

Writing an NIH Grant

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Potential Conflict of Interest Disclosure

I have no relevant personal or financial relationships with any commercial interests noted in this presentation.

W. W. Hay

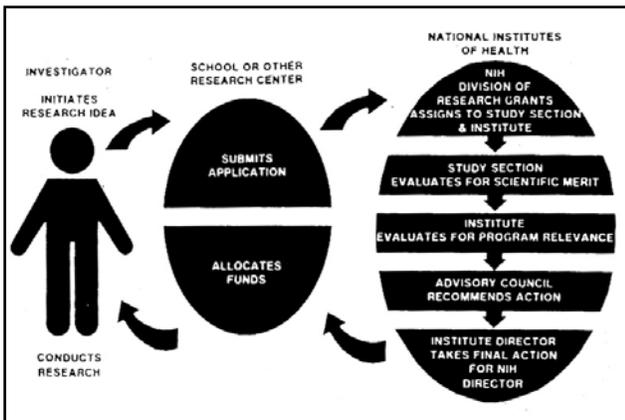


Reality Check _BY DAVID SIPRESS

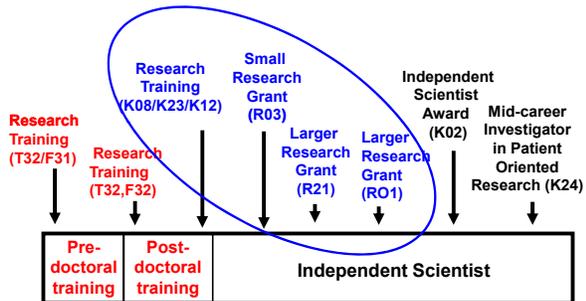


SIPRESS

Hi, Honey—how's everything in the world of academia?



What To Apply For?



Face Page

Description (Abstract)
WHAT you are going to do,
WHY you are going to do it,
HOW you are going to do it,
VALUE of doing it.
 Always emphasize its **IMPACT**.



Personnel engaged on project

Budget

Direct Costs

First Year

Essentials for Grant Proposals

1. Title & Abstract—the idea, what will be done, why, how, long term value (goal), and **IMPACT**
2. Hypotheses and Specific Aims (what)
3. Background and Significance (why, or Rationale)
4. Convincing preliminary data (can it be done and well?)
5. Expertise of the investigator (s) (can you do it?)
6. Methods and Statistical design(how)6.
7. Summary, restating long term value (goal) and overall **IMPACT**

Writing a Grant: General Principles

1. The reviewer evaluating your application is a human being.
2. The reviewer will have several applications to evaluate.
3. To help the reviewer objectively evaluate your application, the following points are crucial:

Organization: Outline first, write second

Clarity: Appropriate syntax, clear and lucid style
Short sentences (active voice helps)
Use Figures to emphasize the important points
Be concise (don't even think about exceeding page limitations)

Assistance:
Have others read it (expert and non-expert)

“There is no form of prose more difficult to understand and more tedious to read than the average scientific paper.”

---Sir Francis Crick

- **Start fresh!** Don't use applications that were rejected.
- Finish early and ask your colleagues to **review** it.
- Tell reviewers the **ultimate utility** of your research - even if it's years down the road.
- Use **specific examples of how it will be important**, don't just say that it will be important.
- Pay attention to **new criteria**.
- Use the word **"impact"** as needed.
- Don't use any words you don't absolutely need. You have only **12 pages**.

Writing a Grant: Getting Started

The absolute requirement for a grant is a good idea.
But do make sure it is about something new.

Hi Daddy, We were talking at dinner tonight about what grandparents do for their jobs. I told Clara (5 yrs old) that you do science experiments to find out how the food gets to babies growing inside their mommies' tummies. Clara looked at me like I was an idiot and said in tones of ringing disgust: "The mommy eats the food and it goes into the baby through the belly button thing." Then she walked off. Sorry, Dad. Guess you need to find a new field of research. Clara already knows all about yours.
Love, Emily

Writing a Grant: Getting Started

The absolute requirement for a grant is a good idea.

Hypotheses or questions or models formulated from this idea must be:

Clear, testable, answerable, verifiable (consult with a statistician)

Of limited scope (i.e., can be completed in a 3-5 year period)

Important, not just interesting

New, unique, extend knowledge, solve an important problem, fill in an essential missing link, predict/generalize to future similar situations.

Focus the research on

better understanding of how mechanisms control a key biological process;

better disease recognition, prevention, or treatment.

**Observation, Hypothesis, Question, Model—
what should you use?**

Study Sections prefer Inductive Reasoning.

They want you to have some preliminary data and a review of the literature to provide a rationale for what you want to do. They do not want to fund you to “go looking” (observe, characterize, describe, and so forth).

“From this preliminary data in our lab and information in the literature, we—

1. will test the following hypothesis (is it not true <5% of the time?; is it true >95% of the time?);
2. answer the following question (how does something work?);
3. prove the generalizability of this model (predicts that the same mechanism or model will behave in the same way in the future).

**Observation, Hypothesis, Question, Model—
what should you use?**

This bottoms up approach prevents preconceived notions, including dogma, from determining an outcome without a rational basis. Emphasizes DISCOVERY (“See, that’s how it works!”) over VERIFICATION (“See, I was correct!”).

Experiments will allow the scientist to make claims as to how things work, based on the process of refining a model (testing a hypothesis, answering a question, showing that a model predicts how something works >95% of the time) by the systematic, controlled (unbiased) gathering of repeatable data consisting of negatives and affirmatives.

“The relation between a thing [*mechanism*] and the rule that controls that thing [*how the mechanism works*] may be shown to be nonseparable by experience [*experimentation*].”

(Bertrand Russell, 1912)

**Observation, Hypothesis, Question, Model—
what should you use?**

If you don’t have much preliminary data—the “idea” you have really is new—how do you frame the first experiment before sufficient data are gathered to produce a model and request funds to test it?

Ask a Question!

You are in a state of ignorance. The question is used as a basis to accumulate new data. From the data one then builds a model, which can be subjected to tests (experiments—gathering “affirmatives” and “negatives” to refine the model) for its inductive ability—the capacity to predict the future.

Substitutes the Question for settings where experiments are performed before sufficient data exist and the “model” for situations where the scientist is working with sufficient data to produce a construct than can be tested for inductive power. (Glass, 2008)

**Observation, Hypothesis, Question, Model—
what should you use?**

True for both biological and clinical research—

Gain a sufficiently large data set that is representative of the variations observed in the lab or the clinic (“in nature”).

Achieve this by demonstrating the reproducibility of the data by experimentation.

Pose a straightforward question of a system and then receive an answer (by experimentation); use that answer to model reality; and then test the reproducibility and predictive power of the model, modifying it as necessary (more experiments and more data) to be sure “probably” (>95% of the time) that the model accurately predicts reality. (Glass DJ, Hall N. A brief history of the hypothesis. Cell 2008; 134: 378-381)

Current Research Plan

Restructured Research Plan

•Introduction to Application (Resubmission or Revision Applications only)

•Specific Aims

•Background and Significance

•Preliminary Studies/Progress Report

•Research Design and Methods

•Introduction to Application (Resubmission or Revision Applications only)

•Specific Aims

•Research Strategy

•Significance

•Innovation

•Approach (methods)

•Preliminary Studies for New Applications

•Progress Report for Renewal/Revision Applications

Specific Aims

The Methods Section begins with a brief (no more than one page) statement of the Specific Aims of the research.

The objectives of the Specific Aims page are to:

- Generate interest
- Demonstrate importance
- Give a concise overview of the Research

Specific Aims

1. More than two or three Specific Aims usually are too many.
2. Each Aim should be stated in one simple sentence, saying as directly as possible what will be done.
3. Each Aim either should be, or include, a hypothesis to be tested or a question to be answered or a model to be tested for predictability.
4. A *brief* statement of the purpose, rationale (including significance, impact, and innovation), and methodological approach for each Aim is useful.

For each Specific Aim, state the--

Expected Outcomes

What your experiments will tell you, why that outcome is particularly important to obtain, and what will be the overall impact on the scientific field of what you will learn.

Potential Problems and Alternative Strategies

Show an awareness of the problems that may arise, and of the alternative approaches that can be used if the problems do indeed occur.

Timelines

Use a chart to illustrate when specific experiments will start and finish.

Research Strategy (Background, Rationale)

Not just a literature review (although this must be included). Provides the rationale for what you propose to do.

Significance

Puts your proposed research in perspective---what it will do and the importance of the results.

How, if the aims of the application are achieved, scientific knowledge will be advanced.

What the effect of these studies will be on the concepts or methods that drive this field.

Innovation

How the project employs novel concepts, approaches, or methods.

How the project challenges existing paradigms or develops new methodologies or technologies.

Approach (Methods)

Your Experiments.

The main part of the grant!

Repeat each specific aim (and hypothesis).

Then the model or general approach.

Then the specific experiments.

Preliminary Data

Demonstrates feasibility. Can it be done? Can you do it?
Will the results be accurate? Are your methods state-of-the-art? Will the hypotheses probably be supported?
Prove that assays and other technical methods in your lab are in working order.

Balance between preliminary data that show feasibility and likelihood of success

vs.

proof of hypothesis which guarantees success and definitive conclusion

Too much prior proof - no reason to fund - it's done; just filling in "n"

Not enough prior proof - too risky; too unlikely to succeed

There is something fascinating about science.

One gets such wholesale returns of conjecture out of such a trifling investment of fact.

Mark Twain

Approach (Methods)

1. Experiments

Emphasize the essential experiments
Refer to literature for established methods
Identify new methods and their value and
proof that they work

State clearly what each experiment will
demonstrate or prove

2. Statistical design and analyses

How will data be interpreted?

3. Pitfalls, and how they will be handled

4. Alternatives (if the primary approach fails)

Summary

What will be learned?

How will the results support the hypotheses (answer the question, test
predictability of the model) and meet the specific aims and goals?

How will the results be new and important?

Gaps in our knowledge that this project will fill:

*"These studies will determine the fundamental mechanisms
responsible for producing cardiorespiratory rhythms that originate in
the medulla."*

Why this is important (essential) to do:

*"These studies will identify which receptors and processes are
probably altered in diseases of the cardiorespiratory system such as
SIDS, allowing novel, specific, more effective therapy."*

Animal Care and Use / Human Subjects

Follow the guidelines in the application exactly

Do not assume that your IACUC or IRB protocol is sufficient.

Document that this work has not been done before, that it
does require an animal model or a human subject and why,
and that all possible non-animal or non-human alternatives
have been considered and shown to be insufficient to solve
the problem(s) that the research addresses.

Above all, show that all possible discomfort of any kind to the
animal or the human subject is known, anticipated, and
prevented or minimized

Timeline:
What will be done when

NUMBER OF ANIMALS AND TIME TABLE:

Protocol	Year 1	2	3	4	5
1. Developmental changes in placental glucose and amino acid metabolism	20	15			
2. Effect of glucose and amino acid supply on placental amino acid metabolism	5	10	25	25	25
Total # of animals	25	25	25	25	25

Budget Justification: Prescribed

All Training Grants

T32, F31/32, KO8, K23, K12

salary (usually for 75% time)

lab support

(usually limited, e.g. \$25K)

travel (limited, e.g., \$1,500)

F & A ("Indirects"; limited, e.g., 8%)

Budget Justification: Modular

\$25,000/module up to \$250,000 (10 modules)

Explain and justify roles of investigators

Rationale for highly expensive

**Budget Justification: Itemized
Direct costs > \$250,000**

Explain and justify each and every item in the budget.

Personnel: name, degree, title, role—justify by specific expertise and what they exactly will do and why the allotted time is essential.

Equipment: Rationale and evidence for cost and need for expensive, unusual, or absolutely essential items (“convenience” or “efficiency” are not sufficient justifications); show cost-sharing if available.

Supplies: As close to “line item” as possible; provide historical and current use and prices; explain per experiment, pre subject, per animal, per year; charts and tables are helpful; include local special or exceptional requirements.

Travel: \$1,500 per year for PI is customary, to attend scientific meeting to present results of research

Other: Do not over inflate costs of communications, publications, etc.

Consortium, Contract, and Consultant costs: get these done well ahead of grant due date; they should accomplish a specific task that you clearly show to be essential.

Budget Justification: Just in Time

- Detailed budget not required—details (how much money you will get) will be worked out by the Institute after funding approved and Institute budget and spending priorities determined
- IRB and IACUC approvals can wait for approval of funding



**Writer's Block
("Block Island")**

Even if you are on the right track, you'll get run over if you just sit there.

Will Rogers

Good Editing—The Most Essential Aspect of Good Writing

- Why? Because bad editing preserves bad writing, which leads to misunderstanding, and all too often to confused and therefore sometimes hostile (or stupefied) reviewers.
- For example, you do not want these in your grant—
- "...causes of which include, but are not limited to, maternal malnutrition, maternal hypertension, and **idiopathic** placental insufficiency."
- "These fetuses are at increased risk of hypoglycemia, hypoxia, and **academia**, as well as spontaneous preterm delivery..."

Fortunately, I am not alone in making this mistake--

"...this report underscores the difficulty for obstetricians to identify...babies destined to develop **academia**,..."

A. Fanaroff MD, 2010 Year Book of Neonatal and Perinatal Medicine

Good Editing—Over and Over Again

“... everything you do you have to do again,
and your capacity for rewriting is the only
thing that separates you from people who do
things in a hurry.”

John Irving

**We are what we repeatedly do;
Excellence, then, is not an act,
But a habit.**

Aristotle

Don't use words you don't absolutely need.

“Utilize” is over used (not over utilized).

“Use” is just fine.

(exception—metabolic rates are “utilization” rates)

Direct, active voice.

We measured three cognitive outcomes.

not, **Three cognitive outcomes were measured.**

Don't run sentences/phrases together with “however”

Confusing-- We found separate effects of glucose and insulin,
however the insulin effect was the strongest.

Better-- We found separate effects of glucose and insulin;
insulin was the strongest.

And many more!

Words NOT to use

Describe
Evaluate
Characterize
Look at
Check
Estimate
Correlate
Study
Ask / Question
Compare

And don't use “alter”
or “change”

Words OK to use

Test
Define
Determine
Measure
Quantify
Prove / Disprove

use “increase” or
or “decrease”—
or “changed from ... to ...”

Be specific!

Good Editing—Over and Over Again

The international scientific literature is now written in English. This is the standard.

Write first, then get help editing into standard English.

Use a standard guide to the English Language. Strunk and White’s “The Elements of Style” is still the classic.

Make the Application look good.

“Appearance is everything”

“Clothes maketh the man (or woman).”

Not quite true, but never, ever underestimate the “power of presentation”

Bad research page, difficult to read, poorly organized.

water content to hematocrit⁸⁸. Blood ¹⁴C-glucose is measured using ion exchange chromatography according to Hay et al.⁸⁹

Calculations. Umbilical and uterine blood flow rates are calculated using tritiated water (³H₂O) by the transplacental steady state diffusion technique.⁹⁰

Net uterine or umbilical uptake rates by the fetus from the placenta of amino acids (including leucine), KIC, glucose, and oxygen are determined by application of the Fick principle.

Uterine or umbilical uptake rate = Uterine or umbilical blood flow (mL/min) x (C_u-C_v) or (C_u-C_v) where C_u and C_v are the concentrations (μmol/mL) of the metabolite measured in the Uterine arterial and venous, or umbilical venous and fetal arterial blood, respectively. Similarly, net fluxes of ¹⁴C-leucine, ¹³C-leucine, and ¹³C-KIC across the umbilical (or Uterine) circulation are measured by the Fick principle as umbilical (or uterine) blood flow times the umbilical (or Uterine) tracer arteriovenous concentration difference.

Tracer fluxes. Maternal plasma leucine disposal rate (DR_m) is calculated as

DR_m = Inf * [(MPE_u/MPE_f)-1] where Inf is the infusion rate of L-[1-¹⁴C] leucine into the mother and MPE_u and MPE_f are the leucine enrichments in the maternal infusate and maternal arterial plasma, respectively. This equation does not account for the disposal rate of the naturally occurring ¹⁴C-labelled leucine which is about 1.1% of the ¹⁴C-leucine.^{88,89} This equation assumes 100% enrichment of the infused isotope. Plasma [1-¹⁴C] leucine is calculated as the product of the leucine concentration and the molar percent excess for ¹⁴C leucine in each vessel.

Tracer fluxes between the placenta and the fetal plasma, and between the fetal plasma and fetal tissues, are calculated according to Carver et al.⁹¹ Loy et al.⁹² and Ross, et al.⁹³

The fraction of fetal leucine tracer infusion taken up by the placenta (F_{pl}) is calculated as:

F_{pl} = [(1-¹⁴C leucine)_{pl} x umbilical blood flow] / [1-¹⁴C leucine infusion rate]

where [(1-¹⁴C) leucine infusion rate excreted as ¹⁴CO₂ via the umbilical circulation (F_{CO₂}) is calculated as:

F_{CO₂} = [(¹⁴CO₂)_{pl} x umbilical blood flow] / [1-¹⁴C leucine infusion rate]

The net ¹⁴CO₂ flux from the fetus to the placenta is calculated as

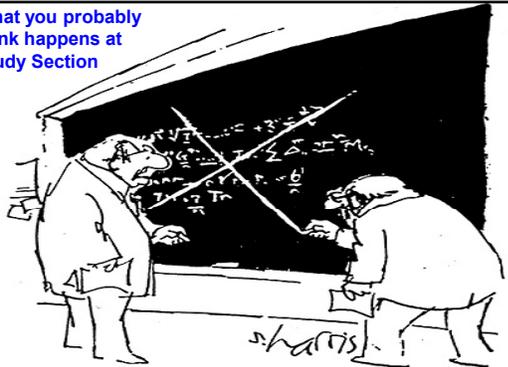
[¹⁴CO₂]_{pl} dpm/min = umbilical blood flow * [(¹⁴CO₂)_{pl} - (¹⁴CO₂)_f]

where [¹⁴CO₂]_{pl} and [¹⁴CO₂]_f are the concentrations of ¹⁴CO₂ (dpm/mL) in the umbilical arterial and venous blood, respectively.

Tracer model: The model (Carver et al. Appen. II, Pub. Man. 8) is adapted from Loy, et al.⁹² van Veen, et al.⁹⁴ and Ross, et al.⁹³ In steady state, the fetal plasma leucine pool is constant in amount, balanced by equal rates of entry (from placenta and fetal tissues) and disposal (into placenta and into fetal tissues). These fluxes of leucine into and out of the fetal plasma, fetal tissues, and the placenta, which apply to the two tracers as well, are shown in the figures below, each flux is labelled with a Roman numeral after Carver, et al.⁹¹

And then your grant goes to study section for review of its overall quality and scientific merit.

What you probably think happens at Study Section



"That's it? That's peer review?"

What *really* happens at Study Section:
9-Point Score Chart for NIH Grants

Impact	Score	Descriptor	Strengths/Weaknesses
High Impact	1	Exceptional	Strengths Weaknesses
	2	Outstanding	
	3	Excellent	
Moderate Impact	4	Very Good	
	5	Good	
	6	Satisfactory	
Low Impact	7	Fair	
	8	Marginal	
	9	Poor	

Non-numeric score options: NR = Not Recommended for Further Consideration, DF = Deferred, AB = Abstinence, CF = Conflict, NP = Not Present, ND=Not Discussed

Score	Descriptor	Additional Guidance on Strengths / Weaknesses
1	Exceptional	Exceptionally strong with essentially no weaknesses
2	Outstanding	Extremely strong with negligible weaknesses
3	Excellent	Very strong with only some minor weaknesses
4	Very Good	Strong but with numerous minor weaknesses
5	Good	Strong but with at least one moderate weakness
6	Satisfactory	Some strengths but also some moderate weaknesses
7	Fair	Some strengths but at least one major weakness
8	Marginal	A few strengths and a few major weaknesses
9	Poor	Very few strengths and numerous major weaknesses

Minor Weakness: An easily addressable weakness that does not substantially lessen impact

Moderate Weakness: A weakness that lessens impact

Major Weakness: A weakness that severely limits impact

What happens?

Either —

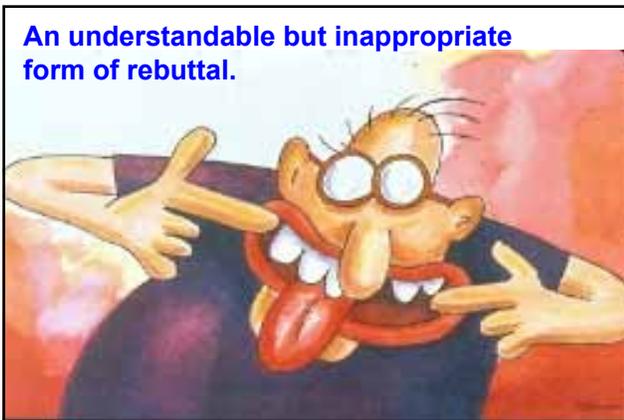
Your grant scores well and gets funded,

Now get to work, and come back and tell the next group of young investigators how you did it.

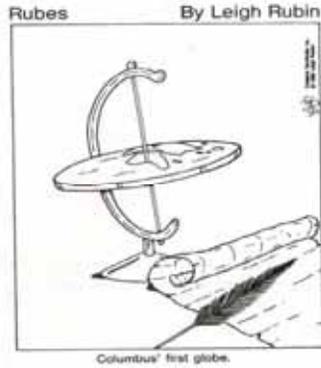
Or—

Your grant is not so well scored and does not get funded.

What do you do now?



Remember, Columbus didn't get it right the first time either.



And remember the *Accenture*TM line—

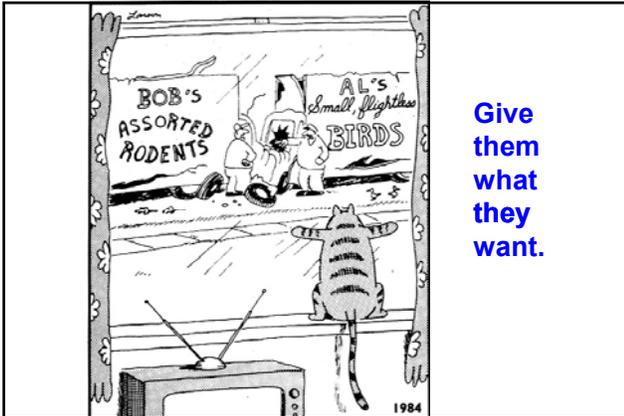
What it takes to be successful—

What you did—10%

What you do next—90%

Resubmission

1. Only one more try !!
2. One page of introduction for response and/or rebuttal.
3. Address exactly each and every concern raised by the review.
4. But--focus response directed at the principal problems.
5. Rebuttal should be well documented to support your position if you disagree with any point in the study section review.
6. Do not expand the grant unless directed to do so.
7. Keep the approved budget, but if you do change, make sure you tie the changes to a specific request of the study section.
8. No grant is perfect; use the revision opportunity to improve yours.
9. Above all, be polite.



Give them what they want.

Critique Oriented Application

NIH now requires that your grant application be written in a template fashion that addresses each of the major review criteria.

1. SIGNIFICANCE

Does this study address an important problem?
If the aims of the application are achieved, how will scientific knowledge be advanced?
What will be the effect of these studies on the concepts or methods that drive the field?

2. APPROACH

Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project?
Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. INNOVATION

Does the project employ novel concepts, approaches, or methods?
Are the aims original and innovative?
Does the project challenge existing paradigms or develop new methodologies or technologies?

4. INVESTIGATOR

Is the investigator appropriately trained and well suited to carry out this work?
Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

5. ENVIRONMENT

Does the scientific environment in which the work will be done contribute to the probability of success?
Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements?
Is there evidence of institutional support?

OVERALL EVALUATION

Summary of the important strengths and weaknesses of the application.
Recommended score reflecting the overall impact of the project on the field, weighting the above criteria as appropriate.
An application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high merit rating.
For example, an investigator may propose to carry out important work, that by its nature is not innovative, but is essential to move a field forward.

Criteria that study section reviewers use to determine their enthusiasm for the grant application and their priority score.

Critique Oriented Application

- Write your grant application to specially address the 5 major evaluation criteria used for the critique: **Significance, Approach, Innovation, Investigator, Environment**, and include a Summary of these for the Abstract and at the end of the Text that emphasizes the overall **Impact** of the research.
- Put the words you want the reviewer's critique to contain in your application.
- Document and justify every statement that relates to these evaluation criteria.

1. Significance

- **State how** this study addresses an important problem.
- **State how**, if the aims of the application are achieved, scientific knowledge will be advanced.
- **State what** the effect of these studies will be on the concepts or methods that drive this field.

2. Approach

State how the conceptual framework, design, methods, and analyses are adequately developed, well integrated, and appropriate to the aims of the project.

State/Acknowledge (with specific examples) potential problem areas and alternative tactics.

3. Innovation

- **State how** the project employs novel concepts, approaches or methods.
- **State how** aims are original and innovative.
- **State how** the project challenges existing paradigms or develops new methodologies or technologies.

4. Investigator

- **State (and document) how** the investigator is appropriately trained and well suited to carry out the proposed work.
- **State how** the proposed research is appropriate to the experience level of the principal investigator and other researchers (if any).

5. Environment

State how the scientific environment in which the work will be done will contribute to the probability of success.

State how the proposed experiments will take advantage of unique features of the scientific environment or employ useful collaborative arrangements.

Show evidence of institutional support.

Overall Impact

- Summarize the important strengths of the application.
- Tell the reviewer what you will learn and why this is essential and important.
- Tell the reviewer how the results of your proposed research—what you will learn—will produce a major **impact** on your scientific field.

RPG/R01/R03/R15/R21 Review

Application #:

Principal Investigator(s):

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 scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact.

Overall Impact Write a paragraph summarizing the factors that informed your Overall Impact score.

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance 4. Innovation 5. Environment
Strengths Strengths Strengths

Weaknesses Weaknesses Weaknesses

2. Investigator(s) 5. Approach
Strengths Strengths

Weaknesses Weaknesses

Preparing a Grant: COMMON MISTAKES

1. poorly written: bad grammar, typographical errors, poor outline, looks sloppy, too many words on a page, too much technical jargon
2. too much work proposed
3. not “crystal clear” what you want to do, why, and how
4. poorly justified; does not advance knowledge
5. necessary expertise is not demonstrated
6. too expensive

Preparing a Grant: COMMON SUCCESSES

1. The grant is easy to read
2. The science is "outstanding"
3. Written with evidence of confidence and enthusiasm for the importance and potential success of the proposed research
4. Figures, graphs, tables, charts, flow diagrams are self-explanatory as well as related to the text
5. The preliminary data/experience are organized to show how they will make the proposed experiments work successfully
6. The budget is accurately and thoroughly justified
7. Descriptive work is acknowledged as such; but the bulk of the research is testable hypotheses

Information

- NICHHD WEBSITE: "Funding by NICHHD"
<http://www.nichd.nih.gov/funding/funding-mechs.htm>
- NIH WEBSITE "Welcome to Extramural Research at the NIH"
<http://grants.nih.gov/grants/welcome.htm>
- NIH CAREER AWARD WEBSITE "K Kiosk"
<http://grants.nih.gov/training/careerdevelopmentawards.htm>
