen to address. You have summarized this information earlier, in the opening paragraph of the *Specific Aims* section. Now, without being redundant, you should extend and embellish what was written earlier with specific details that are supported by citations of the literature.

*Succinct statement of the problem.* The preceding sentences should frame a clear and succinct statement of the gap in the knowledge base or unmet need that is the focus of the proposal. Paraphrase sufficiently and expand the detail to the extent that it does not seem repetitious of the less detailed statement of the gap / unmet need that you offered in the first paragraph of the preceding, *Specific Aims* section.

*Statement of what your contribution is expected to be.* This statement must be both strong and credible, i.e., not just a thoughtless cliché or empty generality that fails to highlight specifically what your contribution is expected to be. This is not meant to be a reiteration of the expected outcomes from the last paragraph of your *Specific Aims* section. Rather, as noted earlier, it should relate to accomplishment of the overall objective of the application. For example, 'As an outcome of the proposed investigations, we expect to have determined the mechanism of / distinguished between / overcome the problem of ____________.' In other words, this should reflect the new knowledge that you expect to obtain.

**Part 2**

*Statement of significance.* Near the middle of the paragraph you should specify why your contribution will be important. This is another one of those times when you can’t be shy: figuratively, this sentence should knock your reviewers right out of their chairs. You don’t want the reviewer to have to interpret for him/herself why your projected contribution will be significant. Rather, you should tell him/her why it is significant, leaving no room for interpretation. This statement should be 'labeled' for what it is (e.g., ‘The proposed research is significant, because ……’); and, as noted above, should be fully highlighted in italics, thereby ensuring that it can be found easily. In almost all cases, the sentence will be completed by underscoring that a vertical step in the field will become possible as a result of the contribution.

**Part 3**

*Validation of the Statement of Significance With a Credible List of Benefits.* The statement of significance you have just written must now be validated by presenting the benefits that will result from the vertical advance in the field that you expect to make? For example, how will it enable subsequent thinking and research? What benefits to human health are likely to ensue? How might it reduce the cost of health care? You don’t have to be the direct contributor of the benefits. If it is credible to project that others will build on what you produce, e.g., through an enabling of their research, you are justified to claim such impact.
EXAMPLE OF A SIGNIFICANCE SUBSECTION

Significance. The subunit of the receptor complex for IFN-γ is the means by which this important cytokine binds to cells and initiates transmembrane signaling (Yang, 1977; Telifer and Gomez, 1988; Homer et al., 1995). Through it, IFN-γ exerts a wide range of immunoregulatory activities (Klein & Klein, 1995). Serious infectious disease problems are experienced by those who become deficient in the cells that produce this cytokine, either because they are lost as part of a disease process (e.g., AIDS; Galbreath, 2002; Toliver, 2003), during chemotherapy (Aikens and Osada, 2000), or as a natural consequence of the aging process (James and Kary, 1997; Zeleny et al., 2004). In addition to its homeostatic and defensive roles, in such diseases as Hashimoto’s thyroiditis and asthma, IFN-γ appears to have a pathogenetic role, either because there is an overabundance of the cytokine (Alcott and Cochrane, 1998; Jones et al., 2000) or because cells become hyper-reactive to normal, physiologic concentrations (Sandoval, 1999). Responsiveness to IFN-γ can be modulated, either up or down, by altering the number of its receptors that are present on a cell’s surface (Carlson et al., 2003). Such findings suggest that cellular functions that are attributable to the effects of IFN-γ could be modulated by altering the number of subunits that are available to bind it. Our contribution here is expected to be detailed understanding of how production of the receptor is regulated transcriptionally. This contribution is significant because it is expected to provide the knowledge needed to develop pharmacologic strategies that will allow the number of a subunits on the surface of targeted cells to be regulated, either up or down. Once such strategies become available, there is the promise that in diseases that are associated with hyper-responsiveness to IFN-γ, cellular responsiveness could be down-regulated by reducing the number of chains that are available to bind the cytokine. Conversely, when greater responsiveness is needed — for example, to ward off pathogenic microorganisms or, in the case of immunocompromised patients, opportunistic invaders — responsiveness of host-defense cells to IFN-γ, could be increased. Thus, important advances in the therapy of diseases and complications that are associated with cellular immune dysfunction could be expected. It is also expected that what is learned will be equally applicable to the prevention/treatment of diseases of agriculturally relevant animals. In addition, the research will be of significance, because what is learned is expected to contribute to broader understanding of how components of other receptor complexes can be modulated as an approach to therapy. Furthermore, better fundamental understanding of how receptor proteins are transcribed can be anticipated.

DEVELOPMENTAL STEPS FOR CHAPTER NINE:

1. Appreciate that, of the five mandatory review criteria used to evaluate NIH grants, “Significance” is the most important. This subsection is where that criterion is primarily addressed.
2. Understand that this section should be written to help justify the need for what you are proposing.
4. Understand and use the three-part approach that is recommended for the development of this critically important subsection.
5. File this ‘Significance’ subsection as the first part of the Background and Significance section, to which you will add ‘Review of Relevant Literature’ subsection later.
6. Seek constructive criticism of your Specific Aims section and significance paragraph from members of your pre-submission review committee (see chapter 22 for details regarding its composition and use).
OVERVIEW: PART THREE

DEVELOPMENT OF THE REST OF YOUR APPLICATION

Once you have finalized your Specific Aims section and significance paragraph using input from members of your pre-submission review committee (see chapter 22 for details) and the Program Officer for the NIH program you are targeting you will be ready to develop the remainder of your proposal. This will be discussed in detail in the following chapters.

Chapter ten, Research Design & Methods Section: Narrative Description of What's to be Done, addresses development of the narrative part of your proposal – the Research Design and Methods section. You should allocate approximately three weeks to complete this section.

Chapter eleven, Background Subsection of the Background & Significance Section and the Bibliography & References Cited Section, summarizes the strategies that should be adopted in preparing the background subsection of the Background and Significance section, as well as what to include in the Bibliography & References Cited section. Approximately two weeks should be allocated for completion of these parts of the application.

Chapter twelve, Preliminary Studies Section / Progress Report, addresses what to include in one or the other of these parts of the application, depending upon whether you are submitting a new application or a renewal (formerly competing continuation). One week should be sufficient to complete this part of your proposal.

Chapter thirteen, Senior/Key Person Profile(s) Component and Biographical Sketches, will allow you to describe your research team in such a way that the feasibility of what is proposed in the Research Plan is maximally supported. Allow one week for completion of these parts.

Chapters fourteen and fifteen. Chapter 14, PHS 398 Modular Budget Component and Justification, describes how to prepare a modular budget and budget justification for R01, R03, R15, R21 and R34 proposals that have an annual direct-cost budget of $250,000 or less. If you will be offering a modular budget, ignore chapter 15, SF 424 (R&R) Budget Component (Breakout Budget), Justification and Cumulative Budget, and devote less than one week to preparation of your modular budget and justification. If you will be offering a breakout budget, skip chapter 14 and substitute the tips and strategies that are included in chapter 15. As its name implies, this chapter guides the preparation of a detailed budget and budget justification. Allow approximately one week to be fully responsive to chapter 15.

Chapter sixteen covers development of the important Facilities & Other Resources and Equipment sections – the physical and intellectual assets that constitute the research environment in which you and your colleagues will be working – as well as the Project/Performance Site Locations component. These sections are also important in establishing the feasibility of what is proposed. They should take less than a week to complete.
Chapter seventeen addresses Human Subjects, Vertebrate Animals, International Collaborations, Environmental Impact, Resource Sharing Plan(s), and Consortium/Contractual Arrangements should one or more of these be applicable to your proposal. This part of the application should take approximately one-to-two weeks to complete, depending on the number of sections that have to be written.

Chapter eighteen offers tips on completing the two cover-page components that are part of an NIH application, the SF 424 Cover Component and the PHS 398 Cover Page Supplement. In addition, this chapter contains suggestions regarding how to use appendix material to your maximal advantage.
CHAPTER 10

RESEARCH DESIGN AND METHODS SECTION: NARRATIVE DESCRIPTION OF WHAT’S TO BE DONE

Instructions for Research Design and Methods Section of the PHS 398 Research Plan Component: “Describe the research design conceptual or clinical framework, procedures, and analyses to be used to accomplish the specific aims of the project. Unless addressed separately in Item 14 (Resource Sharing Plan[s]), include how the data will be collected, analyzed, and interpreted as well as the data-sharing plan as appropriate. Describe any new methodology and its advantage over existing methodologies. Describe any novel concepts, approaches, tools, or technologies for the proposed studies. Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. As part of this section, provide a tentative sequence or timetable for the project. Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be exercised.”

GENERAL TIPS ON WRITING THE RESEARCH DESIGN AND METHODS SECTION

The Research Design and Methods section provides a detailed description of what will be done during the requested period of funding. We assure you that, providing you have been conscientious in the development of your Specific Aims section, although this is the longest section of the application, it will be one of the easiest for you to write. We recommend that you write this section now, even though it is the last one in the Research Plan, for two reasons. First, because Research Design and Methods is primarily an expansion of the Specific Aims section that you have just written, by writing it now you can capitalize on the momentum that you have developed. Second, writing the Research Design and Methods section at this time increases the likelihood that there will be maximal continuity with the Specific Aims section, despite the fact that they appear in the application at opposite ends of the Research Plan.

Before you begin to write, consider the following general points. Development of a strong Research Design and Methods section requires only that you answer the following five questions for each of your aims: 1) What will be done? 2) What are the means that will be used to accomplish the aim? 3) What might go wrong? 4) What alternative strategies will be used if something does go wrong? And finally, 5) What results are expected and why are they important? If you are a New Investigator, be especially clear that the work is feasible in your hands.

It is imperative that you develop your Research Design and Methods section using as its core the specific aims that you have already formulated. If your specific aims have been balanced appropriately, each should have approximately equal weight with respect to the number of pages that is devoted to it. To determine approximately how many pages you will have available for each aim, simply divide the total number of pages you expect to have for the entire Re-
search Design and Methods section by the number of aims. (Although this guideline will generally hold true, we can envision — and have encountered — situations in which this approach isn’t appropriate, i.e., in which the aims must be weighted differently.)

As you conceive this section, remember that you should always put the most interesting and important, i.e., conceptual, material up front. Then, and only then, should you follow with the details. This approach is designed to ‘hook’ the reviewer’s interest and make him/her want to read what you have written. If you think of your presentation as an inverted pyramid, its apex should be the title of the specific aim, i.e., that eye-catching, interest-grabbing ‘headline’ that you have written earlier. That ‘headline’ should be repeated here, verbatim, as the title of the Research Design and Methods subsection that will describe the research associated with the first aim. The title (headline) should be followed by paragraphs that gradually increase the extent of detail. Use the following format (or a similar one):

Specific Aim #1: Title.
1.1 Introduction
1.2 Experimental (or Research) Design:
   1.2.1 Study #1 (write an explanatory title)
   1.2.2 Study #2 (write an explanatory title)
   1.2.3 Etc.
1.3 Expected Outcomes
1.4 Potential Problems and Alternative Approaches

Specific Aim #2: Title
2.1 Introduction
   Continue using the format shown above for this and all subsequent aims.

Timetable
Future Directions

The format for each aim begins with an introductory paragraph that summarizes for the reviewer all of the essential conceptual information that is associated with pursuit and successful completion of the aim. Detailed description of individual studies should next be presented under Experimental Design, one study per paragraph. (For applications that do not propose actual ‘experiments’ you should title this subsection ‘Research Design.’) A separate paragraph with the subheading ‘Expected Outcomes’ should briefly summarize anticipated results and their collective impact. Offering such a paragraph is reviewer friendly because, when the main outcomes are presented together, in one place, an evaluator can more easily appreciate that they collectively achieve the aim’s overall objective — especially when the outcomes are accompanied with one or more integrating sentences. A concluding paragraph, Potential Problems and Alternative Strategies, should acknowledge problems that might arise, as well as your proposed solutions to them (i.e., alternative approaches). NIH reviewers are directed to determine whether applicants anticipate problems and provide alternative tactics / strategies for them. Thus, this last subsection is responsive both to this directive and the instructions that are contained in the text box on page 66. This same format should be used to develop each of your subsequent specific aims. Near the end of the Research Design and Methods section, i.e., after all of your specific aims have been developed, you should include a timetable that relates the important activities that are proposed during the requested period of support. This is required by the instructions (see text box on preceding page). The last paragraph in the section, which should be titled something like ‘Future Directions,’ should be used to tell the reviewer where you expect the proposed research to lead. You want to reinforce that the work described in this proposal is part of
the continuum of research that will ultimately allow you to attain your long-term goal. This last paragraph in the Research Plan is where you project that vision.

As a final general point, we suggest again here that you formally schedule your writing of this section in discrete blocks, i.e., that you write a little every day at a scheduled time. For example, commit to writing an introductory paragraph for one of the aims or the experimental design subsection. If you do this, and do it consistently, you should have no trouble in completing a first-rate Research Design and Methods section over the course of approximately three weeks while, at the same time, you manage all of your competing commitments.

TIPS ON WRITING THE RESEARCH DESIGN AND METHODS SECTION

With these general points and the format just presented firmly in mind, begin by developing the subsection that will tell reviewers how you intend to accomplish aim #1. We recommend that you do so by first writing bullets, which you then convert to text.

Specific Aim #1: Title (Verbatim Repeat from Your Specific Aims Section)

Introduction. You should title the first subsection under each of your aims, ‘Introduction.’ This title should be indented and be presented in bold italics, as it is in this paragraph. Continue with text on the same line, as has been done here, with subsequent lines returning to the left margin. This introductory paragraph should be an overview that will let the reviewer know what is to be detailed in the remainder of the subsection, and why it is important to do what will be proposed. Key words in this paragraph (e.g., objective, working hypothesis, approach, expectations, etc.) should be highlighted in non-bolded italics to allow reviewers to find these components easily.

Begin this paragraph by justifying why the work under this aim needs to be performed. In doing so you should call attention to the part of the overall problem that will be addressed.

Next, write the objective that you have for this aim. Your aim’s objective should be stated in such a way that its attainment will resolve the problem / question that you highlighted with your justification, above. You might begin this component with something like, ‘The objective of this aim is to ___ (solve the problem/answer the question that the aim will address) ___.

Now, tell the reviewer how you will attain the objective that you have written. You will do so by testing the aim’s working hypothesis. You followed the statement of this aim in the Specific Aims section with a working hypothesis. It should be repeated here, verbatim. It is critical that you repeat the working hypothesis in this introductory paragraph, because you want to underscore for your reviewers that the work to be done will be hypothesis-driven. We suggest that you phrase your working hypothesis something like: ‘To attain the objective of this section, we will test the working hypothesis that _______________ etc.’ [NOTE: If you are writing an aim that is better driven by a statement of need, substitute that for the working hypothesis.]

To test your working hypothesis (meet the need), you will employ an experimental approach (strategy). Briefly summarize the principal approaches / methods that will be used to attain the aim’s objective, e.g.: ‘We will test our working hypothesis by using the experimental approach of etc.
The rationale for the work to be proposed under this aim – why you want to undertake this part of the research – should be presented next. The litmus test to be applied here is the same one that you used for testing the overall rationale that you wrote for the Specific Aims section. Does what I have written tell the reviewer what will become possible after the research proposed in this aim is completed, which is not possible now? Write an enthusiastic sentence or two that describe(s) your rationale for this aim. This is an opportunity to convey some of your excitement about the research to your reviewers. Write something like, 'The rationale for this aim is that successful completion of the proposed research will contribute a missing, fundamental element to our base of knowledge, without which the metabolism of compound X cannot be understood. The acquisition of such knowledge is critical to the development of improved therapeutic strategies for disease Y.'

Finally, summarize what the overall outcome(s) of this aim is / are expected to be. Phrase the outcome without parroting the aim, i.e., the title of the subsection. Remember to stay at a general, not detailed, level. You might write something like, 'When the proposed studies for aim #1 have been completed, it is our expectation that the metabolic pathway identified will entail phosphorylation of key amino acids in compound X’s cytoplasmic domain. Such a finding would be of importance, because it would allow, for the first time, the development of novel and much needed approaches to ____________.'

When completed, the introductory paragraph should occupy no more than 0.25-to-0.5 page. As you read it, the flow of logic in this overview must be clear and compelling – it must 'hook' the reviewer's interest in this aim.

**Experimental (or Research) Design.** In this subsection, you will present and discuss the activities that will be undertaken to accomplish the objective of specific aim #1. These activities must grow logically out of the approaches / strategies that you have summarized in your introductory paragraph. Keep in mind that each paragraph in this subsection should be a conceptual unit, i.e., a related group of activities that address a single point. Begin by creating bullets that denote the planned activities. Accompany each with an informative, interest-attracting title — headline — that will be used to introduce the related paragraph in your Experimental (Research) Design subsection. As for the aims themselves, no one of the activities should be absolutely dependent on an expected outcome of an earlier one. Make certain that the range of activities is sufficiently comprehensive that the outcomes will collectively attain the aim's objective. If that isn't clear, then you should revise the Experimental (Research) Design subsection until it is.

**TIP:** Many applicants make the mistake of including too little meaningful experimental detail in their Experimental Plan

Your next step should be to outline what will be entailed under each of the activities that you have listed. Because there is a great range of what might be included, depending on the subject, it is not possible to provide an all-inclusive list here. *You need to provide detail,* but it must be meaningful detail. In other words, it should not be routine methodological detail. Consider each of the following, at least. When something in the list is found to be relevant create a corresponding bullet. Embellish the list with other points that are relevant to your research.

Write the title of your first study:

Approach to be used.
Method(s) required.

Essential reagents needed.

**Critical** equipment required.

Numbers of subjects / animals, and how these numbers were derived.

Statistical analysis needed.

Controls (VERY important).

Replicates that will be needed.

Detailed expectations (VERY important).

How results will be interpreted.

Time required to complete the studies.

**Next, write the title of your second study:**

Consider each of the headings listed above for study #2. Continue this process for other studies that are needed, until you have completed a full outline of the activities that will be undertaken for Specific Aim #1.

Begin writing the Experimental Design subsection for Aim #1 by expanding the bullets you have written. As you write, remember that you **must** engender maximal enthusiasm and acceptance of your proposal. Avoid cluttering the reviewer's mind with material that is tangential to the main point that you want to make in each of your paragraphs. Write in simple declarative sentences that are free of jargon and nonstandard abbreviations and acronyms. Whenever it is credible to do so, use strong words, like 'expect,' and 'can.' Avoid weak words, i.e., those that unnecessarily plant a seed of doubt in the reviewer's mind about what you are proposing (see chapter 4 for examples). Emphasize the conceptual, because that is what is exciting and likely to attract the interest of the reviewer. Make sure, however, that you provide enough experimental detail, e.g., methodological, statistical, and appropriate controls, so that the reviewer will know not only what you plan to do but also how the resultant data will be interpreted. Don't make the mistake of going to the other extreme, i.e., of including too much detail. Doing so usually causes the reviewer to become hopelessly bogged down in a morass of boring minutiae (e.g., how many milliliters of this are added to how many of that, etc).

If you are a little confused about how much methodological detail to include, don't feel like you alone have such a problem; there is **always** the question of how much methodological detail is enough. As a general rule, detail only those methods that are either new to you or that are unique to your group, i.e., that wouldn't otherwise be known by the reviewers. New Investigators should present more detail than established investigators do, keeping in mind that they must convey that what is proposed is feasible in their hands. Also, ask yourself, "Have I erred on the other side and presented so much routine detail that the conceptual aspects of the aim have been obscured?" In other words, the solution to the dilemma can often be found by asking:
“Have I offered just the right amount of detail to convey that what will be done is feasible in my hands?” In other words, put yourself in the position of the reviewer. If you still don’t have a clear idea of how much detail to include, we suggest that you avoid routine methodology – the kind of stuff that could be copied from a methods manual. This is especially true if your Biographical Sketch shows that you have been trained to use the relevant methodology and/or that you have published experience with the methodology in question. As a reviewer, would you require that a formally trained or experienced investigator describe a routine method that is commonly employed in the field? We think not.

If parts of your Experimental (Research) Design subsections are common to two or more of your aims, consider including a Methods and Procedures sub-subsection. If you decide to use this approach, to avoid redundancy we suggest that you put it either at the beginning or end of the Experimental (Research) Design subsection. If you think that it is necessary for reviewers to have methodological detail before reading about what will be done, the Methods and Procedures subsection should be inserted at the beginning of the subsection. The problem with doing so is that reviewers will have to read about methods before getting to the more interesting parts of the Experimental (Research) Design subsection. As an alternative, if reviewers won’t need to have methodological detail early on, you can put the sub-subsection at the end of Experimental (Research) Design subsection, where they won’t need to read it until they know why it is necessary to do so. If you take this approach, include an introductory sentence at the beginning of the Experimental (Research) Design subsection that alerts reviewers to the fact that methods and procedures can be found at the end of the subsection. By putting it at the end of subsection you make methodological detail available to the reviewers, but you don’t force them to wade through it to get to the interesting, experimental parts of what you present. An approach that we recommend AGAINST is inclusion of a Methods and Procedures appendix. Doing so is likely to cause the person who performs the compliance review at the Center for Scientific Review to decide that you have tried to circumvent the page limitation for the Research Plan. Should this happen, your application would be returned without review.

*Expected Outcomes.* It is critically important that this subsection be included for each aim. The summary of expected results that you write here highlights the ‘return on investment’ that reviewers will be seeking. You should pull together the detailed results that were included under each paragraph of the Experimental (Research) Design subsection. As noted earlier, this gives the reviewer an appreciation for how they collectively attain the aim's objective. This overview should be more extensive than the summary sentence (or two) that you wrote about expected outcomes in the introductory paragraph for the aim. What you write here can usually be presented in a single paragraph that does not need to be extensive in its length – 1/3-to-1/2 page, at most.

To create this kind of paragraph, first collect all of the detailed expectations from the preceding Experimental (Research) Design subsection in one place. By doing so, you can then see how they relate to each other and how the overall outcome and importance of these findings can be summarized. As an approach, we suggest that you copy/paste all of your detailed expected results into a new file. After making your analysis of this material, write the paragraph to: (1) summarize the expected outcomes, and (2) convey how they collectively achieve the aim’s objective. The Expected Outcomes paragraph is another opportunity that you have to create excitement, so make every effort to underscore why the expected results are important. There are at least two reasons why they are. First, they collectively attain the aim’s objective and, second, they contribute to attainment of the application’s overall objective. Be enthusiastic when you write this paragraph. However, at the same time, be realistic and provide appropriate caveats, if
they are needed. You must not overstate your expectations to the extent that they (and you) lose credibility.

**Potential Problems and Alternative Approaches.** Your goal here is to anticipate (and then eliminate) justified concerns of your reviewers. You do so by presenting alternative approaches / strategies that will be used to overcome potential problems that you have identified. You are directed to include such information by the instructions for this section, which are repeated again here: "Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims." An additional indicator of the importance of this subsection is included in the ‘APPROACH’ review criterion: “Does the applicant acknowledge potential problem areas and consider alternative tactics?” You know – and the reviewers will know – that no matter how hard you plan and prepare, problems can develop. Failure to address this fact of life by not including this subsection can seriously undercut the fundability of your proposal, as is suggested by the following quote from NIDDK’s website.

TIP: “The typical successful R01 ... [has] proposed experiments [that] are clearly described in detail, with suggestions for proceeding with the work should they fail to produce the expected outcome.”
(see [www.niddk.nih.gov/fund/grants_process/grantwriting.htm](http://www.niddk.nih.gov/fund/grants_process/grantwriting.htm))

If you are doing hypothesis-driven research, first and foremost among problems that reviewers will expect you to address is the possibility that the working hypothesis for the aim will prove to be invalid when it is tested objectively. In that unlikely event, what would you do? To what alternative would you turn? Reviewers will also be concerned about critical reagents: Will they be available and will they perform as expected? Will sufficient patients be available, if a clinical research project is being proposed? And will assays be as discriminating as you say they will be? The problems presented here should not be major ones. Major problems should be addressed under the Experimental (Research) Design subsection, not here. Rather, the problems included here should be ones that are, for example, similar to your getting into your new car on a warm, sunny morning and finding that it won’t start. Although this would be totally unexpected and highly unlikely, it could happen. Alternative strategies that would still allow you to reach your destination might include calling a taxi, renting a car, calling a friend, bicycling, etc. You would have no problem whatsoever convincing even the most critical reviewer of the fact that, should this unlikely possibility actually occur, you would overcome the problem and still reach your destination. You need to list equivalent kinds of problems and alternative strategies here for your first specific aim. You need to assure reviewers that, regardless of what might happen, you will still reach your scientific ‘destination.’ Begin with what you would do, should your working hypothesis for the aim prove to be invalid. Then list other potential problems.

Summarize these potential problems in a paragraph, making certain that you have chosen only the most important and probable problems that might occur. Also make certain that the solutions you have offered are feasible and credible. You should not belabor the problems that you identify. Rather, treat them with the brevity that they deserve. For each problem identified, address 1) the nature of the perceived problem; 2) the reason(s) why you don’t think that the problem is likely to arise; and 3) what alternative approach(es) / strategy(ies) you would employ, should the problem be encountered. Note that all of the studies (alternative strategies) proposed should be addressed in the conditional verb tense, because they all represent things that would be done if,
and only if, they became necessary due to unexpected difficulties (i.e. not 'If this happens, we will ....' but rather 'If this happens we would ....')

For example: ‘Our working hypothesis for this aim is _________. Although our preliminary data (see Preliminary Studies section) and what is extant in the literature (refs) strongly support that this hypothesis will test valid, there is a remote possibility that it will not. In that unlikely event, we would turn to _________ as the next most likely explanation. Another potential problem is the way in which we have proposed to determine whether _________ will result in _________. We expect this approach to work because _______. We acknowledge, however, that this new, rapid and inexpensive technology may not prove sufficiently sensitive to quantify X in up to 5% of the samples. Were this problem to arise, we would employ the labor-intensive, expensive ‘gold standard’ approach (ref) that is known to have the necessary level of sensitivity. We have used this alternative method successfully in the past (ref). Another possible problem that could arise is_______ etc.” Note that your plans to address potential problems should be written using conditional sentences. These are not what you will do. They are what you would do, should the problem actually arise. This subsection should be no more than 1/3-to-1/2 page long. We cannot underscore enough the importance of including this subsection in your Research Design and Methods section. If you think that reviewers are reading your Experimental (Research) Design subsection looking for ways to fund you, you are dead wrong. They will be looking for problems. If you have thought of the same problems and offer the solutions to them here, it will make a very positive impression on your reviewers.

**TIMETABLE**

This important section of the Research Design and Methods section is not included by most applicants, in spite of the fact that they are explicitly directed to include it (see text box at the beginning of this chapter). Its inclusion can be extremely helpful to reviewers, and to the NIH. It is
important to include one like that which is depicted below. A well-conceived timetable can give your reviewers perspective about your project that they would otherwise lack. It should not, however, come across as an afterthought; it should be as detailed as is necessary to convince your reviewers that you have thoroughly thought through how long you expect that it will take to complete each component of your project. Enter the years requested as column headings and your specific aims / studies as labels for the rows. The duration of each aim (bolded double-headed arrows), and the expected duration of the major studies that will be conducted under each aim (non-bolded double-headed arrows), should be indicated in the timetable. The titles of studies in the left column should be sufficiently explanatory that the reviewer will understand the specific tasks that will be required to accomplish the aim. If it would help make the timetable more understandable, enter the titles of specific tasks over the related arrows in the table.

FUTURE DIRECTIONS PARAGRAPH

This should be the final paragraph of your Research Design and Methods section. It is the paragraph in which you tell your reviewers what they can expect in the future, should they decide to fund your proposal. You should begin by briefly summing up where you expect to be at the conclusion of this project. In doing so, you want to leave no doubt that the results of this period of funding will complete a step along the continuum of research that you projected in the Specific Aims section with your long-term goal. You should conclude this paragraph by telling the reviewers what your next steps are expected to be, and why they will be important. Thus, this paragraph provides yet another opportunity to get across to reviewers that you are pursuing a continuum of research that is compatible with the overall mission of the NIH. This paragraph is especially important if you are a new applicant, because a significant consideration for the reviewers may be the extent to which you reflect vision in your application. The ‘Future Directions’ paragraph gives you an outstanding opportunity to assure the reviewers, without being obvious about it, that you have such vision. You want them to know that, if they invest in this project, they can expect it to continue to grow and evolve in important directions that will relate to prevention, diagnosis or treatment of disease.

DEVELOPMENTAL STEPS FOR CHAPTER TEN:

1. Understand the expected content of this section, as described in the PHS 398 instructions.
2. Understand the “APPROACH” review criterion and how it relates to this section.
3. Copy and paste your first specific aim from your Specific Aims section into a new document file.
4. Prepare a first draft of the “Introduction” paragraph for this first specific aim. Be certain that it provides a conceptual ‘overview’ for this subsection.
5. Write the “Experimental (Research) Design” subsection for this aim. Be certain that meaningful, but not excessive or mindless, detail is provided.
6. Summarize results that you expect to obtain for aim #1 in the “Expected Outcomes” subsection; integrate these to show that they collectively attain the aim’s objective.
7. Review your research plan and identify problems that could develop – probably won’t but could. List these, together with your solutions, in the Potential Problems and Alternative Approaches subsection for aim #1.
8. Repeat 3-7, above, for each of the remaining specific aims in your Specific Aims section.
9. Prepare a timetable that summarizes when the major activities proposed in your Experimental (Research) Design subsections will occur.
10. Write a brief paragraph entitled “Future Directions.” Briefly summarize what you expect the outcomes of the proposed research to be and relate them to where you expect your continuum of research will lead in the future.
11. After finalizing this section, covert the document into a PDF file and upload it into the PHS 398 Research Plan Component of the SF 424 (R&R) application package using the “Add Attachment” button on line 5 of section 2.

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### PHS 398 Research Plan

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<th>2. Research Plan Attachments:</th>
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<td>Please attach applicable sections of the research plan, below.</td>
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<td>1. Introduction to Application</td>
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<td>(for RESUBMISSION or REVISION only)</td>
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<tr>
<td>2. Specific Aims</td>
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<tr>
<td>3. Background and Significance</td>
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<td>4. Preliminary Studies / Progress Report</td>
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<td>5. Research Design and Methods</td>
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CHAPTER 11

BACKGROUND SUBSECTION of the BACKGROUND AND SIGNIFICANCE SECTION and the BIBLIOGRAPHY & REFERENCES CITED SECTION

BACKGROUND SUBSECTION

Instructions for the Background Subsection of the PHS 398 Research Plan Component / Background and Significance Section: "Briefly sketch the background leading to the present application, critically evaluate existing knowledge, and specifically identify the gaps that the project is intended to fill. Two to three pages are recommended." [Including the significance paragraph that was formulated earlier.]

DEVELOPING THE BACKGROUND SUBSECTION

You are now ready to begin writing the background component of your Background and Significance section. This is one of the main ways, together with the significance paragraph, that you justify the need for the proposed research. It is a commonly misunderstood component, because most writers of grant applications think that it should be a comprehensive review of ALL of the literature. Nothing could be further from the truth. How could anyone possibly write a comprehensive review of his/her field in the few pages that are recommended? It’s simply not possible. Thus, this important means of justifying what you propose must be viewed in a different light. Its real purpose is to provide a highly selective review that justifies the need for the proposed research.

We recommend that you not write this subsection until after you have written the Research Design and Methods section. Why? Because, if you think of the Research Design and Methods section as the ‘plug’ that will fill the gap in the knowledge base, you can now custom design the ‘hole’ into which the plug will exactly fit. Background subsections that are written before the Research Design and Methods section usually contain a great deal of extraneous information that is not necessary to justify the specific research that is proposed. That problem is avoided by writing the background component after the research plan has been written. We recommend that you title this section, Review of Relevant Literature. Put this title in bolded, italicized letters and then continue to write on the same line with text that is not highlighted. The phrasing of the title anticipates, and is designed to deflect, any criticism by an inexperienced reviewer that your background subsection is not a comprehensive review of the field.

Because the background subsection will vary greatly application-to-application, our recommendations here will be general suggestions as to how you should write this subsection. For exam-
ple, this should be a critical analysis of what has been published, not a passive one (i.e., 'Smith did this, Jones did that.'). Without being overly critical of other workers, if there are relevant gaps in what has previously been published, those gaps need to be identified. You should not rely exclusively (or even primarily) on review articles and books when you write this subsection. Reviewers will want to know how complete your command is of the primary literature of your field. Your treatment of the relevant literature needs to be fully up to date. As noted earlier, we recommend that you cite previously published work using first author/year, rather than numbers.

PURPOSE OF THE BACKGROUND SUBSECTION

The purpose of the background subsection is to justify why the proposed research is necessary. It must substantiate all of the unsubstantiated assertions that you made in the first, introductory paragraph of the Specific Aims section. It should detail and expand upon the fact that there truly is an important gap in the knowledge base, and that such a gap represents a critical need or problem. You should begin the background subsection with a brief historical overview of that part of the literature that is directly relevant to the subject of your application. In the first paragraph, you should summarize the most important older accomplishments and observations.

You should follow this paragraph with one that details the most important recent contributions, i.e., the details that will bring your reviewers to the edge of current knowledge. If there are members of the targeted review panel who have been substantive contributors to your field, be certain to cite their work, as long as it does not appear contrived to do so (In other words, they must truly have made a contribution.). Your own published contributions to the field can also be briefly presented, either as a part of this paragraph or in a third, separate paragraph.

The next paragraph should begin identification of the gap in the knowledge base that will be addressed by your application. The more explicit you can be in identifying the gap, the better. Its identification should then be followed by evidence that supports your earlier assertion (in the Aims section) that the gap is an important problem, i.e., that it is preventing vertical advancement of the field.

At this point, you should begin a new paragraph by again presenting the central hypothesis that will be tested. You do so, because testing of it will fill the gap. You should immediately follow its presentation with strong support for how it was formulated. Remember the single sentence that you wrote in the Specific Aims section about how your central hypothesis was formulated? If it included reference to the work of others, this is where you back up that statement with supporting citations from the literature. Your reasons for selecting this particular hypothesis over alternatives should be given in detail, with discussion of the potential merits/demers of alternative hypotheses, if there are any.

At the conclusion of this subsection, there should be a final sentence or two that bridges to your Preliminary Studies section. This last component of the Background and Significance section should make clear that you and your colleagues have already made progress toward filling the gap in the knowledge base that will be targeted. In particular, you want to underscore that your central hypothesis is supported by the results that you have obtained to date. This ending provides an excellent segue into the next, Preliminary Studies section.

Consider writing your background subsection as an outgrowth of the sample sentences that are provided below. Either modify them or write new ones that will accomplish the same objectives.
Introductory (historical perspective) paragraph(s). 'In 19??, ________ et al. made the seminal observation that _______________. On the basis of these studies, it was concluded that ________________. As a direct result, ________ et al. investigated __________, which led to the additional conclusion that _______________. Etc.'

'Edge of Current Knowledge' paragraph. 'The evidence cited above has led workers in the field to appreciate that ________________. The most recent findings in this area support and extend this concept by ________________. Our own studies have contributed to this contemporary body of knowledge by showing that ________________. Etc.'

'Gap in the Knowledge Base' paragraph. 'Although the work cited above provides convincing evidence that A and B interact, the precise mechanism by which this occurs is completely unknown. For example, the work of Santee and Armstrong (1998) showed very clearly that ________________, but stopped short of identifying the related mechanism. Casey et al. (1999) were similarly frustrated in their attempts to discover the mechanism. Such lack of understanding has recently been highlighted as a problem by Gonzales and her colleagues (2000), as well as by Smith and Brown (2001). Each of these groups underscored that progress in the field is highly unlikely until the mechanism becomes known. We are in total agreement with these earlier investigators, because our own progress has been impeded by this gap in the knowledge base. To resolve this issue, we propose in this application a series of studies designed to identify the relevant interactions between A and B that will allow identification of the underlying mechanism. To do this, we will ________________, using approaches already developed in our laboratory (refs).'

'Central Hypothesis and How Formulated' paragraph (BRIEF). 'To identify the mechanism we will objectively test the central hypothesis that ________________. Considerable published support for this hypothesis derives from the following: 1) ________________ (citation[s]); 2) ________________ (citation[s]); and 3) ________________ (citation[s]). Although it might be argued that ________________ is the mechanism, we consider this alternative is unlikely, because ________________. Etc.'

Concluding, transitional paragraph or sentences. In conclusion, the collective evidence reviewed in this section strongly supports the conclusion that there is a need to identify the mechanism by which _______________ relates to _______________. Such information is important because it would ultimately allow the development of _______________. Previous studies and our own preliminary data, which will now be presented under Preliminary Studies, support the need for such research and provide support for the central hypothesis that we have formulated.

Using this approach, your background subsection should consist of six-to-eight highly focused paragraphs. Refine the material by inserting additional information or transitional sentences needed to improve readability and the flow of logic from one point to the next. There should be no more than a total of three pages for the entire Background and Significance section, including the significance paragraph that you wrote earlier. Have you brought your reviewers fully 'up to speed' with respect to the problem that you want to address? Does the flow of information build logically and persuasively toward what your contribution will be? Is the final paragraph written in such a way that it is a good transition into your Preliminary Studies section? If your answers to these questions are affirmative, you have accomplished your goal for this subsection and are ready to go on to the next step.
The Bibliography & References Cited section should be created as a separate PDF file and uploaded into the application using the “Add Attachment” button on line 8 of the SF-424 Other Project Information Component.

The choice and number of citations included in support of your proposal are important. In fact, the references that accompany your application say a lot about you as an investigator. They should mostly be citations of the primary literature, not reviews. They should be up to date, especially if you are resubmitting an application that wasn’t funded on an earlier attempt. Forgetting to update the Bibliography & References Cited section in resubmitted applications is a relatively common mistake. Reviewers will often check this point to see whether or not an applicant has cared enough to update the literature that is presented in support of the proposal. Citations should be complete, i.e., all authors in their published order, title, accepted abbreviation for the journal, volume, year of publication and full pagination. Finally, it is reviewer friendly to present your references in alphabetical order, based on the name of the first (only) author. Do not open a line after each one is presented, because it unnecessarily increases the length of this part of the application. Set off each citation either by numbering it or by presenting it un-numbered in a ‘hanging indent’ format.

DEVELOPMENTAL STEPS FOR CHAPTER ELEVEN:

1. Assemble a file (either hard copy or electronic) of all of the key literature citations that you will plan to use in writing the background subsection.
2. Be certain that you have familiarized yourself with the information in these publications. This means reading more than the abstract.
3. Identify the most important early seminal publications for the field in which you will be writing your proposal. Use them to write the “Historical Perspectives” paragraph.
4. Decide what the most important issues are that need to developed and write a paragraph for each. Be critical in a positive sense, and make certain that each paragraph allows for a conclusion that justifies the need for what you will propose.
5. Write the “Gap in the Knowledge Base” paragraph that provides the driving force for the proposed activities.
6. Write the paragraph that provides the conceptual framework for the proposal’s central hypothesis, together with the arguments that would support its validity.
7. Develop the concluding paragraph that provides a ‘bridge’ or transition to the next, Preliminary Studies / Progress Report section.
8. Combine the ‘Review of Relevant Literature (Background subsection) with the previously prepared significance paragraph (chapter 9) to create one document. The significance paragraph should be first, even though the title of the section is Background and Significance.
9. Convert the Background and Significance section into a PDF file and upload in the PHS 398 Research Plan Component of the SF 424 (R&R) application kit using the "Add Attachment" button on line 3 of section 2 (see below).

<table>
<thead>
<tr>
<th>2. Research Plan Attachments:</th>
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<tbody>
<tr>
<td>Please attach applicable sections of the research plan, below.</td>
</tr>
<tr>
<td>1. Introduction to Application</td>
</tr>
<tr>
<td>(for RESUBMISSION or REVISION only)</td>
</tr>
<tr>
<td>2. Specific Aims</td>
</tr>
<tr>
<td>3. Background and Significance</td>
</tr>
<tr>
<td>4. Preliminary Studies / Progress Report</td>
</tr>
<tr>
<td>5. Research Design and Methods</td>
</tr>
</tbody>
</table>

10. Compile the citations that you have used in the Background and Significance section, as well as in other sections of the Research Plan into a separate, Bibliography & References Cited section.

11. Convert the Bibliography & References Cited section into a PDF file and upload it into the Other Project Information Component using the "Add Attachment" button on line 8 (see below).