# CHAPTER 11

## *RESEARCH STRATEGY SECTION: APPROACH SUBSECTION (INCLUDING RIGOR, POTENTIAL BIOLOGICAL VARIABLES, TECHNICAL PRELIMINARY STUDIES, AND RENEWAL PROGRESS REPORT)*

> ***Research Instructions for NIH and Other PHS Agencies, Section R.400.3.3:*** "Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Describe the experimental design and methods proposed and how they will achieve robust and unbiased results. Unless addressed separately in Item 14 [Resource Sharing Plan, PHS 398 Research Plan form], 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. Explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans. For example, strong justification from the scientific literature, preliminary data, or other relevant considerations, must be provided for applications proposing to study only one sex. ... 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 appear in item 5 [of the PHS 398 Research Plan form, Protection of Human Subjects]."

Approach is a subsection of the Research Strategy section. Its format is given below:

APPROACH:
- Each Aim:
  - Introduction
  - Research Design
  - Expected Outcomes
  - Potential Problems & Alternative Strategies
- Timeline and Benchmarks for Success
- Future Directions

In this Chapter we will describe for you how to (1) make reviewers *want* to read the details under each aim (purpose of the Introductory Paragraph); (2) write the narrative description of what will be done (Research Design); (3) present what each aim is expected to produce (Expected Outcomes); (4) describe potential problems that might be encountered and, if they are, how they will be avoided/overcome (Potential Problems & Alternative Strategies); (5) depict when the various activities will take place (Timeline), and how you will know if you are succeeding (Benchmarks for Success); and (6) convey to reviewers where the outcomes of this project are expected to lead (Future Directions).

## GENERAL COMMENTS

Descriptive detail in the Approach subsection should be minimized to the greatest extent possible while, at the same time, you give reviewers enough to evaluate what you propose. In other words, you need to strike a "Goldilocks" balance – not too much detail and not too little. From a purely practical standpoint, there isn't enough room in the up-to-12-page length of the Research Strategy section in an R01 or R15 application (even less in an R03 or R21 – just 6 pages) to include excessive detail. Doing so would force you to short other important emphases, such as the quality of the science and the positive impact that your results are expected to have.

If your specific aims have been balanced appropriately, each should have approximately equal weight with respect to the number of pages that is devoted to it. Given the shift of most of the literature review and preliminary data to the Significance subsection, the total length of the Approach subsection should be 7-8 pages. Therefore, if you have three aims, you should have 2+ pages for each – not much! Thus, you must write very succinctly and include only meaningful detail. What do we mean by that? For example, how will you assess statistical significance. How many times will something have to be repeated before you reach statistical significance? If you will be using subjects, how many will you need – and how was that number derived? Did you just pull it out of thin air or did you use an approach, like power analysis, to establish the number? What are the controls? None of those examples could be written by copying part of a methods manual or a publication, which is the operational definition of "meaningful" detail.

Before you begin to write, consider the following general points. Development of a strong Approach subsection requires only that you answer the following five questions for each of your aims: 1) What will be done? 2) What are the means that you will use to accomplish the aim? 3) What might go wrong? 4) What alternative strategies would you turn to if something were to go wrong? And finally, 5) what are the expected outcomes and why are they important? If you are a New/Early Stage Investigator, be especially clear that the work is feasible in *your* hands.

As a final general point, provided that you have conscientiously developed your Specific Aims section, this part of the application should be one of the easiest for you to write even though it is one of the longest. We suggest again here that you write this section by scheduling time each day to work on it. If you take this approach and consistently stick to it, you should have no trouble completing a first-rate Approach subsection in two-to-three weeks. At the same time, you will be able to manage all of your other, competing priorities.

## APPROACH: DEVELOPING EACH AIM

Your already-formulated specific aims should be the core of your Approach subsection. Accordingly, we recommend that you subdivide it along the lines of your aims. The title of each subdivision should be a verbatim repeat of how the aim was presented in your Specific Aims section. Begin by telling reviewers how you intend to accomplish aim #1. We recommend that you do so by first writing bullets, which you then expand into sentences.

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

***Introduction.*** The first paragraph under each aim should be an introductory one. This is consistent with our general strategy of gradually ratcheting up detail as the reader goes deeper into a section. The bolded, italicized title should be "Introduction," indented as shown at the beginning of this paragraph. Continue with text on the same line, as has been done here, with

subsequent lines returning to the left margin. The paragraph should be a very brief "overview" of what will be done and why. It should "hook" the reviewer's interest in the aim and make him/her *want* to read the details that follow. Key words (e.g., *objective, working hypothesis, approach, expectations, etc.*) should be highlighted in non-bolded italics to allow reviewers to find these components easily. If you are using Arial or Helvetica or some other sans-serif typeface, we recommend that you also underline those words.

Begin this paragraph with a sentence that justifies why the work under this aim needs to be performed. In doing so, you should call attention to the part of the overall problem that will be addressed.

Next, write the aim's *objective*. It should be a subset of the overall objective that you wrote in the Specific Aims section. Go on to state that its attainment will resolve the problem/question that you highlighted with your justification, above. The sentence might be something like, "The *objective* of this aim is to (solve the problem/answer the question that the aim will address)."

Next, tell the reviewer how you plan to attain the objective that you have written. In most cases, you will do so by objectively testing the aim's *working hypothesis*. You followed the statement of this aim in the Specific Aims section with a working hypothesis. It should be repeated here, verbatim. It is critical that you repeat the working hypothesis in this introductory paragraph, because you want to underscore for your reviewers that the work to be done will be hypothesis-driven. We suggest that you phrase your working hypothesis something like: "To attain this objective we will test the *working hypothesis* that _____." (NOTE: If you are developing an aim that is *not* hypothesis driven, skip writing this part of the introductory paragraph.)

Follow the working hypothesis (or the objective if the aim is not hypothesis driven) with a sentence or two about the overall strategy or approach that will be used to test (attain) it. For example, "Our *approach* to testing the working hypothesis will be to _____."

The *rationale* for the work to be proposed under this aim – why you want to undertake this part of the research – should be presented next. The litmus test to be applied here is the same one that you used for testing the overall rationale that you wrote for the Specific Aims section: Does what I have written tell the reviewer what will become possible after the proposed research is completed that is not possible now? Write something like, "The *rationale* for this aim is that its successful completion is expected to contribute a fundamental element to our base of knowledge, without which the metabolism of compound X cannot be understood. The acquisition of such knowledge is essential to the development of improved therapeutic strategies for disease Y."

Finally, summarize the expected outcome(s) for this aim and call attention to their importance. You might write something like, "After completing Aim #1, it is our *expectation* that we will have identified how compound X is metabolized. Further, we expect to have shown that metabolism of X entails phosphorylation of key amino acids strategically located at the plasma membrane/cytoplasm interface. Such findings would be important, because they would likely inform the development of novel and much-needed approaches to therapy of disease Y."

When completed, the introductory paragraph should occupy no more than 1/4 to 1/3 of the page. The flow of logic must be clear and compelling – it must "hook" the reviewer's interest in the details that follow.

***Research Design.*** Two of NIH's recent areas of emphasis are (1) rigorous experimental design that will produce robust and unbiased results and (2) consideration of relevant biological variables in such design. The genesis of these emphases stems from NIH's realization that not all of the results produced with its funding have been reproducible. A comprehensive overview of what NIH recommends to correct this problem can be found at https://grants.nih.gov/reproducibility/index.htm.

Extra requirements with respect to experimental design and the consideration of biological variables may be imposed by individual Institutes and Centers, either on their website or in Funding Opportunity Announcements that they issue. Those specific requirements, if they exist, take precedence over the general instructions that follow.

Aids to understanding how you can enhance reproducibility of your own work are in video format. You can access them at the following links:

- Reproducibility of Data Collection and Analysis – Modern Technologies in Cell Biology: Potentials and Pitfalls (11-24-2014)
  https://videocast.nih.gov/summary.asp?Live=15277&bhcp=1
- Reproducibility of Data Collection and Analysis – Modern Technologies in Structural Biology: Potentials and Pitfalls (03-13-2015)
  https://videocast.nih.gov/summary.asp?Live=15910&bhcp=1
- Reproducibility of Data Collection and Analysis – Modern Technologies in Genome Technology: Potentials and Pitfalls (06-04-2015)
  https://videocast.nih.gov/summary.asp?Live=16381&bhcp=1
- NIH Workshop on Reproducibility in Cell Culture Studies
  09-28-2015 Day 1: https://videocast.nih.gov/summary.asp?Live=16876&bhcp=1
  09-29-2015 Day 2: https://videocast.nih.gov/Summary.asp?file=19196&bhcp=1
- Improving Openness and Reproducibility of Scientific Research (10-26-2015)
  https://videocast.nih.gov/summary.asp?live=17454&bhcp=1
- Clearinghouse for Training Modules to Enhance Data Reproducibility
  https://www.nigms.nih.gov/training/pages/clearinghouse-for-training-modules-to-enhance-data-reproducibility.aspx

Rigorous Experimental Design for Robust and Unbiased Results

One of the problems that NIH has identified is that some – many? – investigators have not received sufficient training in "strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results." As a consequence, as noted above, results of their research may not be replicable when the "same" experiments are repeated using appropriate experimental design. If you are one of those persons, it is relatively simple to catch up. For example, since changes in application requirements were announced in March of 2016, NIH has published aids that are designed to enhance rigor and reproducibility (e.g., https://nexus.od.nih.gov/all/2016/07/31/your-one-page-guide-to-rigor-and-reproducibility and https://grants.nih.gov/reproducibility/documents/grant-guideline.pdf). You can also find many texts and journal articles that describe rigorous experimental design for qualitative, quantitative and mixed-methods research online. They range from ones that are general/philosophical (e.g., http://www.sfn.org/Advocacy/Policy-Positions/Research-Practices-for-Scientific-Rigor and http://mbio.asm.org/content/7/6/e01902-16.full) to others (e.g., http://www.stat.cmu.edu/~hseltman/309/Book/Book.pdf) that are point-by-point guides. Many of

the publications would appear to be discipline specific. However, the principles and fundamentals of good experimental design and analysis are generally applicable across disciplinary boundaries. As an alternative approach to finding the sought-after resources, consult your reference librarian.

NIH will also address the problem of insufficient grounding in experimental design and transparency prospectively. Beginning "as early as 2017," NIH (and AHRQ) will require that their trainees receive formal instruction in rigorous experimental design and transparency to enhance reproducibility (see https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-034.html).

Unfortunately, rigorous design alone won't get you all the way to where you need to be. How you implement the design is also important, particularly if you are doing bench research. If you aren't doing so already, adhering to principles of Good Laboratory Practice as closely as is practicable is something that we recommend you consider. Although the original principles were applied to improve studies of drug safety, in our opinion they extend to any laboratory in which investigators want to produce results that are replicable. As defined by the Medicines and Healthcare Products Regulatory Agency (UK), Good Laboratory Practice procedures provide "a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. ... GLP helps assure 'regulatory authorities' [read as 'NIH'] that the data submitted are a true reflection of the results obtained ..." You can find manuals describing Good Laboratory Practice online. For example, the World Health Organization offers a very helpful publication (http://www.who.int/tdr/publications/documents/glp-handbook.pdf) that is titled *Handbook – Good Laboratory Practice (GLP).* Stating in a grant application that you adhere to applicable principles of Good Laboratory Practice would be a strong indicator that you are serious about the issue of reproducibility. Many of the practices are relatively simple to implement and can make a <u>big</u> difference with respect to others being able to replicate your work. For example, having a standardized format and worksheets for record keeping is essential, as is a full set of standard operating procedures for your research group. The latter is even more important if you are proposing a multi-laboratory effort, as would be the case for a Research Program Project (P01) application. Little things, like checking the accuracy of your scale on a routine basis, or storing hygroscopic chemicals in either a desiccator or under a vacuum, or putting dates on reagent containers so that you can monitor shelf life may seem tedious at first, but will prove to be well worth the trouble in the end.

Another approach to standardizing how you conduct research is to adopt applicable methods that PCORI's (Patient-Centered Outcomes Research Institute) Methods Committee has created or endorsed (http://www.pcori.org/research-results/research-methodology/pcori-methodology-standards).

<u>Consideration of Relevant Biological Variables</u>

Experimental design should also take into account biological characteristics that could cause the results of investigations to vary. Sex is a particularly important and often overlooked source of variation. Full consideration of sex in the design and implementation of research requires much more than just the inclusion of both sexes. NIH suggests that applicants and reviewers should additionally consider (i) the extent to which the influence of sex, if any, has been included in the review of literature, (ii) the formulation of research questions and the design of experiments; (iii) stratified randomization of males and females has been included in the experimental design; (iv) the experimental design allows for disaggregation of data, so that results obtained from males and females can be analyzed separately and compared; (v) treatment or toxicity effects can be assessed for each sex separately; (vi) the potential influence

of sex has been included in the interpretation of results; and (vii) the extent to which projected generalizations from the study are appropriate, given the scope of the actual results. (Adapted from FAQs answer IV.2 at https://grants.nih.gov/reproducibility/faqs.htm).

With respect to learning how sex should be factored into research design, we recommend that you take advantage of online training modules that have been posted by NIH's Office of Research on Women's Health (https://orwh.od.nih.gov/research/sex-gender/methods-and-techniques) and the Canadian Institutes of Health Research's (CIHR's) Institute of Gender and Health (http://www.cihr-irsc.gc.ca/e/49347.html). One thing that you will learn is that it is not always necessary to include an equal number of males and females in every experiment. This point, as well as a number of others, have been made in two must-read publications. The first of these (http://www.fasebj.org/content/early/2015/10/28/fj.15-279554.full.pdf+html) was written by Dr. Janine Austin Clayton. She is Director of the Office of Research on Women's Health at NIH. In it, she makes the very important point that "considering sex as a biological variable is not the same as looking for sex differences." Clayton goes on to make the point that the results of rigorously designed preliminary studies can be used to justify why there is no need to include both sexes in subsequent definitive investigations – or, by contrast, that such data could reveal the existence of a potential difference. Part of the definition of "rigorously designed" in the preceding sentence is that the data from each sex be kept separate, so that they can be compared. If such a comparison would suggest a difference, then and only then would there be the need to consider in depth whether (or not) a sex difference exists. One course of action thereafter would be to study each sex in numbers sufficient to reach statistically valid conclusions. Alternatively, if the investigator would elect not to perform additional rigorous, in-depth investigations (not recommended), at the least, in the name of reporting transparency, s/he should describe in related publications that a sex difference could exist. Doing so would appropriately alert subsequent investigators.

The second publication (https://bsd.biomedcentral.com/articles/10.1186/s13293-016-0066-x) includes Dr. Clayton as a coauthor. It extends discussion to metrics that can be used by peer reviewers to assess the appropriateness and extent to which sex has been considered as a biological variable in preclinical studies that propose the use of either human subjects or non-human vertebrate animals. A table of twelve questions is presented that peer reviewers are encouraged to ask. The questions represent a consensus of the NIH and the CIHR, which are the principal funders of biomedical research in North America. CIHR's reviewer checklist, which we find very instructive and helpful, can be downloaded as a PDF at http://www.cihr-irsc.gc.ca/e/documents/igh-checklist-integrating-fund-initiatives-bio-en.pdf.

If you are proposing human or animal experiments in which it would be impossible to include both sexes, you need to state why, even if it is intuitively obvious. For example, it would not be possible to include both sexes in a study of ovarian dysfunction.

If it would be possible but unnecessary to include both sexes, in your opinion, you must include strong justification for that approach. You are required to provide similar justification for not considering other potential causes of biological variation, e.g., age, from your design.

Although NIH does not require it at this time, it encourages investigators to report whether their cell lines have male or female karyotypes and to consider the possible influence of sex on the analysis of results obtained from such cell lines (see FAQs answers IV.3 at and IV.4 at https://grants.nih.gov/reproducibility/faqs.htm).

There are many other biological variables than sex that could potentially cause variation in the results obtained. Three more mentioned by NIH include weight, age, and health status. Others might include race, ethnicity, species/strain of laboratory animal, and diet, for example.

These must also be discussed and accounted for in your research design if the literature or your preliminary data suggest that they could cause results to vary. If you are unclear regarding how to do so, we recommend that you contact the relevant Program Officer.

How to Develop the Research Design Part of Each Aim

Begin by creating bullets that denote the planned activities/studies under each aim. Accompany each list with an informative, interest-attracting title – a *headline* – that will be used to introduce the related paragraph(s) under it. As was the case for developing the aims themselves, no one of the activities/studies should be absolutely dependent on an expected outcome of an earlier one. Make certain that the range of activities/studies is sufficiently comprehensive that the outcomes will collectively attain your application's overall objective.

Starting with Aim #1, create additional bullets that detail under each activity/study what, exactly, will be done. The list will be different for different kinds of research, e.g., bench, secondary analysis, and human-subjects research. Because there is a range of what might be included under each, it is not possible to provide an all-inclusive list here. We underscore again that, whatever your list entails, you need to provide a full range of *meaningful detail*, not just a list of methods and their descriptions. When something in the bulleted list, below, is pertinent, create a corresponding bullet. Then, embellish our bulleted list with other activities that are relevant to this part of your research.

Write an interest-evoking title for your first activity/study:

- Research design/Approach to be used
- Overview of method(s)/Procedures to be used
- Controls
- Data management
- Participants and setting
- Recruitment
- Study Conditions (if a randomized clinical trial)
- Randomization (if a randomized clinical trial)
- Potential sources of biological variation (this Chapter)
- Essential reagents and their authentication (see Chapter 16)
- Essential major/minor equipment (see Chapter 15)
- Number of human/animal subjects needed and how the number was derived
- Replicates needed to reach statistical significance
- Statistical analysis/analyses to be used (e.g., power analysis)
- Expected outcomes (VERY important)
- How results will be interpreted
- Time required to complete the activities/studies

Next, write the title of your second activity/study. Consider each of the headings listed above for activity/study #2. Continue this process for other activities/studies that are needed, until you have completed a full outline of those that will be undertaken under Specific Aim #1.

Begin writing the Research Design subsection for Aim #1 by expanding the bullets you have written. As you write, remember that you *must* engender maximal enthusiasm and acceptance of your proposal. Avoid cluttering the reviewer's mind with material that is tangential to the main point that you want to make in each of your paragraphs. Write in simple declarative sentences that are free of jargon and nonstandard abbreviations and acronyms. Whenever it is

credible to do so, use strong words, like "expect," and "can." Avoid weak words like "hope" and "try," i.e., those that unnecessarily plant a seed of doubt in the reviewer's mind about what you are proposing (see Chapter 4 for more examples of weak words). Emphasize the conceptual, because that is what is exciting and likely to attract the interest of the reviewer. Make sure, however, that you provide enough experimental detail, e.g., methodological, statistical, and appropriate controls, so that the reviewer will know not only what you plan to do but also how you plan to do it, and how the resultant data will be interpreted.

Repeat the above described process for each of your subsequent aims.

If anything is common to two or more of your aims, whether it is methods, subjects or whatever, in later aims refer reviewers to where it is first described in the proposal. There usually isn't enough room under Approach to include a separate Methods & Procedures section and still develop each of your aims fully. And never include a Methods and Procedures appendix. Doing so would be a direct violation of instructions regarding appendix material that are contained in the *Research Instructions for NIH and Other PHS Agencies* (see also Chapter 16 of this *Workbook*) and would likely result in your application being returned without review.

If you are still unsure about how much methodological detail to include, ask yourself the following two questions: (1) Has anyone on the research team published in a peer-reviewed journal using this methodology? If so, reference the relevant publication; don't describe the methodology in your application. Why? Because methodologic description takes up space and makes for pretty boring reading. However, as part of full disclosure we must tell you that NIH does not require reviewers to consult such "off-site" information. Most reviewers will, but they don't have to. Even if they don't, the fact that you have cited a peer-reviewed publication will be taken by most as evidence that you have used the referenced method. (2) Does my training make it obvious that I can do this? For example, would a reviewer require a formally trained molecular biologist to detail how RNA is extracted? We think not.

Especially if you are a New/Early Stage Investigator, there may be a need to offer technical preliminary data here that support your capacity to do what is proposed. Let's consider, for example, an application in which you propose the use of a very demanding technical procedure. You know that everyone on the review panel will know that it is difficult to employ successfully. Neither you nor any of your Co-Investigators has published work that includes use of the procedure. Or, let's imagine that you are you are proposing to recruit parent-child dyads in the context of a rare pediatric disease that rapidly progresses to high morbidity and mortality. Neither you nor any of your Co-Investigators has a demonstrated history of successfully recruiting (and longitudinally retaining) parent-child dyads. Reviewers can be expected, therefore, to anticipate recruitment challenges related to limited overall numbers of children with the rare condition, as well as parental consent issues, given the rapid and emotionally challenging course of the disease. Good proposal writers anticipate problems that they may run into (think like a reviewer) and then do something prospectively to avoid/overcome those problems. In these examples you can anticipate that reviewers will be skeptical of your ability to use the technique successfully/recruit and retain a sufficient number of parent-child dyads. So, to overcome that anticipated concern, you would include technical preliminary results here, in the Approach subsection (rather than under the Scientific Premise subdivision of the Significance subsection), which validate that you will be able to do what you propose.

Technical preliminary may not be generated for publication, but they need to be of publishable quality. In other words, they must have been produced with the same rigor and transparency that would characterize work meant for publication. The results can come from an iso-

lated study, like the one described in the preceding paragraph, which was designed and executed for the sole purpose of providing proof of technical feasibility in your hands.

***Expected Outcomes.*** *It is critically important that this subsection be included for each aim.* It is your opportunity to highlight the "return on investment" that reviewers will be seeking from the aim. Each activity described in the Research Design subsection should have an outcome associated with it. The Expected Outcomes subdivision is where you integrate all of those outcomes to convince reviewers that they collectively attain the aim's objective. In other words, you must provide more than a "laundry list" of expected outcomes. Offering a list is a common mistake, which creates more work for the reviewer. In addition, when that mistake is made, you risk that the reviewer won't/can't make the connection that the expected outcomes collectively attain the aim's objective. What you write here should be more extensive than the summary sentence (or two) that you wrote about expected outcomes in the aim's introductory paragraph. It should be a single, short paragraph – 1/3-to-1/2 page, at most.

The Expected Outcomes paragraph is another opportunity that you have to create excitement, so make every effort to underscore why the expected results are important. There are at least two reasons why they are. First, they collectively attain the aim's objective, thereby contributing to the success of your project. Second, they contribute to attainment of the application's overall objective and, therefore, vertical advancement of the field. Be enthusiastic but, at the same time, realistic. Provide appropriate caveats, if they are needed. You must not overstate your expectations to the extent that you would be perceived by reviewers as overreaching.

***Potential Problems & Alternative Strategies.*** Your job here is to anticipate potential problems that you might encounter during the proposed research. You know – and the reviewers will know – that there is no such thing as problem-free research. No matter how hard you plan and prepare, problems can and will develop. Therefore, to allay reviewers' concerns about such inevitable problems, you should list and accompany them with alternative strategies to which you would turn, should they arise. *Failure to include this subdivision under each aim can seriously undercut the fundability of your proposal.* Evidence that we are correct in that assertion can be found in the text box at the beginning of this Chapter.

If you are doing hypothesis-driven research, the most important potential problem that you must consider is that the working hypothesis for an Aim will unexpectedly test invalid. In that unlikely event, what would you do? To what alternative would you turn? To answer that question, think back to when you were performing preliminary studies. You undoubtedly had a list of alternative hypotheses that you were considering. One by one, your preliminary studies eliminated them, which is how you settled on a working hypothesis - your "best bet" at the time as to what the explanation is. Should objective testing invalidate that hypothesis, you would turn to the last alternative to be eliminated as your next best bet.

As examples of other potential problems, reviewers will be concerned about critical reagents: Will they be available and will they perform as expected, even if you provide proof that they have been authenticated (see Chapter 16)? Another concern may pertain to the assays you propose – will they be as discriminating as you say they will be? The recruitment of sufficient subjects may be another. If you are proposing collection of data remotely, will all of the participants have unfettered access to the Internet?

The problems presented here should *not* be major ones. You should deal with those under the Research Design subsection, not here. The problems included here should be ones that could arise but probably won't. For example, were you to get into your new car on a warm, sun-

ny morning and find that it wouldn't start, that would be a totally unexpected problem – but it *could* happen. Alternative strategies that would allow you to reach your destination might include calling a taxi, renting a car, calling a friend, bicycling, etc. In other words, you would have no problem whatsoever convincing even the most critical reviewer of the fact that, should such an *unlikely* possibility actually occur, you would overcome the problem and get to your destination. You need to list equivalent kinds of problems and alternative strategies here. Reviewers need to be assured that, regardless of what might happen, you would still reach your scientific "destination."

Summarize potential problems in a single paragraph. Make certain that the solutions you have offered – the alternative strategies – are feasible and credible. You should not belabor the problems that you identify. Rather, treat them with the brevity that they deserve. For each problem identified, address 1) the nature of the perceived problem; 2) the reason(s) why you don't think that the problem is likely to arise; and 3) what alternative strategy(ies) you would employ, should the problem be encountered. Note that all of the alternative strategies should be proposed using conditional verb forms (an action [undertaking the alternative strategy] that is dependent on a condition [problems with the original approach]), because they all represent things that would be done *only* if they were to become necessary. In other words, it wouldn't be "If this happens, we will _____" Rather, it should be "If this happens we would _____" What you write might read like the following: "Our working hypothesis for this aim is _____. Although our preliminary data (see Significance subsection-Scientific Premise) solidly support the hypothesis for this aim, and are complemented by recent work published by Strong's group (2009), there is a remote possibility that it could be invalidated when it is tested objectively. In that unlikely event, we would turn to _____ as the next most likely explanation. As noted in the presentation of our preliminary data for this aim, some of our results point to this alternative explanation. Another potential problem is the fact that our new, rapid and inexpensive assay may be insufficiently sensitive to quantify X in 5% of the samples. Should this problem arise, we would turn to the labor-intensive, much-more expensive, "gold-standard" assay (Dickerson & Boyle, 2012), which is known to have the necessary sensitivity. We have not proposed this approach for all of the samples because of the added time and cost that would be required. We have used this alternative method successfully in the past (Goldman *et al.*, 2005). Another potential problem may be that _____. Etc."

This subsection under each aim should be no longer than 1/3-to-1/2 page. We cannot emphasize enough the importance of including it. Not doing so can make you appear naïve; as noted earlier, there is no such thing as problem-free research. A second reason for addressing potential problems relates to how reviewers will be reading your Research Design subsections. If you think that they will be looking for ways to fund you, you are dead wrong. In these hypercompetitive days, they will be looking for disqualifying flaws in what you propose, such as potential problems that could arise. Anticipating such problems and offering solutions to them will prevent such criticism while, at the same time, it will make a very positive impression. The final reason to include these subsections is quite simply the fact that *NIH requires that you address potential problems and offer alternative strategies* (see the text box at the beginning of this Chapter). Given these facts, we hope that you can appreciate why failure to include and address potential problems is often sufficient to knock an otherwise excellent proposal out of the funding range.

## APPROACH: TIMELINE AND BENCHMARKS FOR SUCCESS

This important section of the Approach subsection is not included by most applicants, in spite of

the fact that they are explicitly directed to include benchmarks for progress (see text box at the beginning of this Chapter). Inclusion of this section is extremely helpful to both reviewers and NIH. What you offer here can be something like the table that is depicted, below. Note that it applies to the entire Approach subsection. Therefore, its subheading should be equivalent in format and indention to the titles for the aims (see the format for the Approach subsection at the beginning of this Chapter).

| TIMETABLE | | | | | |
|---|---|---|---|---|---|
| **AIMS/TASKS** | **YEAR 01** | **YEAR 02** | **YEAR 03** | **YEAR 04** | **YEAR 05** |
| **Specific Aim #1** | ← | — | — | → | |
| **Benchmark #1.1** | ⊗ | | | | |
| **Benchmark #1.2** | | ⊗ | | | |
| **Benchmark #1.3** | | | | ⊗ | |
| **Specific Aim #2** | | ← | — | — | → |
| **Benchmark #2.1** | | | ⊗ | | |
| **Benchmark, Etc.** | | | | ⊗ | |
| **Specific Aim #3** | | ← | — | — | — → |
| **Benchmark #3.1** | | | ⊗ | | |
| **Benchmark Etc.** | | | | ⊗ | |

A well-conceived timetable can give your reviewers perspective about your project that otherwise would be lacking. It should not be perceived as an afterthought and at the opposite extreme it shouldn't be overly detailed. *This is where you provide the "benchmarks" that reviewers will be looking for* (see text box at the beginning of this Chapter). What you want is enough detail to convince reviewers that you have thoroughly thought through how long you expect it will take to complete each component of your project, as well as how you will measure progress (or lack thereof). Enter each year for which you have requested support as column headings and your specific aims/studies as labels for the primary rows. The duration of each aim should be reflected using something like the bolded, double-headed arrows shown in the timetable, above. Under each aim, denote when each benchmark will have been reached using an easily seen symbol. The names of the benchmarks should describe them clearly. If there isn't sufficient space to be explicitly clear, name them as shown in the example, above, followed by an asterisk, double asterisk, dagger, etc. Then, in related footnotes fully describe what each benchmark is.

If you are having problems staying within the page limitation for the Research Strategy section, you may be able to save space by providing a narrative timeline, rather than a timetable. If you decide to take such a narrative approach, make certain that it is comprehensible. It is very difficult to provide a narrative summary that doesn't come across as just a list of "stuff." It has to provide the same kind of temporal context and clarity that a timetable would provide.

## APPROACH: PROJECTING FUTURE DIRECTIONS

This should be the final paragraph of your Approach subsection. Its title should also be equivalent in format to the titles of your aims. It is where you tell reviewers what they can expect in the future, should they decide to fund your proposal. In other words, this is in large part about your renewal application, assuming that this project will be successful.

You should begin by *briefly* summing up where you expect to be at the conclusion of the proposed research. In doing so, you want to leave no doubt that the results of this period of funding will complete the next step along the continuum of research that you projected in the Specific Aims section with the statement of your long-term goal. You should continue by telling reviewers what your next steps are expected to be, and why they will be important. Thus, this paragraph provides yet another opportunity to get across to reviewers that you are pursuing a continuum of research that will continue to drive your field vertically. This paragraph is especially important if you are a New/Early Stage Investigator, because reviewers will undoubtedly want to know what your vision of the future is. It is also particularly important if you are writing either a K Award, R03, or R21 application. There is an expectation among reviewers and NIH staff that the results obtained from the proposed period of support will lead to a follow-on R01 application. That should be a clear future direction for each of those grant mechanisms.

## PROGRESS REPORT AND PROGRESS REPORT PUBLICATION LIST FOR RENEWALS

If you are writing a renewal application, the format for the Approach subsection changes to include a Progress Report subdivision, as is shown below (arrow):

APPROACH
- Progress Report ⬅
- Each Aim:
  - Introduction
  - Research Design
  - Expected Outcomes
  - Potential Problems & Alternative Strategies
- Timeline and Benchmarks for Success
- Future Directions

The new subdivision is required in revisions – without any increase in the number of pages that are allowed for the Research Strategy section. That requirement makes staying within the 12-page limit for the Research Strategy section even more difficult. If ever there was a need for succinct writing, this is the place! The text box that follows describes what is required.

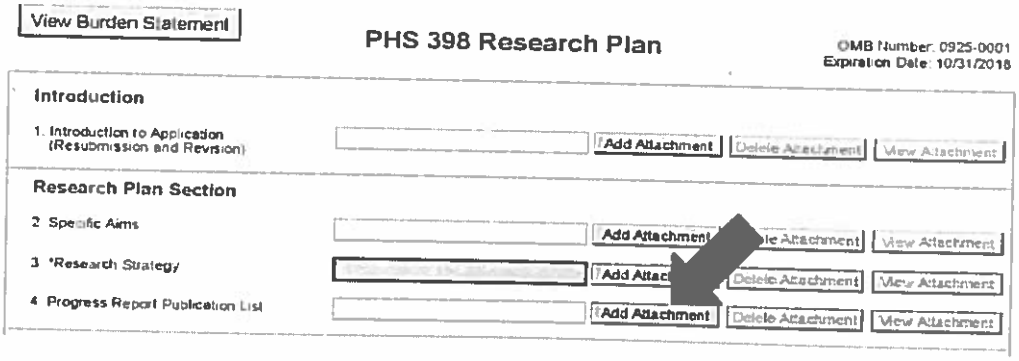
> ***Research Instructions for NIH and Other PHS Agencies, Section R.400.3.3***:
> "For renewal/revision applications, provide a Progress Report [as part of the Approach subsection]. Provide the beginning and ending dates for the period covered since the last competitive review. Summarize the specific 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 to the specific aims and any new directions including changes resulting from significant budget reductions. For any studies meeting the NIH definition for clinical research, discuss previous participant enrollment (e.g., recruitment, retention, inclusion of women, minorities, children etc.) as part of the progress report, particularly if relevant to studies proposed in the renewal or revision application. You should not submit a PHS Inclusion Enrollment Report form unless the enrollment is part of new or ongoing studies in the renewal or revision application."

Many of the principles pertinent to the presentation of preliminary data apply here. However, there are some important differences. First, the section should begin with the duration of time that the *Progress Report* covers. That is not the duration of the grant. It is the period from the date of the last competitive award to the date that you submit the renewal.

Second, you need to present the specific aims for the current period of grant support. They may not be the same as the ones that were submitted in the previous application. For example, if you changed the scope of the project because of budget cuts that were forced on you, that fact should be made clear here, in your Progress Report. You should have backed up such changes by getting the approval of NIH/your Program Officer. In addition, you should have recorded any changes in the annual Research Performance Progress Report (RPPR; see https://grants.nih.gov/grants/rppr/index.htm) that you wrote and submitted through the eRA Commons. (Instructions for preparing and submitting the annual RPPR can be found in the *RPPR User Guide*, which can be downloaded from https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf). As another example of why your original aims might have changed, you found that, in spite of your best projections, one or more of the original aims had to be changed for scientific reasons during the course of the research. Again here, you should have informed NIH/your Program Officer of the need to make a change in one or more of your specific aims and included that information in the relevant RPPR. If there was no objection to the proposed change (and there almost never is), the revised set of aims would become what you would present at the beginning of the Progress Report in your renewal proposal. You should organize and present your Progress Report in the renewal application using the former and/or revised aims as subsection headings.

Third, each paragraph in the Progress Report should be devoted to one discovery that you made. As is the case for presentation of preliminary data, you should include an italicized sentence in each paragraph. The difference here is that you should use such sentences to highlight for reviewers why each discovery was important and how it contributed to attainment of the grant's overall objective.

After you have completed the *Progress Report* you need to create a list of every product that came from the prior funding. The space occupied by this list will not be counted against the 12-page limit for the Research Strategy section. Rather, it will be uploaded as a separate PDF document into field 4 of the PHS 398 Research Plan form (see arrow in figure, below).




It is important to realize in constructing this list that, in addition to evaluating quality, reviewers count. Therefore, we recommend that you use the instructions in the text box, below, to create the list. First, identify everything that could be construed as a product of your current funding. Prioritize those products from most-to-least important. Publications and manuscripts accepted

in peer-reviewed journals will be your most important product. Therefore, begin your list with a subheading, "Publications in Peer-Reviewed Journals." Exclude submitted and "in-preparation" entries from the list. Let's say that these become numbers 1 through 12. The next most important product might be three invited monographs. To include them, you would insert the subheading, "Invited Monographs." However, instead of numbering them 1 thru 3, you

> ***Research Instructions for NIH and Other PHS Agencies, Section R.400.4:***
> "List the titles and complete references to all appropriate publications, manuscripts accepted for publication, patents, and other printed materials that have resulted from the project since it was last reviewed competitively. When citing articles that fall under the Public Access Policy, were authored or co-authored by the applicant and arose from NIH support, .... provide the NIH Manuscript Submission reference number (e.g., NIHMS97531) or the PubMed Central (PMC) reference number (e.g., PMCID234567) for each article. If the PMICD is not yet available ..., indicate "PMC Journal – In Process". .... Citations that are not covered by the Public Access Policy, but are publicly available in a free, online format may include URLs or PMID numbers along with the full reference (note that copies of these publications are not accepted as appendix material)."

would continue the sequence of numbers from above, i.e., they would be 13 through 15. You might continue with patents, if any, as well as any "other printed materials" (e.g., reviews, book chapters, published conference proceedings and the least important, published abstracts, which would be last).

> **TIP:** If you decide to present published abstracts, make sure that most of the earlier ones are reflected as later, full-length publications in peer-reviewed journals. If you present numerous abstracts that do not give rise to subsequent peer-reviewed publications, it will give reviewers the impression that your discoveries either cannot pass the test of rigorous peer review or that you are satisfied to publish primarily abstracts.

When you have completed this exercise, the total number at the end of the list will be larger and much more impressive than a series of smaller totals for the various subsections.

Finally, it is important for you to appreciate that progress made with current funding is a major criterion that is used by reviewers to determine whether or not a renewal application will be funded. If you (and colleagues who you consult) recognize that insufficient progress has been made to merit a fundable priority score, the shortest route to funding is probably not through the submission of a renewal application; you would most likely fail. *In such a case, you should consider changing the proposal enough to convert it into a new application.* By doing so, you would not have to submit a *Progress Report*. If this tactic proves to be necessary you hopefully became aware of it at the time that your most recent Research Performance Progress Report was prepared.

## DEVELOPMENTAL STEPS FOR CHAPTER ELEVEN:

1. Understand the APPROACH review criterion and how it relates to this section.
2. Know the five questions that your completed Approach subsection must answer.
3. Understand how the Approach subsection of Research Strategy should be formatted.
4. Adopt a succinct writing style and include only essential, meaningful detail.

### *Introduction*

5. Copy and paste the title of your first specific aim from your Specific Aims section into a new document file.
6. Prepare a first draft of the introductory paragraph for the first specific aim. Be certain that it provides a conceptual "overview" of everything that is exciting and important about this subsection. The idea is to "hook" the interest of reviewers and make them *want* to read the details that follow.
7. Ensure that the introductory paragraph is not more than 1/4 to 1/3 of a page in length.

### *Research Design*

8. Appreciate that inability to reproduce published research results has been an all-to-frequent problem in recent years.
9. Appreciate that NIH wants to help solve this problem by supporting rigorously designed research that takes sources of biological variation, such as sex, into consideration.
10. Some of the most important application/review changes that NIH made in 2016 pertain to design rigor and consideration of biological variables. You must provide evidence in your application of responsiveness to those changes if you want to get funded.
11. If you need additional information regarding how to increase the likelihood that your results will be reproducible, view the videos that are listed in this Chapter.
12. Consider introducing practicable aspects of Good Laboratory Practice and/or PCORI Standardized Methods to your laboratory operation as a means of helping to ensure the reproducibility of your results.
13. Read the publications at http://www.fasebj.org/content/early/2015/10/28/fj.15-279554.full.pdf+html and https://bsd.biomedcentral.com/articles/10.1186/s13293-016-0066-x to better understand how sex should be considered as a source of biological variation. Download the checklist at http://www.cihr-irsc.gc.ca/e/documents/igh-checklist-integrating-fund-initiatives-bio-en.pdf, which will be of even more help.
14. If you sense a need for better grounding in experimental design, take advantage of the many authoritative resources that are available on the Internet.
15. Begin development of the Research Design for each aim by making a bulleted list of activities/studies.
16. Expand the bullets into sentences under an interest-evoking title for each set of studies/activities.
17. Include technical preliminary results if you need to establish that a method/technical procedure is feasible in your hands.

### *Expected Outcomes*

18. Make a list of the important results that you expect from each Aim.
19. Integrate them in narrative form so that they don't come across as a list.
20. Accompany each Aim's expected outcomes with a sentence that tells reviewers how they collectively attain the objective of that aim.
21. Ensure that the expected outcomes from all of your aims collectively attain the overall objective that you have for the project.

### *Potential Problems & Alternative Strategies*

22. Review your research plan and identify problems that could potentially develop – probably

won't – but could. List these.

23. Develop credible solutions – alternative strategies – for the potential problems.
24. Write in the conditional in this paragraph – these problems are things that *could* happen and the alternative strategies are things that you *would* turn to if the problems would arise.

***Timeline and Benchmarks***

25. Prepare a timetable (or narrative timeline) that summarizes when the when each aim will be conducted, as well as when the benchmarks that will be used to monitor progress will be reached.
26. Make certain that each benchmark is clearly named to denote what it represents in terms of measuring progress. If the table approach is used (compared to a narrative) you can either name them in the left column or, if that isn't fully descriptive,, complement the name with explanatory footnotes.

***Future Directions***

27. Conclude the Approach subsection with a brief paragraph that is entitled "Future Directions." It should mostly focus on what you anticipate the renewal will encompass, assuming that the proposed project is completed successfully.
28. If you are writing a K Award, R03, or R21 application, use this paragraph to emphasize that the immediate follow-on proposal will be an R01, which is what NIH expects. Highlight that the non-renewable funding being sought will enable that application.

***Progress Report for Renewal Applications***

29. Make a decision, based on relative productivity with the current funds, whether or not to submit a renewal. The shortest path to funding may be a new application if you have not made reasonable progress during the current period of grant support.
30. Begin by offering the beginning and ending dates since the last competitive review. The ending date will be the date of submission of the renewal.
31. Summarize the specific aims for the current period of support, including any changes in them that were caused by budget cuts or change in scientific direction.
32. Use the titles of the specific aims to organize the Progress Report into subsections.
33. Use a separate paragraph to present each of your discoveries.
34. Write a fully italicized sentence at the end of each such paragraph that highlights the importance of the discovery and how it helped attain the grant's overall objective.
35. Create a list of the products – most will be publications – from the current period of support, ranked in order of greatest to least importance. Include PMCID or PMC numbers.
36. Convert the list to a PDF file and upload it into field 4 of the PHS 398 Research Plan form, Progress Report Publication List. Do not include submitted or "in-preparation" manuscripts.