

Overall Impact versus Significance

Since the release and implementation of [NOT-OD-09-025](#), "Enhancing Peer Review: The NIH Announces Enhanced Review Criteria for Evaluation of Research Applications Received for Potential FY 2010 Funding," there has been some confusion regarding the distinction between Significance and Overall Impact. In response, the NIH Office of Extramural Research convened a working group consisting of NIH review and program staff to develop additional guidance on this issue.

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DEFINITIONS FROM NOT-OD-09-025

Significance: Does the project address an important problem or critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Overall Impact: Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following five core review criteria, and additional review criteria (as applicable for the project proposed).

KEY POINTS

Overall Impact

- Overall Impact is not a sixth review criterion.
- Overall Impact is not necessarily the arithmetic mean of the scores for the scored review criteria.
- Overall Impact takes into consideration, but is distinct from, the scored review criteria.
- Overall Impact is the synthesis/integration of the five core review criteria that are scored individual and the additional review criteria which are not scored individually.
- To evaluate, the reviewer(s) make an assessment of the *likelihood* for the project to exert a *sustained, powerful influence* on the *research field(s)* involved, in consideration of the scored review criteria, and additional review criteria (as applicable for the project proposed).
 - *Likelihood* (i.e., probability) is primarily derived from the investigator(s), approach and environment criteria.
 - *Sustained powerful influence* is primarily derived from the significance and innovation criteria.

- *Research field(s)* may vary widely, so it would be helpful if reviewers identify in their reviews the research field(s) they believe will be influenced by each project.

Significance

- Significance is evaluated and scored independently of the evaluation and scoring of Investigator(s), Innovation, Approach and Environment.
- The evaluation of significance assumes that the “aims of the project are achieved” and/or will be “successfully completed.”
 - Moreover, reviewers should evaluate the significance of the project within the context of a (research) field(s). For example, autism is a significant field of study but not all studies (projects) of autism are significant.
 - Research field(s) may vary widely, so it would be helpful if reviewers identify in their reviews the research field(s) within which the project addresses an important problem or critical barrier to progress.
 - The research field may be focused on a specific basic research area (enzymology) or a specific disease (*e.g.*, autism), or may be more broadly defined to cut across many health issues (*e.g.*, language training, psychology).

FREQUENTLY ASKED QUESTIONS

Q1: I’ve read the definitions of Significance and Overall Impact but the two still seem rather similar. Can you provide some additional guidance?

A: Significance is a stand-alone assessment of the project’s goals in the context of the relevant field, and to a large extent assumes that the investigator(s), approach and environment are adequate to allow for successful completion of the aims of the project even if later discussion of each of these review criteria will identify problems. When reviewers assess the Overall Impact of an application they are expected to take into account the five core review criteria (significance, investigator(s), innovation, approach and environment) and the additional review criteria to judge the potential of the project to exert a sustained, powerful influence on the field.

Q2: Overall Impact uses the same scale definitions as the five core criteria; how is it different from a sixth review criterion?

A: The Overall Impact score is a synthesis that takes into consideration all of the five core review criteria (significance, investigator(s), innovation, approach and environment) as well as all of the applicable additional review criteria.

Q3: When determining the Overall Impact score, should it equal the arithmetic mean of the scores for the five core review criteria?

A: Not necessarily. The Overall Impact score considers all five core review criteria as well as all applicable additional review criteria. In addition, an application does not need to be strong in all five core review criteria to be judged likely to have a major scientific impact. Therefore, it is possible for one or more review criteria to overshadow the other review criteria, thus driving the Overall Impact score up or down. Please remember that there is no formula to derive the overall impact/priority score from the individual criterion scores. Reviewers are instructed to weigh the different criteria as appropriate for each application in deriving the Overall Impact score.

Q4: Is it possible to have an application receive a moderate score for Significance yet receive a very strong Overall Impact score?

A: One can envision such scenarios. For example, a talented investigator in a very strong environment proposes a highly innovative and very sound approach to address a generally important problem (*e.g.*, breast cancer). However, the proposed project will be relevant to only a narrow area within the larger field of breast cancer research, thus reducing its Significance. Nevertheless, the Overall Impact score could still be strong since the strengths of the project in the other core review criteria give this work the potential to have a sustained, powerful influence on that part of this important field.

Q5: Is it possible to have an application receive a very strong score for Significance yet receive a moderate to low Overall Impact score?

A: Yes. The Overall Impact score synthesizes all five core review criteria as well as all applicable additional review criteria. Thus, while the significance of the project is very strong, the investigator might lack key credentials, the innovation might be minimal, the approach might be problematic, and the environment might not offer adequate support for the project.

Q6: Is it possible for an application with numerous weaknesses in Approach to receive a very strong Overall Impact score?

A: Yes. No single review criterion (*e.g.*, Approach) alone determines the Overall Impact score. A project may have numerous minor weaknesses that affect the score for Approach, yet still have a very strong Overall Impact score if the application is exceptionally strong in the other review criteria and the quality of the team and environment lend confidence that the project will have a major overall impact on the field. "Minor weaknesses" are defined as "addressable weaknesses that do not substantially lessen overall impact."

Q7: Aren't projects that address diseases of large public health importance (*e.g.*, heart disease, cancer, autism or dementia) inherently significant? Should they automatically receive high marks for Significance?

A: Not necessarily. The Significance score reflects whether a project addresses an important problem or critical barrier to progress *within* the field. For example, while a project may generally address a devastating disease with high prevalence, the specific problem addressed in the project may be only tangentially related to the disease, the problem may not be very important for patients with the disease, the proposed work may duplicate already published reports, or the expected results may be unlikely to substantially change knowledge, concepts and/or practice in the field.

Q8: Conversely, are projects that address rare diseases, diseases with modest burden, or highly focused research questions inherently less significant?

A: No. Work on rare diseases, highly prevalent diseases with modest burden, and highly focused research questions can still be extremely important. Reviewers should judge whether the proposed goals and aims address an important problem or critical barrier to progress in the field, whether the proposed work will improve

scientific knowledge, technical capability, and/or clinical practice in the field, or if the project will change the concepts, methods, technologies, treatments, services, or preventative interventions that drive the field.

Q9: The verbal descriptors for high, medium and low overall impact in the [Scoring System and Procedures document](#) indicate that applications with high Overall Impact (i.e., a score of 1-3) have “no to some minor weaknesses.” Is this always the case?

A: Not necessarily. The verbal descriptors and additional guidance on Strengths/Weaknesses are offered only in an effort to provide continuity in scoring between study sections. However, reviewers must not just “count” strengths and weaknesses to arrive at the final Overall Impact score. Remember that the Overall Impact score represents a synthesis of all of the review criteria and what may be a moderate weakness to one reviewer may be only a very minor weakness to another reviewer. For example, a very strong investigator in a very strong environment is addressing an extremely important problem. The approach is very innovative and could revolutionize the field. However, because the approach is so new and has not been tried before, it is not guaranteed that the project’s goals will be met and some reviewers see this as a weakness. However, in the end, the study section concludes that the potential rewards far outweigh the risk(s) associated with the approach and that the application deserves a high Overall Impact score.

Q10: The definitions of Overall Impact and Significance refer to project’s ability to exert a powerful influence or address an important problem within the research field(s) involved. I thought the goal of the NIH is to improve public health. What’s the difference between improving public health and addressing an important problem within a research field?

A: The mission of the NIH is to support research in pursuit of knowledge about the biology and behavior of living systems and to apply that knowledge to extend the healthy life and reduce the burdens of illness and disability. To accomplish this mission, the NIH supports biomedical and behavioral research representing a wide array of research fields as well as tool development, clinical trials and other projects in support of the biomedical research enterprise. In an effort to fairly evaluate scientific and technical merit through the peer review system of a broad range of applications (those that seek cures, not only for diabetes, heart disease, and autism, but also for the lesser recognized orphan diseases and those that ask basic biomedical questions), it is important that Significance and Overall Impact be evaluated within the context of the research field involved. NIH program staff and Institute leadership will evaluate each project’s relevance to their Institute mission in making funding decisions.

Q11. What should be considered in assigning the Overall Impact score for applications submitted for RFAs and other special initiatives?

A. FOAs for *IC-specific RFAs* and *targeted trans-NIH initiatives* (e.g., *Roadmap* or *Common Fund*), including infrastructure and capacity building programs, may include additional FOA-specific review criteria in addition to the five core review criteria and the standard NIH additional review criteria (human subjects, animal welfare, renewal, resubmission, biohazards). The Overall Impact score for applications submitted for these initiatives should reflect the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the five core review criteria as well as all additional review criteria (as applicable for

the project proposed) and the likelihood that the project will advance the stated goals and objectives of the program as articulated in the FOA.

Q12. What should be considered in the Overall Impact score for fellowship (F) applications?

A. For *fellowship applications (Fs)*, the overall impact score should reflect the reviewers' assessment of the likelihood that the fellowship will enhance the candidate's potential for, and commitment to, a productive independent scientific career in a health-related field, in consideration of the five scored (*i.e.*, Fellowship Applicant, Sponsors/ Collaborators/Consultants, Research Training Plan, Training Potential and Institutional Environment & Commitment to Training) as well as all applicable additional review criteria.

Q13. What should be considered in the Overall Impact score for career development (K) applications?

A. For *career development award applications (Ks)* the overall impact score reflects the reviewers' assessment of the likelihood for the candidate to maintain a strong research program, in consideration of the five scored review criteria (*i.e.*, Candidate, Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring, Research Plan, Mentor(s)/Consultant(s)/Collaborator(s), Environment and Institutional Commitment to the Candidate) as well as all applicable additional review criteria.

Q14. What should be considered in the Overall Impact score for institutional training grant (T) applications?

A. For *institutional training grant applications (Ts)*, reviewers are asked to provide an overall impact score to reflect their assessment of the likelihood for the proposed training program to promote the training of pre- and postdoctoral fellows in biomedical, behavioral and clinical research, in consideration of the five scored review criteria (*i.e.*, Training Program and Environment, Training Program Director/Principal Investigator, Preceptors/Mentors, Trainees and Training Record) as well as all applicable additional review criteria.

Q15. What should be considered in the Overall Impact score for shared instrumentation (S10) applications?

A. For *shared instrumentation applications (S10s)*, the overall impact/benefit score reflects the reviewers' assessment of the potential benefit of the instrument requested for the overall research community and on NIH-funded research in consideration of the five scored review criteria (*i.e.*, Justification of Need, Technical Expertise, Research Projects, Administration, Institutional Commitment) as well as all applicable additional review criteria.

CASE STUDIES

- The following case studies are intended to provide further clarity on the distinction between Significance and Overall Impact.
- They are not meant to be comprehensive or to be interpreted literally.
- Rather, they are intended to provide a conceptual framework for how to think about Significance and Overall Impact.

Case Study #1:

An investigator proposes using a novel method of viral vector-mediated siRNA delivery to knock-down the gene for a particular CNS receptor subtype in specific brain regions he/she hypothesizes to be involved in cognitive aspects of a rare mental illness. He/she proposes to use this method to examine disruption of this receptor subtype on cognitive performance in three animal models of the illness.

Scenario 1:

- A. Reviewer 1 is an expert on research of the rare mental illness. He argues that the PI has previously confirmed the proposed hypothesis using pharmacological and genetic approaches. This reviewer felt that the successful accomplishment of the proposed aims would very minimally advance knowledge in the field of study devoted to the rare mental illness. Thus, Reviewer 1 feels the application is of low significance. Reviewer 1 notes that the proposed method is highly innovative, that the models used are appropriate, and that the investigator and environment are strong. Nevertheless, in light of the low Significance of the proposal, Reviewer 1 feels the Overall Impact would be modest and scores accordingly.

- B. Reviewer 2 is an expert on viral vector-mediated siRNA delivery methods. He disagrees that the project's significance is low. He concedes that the proposed hypothesis has already been confirmed in the investigator's previous work. He argues, however, that the proposed technique is highly innovative and if successful, has the potential not only to transform the way scientists manipulate receptor function in the laboratory, but also has potential to provide the foundation for clinical application for many diseases. He suggests that the proposed replication of previous findings is actually a strength because it would confirm the successful implementation of the highly innovative methods. Thus, on the basis of the work's potential to transform technical capability and shape clinical practice in the future, Reviewer 2 argues that the application has high Significance. On the basis of high Significance and strengths in the other review criteria, Reviewer 2 believes the Overall Impact should be rated as high.

Scenario 2:

Both reviewers agree that the application addresses an important problem and that the hypothesis and methods are highly innovative. They believe that if the proposed aims were achieved, the project would significantly advance knowledge in the field and promote substantially new research directions in research on the rare mental illness as well as the broader field of mental health. Therefore, they rate Significance as high. They have strong reservations, however, about the application relative to other review criteria. The investigator and his/her colleagues do not appear to have the relevant training and expertise to successfully accomplish the work and there are some flaws in the approach that may reflect their inexperience with critical methods. Therefore, they rate the Overall Impact as moderate.

Case Study #2:

An application proposes to disrupt a well-known signal transduction pathway in mice and see if it results in an increased incidence of a particular type of breast cancer in mice.

Significance: Breast cancer is an important disease in women. However, that alone is not sufficient to say that this project has high significance. The reviewers should evaluate whether this proposed project addresses an important problem in breast cancer or a critical

barrier to progress in breast cancer research. For example, will research on this signal transduction pathway in mice advance the concepts, methods, technologies, etc, related to studies of human breast cancer?

- Although breast cancer is a very important disease, the reviewers need to address whether the proposed signaling pathway and the work in mice will be important for understanding, treating, or preventing human breast cancer.
- If the signaling pathway under study is also important in another disease, such as colon cancer, the Significance might be higher, since the results of the project will be more broadly applicable.
- A project that addresses a slow growing type of breast cancer that responds well to existing therapies/treatments would be of lower significance because it is less likely to change clinical practice.

Overall Impact: What is the likelihood that this project conducted by these investigators in their environment, with this level of innovation and the proposed approaches, will have a sustained powerful influence on the field?

- If the proposed work in mice will strongly predict what is happening in humans, the investigators are highly qualified, the environment is strong, the approach to disrupting the pathway is innovative, and the approach is flawless the project may be likely to have high Overall Impact.
- Even if the pathway and the mouse model are very significant for breast cancer in humans, the investigators are very experienced and in a great environment, and the approaches are sound, if the proposed work is not innovative or is confirmatory and duplicates many other published reports, the Overall Impact of the project on breast cancer research might be only moderate to low.
- Even if the topic is very significant for breast cancer in humans, the investigators are very experienced and in a great environment, and the project is innovative, the approach may be flawed, reducing the chance of generating useful data, which would reduce the likely Overall Impact on breast cancer research.
- Even if this project is very innovative, well conceived, and likely to have high overall impact, a subsequent project to clone and characterize receptor subtypes for this family of signal transduction molecules may be viewed as having less Overall Impact, since it might not be as innovative. Conversely, such a project might be viewed as having a greater Overall Impact, since the work is essential to develop a new drug treatment for breast cancer.

Case Study # 3:

An application proposes to develop and test an antidote for a chemical agent in an animal model.

Significance: The potential use of chemical agents in wars or related to terrorist activities is of national security concern. However, the significance of the project depends on how the project will contribute to the development of effective therapeutic agents and/or change therapeutic approach.

- Although such agents may directly affect a very limited number of individuals and the therapeutic agent(s) may have no other uses, the project has the strong

likelihood of yielding life saving therapeutic agents should an exposure occur; thus the significance is very high.

- However, if well established clinical practices and multiple effective antidotes are widely available, contribution to the field of development therapeutics for chemical agent exposure will be lower and significance diminished.

Overall Impact: What is the likelihood that this project conducted by these investigators in their environment, with this level of innovation and the proposed approaches, will have a sustained powerful influence on the field?

- The project resolves an unmet need; there are no effective therapies for this chemical exposure with high mortality. The reviewers might note the highly qualified investigators, flawless methods, an excellent animal model, and therapeutic compounds that will work on various chemical agents - High Overall Impact
- While other therapeutic agents exist, the proposed compounds have numerous advantages in terms of side effect, ease of use and efficacy and will likely be the treatment of choice - High Overall Impact
- The project contributes to the enhancement of the therapeutic arsenal but will not result in major changes to current clinical/therapeutic practices - Medium Overall Impact
- While the idea is significant and sound, methodologies are flawed and investigators have very limited experience in the field. The probability of achieving the goals is low - Low Overall Impact
- Technically sound with good investigators but the animal model has no relevance to human condition - Low Overall Impact.