GRANT WRITERS' SEMINARS AND WORKSHOPS, LLC

THE GRANT APPLICATION WRITER'S WORKBOOK

National Institutes of Health Version

SUPPLEMENT – 2016 CHANGES

Period of January 25 through May 24

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The authors gratefully acknowledge M.S. (Peg) AtKisson, Ph.D., John D. Robertson, Ph.D., and Lauren M. Broyles, Ph.D., RN for their contributions to this supplement to *The Grant Application Writer's Workbook – NIH* version.

Queries and comments to: info@grantcentral.com

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***** No Change to these chapters during the period of January 25 through May 24, 2016.

****** Page number (in the current, May 2015 *Workbook*) of chapters with changes.

PREFACE

November 2015

Beginning in June of this year, the National Institutes of Health began issuing Notices designed to alert members of the extramural community to a spectrum of impending changes in how applications will be written and reviewed in 2016. The relevant Notices are:

NOT-OD-15-102 Consideration of Sex as a Biological Variable in NIH-funded Research

NOT-OD-15-103 Enhancing Reproducibility through Rigor and Transparency

NOT-OD-16-004 NIH & AHRQ Announce Upcoming Changes to Policies, Instructions and Forms for 2016 Grant Applications

NOT-OD-16-006 Simplification of the Vertebrate Animals Section of NIH Grant Applications and Contract Proposals

NOT-OD-16-010 Inclusion of Children in Clinical Research Change in NIH Definition

NOT-OD-16-011 Implementing Rigor and Transparency in NIH & AHRQ Research Grant Applications

NIH has also published relevant FAQs at http://grants.nih.gov/reproducibility/faqs.htm and http://grants.nih.gov/grants/forms_updates_faq.htm. It has also added a "Rigor and Reproducibility" section (http://grants.nih.gov/reproducibility/index.htm) to its website.

NIH will implement the changes described in these resources in two phases. Instructions related to Phase-1 are summarized in the above-listed Notices (especially NOT-OD-16-004 and NOT-OD-16-011), as well as in a revised, interim version of the FORMS-C *SF424 (R&R) Application Guide*, which was published November 25, 2015. These instructions are pertinent for applications to be submitted between January 25 and May 24, 2016. Such proposals will use the current FORMS-C application package. *This supplement updates the current version of our Workbook for applications that will be submitted between January 25 and May 24, 2016.*

Phase-2 changes are pertinent to applications submitted on and after May 25, 2016. We will cover those changes in a new FORMS-D edition of *The Grant Application Writer's Workbook*. We will publish it after (i) the new FORMS-D *Application Guide* has been published, and (ii) a new FORMS-D application package has been issued. NIH is promising those sometime in March. By waiting until then we can ensure that all of the Phase-2 changes, in their final form, are covered in the new edition. It will be ready in time for the second round of 2016 submission deadlines.

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OVERVIEW: PART ONE

BEFORE YOU BEGIN TO WRITE

NIH is implementing the changes described in this supplement to help combat the problem of irreproducible results, which is especially prevalent in preclinical studies. Tangible evidence of NIH's commitment is a new "Rigor and Reproducibility" part of its website (http://grants.nih.gov/reproducibility/index.htm).

Upper-level NIH administrators first signaled their willingness to tackle the problem of irreproducibility in a *Nature* policy paper published in January 2014 (Policy: NIH Plans to Enhance Reproducibility; http://www.nature.com/news/policy-nih-plans-to-enhance-reproducibility-1.14586). The authors were Francis S. Collins, Director of the National Institutes of Health, and Lawrence A. Tabak, NIH's Principal Deputy Director.

The authors quickly dispelled the idea that the problem is dishonesty. Rather, in their opinion (and increasingly in the opinion of others), a variety of problems contribute to the challenge of irreproducible results. These range from insufficient training in experimental design, through uncontrolled biological variation laboratory to laboratory, to insufficient "transparency" - insufficient clarity in how investigators conduct and report their studies.

The authors also make the point that there is no single solution to the problem. So, the changes described here regarding how grant applications must be written and reviewed after January 25, 2016 constitute only a single corrective avenue. But it's a start.

The *Overview* page for each of the *Workbook*'s four parts will be used to indicate which chapters contain changes and which do not. As shown, below, we will denote the ones that do with the bolded, all-in-capitals word, "**CHANGES**". Discussion of the changes to chapters so marked will follow the related *Overview* page.

Chapter One "Finding NIH Funding Opportunities and Responding to Them" No changes.

Chapter Two "How to Develop an Irresistible Idea for Your Grant Application" No changes.

Chapter Three "How to Find the Appropriate Program and Grant Mechanism for Your Idea" No changes.

Chapter Four "Influence of the NIH Review Process on Writing for Success" **CHANGES**

Chapter Five "Response to Prior Review" No changes.

Chapter Six "Create a Writing Schedule" **CHANGES**.

CHAPTER 4

INFLUENCE OF THE NIH REVIEW PROCESS ON WRITING FOR SUCCESS

Knowing how reviewers will evaluate your grant proposal helps to inform how it should be written. That maxim is particularly pertinent to coping with NIH's impending, 2016 changes.

The five core-review criteria (SIGNIFICANCE, INVESTIGATOR(S), INNOVATION, APPROACH, and ENVIRONMENT) will not change. Instead, reviewers will be asked to search for evidence that an applicant has been responsive to the areas that NIH deems important to enhancing rigor and reproducibility. They are 1) the scientific premise (foundation of knowledge) for the proposed research, 2) rigorous experimental design for robust and unbiased results, 3) consideration of relevant biological variables, and 4) authentication of key biological and/or chemical resources. In the Spring of 2016, NIH will add new general and/or specific guidelines for reviewers (http://public.csr.nih.gov/ReviewerResources/Pages/default.aspx) regarding how they should incorporate consideration of the changes in their reviews. The directives to reviewers will consist of at least three questions and a request for comments.

Is there a strong scientific premise for the project?

The answer to that question will influence the reviewer's scoring of the SIGNIFICANCE core-review criterion. From NIH's perspective, the scientific premise (foundation of knowledge) for your application includes the strengths and weaknesses of previously published key papers that you cite, including your own, as well as the body of preliminary data that you present in support of your application. That is why we have moved both Review of Relevant Literature and results of Preliminary Studies from the Approach subsection of *Research Strategy* to the Significance subsection (see changes to Chapters 9 through 11, below).

During piloting of the review of scientific premise, one of the implementation strategies was to have at least one member of each study section specifically responsible for evaluating scientific premise. Whether or not that innovation was adopted is not yet known. However, the fact that NIH administrators even considered this approach speaks volumes about the importance that they give to this foundational aspect of a grant proposal.

Does the applicant include strategies to ensure a robust and unbiased approach?

Reviewers will be looking for strict application of the scientific method to your experimental design, methodology, analysis, interpretation, and reporting of results. The reviewer will also be looking for sufficient clarity in what you have written – transparency – that others will be able to repeat and extend what you propose. The conclusions reached by reviewers will affect their scoring of the APPROACH core-review criterion.

If necessary, additional expertise in statistics and experimental design will be added to study sections to ensure full review of scientific rigor.

Has the applicant presented plans to address relevant biological variables?

Examples of relevant biological variables are sex, age, weight, and health status. This assessment will affect the reviewer's scoring of the APPROACH core-review criterion.

Scoring of how you respond to the three questions listed above will contribute to the Overall Impact score for your application. Surprisingly to us, ***Authentication of Key Biological and/or Chemical Resources*** will not influence the Overall Impact score. Reviewers will simply be asked to comment on the "authentication" aspect of your application. In other words, they will be asked to rate this part of your application as either "Acceptable" or "Unacceptable" and, if it is the latter outcome, briefly describe why. Any questions or concerns raised by reviewers will have to be dealt with before NIH will make an award.

CHAPTER 6

CREATE A WRITING SCHEDULE

The following timetable, which is available from our website (www.grantcentral.com/downloads.html), has been updated to reflect the changes NIH will implement between January 25 and May 24, 2016.

	Complete By:
Set up your Pre-Submission Review Committee (see Chapter 21)	
Seek constructive criticism of your idea from the expert members of your Pre-Submission Review Committee	
Refine the idea further, if necessary, using the constructive criticism(s) received from members of the Pre-Submission Review Committee	
Complete the *Specific Aims* section and the Innovation subsection of the *Research Strategy* section (*PHS 398 Research Plan* form).	
Final refinements of *Specific Aims* section and Innovation subsection of *Research Strategy* section; prepare *SF 424 (R&R* [*Cover*] form (except title and Cover Letter attachment) & *PHS 398 Cover Page Supplement* form; complete upper 6 sections of the *Other Project Information* form.	
Send the finalized *Specific Aims* section and Innovation subsection of *Research Strategy* to Pre-Submission Review Committee and to I/C Program Officer	
Prepare Significance subsection of *Research Strategy* section; prepare Bibliography & References Cited section of *Other Project Information* form	
Prepare Title and Cover Letter attachment of *SF 424 (R&R)* [*Cover*] form; if needed, obtain Letters of Support (which should contain the proposal's title)	
Prepare *Research Strategy*-Approach subsection for Specific Aim 1; complete *Project/Performance Site Location(s)* form.	
Prepare Research Strategy-Approach subsection for Specific Aim 2; develop *Senior/Key Person Profile (Expanded)* form and *Biographical Sketch* for each Key Person and Other Significant Contributor.	

If applicable, prepare Research Strategy-Approach subsection for Specific Aim 3; if applicable, develop Multiple PI Leadership Plan and Resource Sharing Plan of *PHS 398 Research Plan* form, as well as International Collaborations and Environmental Impact sections of *Other Project Information* form.	
If applicable, develop the *Human Subjects* sections and *Vertebrate Animals* section of the *PHS 398 Research Plan* form; *Planned Enrollment Report & Cumulative Inclusion Enrollment Report*.	
If your proposal is a renewal, develop the Progress Report subsection of *Research Strategy*-Approach and the Progress Report Publication List of the *PHS 398 Research Plan* form.	
Develop the *Budget* component (Modular or R&R [breakout] form, whichever is applicable) and applicable Budget Justification(s).	
Prepare Facilities & Other Resources and Equipment sections of the *Other Project Information* form; prepare Consortium/Contractual Arrangements section of the *PHS 398 Research Plan* form and *Subaward Budget Attachment(s)* form, if applicable.	
Prepare Project Summary/Abstract and Project Narrative sections of the *Other Project Information* form; prepare Appendix material, if any.	
Assemble the final draft. Proof and make final adjustments.	
Send draft to members of Pre-Submission Review Committee for review of scientific and technical merit.	
Respond to constructive criticisms from members of Pre-Submission Review Committee.	
Send completed proposal to Sponsored Programs/Contracts & Grants Office (or equivalent) 3-5 working days prior to submission deadline (Determine exact number of days by contacting that Office).	
Submit application at least one day before the official agency deadline – not later than:	

OVERVIEW: PART TWO

THE TEMPLATE FOR YOUR RESEARCH PLAN

The 2016 changes mandated by NIH necessitate some significant changes in the format of the Research Plan (see below). The page limits for the Research Plan will not change, however.

Specific Aims (limited to 1 page)
Research Strategy (limited to 12 pages for R01, R15 & R34; 6 for R03 & R21)
Progress Report (only if a renewal)
Significance
Scientific Premise:
Literature and Preliminary Studies in Support of Aims
Significance of the Expected Research Contribution
Innovation

Approach
Each Specific Aim (same format for each):
Introductory Paragraph
Research Design
Expected Outcomes
Potential Problems & Alternative Approaches
Timetable
Future Directions (optional)

Chapter Seven "*Specific Aims* Section: Conceptual Framework for Creating a Bulleted Outline" No changes.

Chapter Eight "Writing the *Specific Aims* Section" No changes.

Chapter Nine "Significance and Innovation Subsections of *Research Strategy*" **CHANGES**

CHAPTER 9

SIGNIFICANCE AND INNOVATION SUBSECTIONS OF THE RESEARCH STRATEGY SECTION

The changes to this Chapter are entirely related to the Significance subsection; there are no changes that affect how the Innovation subsection should be written.

GENERAL CONSIDERATIONS – SIGNIFICANCE SUBSECTION

The purposes of NIH's newly conceived Significance subsection are to: (i) justify the need for what you propose, (ii) establish the scientific premise for your application, and (iii) inform reviewers as to why your research contribution will have NIH-relevant positive impact(s).

The scientific premise – the scientific foundation – on which you build your proposal has become of great interest to NIH. Evidence of that fact is that it is one of the four foci that have driven the changes that NIH will implement in 2016. The underlying reason for NIH's interest is that investigations proposed on weak foundations of knowledge are likely to be seriously flawed from the start. In other words, the outcomes of such research may not be realizable as proposed.

In the context of an NIH grant application, the scientific premise consists of the literature on which you build your application (including your own publications) as well as the body of preliminary data that you offer in support of your application. We recommend that you consider "premise" to mean both the conceptual and/or technical bases for the conclusions that have been drawn in either the literature that you cite or from your preliminary data.

We recommend that you discuss the scientific premise for your application in the Significance subsection of the *Research Strategy* section. We do so because its review will influence scoring

of the SIGNIFICANCE core-review criterion. Reviewers will assess scientific premise by evaluating the strengths and weaknesses of the published and preliminary data on which you build your application. Accordingly, we have moved the analysis of supporting literature and the presentation of preliminary data from the Approach to the Significance subsection of *Research Strategy*. Doing so expands the length of the Significance subsection but, at the same time, it shortens the length of the Approach subsection. Thus, making these changes shouldn't increase the overall length of the *Research Strategy* section by much, if at all. Pilot studies conducted by several NIH Institutes and Centers confirmed the validity of that assumption. That said, it will take the kind of succinct writing illustrated in the answer to FAQs question III.A.2 (http://grants.nih.gov/reproducibility/faqs.htm) to stay within the unchanged page limits.

In our previous approach to writing the Significance subsection, we recommended that you should write it to have three parts. They were (i) details from the literature that justify the need and emphasize the importance of the problem framed in the first paragraph of Specific Aims, (ii) a statement of significance, and (iii) discussion of positive impact – the "benefits" that are expected to accrue from your research contribution. As you will see, those same elements remain a part of the new approach. The differences in the new approach are that you now also include preliminary data and critique strengths and weaknesses of both the published work and of the preliminary data that you offer in support of your application.

How do you critique the material that constitutes the scientific premise of your application? In our opinion, the Notices cited in the Preface of this Supplement and the newly published interim revision of the SF424 (R&R) *Application Guide* aren't of much help in answering this question. They simply tell you that strengths and weaknesses related to such things as "the rigor of previous experimental designs, as well as the incorporation of relevant biological variables and authentication of key resources" should be discussed. Things like statistical power, whether or not studies were blinded, and lack of detail regarding the sex of animals are offered as examples, but without much detail. In making these suggestions, NIH cites a 2012 paper by Landis et al. (http://www.nature.com/nature/journal/v490/n7419/full/nature11556.html). It is much more helpful. Seven of the authors, including the first and last, are senior staff members at NIH's National Institute of Neurological Disorders and Stroke (NINDS). The authors offer a "core set of reporting standards for rigorous study design", including such categories as randomization, blinding, estimation of sample size, and data handling. We highly recommend that you read this paper to appreciate better what NIH is looking for with respect to critiquing strengths and weaknesses.

FORMAT FOR THE NEW SIGNIFICANCE SUBSECTION

The format we recommend for the Significance subsection is:

RESEARCH STRATEGY

Significance:

Scientific Premise:

Overall Scientific Premise

Scientific Premise for Aim #1: Literature & Preliminary Results

Scientific Premise for Aim #2: Literature & Preliminary Results

Scientific Premise for Aim #3 (if applicable): Literature & Preliminary Results

Significance of Expected Research Contribution

Between the “Significance:” subheading and the “Scientific Premise:” sub-subheading you should include an introductory paragraph. It is where you begin ratcheting up detail to verify that the assertions you made in the first paragraph of the *Specific Aims* section are scientifically valid. For example, you should use citations of the literature and other detail (e.g., statistical) to briefly substantiate that the NIH-relevant problem identified in the first paragraph of the *Specific Aims* section does, in fact, exist. You would continue by validating with additional citations and detail that there is a critical or urgent need to address the problem, followed by detail regarding the consequences of not meeting the need.

For example, let’s say that you want to address the problem of hospital-to-hospital variability in the incidence of sequelae following a certain surgical procedure. Your introductory paragraph under Significance would describe the frequency with which the surgical procedure is performed. It would go on to detail the kinds of postsurgical sequelae that can result, as well as the fact that some hospitals have greater success than others in avoiding such postsurgical complications. You would then describe why there is an NIH-relevant need to minimize these complications uniformly. You would conclude by validating that assertion with details of the cost and human consequences of not meeting that need.

Citations that you include in the introductory paragraph are part of the foundation of knowledge on which you will build your proposal. Therefore, strengths and weaknesses of those publications must be discussed as part of your presentation. Such discussion doesn’t need to be extensive – but you must address strengths and weaknesses, even if only briefly. So, for example, you might comment that a study was “well designed”. Or, you might state that the authors made their findings using “the most advanced technology available.” As an additional example, “The gross-anatomic, radiologic, and light-microscopic findings were sufficiently conclusive that we cannot consider the lack of electron-microscopic observations as a weakness that detracts from the authors’ conclusions.” Or lastly, “An apparent weakness of the study is the lack of sufficient subjects to justify the authors’ broad generalizations.”

We recommend that you critique the weaknesses of cited publications as positively and constructively as possible, keeping in mind that you could be commenting on either a reviewer’s publication or one that his/her close colleague wrote.

In addition to discussing strengths and weaknesses, you should include a sentence somewhere in the introductory paragraph that portrays the problem as being relevant to the Funding Opportunity Announcement to which you are responding and/or the mission of the Institute/Center that you are targeting.

Scientific Premise

Overall Scientific Premise:

This brief paragraph should establish the overall premise on which your proposed research is predicated. In other words, this subdivision should lay the scientific foundation on which you have founded the entire project. Continuing with the example introduced above, there are two premises on which the proposal would rest. First, efficacious interventions exist that greatly reduce the incidence of postsurgical sequelae, And, second, such interventions are applied inconsistently, hospital to hospital. If either of those premises is weak, the project would be problematic, if not fatally flawed.

To address the first premise, you would discuss the strengths and weaknesses of published works that speak to the efficacy of existing interventions.

You would support the second premise by, first, presenting your own published and/or unpublished data. You would discuss why your results strongly support your contention that there is variability in use of the interventions, hospital to hospital. You would go on to discuss the strength of your conclusion that hospitals with the least consistent application of preventive interventions were the ones with the highest incidence of sequelae. If the latter conclusion were based on the results of your preliminary studies, you would present the supporting data as part of your discusson here. Further support for the second premise would consist of your discussion of the strengths and weaknesses of others' publications, if any, that complement your findings.

Literature and Preliminary Studies in Support of the Aims:

You would present the scientific premises for your aims similarly. To do so we recommend that you partition the remainder of the Scientific Premise sub-subsection based on your aims. In other words, we recommend that you discuss the scientific premise for each aim independently. Such stratification will help you select support for each aim that is maximally relevant. Also, by offering an integrated continuum of publications and preliminary data under each aim, you will increase ease of understanding and, therefore, the reviewer friendliness of this part of your proposal. It also saves space and eliminates the former problem of deciding whether your published work belongs in the "Review of Relevant Literature" or "Preliminary Studies" section. For citations or data that pertain to the same aspect of more than one aim, you should not repeat them under each aim. In subsequent aims, simply refer back to the first presentation.

Supporting Literature

The papers that you choose to cite here should be the ones that informed your thinking/approach to the related aim. Ideally, some of them should be your own (or those of your Co-Investigators). We recommend that you be extremely judicious in the selection of publications on which you build. The inclusion of publications with demonstrable weaknesses (e.g., poor design or insufficient subjects to establish significance) could, and probably would, weaken the scientific premise for your application. That, in turn, would negatively influence both your SIGNIFICANCE and Overall Impact scores – unless, of course, one of your goals in the proposed project is to address the weakness(es) you have identified in earlier publications.

Another reason for citing fewer publications is a purely practical one. As noted above, NIH now requires discussion of strengths and weaknesses for the publications that you cite in the Significance subsection (you are not required to include such discussion elsewhere in your application). Therefore, including the same number of citations that you may have included in past NIH proposals would lengthen your Significance subsection and, therefore, the *Research Strategy* section. That would be problematic because NIH still limits the number of pages for the *Research Strategy* section to twelve.

The publications you cite should have been peer reviewed and be characterized by experimental and reporting strengths, with very few, if any, weaknesses. If you feel compelled to include a publication that has one or more significant weaknesses, as part of its discussion, you must describe why that weakness/those weaknesses shouldn't be an issue. If that's not possible, you must tell reviewers how you will avoid/overcome the problem(s) that is(are) potentially associated with inclusion of the publication as part of your scientific premise. The best way to avoid those potential problems is not to cite papers that have weaknesses.

You should minimize or – better – avoid citing reviews in this subsection. Why? Because it would be difficult, if not impossible, to discuss strengths and weaknesses of a review article. The rare exception would be one that had focused on strengths and weaknesses of the reviewed literature.

In addition to strengths and weaknesses, you should also discuss why the selected literature helps justify the need for the related aim. To do so, we recommend that you write a sentence at the end of each paragraph that tells reviewers why what you have just reviewed helps justify the work that you propose under the related aim. If you have difficulty writing that sentence, the literature you have just reviewed probably doesn't belong in this part of the application. And that raises a very important point. The Significance subsection is not the only part of the Research Plan in which you can cite literature. Publications cited elsewhere, for purposes other than helping to establish the scientific premise for your proposal, can be important and necessary for other reasons, e.g., framing the status quo in the Innovation subsection of *Research Strategy* (unchanged in Chapter 9).

Additional details regarding the selection and citation of literature, as well as details pertinent to the *Bibliography and References Cited* section, are contained in Chapter 11 of the current edition of *The Grant Application Writer's Workbook*. Those details have not changed.

Preliminary Data

The purpose of preliminary data is to: (i) underpin the conceptual feasibility of your central hypothesis and the working hypothesis for each aim, as well as (ii) support the technical feasibility in your hands of each proposed specific aim.

Just as for the analysis of supporting literature, we recommend that you be highly selective with respect to the data that you offer. You should have produced them with the same kind of rigor and transparency that characterizes what you propose in your application. Why? Because you must discuss the strengths and weaknesses of what you present. If there are weaknesses, you have to acknowledge that fact. Therein lies a problem!

Before NIH announced that it would require discussion of the strengths and weaknesses of preliminary studies, you may have generated data that you want to use, but which have associated weakness(es). You should predicate the use of such data on the extent of the weakness(es), in our opinion. For example:

Severe Weakness:	You discover that the cell line used to produce the data isn't the one you thought it was.
Solution:	Don't submit your application until you have repeated the study with the correct, authenticated cell line.
Moderate Weakness:	You find a few design flaws and sources of biological variation that you didn't consider, but you think that you can salvage most of the data with additional work.
Solution:	Don't submit an R01 now. Use local funds to correct the problems before you submit the proposal. If such funds don't exist, and there are no other sources of funding available to you, submit an R03 to extend and improve

your preliminary data as a steppingstone to a subsequent R01 submission.

Minor Weakness: You included men when you generated your preliminary data, but substantially fewer than women.

Solution: Submit your R01 application with a mitigation plan. You should include the mitigation plan as part of the discussion of your preliminary data. For example, "We acknowledge that our preliminary data include significantly fewer men than women. We found no difference between the two sexes in this cohort. To ensure that the inclusion of fewer men did not mask a difference, we will recruit equal numbers of male and female subjects into the proposed studies. Should a difference or differences unexpectedly be found, we will modify our experimental design to account for them."

Follow discussion of each data set with a sentence that tells reviewers why what you have just presented helps either to support the related working hypothesis or the feasibility of the related aim in your hands. As with your analysis of the literature, if you have difficulty writing that sentence, the just-discussed data probably don't belong in your application as support for its scientific premise.

Technical and editorial details regarding the presentation of preliminary data are unchanged by the new approach. We discuss those details in Chapter 11 of the current, FORMS-C edition of *The Grant Application Writer's Workbook.*

Significance of the Expected Research Contribution

This concluding sub-subsection of the Significance subsection should be written essentially as described in the current edition of our *Workbook*, beginning at the bottom of page 80 with the description of your expected contribution. This sub-subsection should begin with an explicit description of what your research contribution is expected to be. Continue with what we describe in Parts 2 and 3 on page 81.

OVERVIEW: PART THREE

DEVELOPMENT OF THE REST OF YOUR APPLICATION

Chapter Ten. "Approach Subsection of *Research Strategy*: Research Design, Expected Outcomes and Potential Problems & Alternative Strategies". **CHANGES**

Chapter Eleven. "Approach Subsection of *Research Strategy*: Review of Literatures; Preliminary Studies; Progress Report; *Bibliography & References Cited* Section". **CHANGES**

Chapter Twelve. "*Senior/Key Person Profiles* Form, Biographical Sketches, and *Multiple PI Leadership Plan".* No changes.

Chapters Thirteen and Fourteen. "*PHS 398 Modular Budget* Form and Justifications" and "*SF424 (R&R) [Breakout] Budget* Form and *Subaward/Consortial Budget".* **CHANGES**

Chapter Fifteen. "Project/Performance Site Locations, *Facilities & Other Resources* and *Equipment* Sections" No changes.

Chapter Sixteen. Human Subjects Sections, Vertebrate Animals, Select Agent Research, Consortium/Contractual Arrangements, Resource Sharing Plan(s), Environmental Impact, Historical Places, and Foreign Components". **CHANGES***.*

Chapter Seventeen. "*SF424 (R&R)* [*Cover]* Form, *PHS 398 Cover Page Supplement* Form, and Appendix Material. No changes.

CHAPTER 10

APPROACH SUBSECTION OF RESEARCH STRATEGY: RESEARCH DESIGN, EXPECTED OUTCOMES AND POTENTIAL PROBLEMS & ALTERNATIVE STRATEGIES

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

APPROACH:
- Each Aim:
  - Introductory Paragraph
  - ~~Justification & Feasibility~~
    - ~~Review of Relevant Literature~~
    - ~~Preliminary Studies~~
  - Research Design
  - Expected Outcomes
  - Potential Problems & Alternative Strategies
- Timeline
- Future Directions

One of the changes to this Chapter pertains to the format for the Approach subsection, which is reproduced, above. "Justification and Feasibility" and its two subdivisions have been lined out because, with the new approach that we recommend, they are no longer included as part of the Approach subsection. (We have moved them to the Significance subsection, Chapter 9). Without those components, the formatting for each aim "collapses" to include the Introductory Paragraph, Research Design, Expected Outcomes and Potential Problems & Alternative Strategies.

More substantive changes in this Chapter pertain to the Research Design sub-subsection. Two of NIH's new foci, rigorous experimental design for robust and unbiased results and consideration of relevant biological variables should be addressed as part of this sub-subsection. What follows is a general overview of those changes plus those related to authentication of key biological/chemical resources. Extra requirements may be imposed by individual Institutes and Centers, either on their website or in Funding Opportunity Announcements that they issue. Additional specific requirements of that kind would take precedence over the general instructions.

Additional aids to understanding how you can enhance reproducibility are in video format. You can access them at the links listed below:

- Reproducibility of Data Collection and Analysis – Modern Technologies in Cell Biology: Potentials and Pitfalls (11-24-2014)
  http://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)
  http://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)
  http://videocast.nih.gov/summary.asp?Live=16381&bhcp=1
- NIH Workshop on Reproducibility in Cell Culture Studies:
  09-28-2015 Day 1: http://videocast.nih.gov/summary.asp?Live=16876&bhcp=1
  09-29-2015 Day 2: http://videocast.nih.gov/Summary.asp?file=19196&bhcp=1
- Improving Openness and Reproducibility of Scientific Research (10-26-2015)
  http://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, 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. You can find many texts and journal articles that describe rigorous experimental design for qualitative, quantitative and mixed-methods research by searching the Internet using available search engines. They range from ones that are general/philosophical (e.g., http://www.sfn.org/Advocacy/Policy-Positions/Research-Practices-for-Scientific-Rigor) to others (e.g., http://www.stat.cmu.edu/~hseltman/309/Book/Book.pdf) that are chapter-by-chapter guides. In still others (e.g., http://www.stat.cmu.edu/~hseltman/309/Book/Book.pdf), links to resources at other sites are provided. 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.

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 is something that we recommend you consider. Although the original principles were intended 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 by searching the Internet. For example, the World Health Organization offers a *Handbook – Good Laboratory Practice (GLP)* at http://www.who.int/tdr/publications/documents/glp-handbook.pdf. While putting into practice all that is described would probably not be practicable, coming as close as possible should be your goal, in our opinion. 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 big 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.

Routine **Authentication of Key Biological/Chemical Resources** is a very important part of Good Laboratory Practice. NIH's definition of a "key" resource is one that is critical to the conduct of the proposed research and has a characteristic or characteristics that could cause variation laboratory to laboratory. NIH provides the examples of "cell lines, specialty chemicals, antibodies and other biologics". If you have a question about whether or not something is key, we recommend that you err on the side of including it.

The authors’ personal experience illustrates how important authentication can be. Each conducted research that was subject to variation if key reagents were contaminated with even minute amounts of bacterial endotoxin. Endotoxin is ubiquitous in the environment and often contaminates reagents, such as commercially produced fetal bovine serum. The latter is a key resource in most cell cultures and is often contaminated by endotoxin if it is not harvested and processed under the strictest of sterile conditions. Authentication, in this case, would be assurance in your application that the FBS for proposed experiments would be of that quality and that it would be tested chemically for detectable endotoxin before you would use it. Investigators who were unaware of this problem had great difficulty in producing results that were replicable by others and, in some cases, even had to retract published data that were ultimately found to be erroneous due to endotoxin contamination.

NIH does not provide guidelines on authentication procedures. Therefore, you need to describe in your proposal what you would do to authenticate key resources. You should include sufficient detail that it would be clear – "transparent" – in your application how you have and/or would approach the acquisition and maintenance of cell lines, for example. Cross-contamination is potentially a problem when an investigator is using two or more cell lines in the same laboratory. Misidentification of a cell line, though less common, is also a problem. So, you would describe your authentication procedure as acquiring the subject cell line from a reputable source, such as the ATCC (formerly the American Type Culture Collection). After receiving the cell line, you would state that you would expand it and then freeze back a large number of vials. You would then describe using those vials to reconstitute the working population regularly (e.g., monthly). You would describe expanding the last vial, after which the process would be repeated. At some

point, to preclude "drift" of the cell line, you would state that you would reacquire it from the reputable source and start over. That's detail enough – approximately six lines in this case.

Whatever your authentication process(es) is(are), it(they) should be described in a separate attachment, which cannot exceed one page in an NIH application. That's why your descriptions must be succinct. Between January 25 and May 24, 2016, the attachment should be titled, "Authentication of Key Biological and/or Chemical Resources" and uploaded as a PDF document into the "Other Attachments" section of the "R&R Other Project Information" form. In other words, authentication procedures should not be included in your *Research Strategy* section, which means that including them in your application won't encroach on the page limit for that section. If you have followed/propose to follow an accepted standard for authentication, you should cite that standard. NIH does not require that you include the results of authentication as preliminary data, nor is it necessary to have key resources authenticated by an outside entity.

Consideration of Relevant Biological Variables

Experimental design should also take into account biological characteristics that could cause results of investigations to vary. Sex is a particularly important and often overlooked variable. Full consideration of sex in the design and implementation of research requires more than just the inclusion of equal numbers of each sex in proposed studies. NIH suggests that both applicants and reviewers should also consider the extent to which: the influence of sex, if any, is included in the review of literature and design of experiments; the formulation of research questions has taken sex into account; stratified randomization of males and females has been included in the experimental design; the experimental design allows for disaggregation of data, so that results obtained with males and females can be analyzed separately and compared; treatment or toxicity effects can be assessed for each sex separately; the potential influence of sex has been included in the interpretation of results; and whether projected generalizations from the study will be appropriate, given the expected results. (Adapted from FAQs answer B.2 at http://grants.nih.gov/reproducibility/faqs.htm). If you are proposing a single-sex approach, do you provide strong justification for doing so?

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

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 using that cell line. (see FAQs answer II.B.6 at http://grants.nih.gov/reproducibility/faqs.htm)

If you are proposing human or animal experiments in which it would be unnecessary or 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 in the application. You are also required to provide justification for excluding other kinds of variables from your Research Plan that could be relevant.

CHAPTER 11

APPROACH SUBSECTION OF RESEARCH STRATEGY: REVIEW OF LITERATURE; PRELIMINARY STUDIES; PROGRESS REPORT; BIBLIOGRAPHY & REFERENCES CITED SECTION

As noted above, under the changes for Chapter 10, there is a change in format for the Approach subsection. We have moved consideration of supporting literature and preliminary data to the Significance subsection (Chapter 9).

CHAPTER 13

PHS 398 MODULAR BUDGET FORM and BUDGET JUSTIFICATIONS

and

CHAPTER 14

SF 424 R & R [BREAKOUT] BUDGET FORM and SUBAWARD/CONSORTIAL BUDGET

Implementing NIH's changes could add additional costs to your Budget, whether you are using the Modular or SF424 R&R [Breakout] Budget form. For example, if you are doing human-subjects or vertebrate-animal research, appropriate statistical methods should be used to determine the least number of subjects needed to reach valid conclusions. Such a conclusion should be reached independently for both male and female subjects so that the disaggregated data could be compared and contrasted. Such a requirement would likely increase the total number of subjects and, therefore, the related costs. As another example, stepping up the rigor with which you conduct experiments may require the purchase of small pieces of equipment or

the inclusion of fee-for-service costs needed either to maintain equipment optimally or to acquire the services of an unbiased, outside evaluator.

If you are using the Modular approach to budgeting, such costs could push your request up to the next highest module. To determine whether or not such an increase would be necessary, develop a breakout budget *for internal use only*. Add in all costs, including any new ones that are associated with the implementation of NIH's changes. If some of those costs are one-time-only purchases, as would be the case for minor pieces of equipment, the first year of your Budget could be higher by a module, compared to the remaining years. In that case, you would need to complete the Additional Narrative Justification to provide scientific justification for the higher request in the first year.

Subcontractors must also implement the changes mandated by NIH. Therefore, if you have included such a relationship in your proposal, you should also consider potential increases in the costs of the subcontracted work. If you are using the Modular approach to budgeting, the direct cost of a subcontract is part of the total direct-cost figure for each Budget period, with the annual direct cost of the subcontract, rounded to the nearest $1,000, provided in the Consortium Justification. If you are using the R&R Budget [Breakout] approach, each subcontractor must complete its own R&R Budget form, including the Budget Justification. Costs related to implementing NIH's changes at the subcontracting institution would be broken out in the Budget form and explained in the Budget Justification.

CHAPTER 16

HUMAN SUBJECTS SECTIONS, VERTEBRATE ANIMALS SECTION, SELECT AGENT RESEARCH, CONSORTIUM / CONTRACTUAL ARRANGEMENTS, RESOURCE SHARING PLAN(S), ENVIRONMENTAL IMPACT, HISTORICAL PLACES, and FOREIGN COMPONENTS

HUMAN SUBJECTS SECTIONS

The principal change in the Human Subjects sections is a change in the definition of what a "child" is. In the past, any human subject under the age of 21 has been considered to be a child. On and after January 25, 2016, the definition will be anyone under the age of 18. The change is being made to align NIH's definition with the generally accepted age of consent and "the common perception of the age of adulthood" (NOT-OD-16-010).

VERTEBRATE ANIMALS SECTION

Also on January 25, 2016, there will be an easing of descriptive requirements in the Vertebrate Animals section (#8) of the PHS 398 Research Plan form (see NOT-OD-16-006). Specifically, it will no longer be necessary to describe the veterinary care that is available for laboratory ani-

mals. Also, while the number of animals needed is still required in the Vertebrate Animals section (see VAS Checklist at http://grants.nih.gov/grants/olaw/vertebrate_animal_section.htm), justification of that number is no longer required. That requirement will still exist, however. It has been shifted to the Approach subsection of the *Research Strategy* section (see FAQs answer III.C.3, http://grants.nih.gov/reproducibility/faqs.htm). Finally, a description of the method of euthanasia is no longer needed in the VAS section - unless it departs from the guidelines of the American Veterinary Medical Association.

OVERVIEW: PART FOUR

MAXIMIZING YOUR APPLICATION'S COMPETITIVENESS

Chapters Eighteen, Nineteen, Twenty, and Twenty-One. No changes.