Clinical and Translational Research Grantees
-differences from Basic Research-

Tetsuo Ashizawa, M.D.
March 18, 2015
NIH definition of human subjects research

Research with human subjects (Patient-oriented research) that is:

• Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Human subjects research includes:
  • mechanisms of human disease
  • therapeutic interventions
  • clinical trials
  • development of new technologies

• Epidemiological and behavioral studies.
• Outcomes research and health services research.
NIH definition of basic research

Research that does not involve research on human subjects, and is devoted to discovery of biological processes and/or disease mechanisms.

• Under this definition, Basic Research excludes:
  a) All research on potentially identifiable human subjects (e.g., clinical trials)
  b) Therapeutic and/or diagnostic development.
NIH definition of translational research

• The process of making discoveries in the research laboratory or in preclinical studies that will have an impact on human health and may lead to the development of studies in humans,

• The process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans, and

• Research aimed at enhancing the adoption of best practices in the community. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science.
NIH Definition of Clinical Trial

A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

- **Phase I.** Tests a new biomedical intervention in a small group of people (e.g. 20-80) for the first time to evaluate safety and determine efficacy.
- **Phase II.** Study in up to several hundred people to determine efficacy and further evaluate safety.
- **Phase III.** Study to determine efficacy in large groups of people (up to several thousand) and to collect information that will allow the interventions to be used safely.
- **Phase IV.** Studies conducted after the intervention has been marketed.
Exemptions from coverage by the human subjects regulations

• Exemption 1: Instructional strategies in established educational settings
• Exemption 2: Educational tests unlinkable to individuals and no risks from disclosure
• Exemption 3: Educational tests on public officials, or absolute federally mandated confidentiality
• Exemption 4: Existing data/specimens, publicly available, unlinkable to individuals
• Exemption 5: Demonstration projects concerning public benefit or service programs
• Exemption 6: Taste and quality evaluation of foods without additives exceeding regulated levels
Mechanisms of NIH Funding

• Research Grant: R01, R03, R21, R23, R33, R00
• Clinical Trial Planning Grant: R34
• Cooperative Agreement Grant: U01 (Research Project), U10 (Cooperative Clinical Research), U54 (Specialized Center), UH2, UH3
• Small Business Grant: R41/R42 (STTR), R43/R44 (SBIR)
• Career Development Grant: K01, K08, K22, K23, (K25), K99/R00 (mentored); K02, K24 (independent career development)
• Research Program Project Grant: P01 (Program Project), P20, P30 (Center Core), P50 (Center)
• Resource-Related Research Project Grant: R24
• Resource Access Program Grant: X01
• Institutional Training Programs: T32, K12, R25,
• Individual Pre/postdoctoral: F31, F32, F33
Funding Opportunity Announcement (FOA)

Program Announcement (PA)
- Usually accepted on standard receipt dates on an on-going basis
- Remains active for 3 years
- Includes PAR (with special receipt, referral and/or review considerations) and PAS (with specific set-aside funds)

Request for Application (RFA)
- Usually has a single receipt date

Proposals submitted for RFA can be re-submitted for PA. Under the new rule, an application can be re-submitted beyond A1 as a new application.
## This Week's Newest Funding Opportunities * April 4, 2014

Center & Institute Directors [OR-CENTER-DIRECTORS-LIST@UFL.EDU] on behalf of Soma Jaisankar [sjaishan@UFL.EDU]

Sent: Fri, Apr 04, 2014 12:09 PM

Also see: 
- [https://www.grantforward.com/index](https://www.grantforward.com/index)

### Research Funding

All new funding opportunities: To see the most recent funding opportunities go to: [http://research.ufl.edu/funding](http://research.ufl.edu/funding).

Special announcements:
- UF Informatics Institute (UIF) Seed Fund Program (Internal Deadline - May 9 2014)
- UF Office of Research Florida High Tech Corridor Council (FHTCC) - Matching Funds Research Program
- UF Office of Research Register for Workshop on Collaborating with Industry on Sponsored Research, April 24

<table>
<thead>
<tr>
<th>New Limited Submission Funding Opportunities</th>
<th>Internal Deadline</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH, NCCAM Centers of Excellence for Research on CAM (Complementary and Alternative Medicine) R01</td>
<td>Apr 25 2014</td>
</tr>
<tr>
<td>Brain Research Foundation (BRF) Scientific Innovations Award (SIA)</td>
<td>Apr 16 2014</td>
</tr>
<tr>
<td>Edward Mallinckrodt, Jr. Foundation REVISED GUIDELINES AND EXTENDED INTERNAL DEADLINE Request for Grant Applications</td>
<td>Apr 11 2014</td>
</tr>
</tbody>
</table>

### Table

| Centers for Disease Control and Prevention (CDC/NCHDOH) Improving Fetal Alcohol Spectrum Disorders, Prevention and Practice through National Partnerships | Apr 14 2014 |
| Florida Department of State, Division of Cultural Affairs General Program Support and Specific Project Support | Apr 18 2014 |
| Oak Ridge Associated Universities (ORAU) Travel Grants | Apr 25 2014 |
| Health Resources & Services Administration (HRSA) Behavioral Health Workforce Education and Training for Professionals | Apr 25 2014 |
Funding & Funding

Funding Opportunities and Notices

The NIH Guide for Grants and Contracts is the official publication for NIH medical and behavioral research grant policies, guidelines and funding opportunities. Definitions and More Information...

Search the NIH Guide for:
- Active RFAs (Requests for Applications)
- Active PAs (Program Announcements)
- Notices

With Announcement # or Keywords: (Optional)

Browse Active Funding Opportunities
- Requests for Applications (RFAs)
- Program Announcements (PAs)
- Parent Announcements (unsolicited applications)

Browse Recent Policies and Guidelines
- Notices (Released in last 12 months)

Recovery Act Funding
- Current NIH Funding Opportunities and Notices
- Grant Funding Opportunities Web Page

http://grants.nih.gov/Grants/guide/search_results.htm?year=active&scope=pa
Translational Research (NINDS)

Basic Research Grant → Basic Research → IGNITE (R21, R33) → Preclinical preparation for IND, IDE, or 510(K) in Translational Research → BPN & CREATE-BIO (UH2, UH3, STTR (R41) and SBIR (R43)) → Tech innovation, transfer and commercialization; includes small phase I/II Clinical Trials → R/U/P/X/STTR grants → Phase I/II/III Clinical Trials

IGNITE: Innovation Grants to Nurture Initial Translational Efforts
BPN: Blue Print Neurotherapeutics
CREATE-BIO: Cooperative Research to Enable and Advance Translational Enterprises for Biotechnology Products and Biologics
Innovation Grants to Nurture Initial Translational Efforts (IGNITE)

Mission:
To seamlessly advance projects from early discovery (R01 & R21) into late-stage translational programs (BPN & CREATE-Bio) in a manner that is scientifically rigorous, timely, and cost effective.
IGNITE is Meant to Serve as a Feeder Program to CREATE and BPN

*Entry criteria for CREATE and BPN programs:*

1. Essential assays (in vitro and in vivo) to enable optimization of the preliminary bioactive leads(s)
   - **PAR-15-070**: Assay Development and Therapeutic Agent Identification and Characterization to Support Therapeutic Discovery

2. Preliminary bioactive lead(s)
   - **PAR-15-071**: Pharmacodynamics and In vivo Efficacy Studies for Small Molecules and Biologics/Biotechnology Products

3. Either in vivo efficacy using clinically relevant outcome measures and/or in vivo target engagement and/or a path forward that clearly addresses efficacy studies
   - **PAR-15-071**: Pharmacodynamics and In vivo Efficacy Studies for Small Molecules and Biologics/Biotechnology Products
The R21/R33 Mechanism

R21: Demonstrate feasibility and get ready for R33.
(≤2 years R21; ≤3 years for the project)

Go/No-Go Milestone
Does this warrant further investment?

R33: The execution phase
(≤2 years R33; ≤3 years for the project)

Dependent aims; if R21 doesn’t work, NINDS never pays the R33

Extremely clear and definitive milestones are *essential*.
- Only 1 go/no-go point
- Administrative review
This FOA encourages research grant applications to develop in vitro and/or ex vivo assays and conduct iterative screening efforts to identify and characterize potential therapeutic agents for neurological disorders.

R21/R33
FOA #1 (Assay) Start to Finish

Entry Criteria
- Novel targets, mechanisms and pathways
- Strong biological rationale for the intended approach
- Therapy development plan
- Relevance to NINDS mission

End Goal:
- Fulfill the next steps of a bigger therapeutic development plan
- Meet one or more entry criteria for BPN or CREATE
FOA #1 (Assay) Activities

Examples of activities for R21 phase include, but are not limited to:
- Development of assay(s) to support a succinct testing funnel
- A combination of assays may be developed
- Development of in vitro or ex vivo potency/efficacy assay
- Development of assays to evaluate cellular uptake, engagement, infection, aggregation, downstream functional measures in vitro or ex vivo, purity, and specificity.
- Development of assays to evaluate purity and identity of the therapeutic

Examples of activities for the R33 phase include, but are not limited to:
- Preparation and screening of select series of therapeutic agents
- Preparation of therapeutic agent(s) and confirmation of structure, sequence or biological characteristics
- Development and selection of cell lines/vectors to produce bioactive agents
- Assessment of therapeutic agent’s properties using computational analysis and early physicochemical measurements
- Assessment of initial pharmacokinetic parameters such as ADME.
- Assessment of potential off target activities.
- Optimization of therapeutic agent(s).
What FOA #1 (Assay) Should Not be Used For

• Creation of assays or probes to better understand disease mechanisms
• Target identification
• Studies of disease biology
• IND-enabling studies
#2: Pharmacodynamics and In vivo Efficacy Studies PAR-15-071

This FOA provides funding to conduct pharmacodynamics, pharmacokinetics, and in vivo efficacy studies to demonstrate that proposed therapeutic agent(s) have sufficient biological activity to warrant further development to treat neurological disorders.
FOA #2 (PD/Efficacy) Start to Finish

Entry Criteria

• Evidence that the therapeutic agent(s) has the potential to be therapeutically viable
• Evidence to support the robustness of the PD measures and/or efficacy models
• Unmet need for the therapeutic agent(s)
• Justification for how the findings from these studies are relevant to treatments for disorders that are within the NINDS mission.

End Goal:

• Fulfill the next steps of a bigger therapeutic development plan
• Meet one or more entry criteria for BPN or CREATE
FOA #2 (PD/Efficacy) R21 Activities

Examples of activities for the R21 phase include, but are not limited to:

• Preparation of the therapeutic agent(s)
• Characterization of therapeutic agent(s) (purity, stability, ADME, in vitro potency and selectivity, etc.)
• Studies to develop dosage form(s)
• Pharmacokinetics studies
• Studies to confirm that therapeutic agents reach and engage the target site (directly or indirectly) at a level that exceeds pharmacological potency over the desired period.
• Studies to inform design, refinement, and validation of the PD measure and/or in vivo efficacy models and testing procedures
FOA #2 (PD/Efficacy) R33 Activities

At the end of the R21 phase, investigators must exhibit successful completion of

• all necessary preparation and characterization of agent
• pharmacokinetic studies
• design, refinement, and validation of PD and/or efficacy animal studies using the appropriate controls and demonstrating feasibility
• a detailed in vivo study design that meets the NINDS RIGOR guidelines and will allow for demonstration of dose and exposure responses

Examples of activities for R33 phase include, but are not limited to:

• PD and/or in vivo efficacy studies with chemically and biologically characterized therapeutic agent(s).
• Dose (exposure)-response activity with the intended route of administration.
• Studies correlating pharmacokinetic and pharmacodynamics measures (PK/PD)
• Validation and replication studies to confirm observed results.
• Studies to test the agent(s) along with or against positive and negative controls.
What FOA #2 (PD/Efficacy) Should Not be Used For

• Development of de novo animal models and pharmacodynamics measures
• Target identification
• Studies of disease biology
• GLP toxicology studies with optimized therapeutic agents
Review Criteria for Both FOAs

• Therapeutic Development Plan

• Strong biological rationale for the intended approach and supporting data from rigorously designed experiments

• Rigorous study design and reporting

• Multidisciplinary team (disease biology, clinical, statistical, drug development, etc.)

• Go/No-Go Milestones:
  • Well-described
  • Quantifiable
  • Justified scientifically
  • Adequate to justify further investment

• Meeting entry criteria for BPN/CREATE

  Is there a path forward?
Important Points about Milestones

• NINDS uses milestones for measuring success in achieving the project objectives
• Details should be included regarding methods, assumptions, experimental designs, and data analysis plans
• Quantitative criteria should be robust and be consistent with the state-of-the-art in the field
• Timelines should be clear
Additional Review Criteria for FOA #1 (Assay)

• Are the starting compounds chosen based on sound scientific rationale?
• Are there clear, well-defined goals to pursue novel targets, mechanisms and pathways?
• Will the project, if successful, produce a well-validated assay that can support future therapeutic development for neurological disorders?
• Is the process for selecting compounds at each iteration appropriate?
• Is the plan for chemical modification and optimization reasonable?
Additional Review Criteria For FOA #2 (PD/ Efficacy)

• Does the project pursue validated targets, mechanisms and pathways, and treatment approaches?
• Is there a sufficiently developed plan for the assessment of therapeutic agent chemical, biophysical, and biological characterization and on target and off-target in vitro profiling within the proposed grant period?
• Are the proposed in vivo efficacy study and/or pharmacodynamics measures relevant to the proposed clinical indication?
• Are the in vivo models and preclinical outcome measures to assess efficacy and/or PD optimal for the proposed clinical indication?
• Will the project, if successful, produce a robust pharmacodynamics measure or in vivo efficacy results that can support future therapeutic development?
NINDS CREATE BIO Program Summary
PAR-14-286 - NINDS CREATE Bio Discovery (U01), PAR-14-287 (U44, SBIR)

1. Comparison of CREATE BIO Discovery and Development Tracks

**Discovery Track**
- Optimization of therapeutic lead(s)
- Characterize and select a candidate, which has bioactivity, stability, bioavailability, in vivo efficacy and/or target engagement, etc., that are consistent with the desired clinical application
- Funded up to 4 years through the U01 or SBIR U44 cooperative agreement mechanism

**Development Track**
- IND-enabling studies & early-phase clinical trials
- An IND application submitted to the FDA, at a minimum. The program also supports early-phase clinical trials, but these are not required components of proposed projects
- Funded up to 5 years through UH2-UH3 or SBIR U44 cooperative agreement mechanism
2. Important Components of the CREATE BIO Application

• **Target Product Profile (TPP)** and plans for **clinical POC** are required for ALL PARs
• The formation of the **multidisciplinary team** is a requirement prior to entry
• **Rigorous Study Design and Reporting** for all PARs (supporting data package and proposal) is required • Choice of model(s) or assay(s), primary, secondary and exploratory endpoints needs to be explained and clinical relevance justified
• **Power analyses** and associated assumptions for the determination of **sample size, statistical handling** of the data such as criteria for data inclusion or exclusion, as well as procedures for **blinding** and **randomization** need to be described
• Potential **replication of key data** (by the applicants or by independent investigators) should be noted
• Figure should have associated text detailing the **number of animals** per group, how many times the experiments were repeated, and whether the data are **representative or aggregated**
• **Intellectual Property** Strategy has to be clearly outlined for all PARs
• **Quantitative milestones** need to be presented for all PARs • Examples on CREATE Bio website
Out of Scope Activities:

1) Developing animal models
2) Basic research of disease mechanisms
3) Early activities such as target identification and validation
4) Development of risk, detection, diagnostic, prognostic, efficacy prediction biomarkers
5) Stand-alone studies to identify, validate, or qualify biomarkers
6) Activities already performed utilizing other private or public funds to advance the agent
9) Performance of a clinical trial with the objective of demonstrating clinical efficacy
Budget of CREATE BIO

**Discovery Track (U01)**

- <$500 k/yr in direct cost for up to 4 yrs

**Development Track (UH2/UH3)**

- <$1M/yr in direct cost for UH2 for up to 2 yrs
- <$1.5M/yr in direct cost for UH3
- Combined UH2+UH3 for up to 5 yrs
Small Business Innovation Research (SBIR)
Small Business Technology Transfer (STTR)

• Public/private sector partnership to include the joint venture opportunities for small US business (<500 employees) and non-profit research institutions

• R&D effort: Small business >40% and non-profit research institution >30% (STTR only)

• PI may be either from small business or non-profit for STTR and from small business only for SBIR

• To bridge the gap between performance of basic science and commercialization of resulting innovations
  • Technology innovation
  • Technology transfer
  • Commercialization of innovations

  Phase I: to establish the technical merit, feasibility and commercial potential ($150K for 1yr)
  Phase II: to advance the successful STTR Phase I activities ($1M for 2yrs)
  Phase III: to pursue commercialization objectives resulting from STTR Phase I/II activities.*

*Available by only some STTR programs.
**R34: NIH Clinical Trial Planning Grant Program**

- **Supports development of Phase III clinical trials.** This program supports
  - establishment of the research team
  - development of tools for data management and research oversight
  - definition of recruitment strategies
  - finalization of the protocol
  - preparation of an operations/procedures manual
  - **Not** to collect preliminary data

- **Parent R34 Application Characteristics**
  - a project period of <3 years
  - a budget for direct costs of up to four $25,000 modules or $100,000 per year

- **R34 Participating Institutes and Centers**
  (Check for active PA/PAR/RFA)
Writing Clinical Trial Grant Applications

• In principle, same as basic science grants
• Preliminary data, approach – key differences
  • Designs – PDBRPC – bias management
  • Statistics
• Rationale
  • Clinical trials: Equiposed?
Writing Clinical Trial Grant Applications

• Strong biological rationale
• Strong preclinical data
• Preliminary clinical data (Safety records, Phase I data, Phase II data), approach – key differences
  • Designs
    • Rigorous randomization - Study population is heterogeneous
    • Frequently required multicenter design – sample size calculations
    • Blinding
    • Controls (placebo or established intervention)
    • Sample size calculation and statistical analyses
    • Primary outcome measure
Specific Issues

• Read RFA, PA, FOA, etc. from cover to cover. Both PI and grant management office need to understand.

• Follow all the rules.
  • Avoid rejection by the CSR – font, page limitations, format, margins and content.
  • Determine IRB and other requirements.
  • JIT and NOA.

Do not expect any flexibility from CSR or reviewers.
Allow enough time for pre-review and revisions.
Common Elements and Importance from the Reviewer’s Perspective

✓ Title and Face Page
✓ Abstract
✓ Specific Aims
  • Significance
  • Investigator
  • Innovation
  • Approach
  • Environment
    o Human Subjects
    o Vertebrate Animals
    o Biohazards
    o Budget and Period of Support
    o Select Agents
    o Resource Sharing Plans

For translational application
Do not forget “Rigor”.

Review at the Study Section

1. Submission of reviews by designated reviewers
2. Triage
3. Meeting discussion
   1. Stating the overall score by each reviewer
   2. Discussion
   3. Summary
   4. Human subjects, animals, biohazards
   5. Final scores by reviewers
   6. Voting scores – out of range voting
   7. Budget discussion
   8. Data and Material Sharing
   9. IP
10. MPI/foreign organization
WE HAVE STUDIES OF FRUIT FLIES, MICE, HAMSTERS, FROGS, MONKEYS AND MEN WITH THIS CONDITION—but medical research using women as subjects just never occurred to anybody.
### Major Review Issues in National Institutes of Health Grant Proposals (n = 66)

<table>
<thead>
<tr>
<th>Area</th>
<th>Grants, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specific aims/hypothesis</strong></td>
<td></td>
</tr>
<tr>
<td>Goals overstated, overly ambitious or unrealistic</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Poorly focused or inadequately conceptualized</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Hypotheses not clearly articulated</td>
<td>8 (12)</td>
</tr>
<tr>
<td><strong>Background/Significance</strong></td>
<td></td>
</tr>
<tr>
<td>Need for study not well justified</td>
<td>19 (29)</td>
</tr>
<tr>
<td>Too much background, insufficient room for methods, extraneous information</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Overstatement of significance of study</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

From Inouye & Fiellin 2006
Major Review Issues in National Institutes of Health Grant Proposals (n = 66)

<table>
<thead>
<tr>
<th>Area</th>
<th>Grants, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary/pilot studies</td>
<td>33 (50)</td>
</tr>
<tr>
<td>More pilot work needed</td>
<td>27 (41)</td>
</tr>
<tr>
<td>Studies cited with no clear link to proposed study</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Inadequate description of preliminary studies</td>
<td>2 (3)</td>
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</table>
## Major Review Issues in National Institutes of Health Grant Proposals (n = 66)

**Area**

**Methods**  

<table>
<thead>
<tr>
<th>Area</th>
<th>Grants, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study patients</td>
<td>46 (70)</td>
</tr>
<tr>
<td>Inclusion criteria (non-representative, bias, poor description)</td>
<td>36 (54)</td>
</tr>
<tr>
<td>Exclusion criteria (poor justification, overlooked, bias)</td>
<td>23 (35)</td>
</tr>
<tr>
<td>Data analysis (Poor statistics, no Intend-to-treat, unaddressed missing data)</td>
<td>42 (66)</td>
</tr>
<tr>
<td>Outcome (blinding, poor outcome measures, validity, omissions of variables)</td>
<td>40 (66)</td>
</tr>
<tr>
<td>Sample size/power (calculation, attrition rates)</td>
<td>28 (42)</td>
</tr>
<tr>
<td>Controls</td>
<td>21 (32)</td>
</tr>
<tr>
<td>Data collection/procedures</td>
<td>18 (27)</td>
</tr>
<tr>
<td>Intervention (adherence monitor/analyses, randomization flaw, potency)</td>
<td>16 (24)</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Area</th>
<th>Grants, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Issues</strong></td>
<td>24 (36)</td>
</tr>
<tr>
<td>Layout poor (editing/typographical/grammatical errors, inconsistencies, too-small font, omitted lines or tables, poor photocopy, difficult to read)</td>
<td>13 (20)</td>
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<tr>
<td>Use of jargon, abbreviations, undefined terms</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Information presented in wrong sections</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Limitations not adequately discussed (For revision)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Inadequately responsive to previous reviewers' comments</td>
<td></td>
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</tbody>
</table>
Understand the Reviewer’s Perspective

• The reviewers are probably successful, busy researchers.
• They are “experts” but perhaps have little in-depth experience in your area of research.
• Except for the reviewers assigned to your application, study section members who vote their scores will have very limited time to review your application.

Key
• Focus
• Conciseness
• Conceptual clarity
• Transparent language

- Cristal clear significance
- Avoid jargon
- Define acronyms
- Self-contained
- No critical info in appendices
Major review issues for translational grant applications

• Biological rationale
• Rigor in both preliminary data and study plans
• Strong biological rationale conflicting with innovation
• “Go/No Go” - “Go” > “No Go”
• Firm therapy development path – collaborations with NIH, industry, etc.
<table>
<thead>
<tr>
<th>Overall Impact or Criterion Strength Score</th>
<th>Descriptor</th>
<th>Additional Guidance on Strengths/Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>1 Exceptional</td>
<td>Exceptionally strong with essentially no weaknesses</td>
</tr>
<tr>
<td></td>
<td>2 Outstanding</td>
<td>Extremely strong with negligible weaknesses</td>
</tr>
<tr>
<td></td>
<td>3 Excellent</td>
<td>Very strong with only some minor weaknesses</td>
</tr>
<tr>
<td></td>
<td>4 Very Good</td>
<td>Strong but with numerous minor weaknesses</td>
</tr>
<tr>
<td></td>
<td>5 Good</td>
<td>Strong but with at least one moderate weakness</td>
</tr>
<tr>
<td></td>
<td>6 Satisfactory</td>
<td>Some strengths but also some moderate weaknesses</td>
</tr>
<tr>
<td></td>
<td>7 Fair</td>
<td>Some strengths but with at least one major weakness</td>
</tr>
<tr>
<td></td>
<td>8 Marginal</td>
<td>A few strengths and a few major weaknesses</td>
</tr>
<tr>
<td></td>
<td>9 Poor</td>
<td>Very few strengths and numerous major weaknesses</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td></td>
<td></td>
</tr>
<tr>
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</table>

Other Designations for Final Outcome
- **AB**: Abstention
- **CF**: Conflict of Interest
- **OF**: Deferred
- **ND**: Not Discussed
- **NP**: Not Present
- **NR**: Not Recommended for Further Consideration

**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
But first......

• Contact the program officer.
• Review successful grant applications of the type you will write.
• Check NIH Reporter (http://projectreporter.nih.gov/reporter.cfm) to avoid duplication.
• Gauge the priorities of the funding agency.
• Know potential reviewers – study section roster www.csr.nih.gov/committees/rosterindex.asp
• Get advice from a biostatistician!
Specific Issues

• Read RFA, PA, FOA, etc. from cover to cover. Both PI and grant management office need to understand.

• Follow all the rules.
  • Avoid rejection by the CSR – font, page limitations, format, margins and content.
  • Determine IRB and other requirements.
  • JIT and NOA.

Do not expect any flexibility from CSR or reviewers.
Specific Aims – the most important section –
• Hypothesis-driven vs needs-driven
• Goals
• Specific Aims
• Long-term goal
  o Focused?
  o Underdeveloped?
  o Overambitious?
  o Input from mentors, colleagues and collaborators?
  o Study design, sample size, study groups and primary outcomes included? i.e., no surprises to reviewers in later section
  o Achieve answering the central hypothesis or the need if specific aims are accomplished?
  o Specific aims complement one another but independent?
  o Sound rationale for each aim?
  o Clear hypothesis for each aim?

Spend enough time on this page – i.e., until the time of submission
Significance

• This section justifies and builds the case for the project. Say why the proposed project is needed.
• Encyclopedic background is a big “NO-NO” – keep it essential and relevant. Each background sentence should link to the proposed project.
• Show how the proposed study builds on previous work.
• Identify knowledge gaps in previous knowledge and convince reviewers why the gaps need to be filled.
• Prevalence of the problem is not necessarily linked to significance.
• Do not overstate the significance.
• Do not make it too long – other sections will run out of pages.
• Write with your maximal enthusiasm.
Innovation

• Remember that the NIH study section is not necessarily kind to totally innovative proposal – gap filling but with a certain boundary.

• “Your project should move the frontier of knowledge forward. Striving for a paradigm shift is not advisable.” – from the NIAID site.

• Incremental research is safer but needs to be sold as innovation.

• If reviewers think you're wandering too far outside of the box, your application probably won't score well since the likelihood of success will be perceived as low.

• New ways of thinking about known problems and technological innovations are relatively safe.

• Paradigm-shifting innovation requires extraordinary evidence/preliminary data.
Preliminary Data

• Present data directly relevant to the proposed study.
• Justify the rationale and feasibility of your specific aims.
• Include primarily your own data. However, since the page restriction (12 or 6 pages for the narrative) was imposed, many applicants mix key background data with his/her own preliminary data.
• However, you must present your own data to convince reviewers about technical capability of your lab if you have not published the data.
• Show your thoughtfulness, rigor and readiness of your lab.
• Include details (n, error bars, p values, controls, and self-explanatory legends, etc.).
• Align your preliminary data with specific aims.
• The more preliminary data, the better.
Preliminary Data

• If animal data are to justify a clinical study proposal, strong biological rationale, rigor (statistics, randomization, controls, blinded outcome evaluations, target engagement, selection of outcome directly equivalent to clinical primary outcome measure, all thinkable controls) has a key importance.

• If human data are to justify a preclinical or clinical proposal, critically assess quality of the preliminary data (e.g., Class I vs. Class IV data) – remember humans are genetically and socially heterogeneous creatures.
Approach

If your specific aim page can pass the reviewers’ critical eyes, this section is the biggest next killing field.

✓ The art of study design and setting of clinical studies is fundamentally different from basic science research – heterogeneity of study subjects and bias
  • Randomization – describe how you plan to randomize.
  • Blinding – describe the method of blinding of participant allocation to treatment group (smell and taste of pills, physical interventions, surgical interventions).
  • Unbiased selection of case-subjects and control subjects in case-control studies.
  • Enrollment of the representative sample of the target population.
  • Inclusion and exclusion criteria - include justifications and potential biases.
    o Inclusion criteria: is the study sample non-biased and representative?
    o Exclusion criteria: Are the exclusions justified (sufficient and necessary) and not introducing unnecessary or critical biases?
Approach

✓ The art of study design and setting of clinical studies is critically different from basic science research – cont’ed.

• Availability of participants
  o Describe the recruitment strategies, catchment areas, referrals, registry/database, etc. in the context of feasibility and bias.
  o Include a pilot work or similar studies of the population pool.
  o Consider the attrition rate.

• Data collection/procedures
  o Thorough description of study instruments and their validity and reliability (include a table of instruments and their sensitivity, specificity and reliability statistics).
  o Describe all study measurements and data elements and plans to analyze them.
  o Include training and standardization for reliability assurance.
Approach

✓ The art of study design and setting of clinical studies is critically different from basic science research – cont’ed.

• Outcomes
  o Detailed operational definition and specification of each study outcome.
  o Primary and secondary outcome measures with rationale.
  o Blinding evaluators – describe any threats for blinding.
  o How equal surveillance for outcomes will be assured in all study groups.

• Intervention
  o Detailed description of intervention – standardization, potency, adherence, contamination/co-intervention in the control group.
  o The interventions should not be a “black box.”

• Data analysis/Sample size calculations
  o Detailed data management procedures, analytic approach and sample size calculations.
  o Include an intention-to-treat analytic strategy.
  o Handling potential confounders.
  o Handling missing data.
  o Data analysis methods for each outcome with independent variables and covariables to be studied.
  o Use multiple statistical approaches.

Your biostatistician is your best friend.
Pitfalls and Alternative Approach

• If you do not address them, reviewers will with their “dampened enthusiasm.”

• Alternative approach does not have to be detailed to the same extent of your methods.
Budget

• Early communications with the UF Research Administration and Compliance (RAC) and Institutional Review Board.
• Start working early on budget for multicenter clinical studies.
  o Know F&A (indirect cost) rate of home and site institutions.
  o Each institution has its own fringe benefit rate.
  o Understand subcontract rules.
  o Upfront subcontract distribution and per-subject reimbursements.
  o The budget may need adjustments due to the sample size adjustments and changes in the number of sites.
• Making the budget for clinical studies are generally more time consuming – start early.
## Tentative Timeline (5-Year Study)

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1. **Specific aim 1**

2. **Specific aim 2**
   - a. Data acquisition
   - b. Chart review
   - c. Data analysis/manuscripts

3. **Specific aim 3**
   - a. Subject interviews
   - b. Data management
   - c. Data analysis/manuscripts

4. **Specific aim 4**:
   - analysis and synthesis