



Office of Research and Sponsored Programs

1324 W. WISCONSIN AVE.
HOLTHUSEN HALL, 341
414-288-7200
www.marquette.edu/orsp

NIH Research Strategy Guidance

December 2017

Who must complete the "Research Strategy" attachment:

The "Research Strategy" attachment is required for all proposals.

Format:

Follow the page limits for the Research Strategy in the [NIH Table of Page Limits](#), unless otherwise specified in the FOA.

Although multiple sections of information are required in the Research Strategy as detailed below, the page limit applies to the entirety of the single "Research Strategy" attachment.

Attach this information as a PDF file. See NIH's Format Attachments page.

Content:

Organize the Research Strategy in the specified order and use the instructions provided below unless otherwise specified in the FOA. Start each section with the appropriate heading – Significance, Innovation, Approach.

Cite published experimental details in the Research Strategy attachment and provide the full reference in the Bibliography and Reference Cited attachment.

Note for Applications Proposing the Involvement of Human Subjects and/or Clinical Trials:

- Use the Research Strategy section to discuss the overall strategy, methodology, and analyses of your proposed research, but do not duplicate information collected in the PHS Human Subjects and Clinical Trials Information form.
- The PHS Human Subjects and Clinical Trials Information form will capture detailed study information, including eligibility criteria; inclusion of women, minorities, and children; protection and monitoring plans; and statistical design and power.
- You are encouraged to refer to information in the PHS Human Subjects and Clinical Trials Information form as appropriate in your discussion of the Research Strategy (e.g., see Question 2.4 Inclusion of Women, Minorities, and Children).

Note for Applicants with Multiple Specific Aims: You may address the Significance, Innovation, and Approach either for each Specific Aim individually or for all of the Specific Aims collectively.

1. Significance

- Explain the importance of the problem or critical barrier to progress that the proposed project addresses.
- Describe the scientific premise for the proposed project, including consideration of the strengths and weaknesses of published research or preliminary data crucial to the support of your application.
- Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.
- **Additional Instructions for Research:**
 - Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.

2. Innovation

- Explain how the application challenges and seeks to shift current research or clinical practice paradigms.

- Describe any novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, and any advantage over existing methodologies, instrumentation, or interventions.
- Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation, or interventions.

3. Approach

- 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 the Resource Sharing Plan, include how the data will be collected, analyzed, and interpreted, as well as any resource sharing plans as appropriate.
- For trials that randomize groups or deliver interventions to groups, describe how your methods for analysis and sample size are appropriate for your plans for participant assignment and intervention delivery. These methods can include a group- or cluster-randomized trial or an individually randomized group-treatment trial. Additional information is available at the Research Methods Resources webpage.
- 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. Refer to the NIH Guide Notice on Sex as a Biological Variable in NIH-funded Research for additional information.
- Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be exercised. A full discussion on the use of select agents should appear in the Select Agent Research attachment below.
- If research on Human Embryonic Stem Cells (hESCs) is proposed but an approved cell line from the NIH hESC Registry cannot be chosen, provide a strong justification for why an appropriate cell line cannot be chosen from the registry at this time.

As applicable, also include the following information as part of the Research Strategy, keeping within the three sections (Significance, Innovation, and Approach) listed above.

- **Preliminary Studies for New Applications:**
 - For new applications, include information on preliminary studies. Discuss the PD/PI's preliminary studies, data, and or experience pertinent to this application. Except for Exploratory/Developmental Grants (R21/R33), Small Research Grants (R03), and Academic Research Enhancement Award (AREA) Grants (R15), preliminary data can be an essential part of a research grant application and can help to establish the likelihood of success of the proposed project. Early stage investigators should include preliminary data.
- **Progress Report for Renewal and Revision Applications:**
 - Note that the Progress Report falls within the Research Strategy and is therefore included in the page limits for the Research Strategy.
 - For renewal/revision applications, provide a Progress Report. Provide the beginning and ending dates for the period covered since the last competitive review. In the Progress Report, you should:
 - Summarize the specific aims of the previous project period and the importance of the findings, and emphasize the progress made toward their achievement.
 - Explain any significant changes to the specific aims and any new directions, including changes resulting from significant budget reductions.
 - Discuss previous participant enrollment (e.g., recruitment, retention, inclusion of women, minorities, children, etc.) for any studies meeting the NIH definition for clinical research. Use the Progress Report section to discuss, but not duplicate information collected elsewhere in the application.
 - Do not include a list of publications, patents, or other printed materials in the Progress Report. That information will be included in the "Progress Report Publication List" attachment.

Additional rigor and transparency questions reviewers will be asked to consider when reviewing applications

- Significance - Is there a strong scientific premise for the project
- Approach - Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?
- Additional Review Considerations
 - Authentication of Key Biological and/or Chemical Resources - For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

Scientific Premise:

Applications often include data aimed at demonstrating the feasibility of the proposed experimental approach. While this type of data can be important as proof of concept, it does not speak to the project's scientific premise – the strengths and weakness of the data and previously performed work upon which the proposal is built upon.

A hypothetical example might help clarify this point. Let's say an application proposes to investigate whether and how enzyme A regulates a particular cell function. Preliminary data suggest that enzyme A modifies protein B, and there are data in the literature showing that protein B regulates the particular cell function in question. The strength of the proposed project is dependent on the strength of the data suggesting that protein B regulates the particular cell function. Thus, the new application instruction pertaining to premise calls for "consideration of the strengths and weaknesses of published research or preliminary data" to evaluate the rationale for investigating the effects of enzyme A on the particular cell function. Without this information, the scientific premise of the proposed experiment may be built on shaky grounds.

Therefore, **as a part of the Significance section of the Research Strategy**, the updated instructions clarify that applicants should: "Describe the scientific premise for the proposed project, including consideration of the strengths and weaknesses of published research or preliminary data crucial to the support of your application." Weaknesses in scientific rigor or gaps in transparency that preclude the assessment of scientific rigor should be acknowledged. If such weaknesses are identified, the applicant should consider whether or not to include this data in support of the application and how the proposed research will address the weaknesses.

It is important to stress that attention to scientific premise does not impede innovation. Even though innovative research is inherently risky, consideration of scientific premise can help investigators identify the risks and develop a research strategy that enhances the opportunity for success.

Scientific Rigor:

Scientific rigor - the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation, and reporting of results. In published papers, full transparency in reporting experimental details is crucial for others to assess, reproduce, and extend the findings. Likewise, in grant applications, full transparency is necessary for reviewers to properly assess the proposed studies.

Therefore, **as part of the Approach section of the Research Strategy**, updated instructions clarify this expectation to emphasize how the experimental design and methods proposed will achieve robust and unbiased results. Solid, well-controlled experiments can produce robust results capable of being reproduced under well-controlled conditions using reported experimental details. A robust approach might include use of appropriate statistical methods, prospective sample size estimation, replicates, or standards (for example, reference reagents or data standards). Robust and credible results are those obtained with methods specifically designed to avoid bias, such as blinding, randomization, and prospectively defined exclusion/inclusion criteria, to name a few.

It is important to keep in mind that each scientific field may have its own set of best practices or standards to achieve scientific rigor. Reviewers are well-positioned to identify strengths or weaknesses of the proposed plans. Applicants are

encouraged to include a succinct description of the experimental design and methods with enough detail to assure the reviewers that the necessary elements of rigor will be addressed.

Consideration of Relevant Biological Variables:

As with sex, the clarifying instructions on consideration of relevant biological variables do not prescribe that the biological variable itself be studied. If biological variables are known to affect a system or disease model proposed for study, the application should discuss how you will control for these factors, if necessary.

Updated instructions for the Approach section of the Research Strategy ask the applicant to: 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.

What are some biological variables, other than sex, that might need to be considered when doing research in vertebrate animals? Let's start with an example of early vaccine development in mice. It's been well-established that C57BL/6 and Balb/c strains of mice produce different immune responses due to differing genetic backgrounds. Therefore, if an application proposes to study an immune response in mice, it may be necessary to indicate which strain will be used and why. Other variables that might be important include the vendor source or supplier, the age of the animals, since both can affect immune responses. Depending on the field and the research question, housing conditions may need to be considered, including the room temperature and light/dark cycles. Studies with mouse tissues or primary cells should also consider relevant biological variables, including sex, in proposing and reporting research.

The NIH has already established that sex must be considered in proposing studies in humans. Other biological variables that may need to be considered include age, body mass index (BMI), socioeconomic status, or underlying health conditions. Many clinical studies already take these variables into account, but it is important that observations be reported. Variables such as sex, age, BMI, and underlying health conditions may also need to be considered when proposing and reporting studies with human biological samples, including blood and tissue. Consideration of other variables is critical to enable reviewers and the scientific community to assess the internal validity of a study – whether the findings hold up after accounting for confounding and selection biases – and the external validity of a study – whether the findings, even if internally valid, apply to the “real world.”