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WRITING THE APPLICATION, PART I

Scientific Content and Writing Strategies

THE SCIENTIFIC CONTENT

Let's review: You've established that both your institution and you are eligible to apply for the grant mechanism you think most appropriate for you; you have selected a mechanism that is consistent with your experience and credentials and the pilot data you have (or have not) collected; you have lined up your research team; you have a great and possibly important idea for a study that you believe might be funded. Your computer is fired up. You're wired with coffee. Now all you have to do is present your idea in writing in a manner that will be clearly understood by the reviewers, and you have up to 13 pages, including one page for the Specific Aims (depending on the grant mechanism), in which to do it. (Some grants allow fewer than 12 pages, but still require a specific aims page.)

We're going to use the R01 as a model, because this is the most common type of grant; when differences arise for other grant mechanisms, we note them. We also provide details concerning training grants.

To begin with, there are the Specific Aims, one page limit. We've always found that it is helpful to write this section first because it tells the whole story you want to get across. (And, as we emphasize later, you must indeed do that; you must tell the story so that you have all the major points.)

Next comes the 12 pages of text in which you retell the story you told in the Specific Aims, but now with the addition of details; here, you get to lay out your problem and talk about its significance; you describe preliminary work you have done, including the collection of pilot data; you will provide a short section telling why your proposal is innovative; and you have the opportunity to describe in great detail the approach you will take to study that problem. The last section—the approach—will most often be the longest. Twelve pages is not a lot of room, and you may become frustrated that you won't be able to tell all you want to, but keep in mind, it's a level playing field: Everyone has only 12 pages. The reviewers understand that as well and yet they will wish for more detail. And you must write your plan well enough so that you provide the level of detail they will want to see. We have found that the most common reviewer complaint is that an insufficient amount of detail is provided in the Approach section! We spend some time discussing how to work within this framework, how to tell the story you need to tell in those relatively few pages.

GENERAL NOTES CONCERNING SCIENTIFIC WRITING

How important is good writing? Your prose has to be outstanding. Many people were given the notion, in grade school, that essay, or creative, writing required

skill and subtlety, but that scientific writing was meant to be a series of facts to be memorized; little attention was paid to interesting writing. (Remember your Plane Geometry textbook?) We typically did *not* learn how to introduce the writer to the topic, to make clear the relevance to the reader's life or concerns, to make interesting predictions and explain how we would (or did) back them up. We were given the impression that *writing quality* wasn't as important as in other, more literary, pursuits.

But that is not true. It doesn't have to be that way, and your reviews will be stronger because your writing is easier to read—it flows, it tells a story, and this should be true no matter how basic or how applied your research is or how complicated the concepts. It takes a great deal of work to accomplish this—you must carefully consider every word you use and *hear* it, hear it as though you were a reviewer, not the writer. The writing must flow in a natural way, not short choppy sentences; you must have transitions between sentences and paragraphs. And this takes revising and revising and revising until you're sick of it—but that's the job. And, as we always add, have others read it and even better, read it out loud to them. That's how you really find out if you are telling a coherent story. This includes the Methods, by the way. It should be understandable by someone not in your field.

HINT

There are three broad components of a fundable proposal: First, you must have a great idea. It has to strike the reviewers immediately as a potentially important project that will have a significant impact on your field and will push the science forward. Second, you must demonstrate the feasibility of carrying out the proposed work—this is every bit as important as having a great idea. The reviewers want to be confident that you will

be able to do whatever it is you are promising. Third, you must write it so that your story emerges in a logical, orderly, overly simplistic manner (if you try to include all the ramifications of what you are proposing, you run the risk of boring or even annoying the reviewer with material that is peripheral and often not necessary to make your main points. And in addition, it may cost you space you need for other things).

Here are a set of rules we have developed over many years of writing and reading the proposals of others. Some of them are obvious. It is similar to being told, as you're trying to hit a baseball out of the park, "keep your eye on the ball." Everyone knows this, it is obvious that is what one is supposed to do, but knowing this doesn't necessarily lead to doing it. In the same vein, we don't necessarily believe that any one of these rules will come as a revelation, but if you actually pay attention to them, you'll be a better writer.

Rule 1: Write From the Reader's Perspective. You've got to get into your reader's head, hear what they are hearing. Did something not ring true? If the reviewer hears (reads) even a couple of words that raise a question, he or she may carry a sense of doubt as he or she continues reading your proposal, which may color his or her perception about the quality of the work.

A good way to view the reader's perspective is to read your work out loud. Even if you're the only one in the room, you'll hear your writing differently, and you'll most likely find places that will require either minor or more extensive revision. For example, we often tend to repeat ourselves in these proposals, and you may be more likely to hear that when you read the work aloud. Even better, of course, is to read it to someone else and get their impressions. Try to get colleagues, and try to get other friends who are not in your field.

HINT

You can look up the names of all the people on the study section who will be reviewing your application with

little difficulty. (http://www.csr.nih.gov/Roster_proto/sectionI.asp)

However, you will never know specifically which three of them will have your application assigned to them. As you scan the list of reviewers, you may come across one or two whom you definitely feel will be on your panel, and you may guess correctly, or not. You can't rely on that, so you must write the proposal for those who come from sometimes quite different fields than your own. I (first author) have sat on study sections in which I was given proposals that were miles from my own field, and I certainly appreciated the writer's efforts to make this accessible even to a non-expert in his or her study area.

Also, make sure you cite the work of anyone on the study section who has published in the field in which your proposal resides. No matter how senior we get, we get annoyed when someone doesn't cite our groundbreaking work.

You may find yourself short of space: 13 single-spaced pages is not a lot of room, and you will most likely find in your early drafts that you are over the page limit and must cut. One easy temptation is to cut out elements that make the proposal more easily read by the overburdened reviewer, whose eyes are probably already bleary and whose temper may be short by the time he or she gets to your application. For example, it might occur to you to eliminate spaces between paragraphs, or headings but we urge you to resist the temptation. It is easier and

less tiring to read material that has white space to break up the text, and it serves the dual purpose of highlighting the fact that a new thought is about to appear and makes the text easier to read. Pictures and charts also help for this purpose. You can save space, however, by using half a line space rather than a full one to separate paragraphs. (We also think that is more pleasing to the eye than a full space between each paragraph.) If you get desperate, you can squeeze out a couple of extra lines by using 4 points rather than 6 in your "Format Paragraph" window.

HINT

Also, use headings (sacrifice the space; it is worth it), and be creative about making them stand out: Use bold-faced type, italics, or all capitals—you get the picture. Make sure that you have a consistent hierarchy for headings; major headings could, perhaps, appear in bold capitals; and for a secondary heading, you might then use bold lower-case letters.

But never forget: It is not about what you want to tell, it is what the reader needs to hear—cut out material that is peripheral to your main point.

Rule 2: Be Linear. Each point you make should follow logically from the previous one. Your writing should proceed along a straight line, as much as possible. When you must veer off that line, be careful to bring it back again. Think about proceeding up a tree trunk; if you must go off on a branch for some reason, you must come back to the main line (or trunk, if we're still talking trees). This is not a place to allow your ADD free rein—keep the writing tight!

Tell your story without gumming it up with a lot of unnecessary material. Sounds easy, but it isn't. You recognize that the story you are telling is more complicated than you are able to tell, given the space limitations; but going into those complications may detract from the main part of your story. Rule 3 follows up on this.

Avoid the use of jargon. Aim to have the proposal be understandable without anyone having to ask or look up what a particular expression (or acronym) might mean. (It is annoying to have to go back to a previous page to

remind oneself what a particular acronym means—only use standard ones, or perhaps for really long names that do seriously cost you space).

HINT

Remember, one or more of the reviewers may not be in your field, and may even be in a field that has nothing at all with what you do—jargon they may legitimately not understand will not strengthen your case!

Rule 3: *Following up on Rule 2—Keep It Simple.* As you write your idea, you will begin to see other lines of thought that you could add, although they may not pertain to the main focus of the proposal. This is particularly true for the measures you propose: You may decide to add measures that are peripheral to your main hypotheses, measures that would be easy and inexpensive to collect and might contribute something that would add to the depth of your proposed study. You will undoubtedly be able to come up with legitimate rationales for including them, but this may mean you have begun veering off of the main point. Your motivation is a good one: You're already doing the study so it would be easy to tack on extra measures, and if you add these measures to the proposal, you can show the reviewers what a great bargain they are getting, since you would be giving them two or three studies for the price of one.

Resist the temptation to do this. You'll find yourself saying things like, "You know, it would be easy to get blood on these subjects. . . . We could freeze it for later assay for genetic markers . . ." or "It would be great to get depression measures, since we're already getting self-report measures; it would add another outcome, may result in another paper, might find something. . . ." When you hear yourself or your colleagues uttering these sorts of statements, beware. I'm not merely being a purist, although this is not the way good science is done. I'm giving you extremely practical advice. Think about the following: Every primary measure you include should be directly linked to

- A hypothesis
- A power analysis
- A statistical analysis

You will want to mention other measures in which you're interested because (a) you will want the reviewers to know that you know that these might play an important role, and (b) they might cost money, and if you want to take these measures, you may have to find funds for this within your budget. However, you do not necessarily want to power your sample size to them all. Now, there are ways to finesse this. Measures can be listed as "exploratory," for example, but you can only do that to a very limited extent, and we have more to say about this later. For the most part, resist the temptation to start loading up on outcomes. It is very important that the reviewers see your application as highly focused.

HINT

Many inexperienced investigators feel that if they show what a bargain their research will be, because they are collecting measures that will allow them to answer questions other than those posed by the hypotheses, but resist the temptation to do this. You are more likely to appear as inexperienced, not understanding how much work it is to do the work you are proposing as the main part of your

proposal. However, just because you aren't going to mention a particular measure in the proposal doesn't mean you might not go ahead and collect that measure in the course of the study. Just fight the temptation to mention it in the proposal! And make sure that you can find the money if this meeting is going to incur additional costs.

Rule 4: *Tell a Story.* Think of writing a screenplay. Each scene in a good movie is designed to move the story forward. Your proposal should follow the same principal: The story must unfold in such a way that the reader can follow it and be engaged by it, the way you become engaged by a good novel. It should never violate the reader's sense of logic, and it must do this in a manner that makes the reader want to know what will happen next. Good science is interesting, and interesting reading will improve your chances of getting funded.

Rule 5: *Communicate Your Excitement.* Make no mistake, when you write a grant proposal, you are trying to sell something to a specific set of customers. Just like the guy on TV who sells that

great rotisserie oven, you must communicate your excitement about this important research, and you want to excite the readers as well about (a) the importance of the topic, (b) the innovative new methods you have devised for studying the topic, and (c) the broad implications and, more specifically, the public health implications of the study. And how it will move the field forward.

Rule 6: Words Matter. Obvious, but many people write without really critically evaluating their prose. You really have to think about every word you write; the substitution of one word for another can often color the way the entire statement is interpreted. Ask: What point am I trying to make in this paragraph? (Every paragraph should make a point!). Did I succeed in making the point? Is the language I'm using leading to the reader's comprehension in the way I intended?

You must walk a tightrope when you write a grant application: Your proposal has to be ambitious in its scope but must never appear unrealistic regarding what your proposed study is meant to accomplish and in terms of your ability to carry it out. Unlike a paper, a grant proposal must

do more than replicate previous work, such as your pilot study. It must move the field forward! That is what the reviewers want to fund. *You don't want the reviewers to label your proposal as "ambitious"—it will only feed into the concern that you will not be able to deliver what you have promised!*

HINT

Rule 7: Get Feedback Early On. You need to ask your colleagues and mentors to provide feedback on your proposal. Remember, however, you're asking a fairly large favor: If they're qualified to read your stuff, then presumably they have plenty of their own work, and a good critical reading of someone else's proposal can take hours. Presumably, you have done and/or are prepared to do the same for them, but you still have to be careful to show that you understand the amount of effort they are providing on your behalf. The rules are different for co-investigators, of course; you can ask more of them than you can of colleagues who are willing to help, but who are not officially on the proposal. You must begin working on your proposal several weeks, at the very minimum 8 weeks and it would be better to start at least 3 months before the deadline. Among other things, *it will allow you adequate time to work over your ideas until they coalesce into the story you want to tell.* In addition, it will provide sufficient time to ask colleagues for suggestions, without having to ask them to get their reviews to you within an unreasonable amount of time.

Right now, you're nodding your head in agreement, you'll intend to get the project rolling long before the deadline but in the end, many of you won't follow through on this. You'll get busy, you'll fall behind, you'll have great and probably legitimate reasons for not getting it rolling early, and you'll be writing right up to the last minute—but you're hurting your chances of getting funded.

Here are suggestions for specific questions you might ask your readers to address:

- Were you persuaded that the proposed study should be done and that the results would help answer the question or questions asked?
- Did the writing communicate a sense of my excitement about this project?
- Did you find the story easy to follow? Were there parts that sidetracked the story line?
- Did you feel that the assertions made in the course of telling the story were adequately supported by the published literature and/or my own data?
- Do you consider the project innovative?
- Were the methods appropriate to the study questions?
- Did you find the power analysis convincing?

- What limitations do you feel I should have addressed?
- Was the manuscript adequately proofread?

SECTIONS OF THE PROPOSAL

Here we provide an outline of the sections of the proposal reviewers will need to see. We will provide brief details, enough so that you can see the structure; but once again, look at the *Application Guide* for greater detail:

- **Introduction to the Application:** Only if the proposal is a Resubmission or Revision. First time (new) applications should *not* include a cover page.
- **Specific Aims:** We have covered this elsewhere, but it is worth repeating the NIH instructions: (A) *State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved.* (B) *List succinctly the specific objectives of the research proposed (e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or to develop a new technology).*
- **Research Strategy:** Organize these sections in the order specified below (or as stated in the FOA; FOA instructions supersede the general instructions shown here). There are three main section headings: Significance, Innovation, and Approach. In addition, under Research Strategy include a section called “Preliminary Studies” (if it is a new application) or “Progress Report” (for revisions). We discuss in other sections exactly what should go into these sections. Additional sections include human and/or animal protections; these are discussed in Chapter 6.

A. Significance

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

B. Innovation

- Explain how the application challenges and seeks to shift current research or clinical practice paradigms.
- Describe any novel theoretical concepts, approaches or methodologies, instrumentation or intervention(s) to be developed or used, and any advantage over existing methodologies, instrumentation, or intervention(s).
- Explain any refinements, improvements, or new applications of theoretical concepts, approaches, methodologies, instrumentation, or interventions.

On the other hand . . . (of course, there is always another hand!) do not be shy about explaining why your idea and approach is novel—there is a section in the text that you must write

“Innovation” has always been somewhat problematic, because the reviewers have mixed feelings about it. They want to see that your proposal is innovative, but at the same time, perhaps not too innovative, such that there is no continuity between what is already known and what you plan to do. Sorry, wish we could be more specific, but this is simply a judgment that you will have to make. Make sure that you can connect the study you are proposing with a foundation laid by previous research;

also, make sure to use gold-standard measures wherever possible, which may be seen as making innovation less risky from the point of view of the reviewer. Remember: Reviewers want to fund work that is exciting, innovative, and has promise to move the field in a particular direction; however, they also want to make sure that your proposed experiment is feasible and that you have a reasonable chance of finding data that will support your hypotheses.

called “Innovation,” in which you explain how your study is novel, novel in that you are making a meaningful change or addition to, or inventing a new, theory to explain the etiology of a particular illness. And/or, if your methods are novel, this also is regarded as a legitimate focus. In fact, your proposal may be about a new methodology—a new reagent, for example, or a new, presumably more reliable and valid, method of measuring a particular physiological marker or clinical outcome.

Don’t lose sight, however, of the need to link the research to the public health problem or problems your novel contributions may help solve.

Yes, you need to propose great science and appropriate methods and all that, but it is every bit as important to persuade the reviewers that you will be able to complete the project as it’s been laid out in your proposal. As noted earlier,

don’t try to be a bargain! Make sure that you are requesting funding for the resources you will need to ensure that you will be able complete the study successfully. (Our rule was, work out the budget, and then double it.)

C. Approach

- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.
- Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.
- If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high-risk aspects of the proposed work.
- Point out any procedures, situations, or materials that may be hazardous to personnel and precautions to be exercised. A full discussion on the use of Select Agents should be given.

Preliminary Studies for New Applications. For new applications, include information on Preliminary Studies as part of the Approach section. (Again, we suggest you do this in all applications when you can.) Discuss the PD/PI’s preliminary studies, data, and/or experience pertinent to this application. Except for Exploratory/Development Grants (R21, R33), Small Research Grants (R03), Academic Research Enhancement Award (AREA) Grants (R15), and Phase I Small Business Research Grants (R41/R43), preliminary data can be an essential part of a research grant application and help establish the likelihood of success of the

proposed project. Early Stage Investigators should include preliminary data. (However, for R01 applications, reviewers will be instructed to place less emphasis on the preliminary data in applications from ESIs than on the preliminary data in applications from more established investigators.)

Progress Report for Renewal and Revision Applications. For renewal/revision applications, provide a Progress Report as part of the Approach section. Provide the beginning and ending dates for the period covered since the last competitive review. Summarize the specific aims of the previous project period and the importance of the findings and emphasize the progress made toward their achievement. Explain any significant changes to the specific aims and any new directions, including changes resulting from significant budget reductions. A list of publications, manuscripts accepted for publication, patents, and other printed materials should be included.

HINT

The writing of the proposal is not necessarily a linear process. Actually, it should be regarded as interactive, in that not only will some sections need to be written before others, but also, as you modify a particular section, it often will influence other, previously written sections. For example, as you develop the research strategy,

you may find that one or more of your aims just cannot be carried out for some reason—perhaps it is just too expensive, or the power estimates require a sample size to which you do not have access—and so you will have to rewrite the parts of the proposal that relate to that particular aim.

For this reason, you will need to be writing the budget almost as you start writing the proposal (Chapter 7 describes this process). The research will of course influence the budget, but the budget in turn will influence the research you can carry out. Obviously, there are items you can revise later in the grant-writing process, but you do not want to have to significantly modify your specific aims late in the game, as that will likely require rethinking and rewriting the whole proposal.

As mentioned earlier, consider the importance of looking on the web to see precisely who will be on the study section that will be evaluating your proposal. (http://www.csr.nih.gov/Roster_proto/section1.asp). One reason for this is to identify potential conflicts of interest (of which you will inform the NIH), as well as to identify anyone who, for some reason, you feel cannot provide an unbiased assessment of your work. You cannot know exactly which of the panel members will be reviewing your proposal, although you can make guesses. I urge you to look at the study panel early in the writing of the proposal. You may find panel members whom you might not thought to have cited and, needless to say, if one of them were a reviewer on your proposal, that omission would sit poorly. If there are panel members who have worked in the area in which your proposal resides, it would be wise to take account of their particular points of view and to incorporate these in the proposal. You don't have to agree, of course, but you should address them.

THE NIH REVIEW CRITERIA

The first level of review of your application is carried out by a Scientific Review Group (SRG) that will comprise mostly non-federal scientists who have expertise in relevant scientific disciplines and current research areas. The second level of review is performed by the I/C National Advisory Councils. To be recommended for funding, the proposal must be favorably recommended by both.

Obviously you will want to be aware of, and keep in mind, the criteria by which the reviewers will evaluate your proposal. In the following list are the criteria by which NIH reviewers rate

your proposal. These have changed slightly from past years, so be sure to take a look at this. We provide a summary here, but of course this is a topic worth pursuing further on **Grants.Gov**.

Scoring

- Before a review meeting, assigned reviewers and discussants will score applications on the five review criteria (i.e., Significance, Investigator(s), Innovation, Approach, and Environment) using a scale of 1 to 9, with 1 being the best score.
- Each assigned reviewer and discussant will also provide a preliminary overall impact score using the 1 to 9 scale.
- Streamlining: All applications are scored and summary comments (the *summary statement*) provided, but *only the applications that received impact scores in the top half of the distribution will be discussed during the meeting*. Grants that are not discussed are referred to as “streamlined.”
- At the meeting, discussed applications will receive an overall score from each eligible (i.e., without conflicts of interest) panel member and these scores will be averaged to one decimal place and multiplied by 10. The 81 possible priority scores will thus range from 10 to 90

The following list contains the criteria by which NIH reviewers rate your proposal. Obviously, you will want to have these criteria in your mind as you write your proposal.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?
2. Investigators. Are the PIs, collaborators, and other researchers well-suited to the project? If ESIs or NIs, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PI, do the investigators have complementary and integrated expertise and are their leadership approach, governance, and organizational structure appropriate for the project?
3. Innovation. Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches, methodologies, instrumentation, or interventions? Are the concepts, approaches, methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches, methodologies, instrumentation, or interventions proposed?

Note that there are several criteria for what is regarded as “innovative,” not just “has the study ever been done before?” For example, new methods, new statistical procedures,

hard-to-reach, understudied populations, all constitute innovativeness.

4. Approach. Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the

work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

5. **Environment.** Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment, and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

When you begin drawing up an outline of your research proposal, review these five criteria and make sure that you not only address these points, but that you also draw attention to them. Remember, the reviewers must read several applications; they have the criteria in front of them while they do so. You want them to literally be able to check off each one as satisfied.

Additional Review Criteria

RFAs, which are published in the NIH “Guide for Grants and Contracts,” may list additional requirements specific to the RFA under each of the previously mentioned criteria. In addition, the following items will be considered in the determination of scientific and technical, and in providing the overall impact/priority score, but will not give separate scores for these items.

Protections for Human Subjects. For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: (1) risk to subjects, (2) adequacy of protection against risks, (3) potential benefits to the subjects and others, (4) importance of the knowledge to be gained, and (5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate (1) the justification for the exemption, (2) human subjects involvement and characteristics, and (3) sources of materials.

Inclusion of Women, Minorities, and Children. When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for inclusions (or exclusions) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusions) of children to determine if it is justified in terms of the scientific goals and research strategy proposed.

Conference Grant Applications Only: Appropriate Representation. How well do the plans for inclusion of women, racial and/or ethnic minorities, persons with disabilities, and other individuals who traditionally have been underrepresented in science provide for their appropriate representation in the planning, organization, and execution of the proposed conference or scientific meeting? For more information, visit *Inclusion of Women, Minorities and Persons with Disabilities in NIH-supported Conference Grants*.

Vertebrate Animals. The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of procedures involving animals including species, strains, ages, sex, and total number to be used; (2) justifications

for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain, and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other applications proposing the use of vertebrate animals.

Biohazards Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmission Applications. When reviewing a resubmission application, the committee will evaluate the application as now presented, taking into consideration the responses to comments from the previous scientific review group and changes made to the project.

Renewal Applications. When reviewing a renewal application, the committee will consider the progress made in the last funding period.

Revision Applications. When reviewing a revision application, the committee will consider the appropriateness of the proposed expansion of the scope of the project. If the revision application relates to investigation in the original application that was not recommended for approval by the committee, then the committee will consider whether the responses to comments from the previous scientific review group are adequate and whether substantial changes are clearly evident.

There are additional criteria for specific situations, and these can be found in the manual:

Grants.nih.gov/grants/funding/424/sf424_rr_general_verc.pdf

NEW PROCEDURES IMPLEMENTED BY NIH CONCERNING CONTENT OF THE PROPOSAL

Recently, applicants will have to address some new procedures that were implemented for due dates on or after May 25, 2016, which, by the time this book is out, will have passed. The most important of these concerns additional substantive material required for inclusion in the Significance/Approach sections. We report much of what is on the website here, because it is so important. The following text was taken directly from the NIH website:

Scientific rigor and transparency in conducting biomedical research is key to the successful application of knowledge toward improving health outcomes. The information provided on this website is designed to assist the extramural community in addressing rigor and transparency in NIH grant applications and progress reports. See <http://grants.nih.gov/reproducibility/index.htm> for more details on Goals, Guidance, and Resources.

Guidance: Rigor and Reproducibility in Grant Applications

The NIH is committed to promoting rigorous and transparent research in all areas of science supported by a variety of grant programs. Updates to application instructions and review language intended to enhance reproducibility through rigor and transparency have been implemented for research grants and mentored career development

awards. Updates to institutional training grants, institutional career development awards (K12/KL2), and individual fellowships will be forthcoming in 2017 or later.

What does “scientific rigor” mean?

Scientific rigor is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation, and reporting of results. This includes full transparency in reporting experimental details so that others may reproduce and extend the findings. Investigators should apply the elements of rigor that are appropriate for their science. (From FAQs: <http://grants.nih.gov/reproducibility/faqs.htm#4824>)

Note. The FAQs are exceptionally useful for answering questions you may have! We asked various random questions, and always found answers. For example:

How will applicants be expected to address scientific rigor in their applications if they are proposing highly innovative research projects?

Innovative research involves a greater level of risk because of the novelty of the research questions, but innovative research can still be carried out in a rigorous manner. The risk associated with the research can be identified and managed by considering the scientific premise, identifying the factors that are unknown, and incorporating strategies to reduce bias and ensure the methods are designed to generate robust results appropriate for the stage of research. Exploratory research may be able to accommodate more risk than clinical research. Strategies to mitigate risk should increase commensurate with research type or stage, such as moving from preclinical into clinical research. Innovative research projects are expected to generate data that is reproducible and provides a foundation for future studies.

Are guidelines available on how much detail to include in my application regarding rigor and transparency?

As with information typically included in grant applications, one cannot present every detail, yet there are ways to succinctly state what is planned. For example: “10 males and 10 females will be randomized to blinded treatment and control groups, giving 80% power to detect a treatment effect size of 65% compared to a baseline response of 5% at a significance level of 0.05.”

A number of NIH institutes and centers have issued more detailed guidelines in specific funding opportunities or for an area of funding, such as all preclinical research. For examples of guidance that may be helpful for you to consider as you develop your application, see NINDS Guidance, NOT-MH-14-004, and NOT-DA-14-007. For examples of past funding opportunities, see PAR-13-023 (R21) and RFA-NR-15-001 (R01).

Investigators should be aware of the guidelines for publishing preclinical research in journals, which are similar in intent to the new application instructions.

What if an application includes a power analysis that peer reviewers or program staff identify as inappropriate?

The updated review language directs peer reviewers to assess the scientific rigor of the experimental design, including the appropriateness of any justification for the sample size

selection, under the Approach review criterion for research grant applications. The updated review language formalizes NIH's expectations that statistical power be addressed. Program staff also may, at the I/C's discretion, recommend changes to experimental designs, for example, to establish conformity with adopted best practices for the research discipline.

Which relevant biological variables do we need to consider?

Applicants should consider the biological variables that are relevant to the experimental design of the study. The choice of animal model or human population to be included will vary with the scientific topic of the proposed research. For example, sex, age, weight, and underlying health conditions are biological variables that may affect outcome and should be considered where applicable.

In particular, sex is a biological variable that has been frequently ignored in animal study designs and analyses, leading to an incomplete understanding of potential sex-based differences in basic biological function, disease processes, and treatment responses. NIH expects that sex as a biological variable (SABV) will be considered in research designs, analyses, and reporting of vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex.

What are “key biological and/or chemical resources”?

Key resources refer to *established resources* that will be used in the proposed research.

Key biological and/or chemical resources include, but are not limited to, cell lines, specialty chemicals, antibodies, and other biologics. Key biological and/or chemical resources may or may not be generated with NIH funds and

- may differ from laboratory to laboratory or over time,
- may have qualities and/or qualifications that could influence the research data, and
- are integral to the proposed research.

Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals.

Depending on the research study, biological samples may be considered key biological resources that need to be authenticated if they are *an established resource*, particularly if the investigator received the samples from an outside source.

Each investigator will have to determine which resources used in their research fit these criteria and are therefore key to the proposed research.

The quality of resources used to conduct research is critical to the ability to reproduce the results.

Research Grants and Mentored Career Development Awards

The updates to NIH research grant and career development award application instructions and review language focus on four key areas: (Note that the website provided some examples, which we include)

1. The scientific premise of the proposed research
 - The **scientific premise** for an application is the research that is used to form the basis for the proposed research question(s). NIH expects applicants to describe the general strengths and weaknesses of the prior research being cited by the applicant

as crucial to support the application. It is expected that this consideration of general strengths and weaknesses could include attention to the rigor of the previous experimental designs, as well as the incorporation of relevant biological variables and authentication of key resources.

- See related FAQs, blog post
2. Rigorous experimental design for robust and unbiased results
 - **Scientific rigor** is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation, and reporting of results. This includes full transparency in reporting experimental details so that others may reproduce and extend the findings.
 - See related FAQs, blog post
 3. Consideration of relevant biological variables
 - **Biological variables**, such as sex, age, weight, and underlying health conditions, are often critical factors affecting health or disease. In particular, sex is a biological variable that is frequently ignored in animal study designs and analyses, leading to an incomplete understanding of potential sex-based differences in basic biological function, disease processes, and treatment response.
 - NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex.
 4. Authentication of key biological and/or chemical resources
 - **Key biological and/or chemical resources** include, but are not limited to, cell lines, specialty chemicals, antibodies, and other biologics. Key biological and/or chemical resources may or may not be generated with NIH funds and
 - may differ from laboratory to laboratory or over time,
 - may have qualities and/or qualifications that could influence the research data, and
 - are integral to the proposed research.
 - The quality of resources used to conduct research is critical to the ability to reproduce the results. Each investigator will have to determine which resources used in their research fit these criteria and are therefore key to the proposed research.

Institutional Training Grants, Institutional Career Development, and Individual Fellowships

The NIH plans to require formal instruction in rigorous experimental design and transparency to enhance reproducibility for institutional training, institutional career development, and individual fellowship applications no sooner than 2017. See NOT-OD-16-034.

When implemented, applications will be expected to provide the following:

Institutional training grant applications will be required to include within the training program plan *a summary of the instruction* planned for all predoctoral and postdoctoral trainees to ensure the knowledge and skills required to design and conduct rigorous, well-controlled experiments that consider all relevant biological variables, use authenticated biological and chemical resources, and apply appropriate statistical tests for data analyses. In addition, a separate attachment will be required to describe in more detail the instructional content and curricular content.

Institutional career development applications (K12/KL2) will be required to include within the career development program plan *a summary of the instruction* planned for all scholars to

ensure the knowledge and skills required to design and conduct rigorous, well-controlled experiments that consider all relevant biological variables, use authenticated biological and chemical resources, and apply appropriate statistical tests for data analyses. In addition, a separate attachment will be required to describe in more detail the instructional content and curricular content.

Individual fellowship applications will be required to summarize in the research strategy section plans to ensure rigorous, well-controlled experiments that consider all relevant biological variables, use authenticated biological and chemical resources, and apply appropriate statistical tests for data analyses. In addition, more detailed description of instruction in rigorous experimental design to ensure reproducibility will be required in the section on Institutional Environment and Commitment to Training.

RESOURCES

- SABV Decision Tree: **Reviewer Guidance to Evaluate Sex as a Biological Variable (SABV)** (posted 07/20/2016)
- Staff Training Module: **General Policy Overview** (compiled by NIH OER, 10/30/2015)
- **Reviewer Guidance on Rigor and Transparency** (compiled by NIH OER, 03/21/2016)
- **Activity Codes for Rigor and Transparency** (updated 12/06/2015)
- **Frequently Asked Questions**
- **Examples of Rigor in Applications**

*These brief excerpts are taken from awarded applications reviewed under a pilot FOA for rigorous experimental design, which is only one part of the updated instruction and review language for January 25, 2016 and beyond. Note that these examples were selected based on high overall impact scores and positive reviewer comments specific to rigor. **These examples are provided to show how elements of rigor and transparency have been succinctly provided in applications; they may not represent all the aspects and may still have room for improvement.***

Example #1

Aim 3: Male and female mice will be randomly allocated to experimental groups at age 3 months. At this age the accumulation of CUG repeat RNA, sequestration of MBNL1, splicing defects, and myotonia are fully developed. The compound will be administered at 3 doses (25%, 50%, and 100% of the MTD) for 4 weeks, compared to vehicle-treated controls. IP administration will be used unless biodistribution studies indicate a clear preference for the IV route. A group size of N = 10 (5 males, 5 females) will provide 90% power to detect a 22% reduction of the CUG repeat RNA in quadriceps muscle by qRT-PCR (ANOVA, α set at 0.05). The treatment assignment will be blinded to investigators who participate in drug administration and endpoint analyses. This laboratory has previous experience with randomized allocation and blinded analysis using this mouse model [refs]. Their results showed good reproducibility when replicated by investigators in the pharmaceutical industry [ref].

Example #2

Aim 1: Primary screen: In this high throughput screening assay, we combined the SMN promoter with exons 1-6 and an exon 7 splicing cassette in a single construct that should respond to compounds that increase SMN transcription, exon 7 inclusion, or potentially stabilize the SMN

RNA or protein [refs]. The details of the assay and the SMN2-luciferase reporter HEK393 cell line have been extensively validated [refs]. Each point is run in triplicate, the compounds are tested on three separate occasions, and the results are averaged to give an EC50 with standard deviation. Secondary screen: . . . We analyze SMN protein levels by dose response in quantitative immunoblots with statistical analysis by one-way ANOVA with post-hoc analysis using Dunnett or Bonferroni, as appropriate.

Aim 2: Each set of compounds will include a blinded negative control compound that has been determined to be inactive and that is solubilized in the same manner as test compounds. Mice will be randomly assigned within a litter, and data will be collected and submitted to the PI. For compounds that demonstrate extended survival, the PI will be sure to have these tested in (the collaborators') labs, and data will be merged and evaluated. To calculate the number of the experimental mice, we will perform an SSD sample size power analysis to ensure that the appropriately minimal number of mice is used in each experimental context. Typically for each compound in life span studies, we will need ~20 SMA animals in the treated group; ~20 SMA animals in the vehicle treated group; ~20 SMA animals in the untreated group. If we can administer the compound in aqueous solution without expedient, the vehicle and untreated groups might be combined, because these should have identical survival. Therefore, no more than 80 SMA animals will be needed per compound.

Example #3

Aim 2: Intensity signal data will be transformed into log values and then modeled by longitudinal methods (reference cited). Specifically, the composite difference in mean intensity signals over time between the bi-specific T cells vs. control groups is assumed to be 2.8 logs with a composite standard deviation of 2.2 logs. Furthermore, we will assume at least five repeated measurements per mouse after T cell infusion and a within-mouse intra-correlation coefficient equal to 0.50. Thus, a sample size of 10 mice per group will provide at least 80% power to detect the above difference between treated versus control group with a 5% significance level. Log-rank test will be used to compare the survival distribution between groups.

VAS: Animal numbers are based on the requirement to perform each experiment (power and sample size calculations are described in the Research Strategy), which includes an independent experimental repeat.

Example #4

Aim 1: Statistical considerations: In our preliminary studies consisting of this same cohort of DFUs (N= 100) and utilizing 16S rRNA sequencing, we were able to detect dimensions of DFU microbiome, including microbial diversity, that were significantly associated with DFU outcomes. We therefore anticipate that the sample size will provide sufficient power to detect significant differences using metagenomic sequencing, because this is a more sensitive and less-biased assay of microbial identification and diversity.

Aim 3: Random Forests, a machine learning approach for classification, will be used to determine which metagenome features differentiate groups (e.g., antibiotics vs. no antibiotics; pre- vs. post-debridement). Random Forest uses a bootstrap method to assess test error, ideal in our situation of small sample size (N = 18). For diversity and load measures, significance between groups will be assessed using non-parametric Wilcoxon rank-sum tests.

Here is something you may have noticed: You would have presumably done this regardless of the “new procedures” notice; basically, the NIH is requesting that you be very specific and even exhaustive concerning the methods you propose to use, the procedures, the materials; or the measurements you propose to take, such as biological variables. How do you plan to measure them? What research provides reliability and validity for your proposed measurements? Here is a question and answer from FAQs (<http://grants.nih.gov/reproducibility/faqs.htm#4824>)

What does “scientific premise” mean for a grant application?

Scientific premise concerns the quality and strength of the research used to form the basis for the proposed research question. NIH expects applicants to describe the general strengths and weaknesses of the prior research *being cited by the applicant as crucial to support the application*. The NIH expects this consideration of general strengths and weaknesses to include attention to the rigor of the previous experimental designs, as well as relevant biological variables and authentication of key resources.

Recent changes in NIH procedures

In 2015, NIH announced several changes to the application and scientific procedures that were on the books. It would be a good idea to review these changes in the event it applies to your application. Here is the announcement:

Summary of Upcoming Significant Changes to the NIH Grants Policy Statement

The revised NIH Grants Policy Statement (NIHGPS, rev. 11/2015) will represent an update to the 03/31/2015 version and will be applicable to all NIH grants and cooperative agreements beginning on or after the revision date. It incorporates new and modified requirements, clarifies certain policies, and implements changes in statutes, regulations, and policies that have been implemented through appropriate legal and/or policy processes since the previous version of the NIHGPS dated 03/31/2015. When issued, the revised NIHGPS will supersede, in its entirety, the NIH Grants Policy Statement (03/31/2015) as a standard term and condition of the award.

1. Sec. 2.3.7.10 NIH Genomic Data Sharing: Requires that applications proposing to generate large-scale human and/or nonhuman genomic data are expected to include a genomic data sharing plan; requires that applicants who wish to use controlled-access human genomic data from NIH-designated data repositories briefly address their plans for requesting access to the data in the application, and state their intention to abide by the NIH Genomic Data User Code of Conduct.

Reason: Implements provisions announced in NOT-OD-15-083 (“Reminder: NIH Grant Applications and the NIH Genomic Data Sharing Policy”; <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-083.html>)

2. Sec. 2.3.9.5 Application Noncompliance: Reminds applicants that NIH may withdraw any application identified during the receipt, referral, and review process that is not compliant with the instructions in the SF424 (R&R) Application Guide, the Funding Opportunity Announcement, and relevant NIH Guide Notices. Subsequent subsections renumbered.

Reason: Implements provisions announced in NOT-OD-15-095 (“Reminder: NIH Policy on Application Compliance”)

3. Sec. 4.1.3 ClinicalTrials.gov Requirement: Text added to clarify that results reporting is still required after the period of performance has ended.

Reason: To clarify FDAAA requirement.

4. Sec. 4.1.15.9 Informed Consent for Research on Dried Blood Spots Obtained Through Newborn Screening.

Reason: Implements provisions announced in NOT-OD-15-127 (“Preliminary Guidance Related to Informed Consent for Research on Dried Blood Spots Obtained Through Newborn Screening”)

5. Sec. 4.1.14 Human Fetal Tissue Research: The language is changed from “guidance” to “regulatory requirements.”

Reason: To highlight this is a regulatory requirement.

6. Sec. 8.1.1.3 Extension of Final Budget Period of a Previously Approved Project Period without Additional NIH Funds.

Reason: To reduce administrative burden, NIH will allow our recipients to reduce effort during a NCE without prior approval.

7. Sec. 8.1.2.5 Change in Scope: Expands the description of Changes from the Approved Involvement of Human Subjects Requiring Prior NIH Approval.

Reason: Implements provisions announced in NOT-OD-15-128 (“Guidance on Changes That Involve Human Subjects in Active Awards and That Will Require Prior NIH Approval: Updated Notice”) and NOT-OD-15-129 (“Prior NIH Approval of Human Subjects Research in Active Awards Initially Submitted without Definitive Plans for Human Subjects Involvement (“Delayed Onset Awards): Updated Notice”).

8. Sec. 8.2.3.3 Genomic Data Sharing (GDS) Policy: Allows investigators to request permission to transfer controlled-access genomic and associated phenotypic data obtained from NIH-designated data repositories that are under the auspices of the NIH GDS Policy to public or private cloud systems for data storage and analysis.

Reason: Implements provisions announced in NOT-OD-15-086 (“Notice for Use of Cloud Computing Services for Storage and Analysis of Controlled-Access Data Subject to the NIH Genomic Data Sharing [GDS] Policy”).

9. Sec. 8.2.4 Inventions and Patents: Requires recipients to report inventions subject to Bayh-Dole regulation electronically to NIH through iEdison (<http://iEdison.gov>).

Reason: Implements provisions announced in NOT-OD-15-080 (“Notice Regarding Requirement of Grantees and Contractors to Submit Invention Disclosures, Related Reports and Documents Via iEdison”).

News, Notices, and Blog Posts

On January 29, 2016, NIH Deputy Director of Extramural Research, Dr. Mike Lauer, published a series of Open Mike blog posts on each of the four focus areas of the rigor and transparency policy for research grant and career development award applications: Scientific Premise in NIH Grant Applications (<https://nexus.od.nih.gov/all/2016/01/28/scientific-premise-in-nih-grant-applications/>), Scientific Rigor in NIH Grant Applications (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-011.html>), Consideration of Relevant

Biological Variables in NIH Grant Applications (<https://nexus.od.nih.gov/all/2016/01/29/consideration-of-relevant-biological-variables-in-nih-grant-applications/>), and Authentication of Key Biological and/or Chemical Resources in NIH Grant Applications (<https://nexus.od.nih.gov/all/2016/01/29/authentication-of-key-biological-andor-chemical-resources-in-nih-grant-applications/>).

On December 17, 2015, the NIH published guide notice NOT-OD-16-034 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-034.html>) to notify the community of upcoming requirements for formal instruction in rigorous experimental design and transparency to enhance reproducibility. This notice applies to institutional training grants (D43, T15, T32/TL1, T34, T35, T36, T37, T90/R90, and U2R), institutional career development awards (K12/KL2), and individual fellowships (F05, F30, F31, F32, F37, F38, and FI2).

On December 15, 2015, the NIH published guide notice NOT-OD-16-031 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-031.html>) to notify the community of updates to the PHS Research Performance Progress Report (RPPR) instructions to address rigor. New questions about rigor can be found under Accomplishments, Sections B.2 and B.6.

On October 13, 2015, the NIH published guide notices outlining updates to form instructions for applications due in 2016, including an overview (NOT-OD-16-004) (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-004.html>), as well as details on Implementing Rigor and Transparency in NIH & AHRQ Research Grant Applications (NOT-OD-16-011) (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-011.html>) and Implementing Rigor and Transparency in NIH & AHRQ Career Development Award Applications (NOT-OD-16-012) (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-012.html>).

On October 30, 2015, NIH Deputy Director of Extramural Research, Dr. Mike Lauer, published an Open Mike blog post on Bolstering Trust in Science Through Rigorous Standards (<https://nexus.od.nih.gov/all/2015/10/30/bolstering-trust-in-science-through-rigorous-standards/>). NIH OER has also released a staff training module that provides a General Policy Overview (<https://grants.nih.gov/policy/index.htm>) on enhancing reproducibility through rigor and transparency.

Blog entry on “Listening to Our Stakeholders On Considering Sex as a Biological Variable” (http://orwh.od.nih.gov/sexinscience/overview/pdf/NOT-OD-15-102_Guidance.pdf).

Analysis of Public Comments: “NIH Request for Information: Consideration of Sex as a Biological Variable in Biomedical Research” (<https://nexus.od.nih.gov/all/2015/05/20/listening-to-stakeholders-sex-as-a-biological-variable/>).

On June 9th, 2015, the NIH published guide notices Enhancing Reproducibility through Rigor and Transparency (NOT-OD-15-103; <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-103.html>) as well as Considering Sex as a Biological Variable in NIH-funded Research (NOT-OD-15-102).

Annual Research Performance Project Reports (RPPRs): This Notice informs recipients of NIH grants that information on project personnel listed in Section D (Participants) of their annual Research Performance Progress Reports (RPPRs) will be displayed in RePORTER beginning with RPPRs of grants funded in fiscal year 2016. RePORTER, a public database containing the details of NIH-funded research, can be accessed at <https://projectreporter.nih.gov>.

WRITING THE INDIVIDUAL SECTIONS OF THE GRANT TEXT

The Title

See Chapter 7 for suggestions concerning the title of your project.

The Abstract

It is probably best to write the abstract after you've completed the 13 pages of the main text; you'll know exactly what you are doing at that point. The abstract should be written with care, because, unlike the rest of the proposal, it is read by all the reviewers, not just the few who have been assigned your application. It is usually the first thing the reviewers will read and must grab the reviewers' interest immediately. The abstract is important because it provides a context for the proposed work. In addition, if the grant is funded, the abstract becomes public information. Finally, the abstract will guide the assignment of the proposal to a particular study section.

The abstract should describe the nature of the problem or research question, the long-term objectives, the innovative features of the research, the specific aims, and the research design and methods. This is a place where clarity is crucial: Write the abstract only after you have gotten fairly far along in the writing process, and then ask colleagues and co-investigators to read it and provide critical feedback.

Specific Aims

The Specific Aims section assumes a great deal of importance because, along with the abstract, it is often the first thing that reviewers read. Therefore, it is likely to influence their perceptions of the proposed research and, equally important, of your abilities. The Specific Aims must accomplish a great deal in a short amount of space (you have one page, no more than that). So the Specific Aims must be extremely carefully and well-written because it must tell the entire story, or at least enough of it so that the reader goes into the 12-page section with an understanding of the context for the details that will follow. We have provided an (abridged) example of an entire R01 proposal, which will be used throughout the next several chapters. The Specific Aims of this proposal follow; after that, we go, paragraph by paragraph, through the 12-page section, commenting on noteworthy aspects of the writing.

HINT

Do not propose overly ambitious aims. Reviewers may worry that the scope of the work is greater than your budget and/or that the amount of effort you have allocated

to the project will be insufficient. They may regard underbudgeting as a sign of inexperience.

Necessary Elements of the Specific Aims Section

- A clear statement of the problem or question you plan to investigate
- Public health significance
- Background material, to provide context for your proposal
- Why your proposal is innovative, needs to be done
- What you plan to do (i.e., basics of design, primary outcome[s], study conditions)
- Specific aims and, space permitting, hypotheses

In this chapter, we present a proposal, to use as an example, that focuses on lowering blood pressure in hypertensive patients using a behavioral intervention, tested in a randomized controlled trial. An example of the complete Specific Aims page follows. Note the numbers in brackets—{ }—these refer to notes following the example. This proposal is an edited version of an R01 application for a clinical trial that was funded. The example is carried through to the remaining sections in the 12 pages.

Specific Aims Example

Specific Aims {1}

Although drug therapies have greatly improved blood pressure (BP) control, 50% of hypertensives on drug treatment have inadequately controlled BP, which leads to excess risk for morbidity and mortality and produces a huge economic burden on the United States. {2} Promising behavioral approaches to BP control include diet and exercise, as well as stress response-focused interventions, including anger management therapy, tailored stress-reduction approaches, and device-guided breathing and other biofeedback techniques. This application proposes to test the short- and long-term effects of a novel intervention, *guided breathing*. Small studies have shown that guided breathing has positive short-term effects on BP, but

long-term effects are not known. Guided breathing may be a viable ancillary treatment for high blood pressure, because it has been shown to have high patient acceptability, promising initial (short-term) evidence, and no known side effects. {3}

Guided breathing interventions, which slow the breathing rate to the 6- to 10-minute range, have shown substantial effects on BP reduction in several published studies. Although the sample sizes of the studies are small, the results are highly consistent, ranging from reductions in systolic/diastolic BP (SBP/DBP) of 5.5/3.6–15.2/10.0 mmHg. These effects are surprisingly large, considering the relatively brief practice sessions (daily 15-minute sessions for 8 weeks), and if they are found to persist may represent an effective, accessible, cost-efficient way to help control BP in hypertensives. {4}

(Continued)

NOTES FOR THE RESEARCH STRATEGY: SPECIFIC AIMS EXAMPLE

{1} Use these or similar headings to signal that a new major section is about to begin. Also, note the space between Specific Aims and the first paragraph (and between all succeeding paragraphs; we suggest you use a 6-point distance between paragraphs, but if you are really hurting for space (especially in the Specific Aims), try 5 points then 4 points. The point is to make it as easy on the reviewer's eyes as possible (remember, he or she may be reading your application—one of a big pile—at 3AM on the morning of the study group session).

{2} Make reference to the public health implications of the problem right up front.

{3} Note that the introductory paragraph provides a lot of information: It describes the problem (hypertension is poorly controlled in spite of drug therapy), the public health significance of the problem (including noting the 50% prevalence rate), and a proposed solution (“guided breathing” provides a promising adjunct/alternative to medications). Note that the authors might have noted the prevalence rate (around 30% in the United States)—they really did not need to do this. This paragraph also gives a lead-in to the main goal of the study (to test the effects of the intervention on blood pressure in hypertensive patients).

Obviously this example uses an application for a clinical trial, but you may be an animal or bench researcher; however, that doesn't change the fact that the ultimate goal of

your research is to address a public health problem, and it should be mentioned in the first paragraph—the first lines of the first paragraph if you can.

HINT

NOTES

{4} The second paragraph provides support for the rationale by not only describing results from previous studies, indicating that there is reason to think the intervention works, but also, these studies are based on small sample sizes, so additional studies are needed. The paragraph also addresses a subtle point: On the one hand, it demonstrates the possible utility of the intervention by discussing reported blood pressure changes; on the other hand, these changes are larger than one might have expected from such an intervention, and by labeling them as “surprising,” the authors are, in effect, saying, “You are probably somewhat skeptical about these effect sizes, but so were we; however, there are too many studies to dismiss.” You will have different issues to contend with, but the important point here is this: Talk to the reviewers through the language of your proposal if you find yourself wanting to explain or to let the reviewer know that there is a problem but that you are aware of it and are solving it in a particular manner.

Again, this is relevant for all disciplines, right on down to basic work.

HINT

Specific Aims Example (Continued)

Three limitations of the published studies must be addressed before guided breathing can be recommended for widespread use: (1) To what extent are the observed BP changes sustained throughout the day and night? The Food and Drug Administration (FDA) requires that effective antihypertensive treatment lower the BP over a full 24 hours. So far, only one small study (N = 13) has examined the effects on ambulatory BP (ABP). {5} (2) Is there anything special about breathing at 6–10 breaths/minute, or is it a nonspecific relaxation effect? {6} Analyses of behavioral methods of treating hypertension (HTN), such as relaxation training, have generally concluded that the effects are not specific to the treatment modality. (3) What is the effect duration? Only one study, of 6-month duration, examined the effects of guided breathing on BP for more than 8 weeks. {7} It is worth noting that one would not expect 8 weeks of anti-HTN medication to have an effect on BP a year later; however, the expectation has been that effects of behavioral interventions should be sustained for a long duration

after the treatment regimen has ended. Behavioral interventions need to take into account methods to sustain long-term effects, including cost effectiveness, and that is one focus of this application. {8}

Our aim is to conduct a blinded, randomized controlled trial (RCT) to test the efficacy of a guided breathing intervention in poorly controlled hypertensives (N = 400, 100 per arm). 24-hour ABP, shown to be a superior predictor of target organ damage and cardiovascular events, is the primary outcome, and allows inspection of the diurnal pattern. We will include two control groups, usual care (UC) and placebo, using a device that is identical to the guided breathing device, except that it does not slow the breathing rate. The two “intervention” arms actually represent two delivery methods: (1) Standard Duration: Intervention lasts the 8 weeks that is typical of the literature, and (2) Extended Duration: Intervention continues until the 12-month follow up. The Figure shows the design. {9}

(Continued)

NOTES

{5} Ambulatory blood pressure provides a highly stable measure compared to clinic blood pressure and is a better predictor of target organ damage. This is explained in the Significance section of the 12-page section, but the authors are presuming, probably correctly, that most cardiovascular scientists will know this. Note also that the authors get very specific here about the one ambulatory monitoring study; that is some of their most compelling evidence, and they wish to underscore it.

{6} Note the use of the interrogative. It is desirable to break up the prose in different ways, such as this one. It is demonstrative of how the author may communicate with the reviewer without stepping outside the bounds of accepted scientific writing.

{7} Again, the authors provide detail about a particular study they consider important. This is a good practice, but don't do much of this in the Specific Aims section.

{8} Notice that the authors are diplomatically teaching something to the reader—they make an excellent point regarding the expectations concerning behavioral interventions. Not only is it true, and not only does it provide support for their case, but most important, it also stimulated a uniform “hmmm, I never thought of it, but it's true” reaction from several colleagues on whom I tried out the statement.

{9} The authors here move to general aims, including the fact that the study will be a randomized controlled trial (which provides a particularly strong test of intervention efficacy), and they describe the design (the control groups to be used are always an important issue in intervention studies), the patient population, and the study duration.

Specific Aims Example (Continued)

{10}

	Intervention	Placebo
Brief	N=100	N=100
Extended	N=100	N=100

The Specific Aims {11} Are:

1. To recruit 440 hypertensive patients with the goal of ending with a total of 100 in each of the 4 arms. {12}
2. To test the effect of a guided breathing intervention on Ambulatory BP at 8 weeks (Brief) and at 12 months (Extended), compared to usual care and a placebo condition.

Primary Hypotheses:

1. Participants in the two intervention conditions (which are identical until 8 weeks) will have lower ABP compared to participants in both the UC and Placebo conditions.
2. Participants in the Placebo control condition will have lower ABP compared to participants in UC.
3. Participants in both intervention conditions will have lower ABP at 12 months compared to participants in Placebo and in UC.

4. Participants in the extended duration intervention condition will have lower ABP at 12 months compared to participants in the standard duration intervention condition.

Additional Research Question: We plan to evaluate potential mechanisms that may mediate the effects of the intervention on BP, including baroreflex sensitivity, heart rate variability (HRV), changes in ambulatory respiration, and self-reported changes in physical activity and anxiety. {13}{14}

(Continued)

NOTES

{10} The authors have added a figure showing the 2 x 2 study design and sample sizes in each arm. It's not absolutely necessary; however, it is a good thing to do, if you have the room. And the authors have done a good job of explaining it in the text. Again, anything to make it easier for the reviewers to understand and easier for them to read is helpful (a figure breaks up the page and gives the eyes a bit of a rest).

{11} This next one is a controversial and subtle point, worth paying particular attention to. Do you use aims, do you use hypotheses, why are some "primary" aims or hypotheses and some "secondary," what is the distinction for "research questions" sometimes tacked on after the last of the aims or hypotheses? The thing is, talk to 10 experienced and successful grant writers and you'll get 10 opinions. This is true even when you talk to several NIH program officers. No criticism of them; it is simply ambiguous. Moreover, look at 10 funded grant applications and they'll have done them in 10 different ways. If you can do both, as in this example, great. If not, stick with Specific Aims; make sure they are focused, and try to keep the number of them down (to 3, or 4 say).

{12} This is a somewhat unusual aim; researchers usually stick to statements that correspond with their hypotheses. However, it is a good idea to let the reviewers know what you actually aim to do.

{13}{14} Primary and secondary hypotheses and research questions. Frankly, there is often a good deal of hand waving here. Of course, your primary hypotheses should be those that are the main points of the study. The question is, what are the implications of labeling them one or the other? Reviewers tend to look at the power analyses, and a question that always comes up is, toward which outcome measures are they geared? If a researcher has laid out a hypothesis, I assume he expects to test it; does he have the statistical power—that is, a sufficient number of subjects—to do so? In this particular instance, you can see at once the authors' logic. The sole difference between the primary and secondary hypotheses is the follow-up period to be used, 8 weeks (which is well-supported by the previous studies) or 12 months (no data at all on which to base a prediction). Thus, the authors do not power to the 12-month analysis as they really have little basis to do so.

When should you label an aim as a "Research Question"? Well, again, this is controversial and there is no clear guide. If your goal is to accomplish something that is relevant but not directly involved, you might label it as an Additional Research Question. However, the subtext is that you probably are not aiming to power to this analysis, not a strength of the proposal. If you are lucky, however, you will have a sufficient sample size to test this question because of the power analyses for your main variables. But be wary of using "additional research questions."

It is easy to get carried away with hypotheses. Try to limit the number of them—there is of course no hard and fast

rule, but we suggest you try to limit yourself to two or three hypotheses.

HINT

We have urged you to write from the point of view of your audience (the two or three reviewers who will score your application). **THIS IS THE SINGLE MOST IMPORTANT POINT WE CAN MAKE! YOU MUST HEAR YOUR WRITING AS THOUGH YOU WERE A REVIEWER!** Also, keep in mind the larger audience: the NIH as an organization and its agenda. The NIH leaders must convince Congress to allocate a great deal of taxpayer money for the funding of research. To do this, they must show that they are solving a problem for those representatives and senators; the NIH has to address the public health implications of the research it funds. Most members of Congress will not be particularly excited to learn that a particular inflammatory factor tends to stimulate platelet activation when passing through the artery of a pig. However, they will get excited when they hear that progress is being made in basic processes that will reduce morbidity and mortality, as well as the economic burden associated with them, in the United States. Hit the public health implications hard very early on—often in the first sentence—and emphasize how your study will address them, whether you are a basic or a clinical researcher.

Hypotheses should be worded carefully, in a manner that clearly specifies a relationship between an independent and a dependent variable and that relates to the proposed research, which is presumably an empirical test of that relationship. The hypotheses should be

simple. If you have a compound prediction—for example, one that involves an interaction—break it down. Rather than saying, “We predict that both variables A and B will have main effects on variable C, and that further, variables A and B will interact to produce an independent effect on variable C . . .” it would be better to write,

Hypothesis 1: We predict a main effect of variable A on variable C.

Hypothesis 2: We predict a main effect of variable B on variable C.

Hypothesis 3: We predict an interaction effect between variables A and B on variable C.

The additional research questions in the example were labeled as questions, not hypotheses, for a strategic reason: This study is meant to focus on clinical outcomes, not on mechanisms, and the authors want to emphasize this focus. However, they thought that testing these putative mechanisms was important and that their absence would raise questions in the reviewers’ minds, so they included them, even though it makes the story more complicated. Moreover, you are expected to base your statistical power on the anticipated effects for hypotheses (at least, primary ones), but not so with additional research questions.

You must tell the reviewers why you think your total body of work is new, important, and integrative. Don’t be bashful about this: Hammer home the strong points, and

do it early and often. Your goal is to communicate your excitement about your proposal and to get the reviewer excited as well.

RESEARCH STRATEGY

This is the 12-page section that must incorporate the following headings:

Research Strategy

A. Significance

B. Innovation

C. Approach

- Preliminary Studies (for new applications)
- Progress Report (for renewal/revision applications)

A. Significance

Here are the important points that should be included under the Significance subheading:

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

Note. If you've done a good job on your Specific Aims, a lot of this should already be in there. Don't be too redundant, because 12 pages is not a lot of room. (However, be redundant enough concerning more abstruse or difficult-to-remember points so the reader doesn't have to go back to find the details.) In general, make sure that the reviewers never have to look elsewhere in the proposal to clarify a particular point!

Necessary Elements of the Significance Section

There used to be a section called "Background and Significance"; it immediately followed the Specific Aims section. The Background and Significance section is now gone, but it is still necessary to get some background information in there. As I mentioned earlier, some, actually, all of the following can be mentioned in the Specific Aims, but you often will have to elaborate on some pieces in the 12 pages of the Research Strategy section. Thus, here are the pieces you need to include:

- The problem your study will address
- Why the problem is a public health concern and therefore important to the NIH
- How your research will have an impact on public health

As you will see, the authors of the sample proposal begin the Significance section by repeating some of what they described in the Specific Aims section. It's often necessary to do this, but keep in mind the space limitations. You are going to want to devote most of the 12 pages to Approach, so take care to limit yourself in the Significance and Innovation sections. I suggest you keep these to about two to three pages total. You will want as much space as possible for your methodology.

In the telling of your story, you will need to use redundancy; your reader, who is not necessarily an expert in your specific area, will need to be reminded of some of the elements of your story more than once. Find a

balance between providing the necessary prompts and being over-redundant. It may be difficult for you, the writer, to make this judgment, so ask your external readers for feedback on this.

HINT

Research Strategy: Significance Example

Research Strategy

A. Significance

Overview: {1} Drug treatment has fallen short of getting most treated hypertensives to goal (BP below 140/90 mmHg). A promising behavioral treatment to reduce BP is guided breathing, which uses a portable device that guides the patient to slow the breathing rate to 6–10 breaths/minute (the typical respiration rate is 16 breaths/minute or more). The guided breathing intervention is typically used 15 minutes a day for 8 weeks, and several small studies have reported that after 4–8 weeks, a BP reduction was observed. However, the existing studies are not adequate to establish the efficacy of the treatment due to small sample sizes and short follow-up durations. We propose an RCT, powered to detect effects of the intervention compared to both placebo and UC at 8 weeks (the typical intervention period), and at 12 months. In addition, we will evaluate a potential mediator {2} of the effect of guided breathing on BP.

- Pharmacologic treatment of HTN is effective, but is limited in practice. {3, 4, 5} Drug treatment alone has

limitations. Only 53% of hypertensives on drug treatment, and only 1/3 of all hypertensives, in the United States have controlled BP. Medications are often expensive and may have side effects that limit adherence. Thus, treatment guidelines recommend adjunctive behavioral treatments.

- Non-pharmacologic treatment of HTN provides a useful adjunct to drug therapy. In this review, we focus on interventions that involve relaxation, biofeedback, and guided breathing. {6} Specific Relaxation-Based Interventions. Various relaxation interventions reported beneficial effects on BP, with effect sizes of 9.0–9.7 mmHg (SBP) and 6.1–7.2 mmHg (DBP).

{7} Interventions included autogenic training, progressive muscle relaxation, meditation, and biofeedback. However, it has been difficult to demonstrate replicable differences between any specific treatment modality and active control conditions (i.e., other relaxation techniques or placebo relaxation interventions).

(Continued)

NOTES FOR THE RESEARCH STRATEGY: SIGNIFICANCE EXAMPLE

{1} You may find yourself in the position where you need to describe A, but that to understand A you will have to have told your readers about B first. Simultaneously, it may be difficult to describe B if your readers have not yet been told about A. An overview is a device that allows you to introduce concepts that your readers will need to know before you can tell them about other concepts. Here, many of the salient points you will want the reviewers to have in mind while they read are presented concisely. The authors have done a great job presenting a large amount of necessary material in one paragraph.

{2} Statistical methods are changing rapidly. If the statistics you plan to use are complicated, and beyond your area of expertise, find a good statistician, who preferably will be a co-investigator rather than a consultant.

{3} In the Significance section, consider using a technique in which you set off the main point in bold type and with a bullet; the paragraph that follows the bulleted heading provides detail and support from the literature. If you do this carefully, the main points of the story can be followed by just reading the bulleted statements. Again, it makes it easier for your readers to follow your story line and easier to read. If you do this, try to keep your bullet points on one line, when possible; they seem neater and more focused that way. Yes, it takes up some extra space; again, however, don't sacrifice techniques that will make the reviewers happier (or at least, less unhappy) about reading your proposal.

{4} In this paragraph, the story begins with a statement of the problem. The authors could have begun with a bullet point that might have read, "Hypertension remains a large problem in the United States in terms of morbidity and cost," but when you find that you are over the 12-page limit—and you will—you will have to look for places to cut. The authors decided that reviewers did not have to be convinced of the dangers of hypertension and cut it out. Cutting is an important part of the process, and the inviolate rule is that when you are over the page limit, something has to go. Obviously, look for stuff that doesn't undermine the story; but even after cutting out optional bits, you may still be over the page limit. Begin rewriting: Tighten up the narrative and give it to colleagues who can see places where cutting can be done. Finally, you have to be ruthless: If it's a choice between the critical and the very important, cut out the very important. Do not play games like reducing the font size.

{5} Note that we are not presenting the full text of this grant proposal here, only enough to illustrate the points I am trying to make; thus, the story will skip here and there. (The point actually wasn't to turn you into an expert on guided breathing!)

{6} Provide a context for sections to come. You don't want readers to have to go through three paragraphs before they figure out why you have put in this material.

{7} Provide data (e.g., means or effect sizes) for important studies you have cited, including, when we get to it, your own.

Research Strategy: Significance Example (Continued)

- **Device-guided breathing shows promise for non-pharmacologic control of HTN.** Advances in technology and increased interest in heart rate variability (HRV) as an index of cardiac health have led to studies that use HRV biofeedback coupled with devices that guide the breathing to the 6–10 breaths/minute (0.1 Hz) range. {8} It is in this range that respiratory sinus arrhythmia (RSA; the differences in heart rate during inhalation and exhalation) {9} has its greatest amplitude. Although much

lower than the typical 16 breaths/minute respiration rate, breathing in the 6 breaths/minute range has been extensively studied in the laboratory and is apparently safe. {10} It appears that people compensate by breathing more deeply, and pulse oximetry and end-tidal carbon dioxide (CO₂) indicate that there is little effect on blood gases. All the studies to be discussed here have in common that the patient is instructed in and guided by visual and/or auditory feedback to breathe in the 6–10 breaths/minute range. {11} The results of the studies of guided breathing effects on BP are summarized in Table A. {12}

Table A Results of Studies on Guided Breathing Effects

Author, Year	N	Study Design	Control Condition	Dependent Measure(s)	Follow-Up Period	Outcome
Jones, 2004	79	Open label; Matched Controls Tx: Paced breathing + home BP	Home BP monitoring	Office and home BP	4 weeks	SBP/DBP reduction: 5.4/3.2 mm Hg vs. 1.9/1.0 mm Hg (home BP) for SBP and DBP: $p < 0.001$
Smith, 2007	42	RCT: Tx: Paced breathing	Relaxation (Recorded music)	Office BP	8 weeks	SBP reduction: 8.2/5.0 mm Hg vs. 2.3/1.2 mm Hg (control) $p < 0.03$
Trace, 2004	61	RCT Tx: Paced breathing + other stress mgmt techniques	Wait list control	Office and home BP	3 mos.	SBP reduction ($p < 0.05$): 2.6 mm Hg vs. 1.2 mm Hg (control)
Watkins, 2008	38	Open label; Matched Controls	Attention control	Office and home BP	8 weeks	SBP reduction (results NS): 8.5 vs. 6.4 mm Hg

(Continued)

NOTES

{8} As noted previously, in addition to the clinical outcome, the researchers also plan to collect data on a mechanism by which the intervention might work to reduce blood pressure. It is always crucial to provide biologically plausible pathways by which your effect could occur. Here, the authors foreshadow events that will come later. In the Approach section, for example, they will describe methods by which heart rate variability will be assessed; so here they lay the groundwork and rationale for including those methods. You do not want to bring in concepts late in the proposal for the first time; this is akin to the dastardly device of bringing a new character into a novel in the final chapter who we discover to have been a secret lover of the murdered victim. Carefully lay your groundwork.

{9} Don't assume that your readers know about technical matters that you may consider commonplace. Be diplomatic when you explain such matters; don't sound condescending!

{10} Anticipate reviewers' questions and deal with them immediately. If you wait, for example, until the Approach section, the reader will read several pages with this question, or doubt, in mind. A particular mind-set can influence the way subsequent material is perceived, and by the time you set things straight, the reader may already have formed a negative impression. Here, the authors were apparently concerned that the reviewer might worry about safety issues, and they do not want that concern to continue, so they put it to rest immediately when the point is raised.

We cannot emphasize note 10 enough. A main point of hearing your writing as though you were a reviewer, not the writer, is to anticipate areas that may cause even a small alarm bell to ring and to deal with them on the spot. Don't wait to put these explanations in a "Limitations"

section at the end. In fact, given the new page limits, I suggest you don't have the traditional Limitations section, but rather have already have addressed the points as they arise. If you wait until the end, the damage may already have been done.

NOTES (Continued)

{11} Again, the authors have provided a context for what comes next.

{12} In the Specific Aims section, the literature concerning the interventions (e.g., biofeedback) was summarized with just enough detail to presumably convince the reviewer that the conclusions being presented are a fair representation of what is likely to be a larger literature. That won't do here. The author needs to provide substantial evidence that (a) this particular intervention has been shown to be effective in other studies, and (b) in the present case, although the evidence is suggestive, the work you are proposing needs to be done. You will recall that in the Specific Aims section, the writer used a subtle means of letting the reviewer know that the very strong results of these studies were "surprisingly large." Here, the authors specifically present the results from each of the studies.

The new 12-page format (not including the Specific Aims section) means that you need be very selective about what you include. Table A, for example, takes substantial room; however, the authors apparently felt it was necessary, and we agree with them.

Research Strategy: Significance Example (Continued)

- Guided breathing may be effective as a means of lowering BP in hypertensive patients. The results of the studies shown in Table A are overwhelmingly positive but are limited by several factors: The sample sizes in many are small, two do not have control conditions, and only one small trial (N = 13) used ABP as an outcome. {13}

The consistency of the effect sizes across the studies suggests that guided breathing may be a useful intervention to test in an RCT that is adequately powered. Some of the results seem larger than might be expected from a relatively mild intervention (the intervention involves breathing in time to feedback, such as a series of musical tones, that guide the breathing to a slower rate—6–10 breaths/minute—for 15 minutes a day for 8 weeks). {14} Of the eight published studies, four of them show SBP reductions of 12 mmHg or greater, a very large effect. Potential advantages of the guided breathing intervention are that it is easy to learn, has good patient acceptability, and is relatively inexpensive (Respirco monitors cost around \$200). There are no known side effects, and it is accessible to a wide range of at-risk populations.

As impressive as the evidence shown in Table A is, only one small study used ABP; however, it is ABP that must serve

as the gold standard for this intervention, because it is not susceptible to the so-called white coat effect (a systematic BP elevation that occurs in the presence of the physician and that may lead to misdiagnosis of HTN), has been shown to be a superior predictor of target organ damage compared to office BP measurements, and provides a means to assess BP during sleep. A strength of the present study is that ABP will serve as the primary outcome. Although home BP is a more useful outcome than clinic BP, home readings cannot be taken during sleep, though they are usually taken when the subject is relatively relaxed; moreover, it is critical to know if the treatment also lowers BP when the subjects are active. Only ABP can answer this question, and the only study to use this included only 13 subjects. {15}

Mechanisms: The main focus of this application is on the clinical outcome (i.e., ABP), and it is the measure on which our power estimates are based. However, because we will be seeing the participants over a sustained period of time (1 year) and at several visits, we have the opportunity to collect data that will allow us to evaluate potential mechanisms at little additional cost or burden to the subjects.

It is unclear why slowing the breathing rate a few minutes a day should affect BP. In addition to the clinical outcome, we will also collect data on a candidate mechanism: alteration of baroreflex sensitivity. Other potential mechanisms include HRV and increased arterial compliance. {16}

NOTES

{13} Here, coupled with the following paragraph, the authors have made the transition from describing the background to focusing on the rationale for the proposed study. In the old days (that is, until a few months ago) this section was called “Background and Significance”; it is now, as you know, called simply “Significance” and there is no “Background” heading. However, you need to get some background in there to set the stage for the rest of it. Presumably you have done a fabulous job of this in the Specific Aims section, but here is the chance to elaborate a bit. Notice that the “background” piece has taken up around a page or so. The present paragraph makes the important point that although there is already a literature, it has not been adequate to answer the question; and improving the methodology (more subjects, ambulatory blood pressure monitoring, more sophisticated data analysis strategies, and a 12-month follow-up period) will address this problem.

{14} The point is a subtle one: The results of the published studies are actually surprisingly large; the authors are anticipating that the readers will notice that and are addressing the point, and they are also letting the reviewers know that they (the authors) are sophisticated concerning the larger picture. This is very important! Insert your comments when you need to and talk to the reviewers about such points. Don't let them think that you are naïve or not knowledgeable about such things.

{15} A big part of the rationale for this project is given in this sentence. The authors have made a case for ambulatory blood pressure being a more useful measure than the ones used previously, and they are showing that in the one study that did use ABP, the sample size was tiny. This area clearly requires additional work, which is what the researchers are proposing.

{16} The authors are taking a risk here. Remember the writing rules: You want to tell a simple—oversimple—story that moves along a straight line. You do not want to distract the reader from the main point. This discussion of mechanisms (and then later) needs to provide details in what is now a relatively short amount of space, may lose you points rather than gaining them. This is always a judgment call, pretty much a strategy decision. The authors risked it, and did get funded, so it was worth the gamble, but be careful!

Take a moment to focus on the wording of these sections. This is a well-written application; the authors have taken pains with their phrasing, such that although now more technical in subject matter, such as the proposed biological mechanism discussed in the first paragraph, it is not difficult to read. Throughout, for example, notice that synonyms are used rather than repeating the same term over and over; the wording is terse, as it must be;

however, when necessary the authors use extra words they might otherwise have avoided to make it easier to read. Remember: It is not about what you want to say, it is about the impression you want to leave in the reviewer's mind. Once the reviewer's awareness has been activated because of some error, or lack of clarity, he or she may then read all the rest with a different, slightly more critical, eye.

HINT

Summary

We have used the Significance example to illustrate several principles or rules. First, the narrative here considers the reader: Terms are well defined, abbreviations explained, headers provided, and large blocks of type are broken up with white space. In addition, the section is written in a way that takes into account what the reviewers may be thinking as they read. So new sections are set up with a preliminary statement explaining what is about to come and why; therefore, the authors have written this section and the reviewers are reading it. When issues arise that may be questionable or controversial in some manner, the authors explain their decisions. Note that they do not wait until the end of the proposal to discuss them; if they were to do so, by the time the reviewers would see the discussion, they may have already formed a negative impression.

The story the authors are telling is a simple and clean one, and it is presented in such a way so as to make the story line easy to follow. The logic is explained, and no part of the story line has been allowed to sag. When the study hypotheses are strongly supported, that is made clear; when hypotheses are less well-supported and treated as exploratory, that is evident as well. Again, the narrative was presented in such a way that the reviewers were made aware of the implications of having, or omitting, the more controversial hypotheses. Finally, the authors really are telling a story. By now, you may feel

that you know more about the potential effects of device-guided breathing on blood pressure than you ever wanted to, but you certainly were able to easily follow as much of the story as we have provided.

B. Innovation

Here is where you get to tell why your research pushes the boundaries forward, how it is going to change the field and add to the knowledge base concerning the problem you propose to study. Don't take too much space to do this, a page at the most, probably less. It may be short, but it is an extremely important section—here is where you get the reviewer excited about what you plan to do.

You want to

- Explain how the application challenges and seeks to shift current research or clinical practice paradigms.
- Describe any novel theoretical concepts, approaches or methodologies, instrumentation or intervention(s) to be developed or used and any advantage over existing methodologies, instrumentation, or intervention(s).
- Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation, or interventions.

Again, you presumably will have foreshadowed some of this material in the Specific Aims section. The main points that need to be addressed in the Innovation section are

- What you plan to do that is different from previous studies: Give a definitive account of the rationale for the proposed study. You have given some of this information earlier in both the Specific Aims and Significance sections. Here, I suggest you summarize that in one or two paragraphs (at most).
- Why your plan is novel, cutting edge, and should excite the reader: That's not just lip service; you want to get the reviewer excited about your proposal. What are the seriously cool aspects? A new approach, a new underlying theoretical model, improvements in study variables (more reliable instruments, objective rather than self-report measures, longer follow-up periods, new technology, a comparison of competing theories, manipulated rather than measured independent variables, and others.

Necessary Elements of the Innovation Section

- Why your plan is novel, cutting edge, and should excite the reader (what are you planning to do that hasn't been done before?)

Research Strategy: Innovation Example

Research Strategy

B. Innovation

Ambulatory Blood Pressure (ABP) as the primary outcome: As impressive as the evidence shown in Table A is, only one small study used ABP; however, it is ABP that must serve as the gold standard for this intervention, because it is not susceptible to the so-called white coat effect (a BP elevation that occurs

in many individuals in the presence of the physician, which may lead to misdiagnosis of HTN) and has been shown to be a superior predictor of target organ damage compared to office BP measurements. A strength of the present study is that ABP will serve as the primary outcome. In addition, we propose to study a large number of subjects (N = 400), based on the power analysis. Previous studies have used small sample sizes (largest was 79). Finally, we propose to study a longer follow-up duration (12 months) than any previous studies (longest was 12 weeks). [17]

NOTES FOR THE RESEARCH STRATEGY: INNOVATION EXAMPLE

[17] I repeat here the NIH definition of Innovation: Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

As you can see, “Innovation” can refer to different things: (1) A new idea. In this proposal, however, the authors have taken pains to explain that the underlying idea has already been tested in several studies. (2) A new, preferably understudied, population. This might refer to a constitutional variable, such as sex—many studies have used men only, and NIH is very concerned about studying the same phenomena in women. Same for race/ethnicity—you get points for going into a minority population, especially since the members are often at greater risk for acute and chronic illness than the majority. In fact, NIH insists that you study minority individuals as part of any (human) study. (3) Novel technology/statistics. If new devices or statistical methods have been developed that show promise for doing a better job than previous ones, then that may constitute innovation. That is one focus of this proposal. Although ambulatory blood pressure monitoring was developed many years ago, it still is underutilized, in spite of the advantages in the interpretability of the data, and the authors are correct to highlight this. (4) Untested methodological improvements. This may involve a larger sample size than previous, longer follow-up duration (both of which are elements of this proposal), and others.

Let’s further discuss an issue with which you will always have to contend: Inevitably, the science you are proposing (or are writing up for publication) is a simplification of what both you and your reviewers know to be a much more complex picture. You should find ways to let your reviewers know that you are aware of these complexities, but you must not allow your proposals (or manuscripts) to get sidetracked by those complexities. It is difficult to

avoid. Do not fall into the traps of getting more complex than you need to in order to make your point, or finding that your work never gets out the door because you have become frozen due to the innumerable pathways and systems, both inside and outside the body, that are genuinely relevant to your work but not necessarily to the specific issue you mean to address.

HINT

You have to be ruthless with your own prose. You may write a paragraph that you think was worthy of Shakespeare, but if it does not move the action forward, if it does not fill in a necessary piece of the story you are trying to tell, cut it. You

must think of yourself as a lean, mean, editing machine. Kidding aside, “lean” is what you’re going for. Lean, but it must tell the story and do so in a way that is readable and that makes sense. If it was easy, everyone would do it!

HINT

C. Approach

Finally, you are now going to write about how you will address your Specific Aims. In this section, you will describe the methodology you propose to use. You should, hopefully, have at least eight or nine pages in which to do it.

Approach: Preliminary Studies

Describe:

- (1) Preliminary Studies (new application) or a Progress Report (Renewal/Revision), and

- (2) The methods you propose to use to carry out your study.

Because this is a new application, the authors have written a Preliminary Studies section rather than a Progress Report. This is where you get to impress the reviewers with your capabilities to carry out the research you have proposed and with the pilot data you have presumably collected to show that your hypotheses are on the right track.

The Preliminary Studies section gives you a chance to tell the reviewers about the following:

- (1) The skills you and your team possess that are necessary to the project. For example, you may want to provide research abstracts that may not relate directly to the hypotheses or outcomes of the present study but that demonstrate your competence, or that of a member of your team, in an area that will contribute to the conduct of the study. In the example, for instance, the authors plan to measure heart rate variability and baroreflex sensitivity; presumably, at least one member of the team has that expertise and can provide abstracts or other support for the demonstration of those skills.

HINT

If anyone on the grant has data that back up your capabilities and/or your assertions about how you expect the experiment to turn out, that becomes part of the

experience you may cite in this section. In effect, it becomes part of “your” experience—you the PI—but most of this section should represent your work.

- (2) Data that you and/or other members of the team have collected that bear directly on the research question at hand (i.e., pilot data). Pilot data are more or less important depending on the mechanism you plan to use. For some K (career) awards or the R21 exploratory research mechanism, they are less important.

Smaller grants, notably, the R21, may be billed as “exploratory,” and therefore ostensibly do not require pilot data. Don’t necessarily place your faith in this. Sometimes, an ad hoc study group will convene to review only these applications, and under those conditions at least they are all on board with the fact that they are reviewing a small, exploratory grant rather than, for example, an R01. However, this is often not the case, and the R21 may be mixed in with R01 or other applications, and the reviewers may tend to apply the same criteria regarding pilot data as though you were submitting an R01. Moreover, if you are one of several R21s and some of them do include pilot data, the reviewer may give those applications higher scores, and your application will then suffer by comparison. Pilot data are one of the most important arrows in your quiver; always try very hard to at least obtain feasibility data—even on only a few subjects.

For an R01 research award, however, pilot data are crucial. Having gathered pilot data provides evidence concerning three important issues: (1) your experience in conducting research in the area in which you are requesting funding; (2) the feasibility of the project—that is, your ability, including appropriate institutional support, to carry out the proposed study; and (3) at least some support for your hypotheses, some evidence that you are on the right track.

Necessary Elements of the Approach: Preliminary Studies Section

- Studies conducted by the PI and key personnel that are relevant to proposal
- Pilot data

Research Strategy: Approach

Preliminary Studies Example

Preliminary Studies

Subject Recruitment. Dr. Okata is site PI of a trial currently being conducted at the New York Medical Center (NYMC). This trial will complete patient accrual in October 2007. It is an RCT testing the effect of a stress management intervention on BP in hypertensives. {1} The proposed trial will recruit in this same population.

RCT of a Stress Management Intervention (K. Okata):

The project focuses on patients at 10 community health centers, and in it, we have used several of the methods we are planning for recruitment in the currently proposed project. Thus far, the study has screened approximately 6,000 people. We have seen an average of 460 people at each screening and have found a 22% prevalence of HTN. Approximately 14% declined participation at the time of screening. Overall, of the eligible people we screened, we enrolled 55%. By the end of October 2007, we will have recruited a total of 400 hypertensives. We have, at this time, successfully retained approximately 90% of the participants whose 12-month evaluations have come due for 1-year follow-up. Based on this experience, we feel comfortable that our accrual goals for this study are feasible. {2}

Dr. Ruggiero has published several studies concerning the relation between psychological factors and autonomic control, using spectral power analysis as the main outcome. He has examined these relationships both in the laboratory and in the subjects' natural environments using 24-hour Holter monitoring. He recently published the results of one such study in the *Journal of Important Psychophysiological Results*, 16:10–15,

2005. Dr. Ruggiero will supervise the laboratory procedures for the assessment of baroreceptor sensitivity. {3}

Cardiovascular Autonomic Control and Hostility (R. Ruggiero)

We examined the relationship between anxiety and 24-hour HRV in 126 hypertensive patients who completed the Jones Anxiety scale and wore 24-hour ambulatory ECG recorders. We predicted that anxiety would be inversely related to the high frequency (HF) power response to psychological challenge. Support for this hypothesis would be consistent with the view that anxious people engage in multiple episodes of anxiety throughout the waking day, with each episode causing a decrease in HF power. The cumulative effect of such episodes is lower levels of cardiac autonomic control in highly anxious subjects. As expected, there was a significant correlation ($r = 0.39$, $p < 0.05$) between anxiety score and HF power. {4}

Pilot Study

We studied 5 hypertensive patients (3 male, 2 female) from our practice in an open-label trial with no control condition (approved by the institutional review board [IRB] and with informed consent for participation). All participants wore an ABP monitor for 24 hours at baseline, then were trained in the use of the guided breathing technique and instructed to practice 15 minutes daily for 8 weeks. ABP monitoring was then repeated. After 8 weeks of home practice, we found mean reductions of 11.6/5.4 mmHg

SBP/DBP in 24-hour ABP. We found that 3 of the 5 patients had a BP reduction that we would regard as clinically significant (> 5 mmHg SBP). These results are in line with the one small, published study that measured ABP levels and support our primary hypotheses that the guided breathing procedure will reduce 24-hour BP at 8 weeks. {5}

{1} Do not simply provide a list of several abstracts; an explanation about each should be given first, so the reviewers immediately understand why you are asking them to read this material.

{2} The authors have correctly provided a lot of detail, because the reviewers will be concerned about recruitment. Note also, they gave a nice plug to Dr. Okata, mentioning that he was already supervising a randomized clinical trial. The authors are taking the opportunity to showcase Dr. Okata's background, which we have deliberately made somewhat skimpy for this example regarding what NIH reviewers might expect.

{3} Notice that the authors have provided two paragraphs providing evidence that Dr. Ruggiero has a track record in the area in which he will be in charge, the laboratory procedures. As you can see, he is specifically mentioned by name.

{4} Note the level of detail provided concerning the results; this is important to do, don't just say "the results were significant" or something similar. Provide test statistics and p-values.

{5} These are useful pilot data. The number is very small ($N = 5$), but the results are in the predicted direction, and this little paragraph provides good support for going further with this part of the proposed study. Remember, you saw in the Research Strategy: Significance section that there were several small published studies (although not as small as this one), and only one that used ambulatory blood pressure monitoring—a much more convincing measure than clinic blood pressure. So, all in all, this paragraph provides very important information. Also, the authors, having several months between the due date of the proposal and the reviews (Chapter 8 discusses the timetables), are allowed to send in supplementary material, in which the sample size could be expanded.

Dr. Okata's lack of experience places him at a disadvantage relative to other PIs who inevitably will possess far greater experience. However, the NIH is very interested in encouraging junior investigators, so they have acted to level the playing field a bit. There will be a place in your eRA Commons profile to note that you are—or are not—an NI or an ESI.

The NIH has specific definitions of these, and if you fall into either of these categories, you may reap an advantage: For some grant mechanisms, the NIH will, in effect, give you a “handicap” (like in golf)—you will have to attain a lesser score, compared to more senior investigators, to get you into the funding range. Details are provided in Chapter 4.

For those who have been involved in the conduct of clinical trials, you know that one thing that can kill your grant is recruitment. We have been in situations in which we had to enlist one or more additional sites, so as to find enough patients that we were adhering to the quarterly commitments we had with NHLBI, and of course, enough so that we would be able to detect effects if indeed they were present. Thus, the authors are giving the reviewers chapter and verse on prevalence in their sample, patient flow, and so on, and this will be regarded as an important strength by the readers. But the larger point is that there will be one or more potential issues, specific to your discipline or methodology, that the reviewers will worry about and about which they will need reassurance. Remember, it is psychological: You don't want the reviewer to ever experience worry or doubt, if you can avoid it, because it will color their perceptions of the remainder of the proposal.

You have to think like a reviewer, see where a possible provocation of doubt might occur, and cleverly undermine its possible effect by showing that you have anticipated the concern and allay it before it occurs. In the event that there is a weakness you cannot avoid, perhaps due to a characteristic of a particular patient population, if you are conducting clinical research, or if you have a need for an assay that simply doesn't yet exist, or some other lack that cannot be addressed using any available methodology, you have to describe the conundrum right then and there—at the exact point where the reviewer is going to spot the weakness—and explain why you chose the route you did. If you do so carefully, the reviewer will get it. If it is a fatal flaw, well, you shouldn't have submitted the proposal in the first place. The presumption is that in spite of this flaw, the study will provide important knowledge. Thus, you should be able to avoid concern on that point.

Approach: Research Methods and Design

There is no “official” heading required or suggested by the new format, but that's the next section, so you might as well label it. The Research Methods and Design section presents some particular challenges. It is the fussiest section, meant to be presented in what is often exhaustive (and exhausting) detail. In particular, you must address in detail how you plan to accomplish each of the specific aims.

There is also the issue of precisely how much detail to present, and the example addresses this question. Finally, this can be a section in which reviewers find points on which to downgrade your score. It is easier to ding an application on a solid methodological point than a more general one, so this section must be crafted extremely carefully. Once again, you are going to learn more about how to conduct a clinical trial to evaluate the efficacy of guided breathing than perhaps you wanted to know, but it will serve as a means of illustrating these points.

Please note that, as with the previous sections, we have removed paragraphs that do not particularly illustrate any point we would like to make; thus, there may appear to be discontinuities in the section, but this is not due to the authors' lack of attention.

Here are the important points that should be included in the Research Methods and Design section:

- Describe the overall strategy, methodology, and analyses to be used to accomplish the Specific Aims of the project. Include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.
- Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.

- If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high-risk aspects of the proposed work.
- Point out any procedures, situations, or materials that may be hazardous to personnel and precautions to be exercised. A full discussion on the use of Select Agents should be given.

Reviewers are very interested in methodological details. The new 12-page limit obviously means that you will have to cut somewhere in comparison to the previous 25-page length, but you should avoid skimping on methodological details. How to reconcile these seemingly irreconcilable imperatives? Go over your writing; go over it again and again and again. Every time you start from the beginning, you will find places that you can cut: phrases that are unnecessary and sentences and paragraphs that can go. The reviewers know as well as you do that space is limited, but they want those methodological details! And as long as we're discussing it, it is worth noting that the shortage of space doesn't mean you don't want your sentences to flow in a natural and pleasant cadence. Avoid sounding like you are using a telegraph—use the extra words and transitions you really need so that your proposal, even the methodological details, reads well.

Here is something you'll hear again and again from us: Revise. Every time you open up the file, read with the goal of cutting—no matter how carefully you have written; no matter how convinced you are that you have removed every single bit of fat, there is always more. Don't always start at the beginning; you can end up with

a finely crafted beginning but the middle and ending, not so much. This kind of focused editing will force you to choose your words carefully. Remember, as in poetry, *every word should be there for a reason!* Hear the sentence in your head. Are the connections still there? Is the meaning clear?

HINT

We've said this before, but we'll say it again: Read your stuff out loud to others. They will often hear something you would have missed. They may give you feedback that

your story is out of order or that a particular paragraph needs to be moved, or that they just don't understand something.

HINT

Necessary Elements of the Approach:

Research Methods and Design Section*

- An overview of the methods you plan to use
- Hypotheses (given earlier in this example)
- The study design, including strengths and advantages, and a discussion of possible alternatives and the reasons for not choosing them
- Subjects (population characteristics, inclusion and exclusion criteria)
- Informed consent procedures, animal handling, and care specifics
- Recruitment and attrition information, including a flowchart and a backup plan if recruitment is slower than expected
- Sample size and power calculations that address each primary hypothesis and each primary outcome measure
- Description of manipulation, intervention, independent variables, and control conditions
- Description of outcomes
- Procedures, including quality control measures to ensure high-quality data collection

- Randomization method and considerations (e.g., stratification, matching)
- Study timeline
- Measures used in the study
- Data management and missing values
- Statistical analysis
- Dissemination of results
- Potential limitations and solutions

* This list of elements is of course specific to the type of methodology and problem under study in this example.

Research Strategy: Approach

Research Methods and Design Example

Research Strategy

C. Approach: Research Methods and Design

Overview and Design: We propose an RCT with two intervention conditions, standard duration of treatment (N = 80) and extended treatment (N = 80), and two control conditions, placebo (N = 80) and usual care (UC) (N = 80). We will use a mixed design, examining the effects of the intervention on change in ABP (a within-subjects factor) across the intervention and control conditions (a between-subjects factor). {1}

Participants in the two intervention conditions are treated identically during the first 8 weeks (the typical period for this type of intervention); at 8 weeks, participants in the standard duration intervention discontinue the intervention, but continue in the study; those in the extended duration intervention continue the intervention throughout the 12-month period. A summary of the conditions follows:

Control 1: UC (no device given);

Control 2: Placebo (placebo device given, but only during first 8 weeks);

Intervention 1: Standard Duration (device used only during first 8 weeks);

Intervention 2: Extended Duration (device used for entire 12-month period) {2}

The intervention consists of the use of a device (Respirco, Taos, NM) that guides participants to reduce the breathing rate to 6 breaths/minute. Participants in the placebo condition are provided with devices that are identical in appearance to those used in the intervention, with the exception that the placebo device does not guide to 6–10 breaths/minute. Instead, the placebo participant listens to a set of random musical tones. The manufacturer has agreed to reprogram devices for this purpose (see letter in Chapter 7). {3} In the placebo condition, the device serves to create a 15-minute relaxation period, which provides a control that will allow us to evaluate (a) the effect of relaxation on BP and (b) the effect of guided breathing on BP over and above that of relaxation. As in the standard duration intervention condition, the use of the placebo device ends at 8 weeks. {4}

The primary outcome is the difference between conditions in change in ABP between baseline (prior to randomization) and at 8 weeks; a secondary outcome is the difference between conditions in change in ABP between baseline and at 12 months. Additional outcomes are changes in ambulatory respiration rate, HRV, and baroreflex sensitivity, as well as in self-report measures of activity level and anxiety. {5}

Our primary hypotheses address the outcome at 8 weeks. It is this period for which we have the strongest evidence. However, the 12-month outcomes (secondary hypotheses) are also very important to observe the sustainability of the effect of the intervention.

NOTES

{1} The Progress Report for Renewal/Revision Applications section begins with an overview statement. By this time, the reader is somewhat familiar with much of this, so it becomes easier to read and understand. However, you will also notice that each of the methodological points now becomes sharpened; that is, presented in finer detail. Thus, this is the first time a formal statement of the study design has been given.

{2} Although the conditions (or “arms”) have been mentioned before, the authors now provide a summary to which readers can refer, making it easier for them.

{3} The authors specifically mention a letter from the supplier of the device to be used in the trials. It is easy for the authors to make claims about what will occur, but readers like to see evidence that such matters have actually been arranged. There is a separate section for letters (see Chapter 7).

{4} I think that this is a very creative and useful control condition. The authors carefully justify its inclusion: Without this control, the data would have been subject to an ambiguity that could not otherwise have been teased out. This is precisely the sort of detail that the reviewers will like.

{5} Once again, the authors give a very clear, straightforward statement, this time concerning the primary outcome.

Research Strategy: Approach

Research Methods and Design Example (Continued)

Primary Hypotheses (based on systolic ABP at 8 weeks): {6, 7}

1. Participants in the two intervention conditions (which are identical until 8 weeks) will have lower ABP compared to participants in both the UC and placebo conditions.
2. Participants in the placebo arm will have lower ABP compared to participants in UC.

Secondary Hypotheses (based on systolic ABP at 12 months):

1. Participants in both the extended duration treatment condition and in the standard duration intervention

condition (in which intervention ends at 8 weeks) will have lower ABP at 12 months compared to participants in placebo and in UC.

2. Participants in the extended duration intervention condition will have lower ABP at 12 months compared to participants in the standard duration intervention condition.

Additional Research Question: We plan to evaluate potential mechanisms that may mediate the effects of the intervention on BP, including baroreflex sensitivity, heart rate variability (HRV), changes in ambulatory respiration, and self-reported changes in physical activity and anxiety.

NOTES

{6} The hypotheses should be copied and pasted from the Specific Aims section; they should be identical.

{7} The placement of the hypotheses is controversial; some do it at the beginning of the section, as we have done in this example; others prefer to place it directly before the Power Analysis section, because it is the hypotheses that the power analysis is designed to address. There are no hard and fast rules here—use your judgment. If your power section is very complicated, you might consider the latter option.

Research Strategy: Approach

Research Methods and Design Example (Continued)

Design Consideration {8}

Why Not Use a Crossover Design. We considered a crossover design. Such a design is useful when there is no possibility that the intervention will have carryover effects. Here, however, we are particularly interested in the possibility that the intervention will have carryover effects. Thus, a crossover

design would not have allowed us to test the primary and secondary hypotheses in this study.

Note. UC Condition Is Not Really Usual Care. An issue faced by all RCTs is the design of the control conditions. Usual care, in particular, presents a specific challenge, in that *simply participating* in the trial often affects patients' behavior. Our decision to use home BP monitoring in the UC condition was the result of a compromise: We must have comparable measures across conditions to allow us to understand the processes by which effects may be occurring; however, we do not wish to impinge on that effect. The main focus of the proposed trial is the clinical outcome;

NOTES

{8} This portion of the Progress Report for Renewal/Revision Applications section is very important. The authors provide explanations of methodological decisions they anticipate will arise in the reviewers' minds. Notice that these explanations are quite close to the beginning of the section so that they are able to defuse those concerns almost as soon as they arise. Many authors put these in a section at the very end; by now you know why that may not be wise, although I recommend you also include a limitations discussion at the very end of the Progress Report for Renewal/Revision Applications section. Worse, many authors don't put them in at all, perhaps hoping they will not occur to the reviewers. That is not a good idea.

(Continued)

however, this is meant to be an efficacy, not an effectiveness, trial. {9} Thus, we felt that the current configuration was the best compromise.

Participant Population

Clinical Sites and Participant Population. {10} The NYMC is a tertiary care teaching facility and medical school that draws its patients from the greater New York metropolitan area. There are 22 community health centers that fall under the NYMC umbrella, and the study will be conducted in 12 of these. Across the 12 centers, the patient population is very diverse, with 35% Caucasian, 29% African American, 19% Latino, and 16% Asian,

and there are a total of 46,000 patient visits annually. (See the Letters of Agreement section in Chapter 7.) {11}

To recruit patients, we will use a strategy that has proved successful in a trial that Dr. Okata is currently running in this population. {12} We estimate that approximately 30% will have a screening SBP greater than 140 mmHg, or DBP greater than 90 mmHg. More than 40% of those with hypertensive screening BP levels are African American, and this group is overrepresented in the hypertensive diagnostic group, as would be expected. Our experience with this population suggests that of those with screening BP in the hypertensive range, 15% will have normal BP when assessed using ABP.

{9} This takes a bit of nerve. The author is acknowledging that his “usual care” condition—a staple of such trials—is somewhat of a farce. The subjects are aware they are in a trial; of course contact must be kept with and measurements taken on subjects in the control conditions, thus reinforcing the subjects’ awareness that their behavior is being monitored and with presumptive effects on that behavior (Heisinger was correct!). The larger point, however, is that the author made a choice, here, whether to hope that the reviewer would not trouble over this point, or whether to lay it out on the table. You will be confronted with such issues in your applications that are relevant to your own methodologies. The thing to consider is, if you mentioned the shortcoming, but the reviewer wouldn’t have noticed it if you hadn’t, you may take a small hit. However, if you failed to mention it, but the reviewer was familiar with the issue, you would take a large hit.

{10} Whether you are proposing basic or clinical research, you must persuade the reviewers that you have the capabilities to carry out the research. If you can’t do that, no matter how good or innovative the science, your score will suffer. Give specifics about the sites, the patient flow, the patient demographics, and so forth; or, in the case of basic research, provide details concerning the laboratory space and equipment and, if appropriate, facilities for maintaining animal subjects.

{11} Whenever you are claiming resources outside your control (in this case, outside clinical sites), it is a good idea to provide letters. These can be faxed, even in your original application, although it is of course better to have originals. Also, in this instance, the authors are implying that, if you look in the Letters of Agreement section, you will find 12 letters from these sites (that is, from someone who has the authority to provide access); however, if you were missing a couple of them, that would probably pass without comment.

{12} Note the reminder that the researchers have experience in this particular patient population, which will increase the reviewers’ confidence that recruitment will go as planned.

Research Strategy: Approach

Research Methods and Design Example (Continued)

Screening, Recruitment, and Attrition

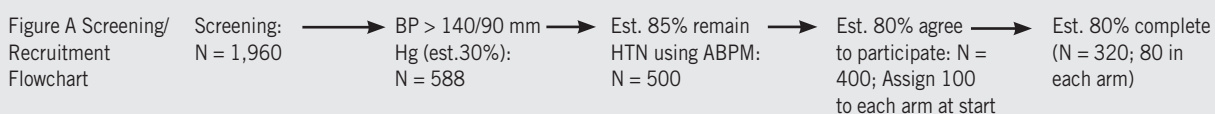
Physician Referrals. The 12 referring physicians (one at each site) have a total of 52,800 patient visits/year with, between them, 15–20 new patients each week. We estimate that we must recruit 692 patients over the 4-year recruitment period. Assuming a 20% refusal rate, and 15% who are normotensive by ambulatory monitoring, that total will yield 400 patients to be randomized for the study. Given the patient flow, we anticipate that we should easily be able to recruit the required number. Figure A shows the screening and recruitment goals. {13}

Screening. Based on the prevalence of HTN in this population and our experience with the proportion of people who

will remain hypertensive using ABP monitoring, we anticipate that we will need to screen a total of 1,960 participants (there will be 12 screening periods, with an average of 163 people screened at each). Based on our current study, which uses the same techniques, we anticipate that we should be able to recruit the required number of patients.

Attrition. We will over-recruit by 20% to allow for dropout, so we will begin with $N = 100$ and end with $N = 80$ in each condition. This means that, beginning at Month 6, we will recruit 11 participants per month throughout the recruitment period. To enhance retention, we are offering a financial incentive for study completion. Further, we will request the names, addresses, and telephone numbers of three friends, neighbors, or relatives who would know how to get in touch with the participant in the event of a missed appointment. {14} Figure A shows the recruitment flow.

Figure A Screening/Recruitment Flowchart



NOTES

{13} Give sufficient detail concerning issues of recruitment and attrition. Explain your plan to over-recruit, and by what percentage, to allow for dropout; explain what procedures you will institute to retain subjects.

{14} It is helpful to provide a figure showing how you got from your screening to your final cell sizes.

Describe in detail your plans to sample—or oversample, if necessary—in different minority populations. Chapter 6 describes the NIH requirements to recruit women and minorities; it is incumbent on you to describe outreach efforts, in the event they are needed, to recruit from populations that may not necessarily be represented in what

you might consider your main population or populations. You do not want the reviewer experiencing doubt about your ability to recruit not only the absolute number of participants but the appropriate composition, by sex and minority status, as well.

HINT

Research Strategy: Approach

Research Methods and Design Example (Continued)

Sample Size and Power. {15, 16} We propose a design in which there are 4 arms, with 80 subjects completing the 12-month study in each arm. {17} ABP is assessed at baseline. In addition to the baseline measures, ABP outcomes are assessed at 8 weeks (i.e., at the end of the intervention period) and at 12 months. The power estimates are broken into two sections, corresponding to the two follow-up assessment points. Primary outcomes are changes in SBP from pretreatment.

ABP Comparisons at 8 Weeks. Based on previous studies, we hypothesize the ABP changes shown in Table B. We further assume a homogenous within-group variability corresponding to a standard deviation of 13 mmHg. Based on these assumptions, our standardized effect size (f) for the overall analysis of variance (ANOVA) is 0.26, which is conventionally characterized as a medium effect size. With 80 patients in each of the two intervention conditions and 80 patients each in the placebo and UC groups, we will have a power of 0.98 to detect an overall effect using a nominal alpha level of 0.05. The planned orthogonal comparisons that reflect the specific study hypotheses and that will follow up the overall ANOVA are described next. {18}

NOTES

{15} We usually put the discussion of sample size and power after our description of the sample because it explains how we arrived at the proposed sample size. However, you may sometimes prefer to put it just before the discussion of statistical analysis, which often comes much later. As with every section, where you place it in the narrative should be a function of how the story unfolds, such that each section advances the storyline, even here in the Progress Report for Renewal/Revision Applications section.

{16} The discussion of power is very important. If you are not intimately acquainted with this topic, take the trouble to learn about it. If you cannot find a course at your institution, then look for workshops given at conferences, and, of course, there are any number of texts that will provide the basics. If you are not a sophisticated statistician, hook up with one who is well-versed in power calculations. You can find programs that will allow you to perform simple power calculations in many lower-level statistics texts or on the web. However, these are usually appropriate for only the most basic and straightforward designs. Once you move into more complex realms, you need someone who really knows this topic to help you. The reviewers pay close attention to the power calculations. Most researchers agree that it is desirable to have a minimum of 80% power for a given effect; sometimes, you may end up with greater power than that, as in the example. The only reasons to avoid very high power levels, like those we see in the present study, are (a) that you may end up with more subjects than you needed, and therefore greater expense; and (b) that you may, ironically, end up finding statistical significance in comparisons that fail the test of clinical significance. Be aware of the controversy over the value of statistical tests. The direction we take is not only to have a high regard for statistical significance, but also to have an equally high regard for effect size. In the sample study, we have saved space by omitting the power estimates for the secondary measures in which the power declines to just above 80%; you may need to provide yourself with very high power for some variables when the power declines for other analyses.

Having said all that, if your statistics are fairly simple, there are books and programs to help you calculate power, and you probably don't need to have a professional statistician on the grant for that reason alone.

{17} The authors make a clear distinction between assignment of participants ($N = 100$ in each arm) and the anticipated completion ($N = 80$ in each arm) of the program by those participants—and note that the authors highlight the distinction by using italicized type. These are precisely the kinds of details that you do not want to miss.

{18} Note the clear explanation of how the power estimates were determined.

(Continued)

Table B ABP Comparison at 8 Weeks

Comparison	Expected SBP Change at 8 Weeks	Standardized Effect Size (Cohen's d)	Power to Detect Effect
Intervention (standard + extended) plus placebo vs. UC	Intervention + placebo: 8 mm Hg UC: 2 mm Hg	0.32	0.84
Intervention (standard + extended) vs. placebo	Intervention: 10 mm Hg Placebo: 5 mm Hg	0.36	0.89

The first comparison tests the effect of the device (whether guided breathing or placebo) relative to UC; the second and most critical comparison establishes the effect of the intervention relative to the placebo device. (See Table B.)

ABP Comparisons at 12 Months: In these analyses, the placebo and UC groups are each expected to have a 2 mmHg (SBP) change at 12 months relative to baseline. Thus, participants in the placebo condition (those who gave up the device at the end of 8 weeks) will be combined with the UC group (N = 160), and the main focus will be on the standard duration and extended duration intervention groups. We expect that

the extended intervention group will continue to maintain a 10 mmHg decrease in SBP at 12 months relative to baseline, whereas we anticipate that the standard duration group will only partially maintain the treatment effect, showing a decrease of 6 mmHg after 12 months relative to baseline. Based on these hypothesized effects and a homogenous within-cell standard deviation of 13 mmHg for the SBP change, our overall ANOVA will have an effect size of $f = 0.19$ and our power will be 0.86 (using a nominal alpha level of 0.05). {19, 20}

The two more critical follow-up orthogonal planned comparisons are summarized in Table C. {21}

Table C ABP Comparison at 12 Months

Comparison	Expected SBP Change at 12 Months	Standardized Effect Size (Cohen's d)	Power to Detect Effect
Intervention (Standard + Extended) vs. UC plus placebo	Intervention + placebo: 8 mm Hg UC: 2 mm Hg	0.18	0.77
Extended vs. Standard Intervention	Extended Intervention: 10 mm Hg Standard Intervention: 3.3 mm Hg	0.41	0.83

{19} A table is a good way to present the estimates that pertain to each of your hypotheses. The authors here give specific contrasts, with estimated differences between them.

{20} Recall that the hypotheses were broken into primary and secondary hypotheses. However, the authors do not use this split to avoid powering the study to be able to detect effects in the secondary hypotheses (the smallest estimate is still close to 80%). Thus, this section, and Table C, addresses the secondary (12-month follow-up) hypotheses.

{21} Its true that these tables take up a good amount of room (but note that they have been produced much larger for this book than they were in the actual grant application) but it is precisely this level of detail that the reviewers want to see. You have to pick and choose which elements to detail—it used to be (under the 25-page-limit days) that every detail needed to be provided, but it just can't be done in 12 pages. However, power is one issue on which reviewers like to see exquisite detail.

You probably know that there are different approaches to power estimates. You can begin with an effect size, gleaned from the literature, or, preferably, from your own pilot data, and this can lead to a sample size. Often, however, you will—for various reasons, including economy or limited access to subjects—have a sample size in mind when you begin. Researchers can and often do fool a bit with the effect sizes so that they end with the sample sizes they want. There is

some give, here, if it will really help you, but be careful about getting carried away. Do not fall into the trap of saying whatever you think you must get the money, although you will be tempted. If you under-power your study, you are likely to fail to see significant effects, may end up wasting years of your time, and have little to show when you apply for your next grant. If you find yourself sorely tempted in this regard, rethink your research strategy.

Let's return to the question of whether to label hypotheses as primary or secondary, or presenting them as "Research Questions." As discussed earlier, you may have framed your predictions as "specific aims" or as "hypotheses," or both. In addition, you may have "primary aims" and "secondary aims," and "primary hypotheses" and "secondary hypotheses." To which of these must you power to? This is a complicated and important question. Basically, you should power to any aims and/or hypotheses that are of importance to your study. In the past, researchers have often powered to their primary aims, and basically ignored other aims, especially, of course, if those other

aims would have called for more subject inclusion than the primary hypotheses and aims. Reviewers have gotten fussier about this, with good reason: You can't legitimately draw conclusions from data supporting an aim based on an insufficient number of subjects. You can't get away with doing so by labeling the under-powered aim as a "secondary" aim. If you absolutely cannot afford to power to all your aims/hypotheses, you may need to rethink your approach. Can you "demote" a primary or secondary hypothesis to an "exploratory aim"? If you do, though, be careful about how you plan to interpret the data supporting this aim or hypothesis.

Research Strategy: Approach

Research Methods and Design Example (Continued)

Eligibility Criteria {22}

Inclusion Criteria: Aged 18+ years; screening BP of < 140/90

Exclusion Criteria: Being deemed unable to comply with the protocol; participation in any other HTN-related clinical trial

Description of the Intervention

The device (Acme, Inc., Paramus, NJ) consists of . . . {23}

Description of the Control Conditions: {23}

Procedures

Personnel. The research assistants (RAs) will conduct the screenings, patient scheduling, consent, enrollment

procedures, and chart reviews. The RAs will be supervised by Dr. Okata.

Screening and Recruitment . . . {23}

Reminder Telephone Call. People who are eligible at the initial screening and who desire to participate in the study are given an appointment for the initial visit and are told that they will receive a phone call the night before the appointment. {24}

Randomization Procedures. {25} We shall follow the Consolidated Statement of Reporting Trials (CONSORT) guidelines wherever appropriate in this application, including in the description of the randomization procedures.

Unit of randomization: Individual.

Method Used to Generate the Allocation Schedule. Dr. McBurney, the project statistician, will create the

NOTES

{22} Think out your eligibility criteria carefully. When the rationale for a particular criterion is not obvious, make sure to provide it. This is a point on which reviewers will fault you if you do not provide sufficient and clear information. Finally, you should copy this discussion in its entirety and place it in the Ethical Concerns section (see Chapter 6).

{23} Omitted to save space.

{24} This discussion of the reminder call illustrates the level of detail you need to consider. Try to anticipate every problem you could conceivably run into and incorporate a methodological procedure to address it at the outset. Probably no reviewer would have criticized you for failing to have included this section, but they will certainly note your attention to detail because you did include it.

{25} Not all studies involve randomization, but many do, and this is an issue to which reviewers pay close attention. In a basic study, simple procedures are appropriate, but sometimes they need to be more elaborate. The present example is of a clinical trial, concerning which several journals have endorsed the CONSORT (Consolidated Statement of Reporting Trials) guidelines. CONSORT seems like a very neat method of breaking down the procedures, so I suggest using it for your clinical trial proposal, and it sets the stage for the later publications to come.

(Continued)

randomization allocation by generating random numbers and placing subject assignment in sealed envelopes.

Method of Allocation Concealment and Timing of Assignment. Assignments will be generated within randomly sized blocks, so it is impossible for project staff to anticipate the likely group assignment of an individual at the end of a block by process of elimination.

Method to Separate the Generator From the Executor of Assignment. The sequence of assignments will be held by

Dr. McBurney or a data manager in his office in Queens, New York, off-site from the project, and they will be contacted by phone by project staff when the staff are ready to randomize a participant. Nobody who is connected with the conduct of the trial will have access to the records. Dr. McBurney's office will keep a record of who was randomized to which group and will check that those randomized are analyzed in the correct group.

Research Strategy: Approach

Research Methods and Design Example (Continued)

Measures Used in the Study {26}

All study measurements obtained from patients will be assessed by trained RAs. Study measures are divided into

three categories: (1) self-report measures, {27} (2) physiological measures taken in laboratory, and (3) ambulatory physiological measures. Table D summarizes the measures (by modality) and notes which measures will be given at screening, baseline, and 12 months. {28}

Table D Measures Used in the Study at Specific Visits

Measure	Screening	Baseline	8 Weeks	12 Months
<i>Self-Report Measures</i>				
NYMC demographic form	X			
Branson self-reported adherence questionnaire		X	X	X
Current medications (from patients' medication vials)		X	X	X

NOTES

{26} Always include a section about each of the measures you plan to use. Explain the purpose of each (e.g., is it meant to be an outcome, to provide a basis for stratification, or to be used as a statistical control?). I have actually cut out most of the measures in the example to save space, but I'm sure you get the point with these few.

{27} If you are going to use self-report measures, use standardized, validated measures whenever possible. If no measure that does the job you need exists in the literature with which you are familiar, search on the construct to see if a measure has been developed for use with, say, a different patient population; you may be able to modify such a measure and still retain some of its reliability and validity. If you must make up a measure from scratch, try to keep it simple—preferably, one that requires self-report of a set of behaviors rather than items from which you attempt to infer a personality construct. Doing the latter just gives the reviewer an easy opportunity to criticize your proposal. In addition, when you do use self-report measures, acknowledge the limitations on the interpretation of such data.

{28} It is not always necessary to include such a table on measures; doing so depends on the complexity of your design and the amount of space you have to work with. In the example, I have simplified the table: There were actually several more visits than I have mentioned, and several more measures as well. You can see, however, how the table helps avoid any possibility of ambiguity concerning the timing of the measures.

Be careful not to incur too much patient burden. It is tempting to pile on measures and visits, but reviewers will consider whether they believe that patients will actually do it all. Pilot data regarding this aspect of the

study will provide important ammunition; if you don't have your own pilot data, data from a different study using a similar population and with a similar patient burden may suffice.

Research Strategy: Approach

Research Methods and Design Example (Continued)

Branson Medication Adherence Questionnaire. Data on medication adherence will help us interpret the effects of the intervention on BP control. Adherence to prescribed antihypertensive

medications will be assessed using the well-validated 6-item scale developed by Branson that specifically addresses adherence to prescribed medication regimen. It has been utilized in other studies of hypertensive patients and found to have a Cronbach's alpha of 0.9. {29}

NOTE

{29} Here, the authors provide a measure of reliability, Cronbach's alpha. (If you are not familiar with these and other measures of reliability and validity, I strongly advise you to learn about them. They are relevant for all types of measures, not just self-report.) Is alpha sufficient? Probably not. Cronbach's alpha gives you an estimate of one type of reliability (the extent to which the items tend to cluster), but most reviewers will want to see an estimate of test-retest reliability (the extent to which a person's score remains stable over time). Also, reliability is necessary, but by no means sufficient: Why should we believe that a score on this measure, even if it is stable over time, is actually indicative of how adherent a person is? We also want to see evidence of validity of the measure. Such data should be available in the literature; if they are not, find a new measure, if one exists.

Research Strategy: Approach

Research Methods and Design Example (Continued)

Physiological Measures Taken in Laboratory {30}

Ambulatory Physiological Measures

ABP. We will use the well-validated Kaplan (Pomona, CA) model 1234 ABP monitor. Monitors are validated for each person. BP readings will be taken simultaneously by the monitor and the RA, who has been trained in these procedures by Dr. Smith. The RA uses a T-connector and a mercury sphygmomanometer and stethoscope; readings are then compared. For validation to be considered successful, the mean agreement between the two sets of readings must be within 5 mmHg. Subjects are instructed about reading failures, which are usually attributable to arm movement. In the event of a failed reading, the monitor will make one attempt, 2 minutes later, to obtain a valid reading. Subjects are also given a telephone number that they can call to speak to an investigator or technician if a problem with the ABP monitor occurs. {31}

Chart Measures

At discharge, the RA will conduct a chart review to abstract data on comorbidities and antihypertensive medication changes. The purpose of these data is to assist in the interpretation

of the BP outcome. A random sample of 20% of the charts will be reviewed by a second coder, who is blind to the first coder's ratings, and interjudge ratings will be calculated to ensure reliability.

Data Analysis/Statistics

Overview of Approach. The proposed research is an RCT with an intervention arm, a placebo arm, and a UC arm. The primary aim of this trial is to determine if a guided breathing intervention has a significant and positive effect on lowering SBP, measured with an ABP monitor, after 8 weeks of intervention. {32} Thus, our primary analyses will be based on the intention-to-treat, with results from baseline carried forward for subjects who do not complete the trial. Subsequently, we will examine the long-term effects of device-guided breathing at 12 months. This phase of the study (i.e., involving the 12-month outcomes) will have two treatment arms representing subjects whose use of the device was of standard or extended duration as well as two comparison arms that include the placebo and UC groups.

We again propose an intention-to-treat approach in our primary analyses. Our general analytic strategy is, therefore, a one-way ANOVA on the change scores between baseline and 8 weeks (the primary aim) and between baseline and 12 months (the secondary aim). Our power and sample size calculations are based on this analytic strategy. {33}

NOTES

{30} In the interests of saving space, we are only showing you particular sections on which we wish to comment. Of course, a paragraph should be provided for each measure, including physiological measures. The next section provides an example.

{31} The authors give a lot of detail about the validation and use of the monitor. As always, you cannot assume that your readers are familiar with the device you plan to use or that they will make the assumption that you will conduct the necessary validation procedures (there will be analogous issues for most physiological measures you may take). As always, put yourself in the place of your reader and assume you don't know much about this device. What information would you require? What will you be looking for?

{32} We have deliberately kept this section as short as possible, because the statistical analyses will differ widely in each study. In this case, however, the design is a simple and straightforward one (somewhat more so, since I cut some complexities out of the design). Note that the authors give a very brief summary of the study design to set up the context for the analyses. You can see that the authors point out that the analyses will be conducted separately for the 8-week and the 12-month outcomes.

{33} Note that, before launching into the specific statistical methods, the authors have provided a clear statement that recaps the design and provides a context for the specifics. The use of the main analytic procedure (a mixed-design ANOVA) is justified, the computation of the within-subjects changes are explained (i.e., the difference in the outcome between the 12-month follow-up and the baseline measurements), the two different phases of the study (8 weeks vs. 12 months) are again touched on, and the data analyses are tied to the power analyses.

It is worth noting that one section we cut here concerned data editing. Your narrative should, for example, address what algorithms will be in place when outlier readings occur. You are presumably the expert regarding whatever measures you plan to take (or your co-investigators and/or consultants are); you should know—or learn about—the less obvious questions that may arise.

HINT

Unless your design is very simple and requires only t-tests, chi-squares, or simple ANOVAS, I would describe the statistical models, using the appropriate Greek symbols, and provide details concerning any nontrivial part of the

analysis. Moreover, if your analyses are complex, and neither you nor your co-investigators have a strong statistics reputation, reviewers will want to see that you have a good statistician on the project, preferably as a co-investigator.

Research Strategy: Approach

Research Methods and Design Example (Continued)

In the process of addressing these aims, we also will be able to explore a number of other secondary questions, including mechanisms that may underlie the effect of guided breathing on SBP and the possible moderating or conditional effects of other variables on the results. For these analyses, we will use multiple regression/correlation approaches to take advantage of the continuous nature of many of the proposed mediating or moderating variables. Although motivated by prior research and scholarship, we recognize the exploratory nature of these analyses in the context of this treatment-outcome study. We will be appropriately cautious in our inference strategies (e.g.,

adjustment of probability levels for claims of statistical significance), and we have focused our analyses and power (and sample size) on the primary aim. {34} More specifically, we intend to test the possibility that the effect of guided breathing on SBP change will be mediated by the effect of guided breathing on the baroreflex. And we intend to test the moderating effect of adherence on the treatment group-SBP change relation, with the specific prediction that increased adherence will enhance the treatment effect. {35}.

Data management. We will use a system in which data are entered by the RA (and the subject, if there is self-report data) directly into a tablet PC with a touch-sensitive screen. Data are then directly entered, via an interface, to a central database.

NOTES

{34} Labeling a particular analysis as “exploratory” does not relieve you, the principal investigator, of the responsibility to explain how you are going to control for Type I error (the probability of rejecting your null hypothesis when it is true). In the unlikely event you are not intimately acquainted with the issues of Type I and Type II errors, I advise you to learn about them before you submit your proposal. The reviewers will be well-versed in them and will be looking for instances in which your results may capitalize on chance. Here, the authors explain that they

are aware that these analyses are exploratory, but they also explain (albeit possibly in too little detail) how they plan to correct for it.

{35} The authors could have gone into more detail concerning the statistical models they plan to use, for example, the equations that underlie the procedures. In the example, however, the design is very straightforward and so are the analyses. It is worth noting, though, that the first ANOVA they plan involves the three study arms, but they do not mention what they plan to do subsequently if the ANOVA is significant. That is, do they propose planned orthogonal comparisons (which would be legitimate in the present case) or more conservative post hoc analyses?

In any case, it should have been discussed.

Research Strategy: Approach

Research Methods and Design Example (Continued)

Preliminary Analyses and Data Preparation. Prior to conducting the main analyses, all variables will be screened for inconsistent or abnormal values, and continuous measures will be assessed for skewness and outliers. Transformations to reduce heteroscedasticity and/or the effect of extreme values on the statistical analyses will be used, if necessary. We will also use exploratory graphical methods to assess the effect of these transformations on the linearity of the data.

Missing data rates and patterns will be assessed; in particular, missing data rates by treatment group will be studied. For the primary analyses, we will use intent-to-treat approaches and carry observations forward. However, for the secondary measures, including questionnaires, we will consider several approaches to handling missing data: maximum likelihood estimation of scattered missing responses, assessment of correlates of “missingness,” and complete case analysis. Reasons for withdrawal from the study and loss to follow-up will be tabulated by experimental group. {36}

Dissemination of Results {37}

We will disseminate results at conferences and in peer-reviewed journals on the following schedule:

End of Year 1: We will submit a methods/baseline paper to *Controlled Clinical Trials*.

End of Year 2: We will present preliminary findings at a national conference.

End of Year 3: We will present interim findings at a national conference and publish the findings.

End of Year 4: We will present further findings at a national conference.

End of Year 5: We will present the first set of basic results at a national conference and publish the findings.

Middle of Year 6: We shall present at a national conference and publish more extensive findings concerning both the clinical outcomes and mechanisms.

NOTES

{36} Missing data are almost always an issue in a study, and many researchers do not provide information on what they plan to do in the event data is missing. These authors address two issues here: (1) the imputation techniques they will use in the event of missing data, and (2) an analytic strategy that will allow statements to be made concerning the comparability of data from those who withdraw from the study and those who continue. Missing data issues are always important, and if you do not address them in a clinical trial, it will probably be regarded by the reviewers as an important omission.

{37} Dissemination of results is an important feature of the project that is often overlooked in the proposal. One assumes that the authors, once they have data in hand, will plan to present at conferences and write papers. However, when you consider that the talks and papers are the only product produced in return for large sums of money NIH has invested in you, make your dissemination intentions specific. The authors have provided a clear list giving the approximate times in the course of the study that they will publicize their findings, which is an excellent idea. It also, incidentally, helps justify the travel money you will be requesting (see Chapter 7).

Many researchers do not provide citations for their proposed statistical analyses. Obviously, if the statistics are to be fairly simple (e.g., t-tests, correlations, analyses of variance [ANOVA], regressions, or simple nonparametric tests), you don't need to provide citations. However, when using more complex procedures (e.g., multivariate analy-

sis of variance [MANOVA], simultaneous equation modeling, hierarchical modeling procedures, and so on) or a procedure that is in any way controversial (e.g., contriving a post hoc test to examine differences between groups in a mixed design), provide references to provide validity for your statistical approach.

HINT

A reviewer will jump all over a proposal that looks as though it seeks to capitalize on chance—that looks like a “fishing expedition.” To the extent that a hypothesis is strongly justified on the basis of theory and prior results, a Type I error is less of an issue (but it is always an issue). Thus, I have seen proposals in which “cardiovascular change” is given as the outcome, measured as systolic and diastolic blood pressure, heart rate, heart rate variability (of which there can be three or four measures), and hemodynamic pattern (i.e., peripheral resistance, cardiac output, and several other measures). If you have multiple

outcome measures, you should be prepared to make specific predictions for each of them separately. If, say, only one or two of those measures show the predicted effect, is that sufficient to say that a hypothesis concerning cardiovascular change was supported? If you do not have specific hypotheses about each individual outcome, you should be prepared to use statistical controls of some sort to protect against Type I error. And this is an even greater problem when you are analyzing research questions or exploratory hypotheses rather than your primary, well-grounded study hypotheses.

Research Strategy: Approach

Research Methods and Design Example (Continued)

Potential Confounding Due to Changes in Medication, Especially in the Control Condition. In an intervention in which the experimental group is predicted to show an improvement in the outcome measure, and participants in the control condition are predicted to show no change, there is always a concern that the attending physician may use other methods to control the illness, making it difficult to interpret the results. To minimize this possibility, we shall take the following steps: At screening, potential participants (i.e., those found to be hypertensive) will be informed that their BP is higher than recommended levels, and the RA will suggest that they see a physician. They will be told that if, as a result of the screening, they do plan to see a physician for possible treatment, they will not be admitted to the study immediately, but only after they have seen their physicians; if no new treatment has been prescribed at that physician visit, they may then be admitted to the study; if new treatment has started (either new medications or increased dosages of medications the participant is already taking), the participant will be told that after 2 months, he or she may be rescreened (to allow the change in treatment to take effect and stabilize), and, depending on the results, may then be admitted to the study. {38}

Monitoring and Promotion of Adherence. We will ask participants in the standard intervention and placebo conditions to use their device 4 days/week for 8 weeks; we will ask those in the extended duration condition to use their device 4 days/week for 12 months. Finally, we will ask all participants to take their BP 2 days/week for 12 months (three readings each time). This obviously represents a large burden, especially for those in the extended duration condition. We will know precisely when and for how often the guided breathing and placebo devices are used, as the devices automatically record the date, time, and duration of the sessions, as well as other statistics regarding performance of breathing in the < 10 breath/minute range. Similarly, the home BP device also stores the readings with the dates and times of measurement. The data from the guided breathing and the placebo devices will be used in sub-analyses to examine the effects of amount of practice on change in BP (and HRV and baroreflex sensitivity). {39}

Study Timetable

(Note. Reviewers like to see a timetable that shows what you intend to be the chronological process of the conduct of your grant. Here is an example of what one might look like if conducting a 3-year human study in which subjects are seen at baseline and at follow-up 6 months later. The study calls for 180 subjects, and they will be scheduled at 30 per quarter (10 per month):

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter
1	Setup/Hiring	Training	Screening/Enrollment	Cohort 1 Baseline
2	Cohort 2 Baseline	Cohort 3 Baseline	Cohort 4 Baseline	Cohort Baseline
3	Cohort 6 Baseline	Cohort 4 Follow-Up	Cohort 5 Follow-Up	Cohort 6 Follow-Up Data analysis, Report Writing

Review Criteria {40}

1. **Significance.** The proposed study addresses an important public health problem {41}—the excess morbidity, mortality, and economic burden due to uncontrolled HTN. If the aims of the application are achieved, the scientific gains include a better understanding of the role characteristic breathing patterns and the RSA play in BP regulation; and of the role that non-pharmacological approaches to HTN treatment may play as a supplement and, when necessary, as an alternative to pharmacological therapy.
2. **Approach.** We have proposed the use of an RCT, a powerful design that provides important scientific information concerning the causal relation between the intervention and the outcome and about the feasibility and utility of the proposed intervention. The proposed measures are based on the assessment in the current literature of the most useful, cutting-edge techniques: for example, ambulatory assessment of BP and respiration. The proposed statistical analyses use cutting-edge techniques as well. Alternative research strategies and the rationales for methodological decisions have been described, as in the case of the design (we considered, for example, a crossover design) and control conditions.
 - a. NYMC has provided strong support for the research of this group over the past several years. The group itself has the resources necessary to successfully carry out the research in terms of research space, computer and Internet resources, clinical needs including ABP monitors, Holter monitors, and ambulatory respiratory assessment monitors. The patient population at NYMC is diverse and composed, to a large degree, of economically disadvantaged patients who are especially in need of non-pharmacological treatments. The outpatient clinic has a substantial patient load, and a large proportion of the patients seen there are minorities with poorly controlled HTN. {42}
 - b. NYMC has provided strong support for the research of this group over the past several years. The group itself has the resources necessary to successfully carry out the research in terms of research space, computer and Internet resources, clinical needs including ABP monitors, Holter monitors, and ambulatory respiratory assessment monitors. The patient population at NYMC is diverse and composed, to a large degree, of economically disadvantaged patients who are especially in need of non-pharmacological treatments. The outpatient clinic has a substantial patient load, and a large proportion of the patients seen there are minorities with poorly controlled HTN. {42}
3. **Innovation.** The proposed study represents an innovative treatment intervention that is a departure from the traditional manner in which HTN treatment is usually considered and that represents a potentially important advancement in public health.
4. **Investigators.** This research team has done much of the seminal work in the areas of BP measurement, psychosocial causes of essential HTN, and behavioral interventions for the treatment of HTN. They also have a great deal of experience in the conduct of behavioral clinical trials.

NOTES

{38} The authors have discussed the limitations in the narrative as the concern would have arisen in the reviewer's mind. That is how you want to do it—you don't want the reviewer to have carried that doubt as she continued reading your proposal. However, some researchers also like to see a "limitations" section. Reviewers tend to look for it, and it is a useful place to describe your logic concerning potential pitfalls. If you do include this section, you should

- Discuss potential weaknesses in the proposed procedures, especially those that may interfere with a clean interpretation of the data.
- Describe alternative approaches you have considered and why you chose not to use them (it is often the case that there are a limited number of approaches you can take concerning a specific issue, and whichever one you choose is associated with some weakness).
- Specifically note that the case you plan to make is not compromised by the weakness in design.

{39} Participant compliance to the study protocol absolutely must be addressed. People, even those who have volunteered for your study and who have agreed to comply with the study requirements, will routinely violate one or another part of the protocol, which leads to missing data or worse, poor-quality data. If there is a differential incompliance between your conditions (i.e., participants are less compliant in one condition than in others), you begin to lose the power of your random assignment, as subjects are self-selecting out of some portions of the data. It is common for applicants to lose points on this issue.

{40} The following section comprises the five criteria that NIH reviewers use to evaluate each application. Each criterion is addressed without false modesty and, at the same time, without unjustified crowing. Make your argument matter-of-factly, but don't hesitate to highlight your strengths. Note that I encouraged researchers to always do this at the end of the proposal when 25 pages was the rule; there is a good chance that you won't be able to squeeze this in, but I have left it in this example as an illustration.

{41} Note the authors' reference to a public health problem. You should tie the research to the public health considerations as often as you can justify it. This is true whether your research takes place in a test tube, in an animal model, or in a community sample. Ultimately, as far as the NIH is concerned, there is no reason to do the research if it will not eventually have implications for treatment.

{42} Access to particular patient populations that are of interest to the NIH for one reason or another (e.g., because they are underserved, understudied, economically disadvantaged, or culturally diverse) is an important resource in which the reviewers will absolutely be interested.

COMMON REVIEWERS' CRITICISMS

In Chapter 8, we set out common reviewers' criticisms of proposals. They are provided there rather than here because Chapter 8 is where we discuss the feedback you will receive on the summary sheets and the resubmission process. However, it would obviously be just as well to have these common criticisms in mind while you are writing the original draft, so please consult these criticisms as you are developing the proposal.

PROPOSAL DEVELOPMENT TIMELINE

Allow yourself sufficient time to write any proposal you plan to submit to the NIH—or any other funding agency. I have seen otherwise-competent scientists begin their proposals 2 or 3 weeks before the deadline. Can you get it done in that amount of time? Sure. Probably. Maybe. Will it get funded? You should have a pretty good sense by now that the answer is, “Not likely.” I suggest you begin writing your Specific Aims at least 3 months before the deadline. In fact, Table 5.1 shows a possible timeline for some of the major aspects of the development of the proposal. Note that I regard 3 months as a minimum; you may decide you require more time.

HINT

Why so long, really? You can write the proposal in considerably less than that; it is not the writing of the proposal that requires such a long preparation period. It is allowing sufficient time to develop the story you want to tell,

especially how you plan to your approach. This often will involve consultations with others, reference to the costs (which may cause you to have to revise your initial plans), time allowed to get feedback from your colleagues.

Table 5.1 Suggested Writing Time Table

	12 Months	16 Weeks	14 Weeks	12 Weeks	10 Weeks	6 Weeks	4 Weeks
Develop initial conceptualization	X						
Begin collecting pilot data	X						
Contact PO	X						
Compile research team		X					
Obtain application forms		X					
Begin Specific Aims section		X					
Begin budget		X					
Begin Research Design and Methods section			X				
Begin IRB application			X				
Determine potential reviewers				X			
Begin Preliminary Studies section				X			
Enlist consultants				X			

	12 Months	16 Weeks	14 Weeks	12 Weeks	10 Weeks	6 Weeks	4 Weeks
Finalize budget					X		
Obtain letters of support					X		
Finalize Specific Aims section					X		
Finalize Research Design and Methods section						X	
Finalize Preliminary Studies section						X	
Finalize sections E–K						X	
Send to colleagues for review						X	
Write abstract							X
Send for budget review and departmental signatures							X
Revise until deadline							X

REVISE, REVISE, REVISE, PROOFREAD, PROOFREAD ...

To revise and proofread your proposal may seem obvious, but two things tend to happen that interfere. First, you start coming down to the wire, and haven't left yourself enough time. Second, there does arrive a point at which you just can't look at the damn thing another time. I know that there is a point at which I hit a wall, and my eyes slip off the text without being able to process it. These are both great excuses, but they will not provide a lot of comfort if you don't get funded. So what to do? This is obvious, too, and I've made the point as strongly as possible in other parts of this book. Start early. Start earlier than you would have guessed, because your deadline should not be the NIH submission date; it should be at least a month earlier. That will take care of the running out of time problem. It will also take care of the other problem, because the obvious solution is that you need to take a few days, even a week, off from the process so that you can approach the writing afresh.

I absolutely guarantee that if you do this, you will find problems in the text that passed you by on all previous readings! At the least, you will find places in which you have been redundant and can word things more clearly and efficiently. Myself, I will have read the entire proposal through 30 or more times before submission. There are things you cannot control: whether the reviewers will like your idea, whether NIH funding levels are up or down, and so on; but as a professional, you want to control everything you can. No typographical errors, no inconsistencies in numbers, no mismatch between section numbers, no inappropriate paragraphs left in from when you cut-and-pasted from someone else's proposal or your most recent publication. . . . Such mistakes do more than annoy the reviewers; they also reflect badly on you in general.

SUMMARY

Here are the points we have emphasized:

1. Scientific writing has to be good writing. It is your job as the writer to create a series of impressions in the mind of the reader, and to do so, you must read your own writing as

though you were a reviewer. If it were someone else's proposal you were reading, did anything arise to trigger a question? Did the Background and Significance sections tell a story that made sense, in which one point led logically and fluidly to the next? Was each contention adequately supported? Did you see a proposed strategy or procedure that might be deemed controversial, even unacceptable by some? (And if so, did you address that concern right at that point in the proposal?)

2. You have to use your judgment concerning the relative levels of detail you can provide concerning the background and significance, the preliminary studies, and the research and design methods. You probably can't give the level of detail you would like on all those sections, and when allocating space, "research and design methods" should get priority—reviewers want specifics concerning procedures, measures, and analyses.
3. You have to communicate your excitement about the proposal—that you are passionately convinced that this is important research that will have a substantial impact on the field. You must be clear about why it is important regarding the public health issue you are addressing. And no matter whether your research is closer to bench than bedside, translational is one of the key watchwords these days: Make sure that your reader understands that no matter the level of your work, it is a necessary step to influencing the public health.
4. Start early, at least a few months before the deadline. This isn't because it takes so long to do the writing—it doesn't, or anyhow, shouldn't—it is to allow colleagues to read drafts as you progress toward the finished product, to allow you time to integrate their comments, and then to send it out again. Get as many eyes on the proposal as you can, and don't wait to do this until the end: Send it out as soon as you have finished your Specific Aims.