Institutional K Awards Tutorial

Planning and writing a GA CTSA KL2 and BIRCWH K12

Session #2
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Class #2 Objectives

Candidate Section

Letters of Support

- Plans and Statements of Mentor and Co-Mentor(s), Consultants, Collaborators
- Chair or Division Chief's statement of commitment to you for this award

Research Plan (Specific Aims & Research Strategy)

- Examples
- Organization
- Clarity
- Styles of writing

Using reviewers' comments to highlight:

- Qualifications issues
- Level of detail in writing
- Integration of Research Plan in other sections
- Integration of Training Plan

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Candidate Section

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Candidate Information

(Candidate + Research Strategy = 12 pages)

a) Candidate's Background

b) Career Goals and Objectives

c) Career Development/Training Activities During the Award Period

- Refer to the NIH Career Development Application Guide for more detailed instructions
  https://grants.nih.gov/grants/how-to-apply-application-guide/forms-h/career-forms-h.pdf

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NIH Review Criteria

K - Career Development	Standard Grants
Candidate	Significance
Career Development Plan / Career Goals	Investigator
Research Plan	Innovation
Mentors, etc.	Approach
Environment Commitment to Candidate	Environment

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Candidate Information

c) Career Development/Training Activities During Award Period

- "Stress the new, enhanced research skills and knowledge you will acquire..."
- Who comprises your Mentoring Team? Who will train you to do what for which aims? Mention people by name/role. This section will complement the *Letters of Support by Mentors*
- Be specific – what is the real new training you will receive
- Describe structured activities in DETAIL
  - formal supervision/mentoring – weekly time with mentors
  - coursework (course number and descriptive title – no elaborate discussion)
  - seminars, lab meetings
  - preparation for mentored NIH K award independent research, etc.
- You must propose Research and Training Activities for each of the 2 years
- Plan to submit your NIH K must occur by the end of your first 12 months as KL2 / K12 Scholar
  - State you will take my 6-hour NIH K grant writing tutorial and MSCR594 Grant and Scientific Writing (required) to prepare for your NIH K application

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Important Considerations in Selecting a Mentor

1. ***Highly qualified, senior academic scientist*** who takes overall responsibility for overseeing your training activities and your original research
2. 'Apprentice model' of mentorship is highly valued
3. This person must be 100% committed and this must be crystal clear in this section
4. Mentor must have a 'stable financial environment' – R01 funding is excellent but not required (but there is a big bias for an NIH funded mentor for the NIH K award)
   - Answers the question "Where will the resources come from to support the research that is not supported by the grant?" Resources can come from lots of places – they must however be available (not anticipated through future grants).
5. All mentoring/consulting/collaborating must be coordinated and spearheaded by the mentor

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Describe the Advisory / Mentoring Team

Everyone who is involved in 'helping you' with the K award has a job title.

- **Mentor**
- **Co-mentor**
- **Consultant**
- **Collaborator**
- **Advisory Committee**

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Mentorship Team

I recognize the importance of mentoring throughout one's career, but particularly in making the transition from junior to independent investigator. I have established a team of mentors that are national and international experts in transplant immunology, immunotherapy, sickle cell disease, and HSCT. My primary mentorship team of Dr. Galipeau and Dr. Krishnamurti, who are both based at Emory, will provide the necessary expertise in scientific study design and implementation, clinical trial development, grantsmanship, and mentoring.

Primary Mentor: Jacques Galipeau, MD is a tenured Professor of Hematology and Oncology in the Departments of Pediatrics…… I will attend the weekly Gallipeau lab meetings where I will be expected to present …. (describe the components of the hands-on training you will receive by who, where and when)

Co-Primary Mentor: Lakshmanan Krishnamurti, MD is a Professor of Hematology and Oncology in the Department of Pediatrics and Director of Pediatric Blood and Marrow Transplantation. ……

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Table 1. Training and Research Plan by Year *Shows work x time for each semester*

Planned Activities by Year/Period		Year 1 (8/1/14-8/31/15)		Year 2 (8/1/15-8/31/16)		
Academic Semester		Fall	Spring	Summer	Fall	Spring
Training Plan						
MSCR Coursework	Analytic Methods for Clinical Research I	X				
	Biostatistics	X				
	Data Management	X				
	Community Engagement & Health Disparities	X				
	Fundamentals of Bioinformatics		X			
	Analysis of Clinical Research Data		X			
	Analytic Methods for Clinical Research II		X			
	Clinical Research Colloquium		X			
	Clinical Trial Design and Analysis		X			
Thesis	Preparation	X	X	X		
	Defense			X		
National Conferences	American Society of Hematology (ASH)	X			X	
	Tandem meeting (ASBMT/CIBMTR)		X			X
ASH CRTI	Submit application		X			
	CRTI program			X	X	X
Research Plan						
Specific Aim 1	Prospective sample collection	X	X	X		
	Ex-vivo expansion of MSCs		X	X	X	
	Phenotypic analysis of MSCs		X	X		
Specific Aim 2	Retrospective sample collection	X				
	Analysis of MSC function	X	X	X	X	X
Specific Aim 3	IFN-γ priming of MSCs	X	X	X	X	X
	Analysis of MSC function	X	X	X	X	X
Data analysis			X	X	X	X
Abstracts	ASH	X			X	
	Tandem meeting		X			X
Manuscript	Preparation	X	X		X	X
	Submission/publication		X	X		X
Haplo-BMT platform	Protocol development	X				
	Submit IND application		X			
	IRB submission for MSC clinical trial			X		
Funding	Preparation of K23 application		X	X		
	Submission of K23 application			X		
Clinical Plan (remaining 25% effort)						
Inpatient and outpatient BMT service (<12 weeks per year)		X	X	X	X	X

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Table 1. Career Development Plan over K23 Award Period

TRAINING OBJECTIVES	ACTIVITY	YEAR 1	2	3	4	5
A. Multidisciplinary mentorship	Structured mentoring and apprenticeship with Drs. Ofotokun (weekly), Acosta (monthly), and Schinazi (monthly)	✧	✧	✧	✧	✧
	DOM Career Development Mentoring for K Awardees	✧	✧	✧	✧	✧
B. Training in experimental Pharmacology and PK/PD Modeling	Basic pharmacology (IBS 531, 532)		✧			
	Advanced biostatistical analysis coursework (BIOS 502)			✧		
	Buffalo Pharmacometrics PK/PD Modeling Workshops			✧	✧	✧
	UAB Pharmacometrics Workshops	✧	✧	✧	✧	✧
	Hands-on experimental pharmacology and PK/PD modeling practicums at UAB			✧	✧	✧
C. Scientific communication (writing and presentation skills)	Emory K Club lectures (monthly)	✧	✧	✧	✧	✧
	Emory DOM Faculty Development Seminars (monthly)	✧	✧	✧	✧	✧
	ID Division seminars (weekly)	✧	✧	✧	✧	✧
	Proposal Development and Grant Writing Course			✧		
	Keck Scientist-Writer Workshop				✧	
	CROI Conference (annually)	✧	✧	✧	✧	✧
	IAS or International Workshop on Clinical Pharmacology of HIV Therapy (annually)	✧	✧	✧	✧	✧
D. Maintenance of clinical skills in HIV disease management	Women's IDP clinic (1 half day/week)	✧	✧	✧	✧	✧
	Grady inpatient service (6 weeks/year)	✧	✧	✧	✧	✧
	IDP provider didactic (weekly)	✧	✧	✧	✧	✧
	CME activities (annually)	✧	✧	✧	✧	✧

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Task	Year 1 Q1 Q2 Q3 Q4	Year 2 Q1 Q2 Q3 Q4	Year 3 Q1 Q2 Q3 Q4	Year 4 Q1 Q2 Q3 Q4	Year 5 Q1 Q2 Q3 Q4
TRAINING PLAN					
Focused Mentorship/Self-study					
Clinical Research Fundamentals (Goal 1)	XXX XXX XXX XXX	XXX XXX XXX XXX	XXX XXX XXX XXX	XXX XXX XXX XXX	XXX XXX XXX XXX
Clinical Trials (Goal 2)	XXX XXX XXX XXX	XXX XXX XXX XXX	XXX XXX XXX XXX	XXX XXX XXX XXX	XXX XXX XXX XXX
Clinical OFP Interpretation (Goal 3)	XXX XXX XXX XXX		XXX XXX XXX		
Advanced Data Analysis (Goal 4)	XXX XXX XXX XXX	XXX		XXX XXX	XXX XXX
Telemedicine (Goal 5)	XXX XXX				
Formal Coursework					
MSCR Program (Goal 1)	XXX XXX				
Clinical Trials (Goal 2)			X	X	
Statistics Electives (Goal 4)	XXX XXX				
Telemedicine (Goal 5)	X		X		
RESEARCH PLAN					
Emory Study					
Start-up (form design, database, training)	XXX				
Phase 1: DO only by ED physicians (Aim 1A,2A)	XXX XXX				
Phase 2: OFP read by ED physicians (Aim 1B,2A)	XXX XXX				
Precision/reliability studies (Aim 1C)					
Expert reviewers	XXX XXX XXX XXX				
ED physicians	X X				
Phase 3: Complete follow-up (Aim 2B)	XXX XXX				
Grady Study					
Start-up (form design, database, training)			XXX XXX		
Enrollment (Aim 1B/C validation)			XXX XXX XXX		
Complete follow-up (Aim 2B validation)				XXX XXX	
Close-out					
Data Analysis	XXX XXX XXX XXX	XXX		XXX XXX XXX XXX	
Publication			XXX XXX		XXX XXX
Grant Writing			XXX XXX	XXX XXX XXX XXX	XXX XXX

Figure 2. K23 overall timeline for the training and research plan.

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What are Reviewers Looking for?

- What scientific skills / techniques / areas don't you know?
- Who is spearheading your training and looking out for your career development?
- Where will the balance of research funding come from?
  - Lab tech, materials, cells, animals, datasets, staff support (research tech, clinical coordinator, recruiter, assessors, etc.)
- What new skills will you learn?
- How will the new training support your ability to carry out the proposed aims?
- All this can be very concrete and specific; write in the 1st person to make this flow nicely

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"Future Plans for NIH Research"

Describe a plan to submit your NIH K by the end of your first 12 months as KL2 / K12 Scholar

- Training Activities:
  - Take my NIH K grant writing class (offered 2x/yr, sponsored by the Office of Postdoctoral Education)
  - All KL2 / K12 scholars will enroll in MSCR 594 Scientific and Grant Writing (even those following the personalized pathway)
- What to write about:
  - Preview what your NIH K goals will be in terms of further training, future research, professional career goals (short and long term)
  - To do this you must familiarize yourself with the K award options
  - https://researchtraining.nih.gov/programs/career-development
  - New considerations for clinical trials and any independent and prospective human subjects data collection. Be sure you understand all this as this is all new.

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Mentor / Co-mentors Letters of Support Section

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NIH Review Criteria

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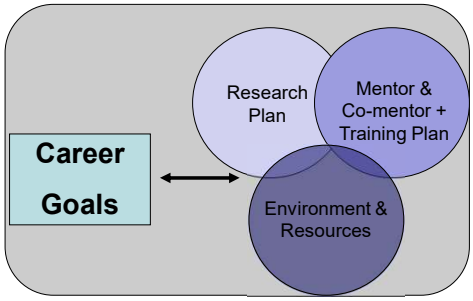
Career Development Award Theme: Integration & Consistency



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Letters of Support: From Department Chair or Division Chief

- Guarantee that the applicant will have protected time (equivalent to the salary support provided by the Department) to carry out clinical research training if accepted by the program
  - 75% for non-surgical specialties
  - minimum of 50% for surgical specialties
- For Department of Medicine, Letter of Support from Division Chief is required in lieu of Chair's letter
- *This is **not a letter of recommendation** but rather a statement that your department will support your salary and give you protected time to do the proposed work*

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- This is a good place to explain what the division / department commit to this CDA

"As Division Chief of Digestive Diseases, I guarantee that Dr. Smartypants will receive 75% protected time to conduct the proposed research for this KL2. She will continue to devote 10% time to clinical duties involving digestive diseases.

The Biomarkers Core in the Department of Medicine will cover all costs in excess of those described in the Research Support budget to allow Dr. Smartypants to complete the proposed aims.

- This description of Biomarkers Core support should be repeated in Budget Justification

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Letters of Support: From Lead Mentor

- Lead mentor and all co-mentors and other key personnel (including advisory committee members) will upload a Letter of Support to the grant portal
- Contents of "Letter of Support"
  - Mentor's qualifications to serve as lead mentor including current federal support
  - Willingness to serve as lead mentor
    - This would include willingness to convene any advisory committee meetings to review progress, etc.
  - Mentor's assessment of candidate
  - Prior trainees the mentor has mentored (including any K or K-equivalent trainees)
  - Brief summary of the applicant's research proposal
  - Brief summary of plans for mentoring and enhancing the research capabilities of the applicant

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Mentor's Letters of Support

This section is (supposed to be) completed by Mentor, etc.

- In the mentor's voice and clearly from the point of view of the mentor – has a distinctly different tone and presentation from your writing.
- Mentor may ask you to 'prepare' the first draft

Work collaboratively with the mentor on this section. This is YOUR proposal.

THESE ARE NOT LETTERS OF RECOMMENDATION

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Planning the Mentor's Letters of Support

1. What format will your mentoring take – Mentoring team, multiple independent contributors to your training, single mentor or mentor and multiple co-mentors, etc.
2. The Mentor's section must complement and expand upon your *Training Activities During the Award Period* in the Candidate Section
3. The mentor describes all relevant areas of expertise and how the mentor's background and current research agenda relate SPECIFICALLY to your research plan and career goals.
4. Strike a balance between describing the Mentor's achievements and discussing your training.
   - *"Dr. Smith appears to be highly qualified to serve as a mentor, but it is not clear from her statement exactly how the candidate's career development will be fostered."*

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TIP: Create a template for your mentor

- Organize main mentor's section to reflect these main points
- Copy/paste all directions from KL2 / K12 RFA for each bullet point
- Review and include the "Review Criteria" from the NIH K FOA to get a sense of what reviewers are looking for
- Statements of support and biosketches are required for each
  - Consultant
  - Collaborator
  - Contributor

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Mentor's Letters of Support: Objective

Overall Objective of this section: How the K award will enhance the development of the candidate's research career – this defines the CDA. *You cannot be funded with a lukewarm Mentor's section no matter how accomplished the mentor may be.*

There are 5 points that must be addressed (from the RFA):

1. Willingness to serve as lead mentor
   - This would include willingness to convene any advisory committee meetings to review progress, etc.
2. Mentor's assessment of candidate
   - *Brief* 'open' letter of recommendation (very brief) stating why the KL2 is a good match for you
3. Prior trainees the mentor has mentored (including any K or similar trainees)
4. Brief summary of the applicant's research proposal
5. Brief summary of **plans for mentoring** and enhancing the research capabilities of the applicant

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Key Points to include:

- This section must be very specific and about you and your current specific aims. YOUR NAME MUST BE MENTIONED OVER AND OVER AGAIN. Do not let this be VAGUE/GENERIC
  - What is the plan for attending scientific meetings, lab responsibilities, seminars?
  - What are the expectations for publications?
  - How will you be trained or mentored in writing, authorship, grant writing, etc.?
- Have the mentor refer to your aims and speak about the science
- This is a good place for the Mentor to introduce the Advisory Team or other co-mentor and/or Consultants, Contributors
- Relationship with all co-mentors, advisors, collaborators in training you (e.g., relationship with Advisory Team)
- Make clear what aspects of the proposed research are for the candidate to take with him/her when he/she transitions to independence – very important for mentored CDA proposals
- Financial resources available to you (the candidate), mentor's other support, departmental $$ to cover the balance
  - Materials, animals, tech support, recruitment of patients, expensive analyses
  - *I [i.e., the mentor] have a funded R01 through 2026 that will cover a laboratory technician to assist Dr. Brain with the cell cultures necessary for this proposed research.*

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- What exactly will the mentor do to train you in the proposed science described in the specific aims?
  - Hands on laboratory training or training in mentor's area of expertise
  - Access and availability to resources (space, technicians,...)
  - Access to patients or data sets
  - Commitment to meetings with you - how will communication occur?
- How will you be trained to conduct presentations, attend certification for responsible conduct of research
- How will you be supported/mentored to prepare the NIH K (or similar)?
- Describe the mentoring activities/tasks that will help you with the transition to becoming an independent scientist:
  - Evaluation protocol – e.g., twice yearly reviews / progress reports
  - Promotion issues
  - Lab leadership issues – team leadership, training of students
  - Publications – discussed strategies, goals, deadlines
  - Grant preparation – name the opportunities

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Letters of Support: Consultants and Collaborators (up to 5 Advisory Committee member slots)

- Work with your mentor on the selection of the rest of the team
- An *Advisory Committee* is desirable especially if it contains people who will work with you on the NIH K as well
  - These can be also called consultants / collaborators
  - The best layout of the team is up to you
- What will each of these people do to train you in a specific skill (use of equipment, special assay) or provide you with (ongoing recruitment platform, biospecimens, datasets or registry data)?
- Consultants/collaborators can apply to only 1 aim or 1 experiment or one skill
- Biostatistical consultation can be hired but be careful that you are not missing out on a legitimate training experience
  - - better to have mentored biostatistician training - explain fully the data analysis training goals

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Criticism of vagueness in describing work with an outside collaborator (poor score)

"It seems unreasonable that all the experiments described in Aims 1 and 2A can be completed by visiting Dr. Smith's lab in Boston '4-5 times over 2 years'."

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Better, with more detail (excellent score):

"Dr. Gross will participate in training for 6 weeks in May 2011 in my lab at MIT's Biomatrix and Vector Productions program. I and my staff will provide hands-on training to Dr. Gross in methods to produce vector C which is the basis for specific aim 3 in the proposed K01. All laboratory equipment and supplies will be provided by me. I will also be available for as needed consultation by phone and email for the duration of the award with Dr. Gross and the Advisory Team on proper analytic procedures and trouble shooting after the candidate returns to Emory.

I am particularly interested in Dr. Gross' aims because ……

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Research Plan Section

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New Criteria for Rigor and Reproducibility

- **Enhancing Reproducibility through Rigor and Transparency**
  https://grants.nih.gov/policy/reproducibility/index.htm

Notice Number: NOT-OD-16-012

See my folder on Dropbox

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Research Plan

Specific Aims – limited to 1 page, not part of 12

Research Strategy – part of the12 pages that includes Candidate section

a) **Significance**
b) **Innovation**
c) **Approach**

Bibliography and References Cited are at the end (not part of page limit)

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Research Plan: General Writing Considerations

- Pick a presentation style and keep it consistent throughout (e.g., font, underlining, italics, figure and table formatting, etc.)
- Subheadings are good - helps you and the reader stay focused; makes it easier on the eye
- Clear, concise language – nothing extraneous, everything in the right section, all points towards the Research Plan of Career Development Award recipient
- Not an R01 – language in narrative can refer to new training activities, you can write the entire proposal in the 1st person

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Specific Aims (1 page maximum): Traditional format and presentation

1. Collect many copies of Specific Aims pages from all types of science and study them
2. Typically, there is an introductory section followed by a listing of the aims.
3. Goal is to be succinct and compelling – SELL your idea!
4. This is your first chance to engage your reader in the Research Strategy - **make an impact!**
   - May be the only section that the rest of the reviewers read
   - Work on this repeatedly until nearly the very end
   - **Get lots of very high-level feedback on this page (you may have to have 20 drafts!)**

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Key issues for the Specific Aims page

- KL2 RFA http://georgiactsa.org/training/kl2/index.html states (under Additional Information): An investigator initiated, *hypothesis driven proposal with specific aims* will be developed by each trainee. Research proposal must have a "*human component*," i.e., interaction with human subjects or specimens obtained from identifiable humans. This will be initially outlined in the application submitted by candidates for the program and will be further refined after enrollment in the KL2. If the research project involves a clinical trial, per NIH rules, ONLY clinical trials through the end of Phase IIA are eligible.
- BIRCWH K12 RFA states: Scholars will formulate and execute an interdisciplinary research plan relevant to sex, gender, and women's health, with an emphasis on (but not limited to) communicable disease
  - http://www.bircwh.emory.edu/index.html

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From the Specific Aims page, a reviewer must learn: *why is this science important?*

- Make a connection with the mission of the funder
  - your funder in this case will be the GA CTSA or BIRCWH
- The review committee will be generalists
- Make a brief introduction/overview of your methodology
  - Maybe include what have you done to date; notable findings?
  - Any notable, novel, cutting-edge, interdisciplinary aspects?
- How will your findings add to the body of knowledge?
  - WHY is this important? (don't take this for granted – reviewers may be naïve)
- My pet peeve: The lack of research on a topic is not a sufficient scientific justification for asking for funds. Lots of things are unknown.

"is unknown" ≠ scientific rationale

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From the SA page the reviewer must learn: *what will you have when the grant is over?*

Deliverables don't have to be earth-shattering.
Rather, they must:

- Offer a new, expanded direction in your work (something that will clearly lead to the NIH K23 or similar)
- You will have generated decent preliminary scientific support for your NIH K aims
- Be scientifically important, in context, and appeal to the funder
- Have operationally-defined outcomes; *Primary outcome* must be crystal clear – this will help with concerns about lacking 'research focus'

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Specific Aims (1 page; standard NIH format)

…introductory paragraphs…

Hypothesis: State an overriding hypothesis (optional)
Aim 1. .....
Hypothesis 1. .....

Aim 2. .....
Hypothesis 2. .....
Training Opportunity: a brief statement to link your training to the aims per se

- Do you have too many aims?
- Are they logically interrelated?
- Are subsequent aims dependent on successful outcome of preceding aims? (bad idea)
- Do they belong in the same proposal?
- *Most proposals are overly ambitious.*

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KL2 (funded) Specific Aims:

Aim 1: To develop an electronic decision support tool to communicate estimated risks of poor health outcomes for dialysis vs. kidney transplantation. There are three objectives for this aim:

1) To develop and validate predictive models for 3-year mortality for three treatment options: a) dialysis, b) deceased donor (DD) transplant, and c) living donor (LD) transplant.
2) To develop and validate predictive models for length of stay for 1) dialysis, b) DD transplant and c) LD transplant.
3) To translate these predictive models into a decision support tool (i.e., iPad App).

Aim 2: To determine the feasibility of implementing the decision support tool among a metro-Atlanta dialysis patient population. Our primary objective of this feasibility study is to gather preliminary data to inform a future, randomized study of the tool in a metro-Atlanta dialysis population to improve outcomes.

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K23 (funded)

AIM 1: To determine the pharmacokinetics of levofloxacin (LEV) and capreomycin (CAP) in patients with MDR-TB including the examination of drug levels in plasma, pulmonary tissue, and tuberculous cavitary lung among patients undergoing adjunctive surgical therapy.
Hypotheses: LEV and CM levels will be lower inside tuberculous cavitary lesions compared to plasma, and non-cavitary lung samples due to xxx. Utilizing a cohort of MDR-TB patients undergoing adjunctive surgery and an innovative microdialysis method we will be the first group to assess SLD levels among various compartments including within pulmonary cavities, the site of the highest concentration of *Mycobacterium tuberculosis* (MTB). *Training will include coursework in pharmacology, learning the technique of microdialysis, and practical experience in pharmacology research.*

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Example of Inter-dependent Aims

To test our hypotheses, we propose the following **3 Specific Aims:**

Aim 1. To determine if patients with chronic renal failure (CRF) have an exaggerated sympathetic response during exercise.

Aim 2. Test a pilot therapy of BH4 for patients with an exaggerated sympathetic response during exercise.

Aim 3. In patients with a good treatment response to therapy, determine if there is improvement in resting and exercise-induced sympathetic over-activity, endothelial dysfunction, and oxidative stress.

Consider:
- *Why are these aims inter-dependent?*
- *Is this a good strategy?*

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Example of Independent Aims (K23)

To test our hypotheses, we propose the following **3 Specific Aims:**

Aim 1. To determine if patients with chronic renal failure (CRF) have an exaggerated sympathetic response during exercise.

Aim 2. To determine if the exaggerated sympathetic response during exercise is due to: a) impaired NO-mediated vasodilatation during exercise, and b) exaggerated increases in exercise-induced oxidative stress.

Aim 3. To determine if short-term treatment with BH4 will improve both resting and exercise-induced sympathetic over-activity, endothelial dysfunction, and oxidative stress in patients with CRF.

This demonstrates:

- *You will learn something interesting for each aim.*
- *Each aim could be a single aim small grant*
- *Each subsequent aim (i.e., Aims 2 and 3) ARE NOT dependent on an anticipated outcome from Aim 1*
- *These kinds of aims require strong preliminary data*

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Each Aim should yield interesting findings

- All aims can study the same subjects or different subjects (be clear)
- You should be able to test hypotheses (or conduct the research) for each aim regardless of the outcome of the other aims
- Being able to conduct Aims 2 and 3 cannot be dependent on an anticipated outcome from Aim 1
  - Unless you have very compelling preliminary data for what you anticipate you will find in Aim 1 (i.e., Aim 1 is a replication of previous work),
  - You might have preliminary data from a similar patient sample. If you have a good scientific rationale, you can use these data (from a different patient group) to support your new proposed aims.
  - Sometimes you'll move from evidence in animals to humans – be clear about possible pitfalls / limitations

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Specific Aims (KL2)

Specific Aim 1. To test the hypothesis that the risk of NEC is greater in VLBW infants exposed to RBC transfusion compared to unexposed VLBW infants.
Rationale: Exposure to RBC transfusion has been associated with NEC, although this association may be confounded by inadequate control for illness severity and enteral feeding in prior studies. A prospective cohort study controlling for known confounders including illness severity and enteral feeding and monitoring for the development of NEC following exposure to RBC transfusion will allow us to:

A) Determine the relative risk of NEC in VLBW infants exposed to RBC transfusion compared to unexposed VLBW infants *(primary objective)*.
B) Estimate the incidence of NEC within 48 hours of exposure to RBC transfusion in VLBW infants.
C) Estimate the risk of severe anemia (hemoglobin <8 mg/dL) on the subsequent development of NEC before and after controlling for RBC transfusion exposure.

Specific Aim 2. To test the hypothesis that an increased duration of RBC storage age between irradiation and transfusion is associated with a greater risk of TR-NEC in transfused VLBW infants.
Rationale: Deterioration of RBCs after prolonged storage has been associated with detrimental effects in transfused patients and irradiation can accelerate the RBC storage lesion. We will measure each transfusion episode, including duration from RBC irradiation to transfusion, in order to:

A) Determine the relative risk of TR-NEC in VLBW infants transfused with RBCs stored beyond 5 days after irradiation compared to infants receiving RBCs stored ≤ 5 days after irradiation *(primary objective)*.
B) Evaluate the interaction between severe anemia and transfusion of RBCs stored beyond 5 days after irradiation on the risk of TR-NEC.
C) Estimate the risk of TR-NEC in transfused VLBW infants receiving repeat donor transfusions and compare this to those receiving single donor transfusions.

Notes:
- NEC = necrotizing enterocolitis – leading cause of neonatal morbidity and mortality among premature infants; poorly understood pathogenesis; complicated by transfusions which are common in premature infants because they have anemia.
- This is an observational cohort study with repeated measures over time.
- Challenging data collection and data management tasks.

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OVERALL IMPACT = SO WHAT factor

- After reading the first 5 sentences of the introductory narrative of the SA, the reader should think - ***wow, tell me more***
- If the reader wants to say ***SO WHAT*** to this intro, think about editing
- Can you state the real-world relevance of your findings?
  - Measure therapeutic effectiveness
  - Identify drug targets
  - Change in standard of care or treatment guidelines

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NIH advice for writing the research plan

Please read these:

https://www.nimh.nih.gov/funding/grant-writing-and-application-process/common-mistakes-in-writing-applications.shtml

https://www.niaid.nih.gov/grants-contracts/write-research-plan

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RESEARCH STRATEGY

a) *Significance*

b) *Innovation*

c) *Approach*

- For the KL2 and NIH K, you get up to 12 pages to write the Candidate section + this Research Strategy section
- Usually, I see 4-5 pages for Candidate, and the rest for research
- You get the equivalent of 12 pages of writing (so you can have unused white space – e.g., 4.5 + 7.5 pages)

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Significance

- Explain the importance of the problem or critical barrier to progress in the field 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.
- Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.
- **This should not be a literature review but rather a synthesis of the relevant literature with an eye to *rigor of prior research.***

49

Significance Versus Overall Impact

- Review handout posted on Dropbox to get good ideas about being clear in grant writing

50

When reading the Significance, the reviewer is thinking .....

- What would be the greatest potential contribution of this work were you to get the funds and succeed in your work?
- How would your findings contribute to the field?
- This section motivates the reviewer to think "*Tell me more*".
- Writing style must be engaging. The length will depend on many factors.
- Subheaders can be very effective in conveying an 'argument' or persuasive case and in a short presentation can be very helpful in forcing you to synthesize quickly and get to your point.
- What is your 'case'?

51

Using subheaders in Significance to convey your 'case'

SIGNIFICANCE

Critical Barriers to Eye Examination in the Emergency Department

Technical Improvements to the Funduscopic Exam

Telemedicine in Neuro-ophthalmology of the Future

52

RESEARCH STRATEGY

A. Significance

A.1. Kidney disease is a substantial public health problem in the Southeastern US. Kidney transplantation is the optimal treatment for ESRD patients…….

A.2. Racial disparities exist in access to optimal treatment for ESRD patients.

A.3. AA ESRD patients are less likely to be informed of kidney transplantation.

A.4. Patients who are most at risk for poor outcomes have the greatest difficulty in accessing health information.

A.5. Critically important treatment decisions are often made without evidence-based information about a patient's prognosis.

A.6. Shared decision making through decision support tools can increase patient involvement in the health care decision making process, leading to better health outcomes.

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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.

- *WORDS IN RED ARE GREAT GRANT WRITING WORDS*

54

INNOVATION

This application is proposing the first prospective, multicenter study to investigate the epidemiology of TR-NEC. An immense strength of this study is the use of the TT-CMV birth cohort, which has detailed data collection of the blood bank processing and timing of each RBC transfusion exposure. As prior studies have been retrospective with inadequate measure of explanatory variables and control of confounding variables, there is a significant potential for bias in interpreting the factors associated with an increased risk of NEC following RBC exposure. This potential for bias was underscored in a recent meta-analysis of twelve studies (including 5 abstracts) reporting an association between transfusion and NEC in which the authors emphasized the critical need for prospective studies that investigate all transfusion episodes in neonates with a primary endpoint of NEC[9]. This proposed study, through the use of the TT-CMV study cohort, will allow the investigators the unique opportunity to systematically and rigorously follow all enrolled VLBW infants for the primary endpoint of NEC. As a result, this study will address the significant knowledge gaps that exist regarding neonatal RBC transfusion practice and the contribution of RBC transfusion to the development of NEC. **Data generated from this study will be directly relevant to designing prevention strategies for TR-NEC, including studies aimed at determining the optimal lower hemoglobin thresholds for transfusion and the safe duration of RBC storage between irradiation and transfusion in premature infants.**

Notes:
- TR-NEC = transfusion-related necrotizing
- TT-CMV birth cohort – name of the database
- VLBW = very low birth weight
- RBC = red blood cells

55

Innovation (KL2)

Figure 2. Clinical and Translational Framework for Research

56

INNOVATION

1) Research questions and hypotheses that have never been clinically tested:

2) Studying a unique patient population:

3) Utilizing advanced technologies in an innovative fashion:

57

APPROACH

- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project.
  - Describe plans to address weaknesses in the rigor of the prior research that serves as the key support for the proposed 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.
  - Resources and tools for rigorous experimental design can be found at the **Enhancing Reproducibility through Rigor and Transparency website**.

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APPROACH (continued)

- 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

59

APPROACH (continued)

- 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.

60

APPROACH (continued)

Preliminary Studies for New Applications:

- For new applications, include information on preliminary studies.
- Discuss the 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.*

61

Presenting Preliminary Data

- Use of first person is appropriate; has an element of 'essay' writing.
- Use a single consecutive numbering system for figures and tables from beginning to end of document.
  - For example, if you have a Table 1 in the Candidate section, the next table in the Research Strategy would be Table 2.
- Use a consistent citation system
- Use dates when appropriate
  - *During my clinical fellowship from 2008-2010, …*
- There should be an important rationale for every finding / figure / table.
  - *These now published preliminary data (Figure 1) strongly suggest that vitamin D plays a crucial role in macrophage recycling of iron by increasing expression of ferroportin.*
  - *Therefore, these data, as shown in Figure 5, give us confidence that our proposed vitamin D treatment regimen will be safe and efficacious in…..*

62

Help Reviewers "get" what you are doing

- Name names and places to remind reviewer of new training or any work off location
  - Remember, this is a local Emory review committee

C. PRELIMINARY DATA SUPPORTING THIS APPLICATION: The following work has allowed me to develop important experience conducting clinical research in the Republic of Georgia, form successful research collaborations, and generated the research hypotheses for the K23 projects in this proposal.

1) ……

2) *Surgery for patients with highly drug-resistant TB: A report of 82 patients (presented at World Union Conference, Lille, October 2011)*: We reported a favorable outcome rate of 81% in a treatment outcome study for pulmonary M/XDR-TB patients (31% XDR) with cavitary disease undergoing adjunctive surgery in Tbilisi, Georgia. These results provide further evidence that TB cavitary lesions may adversely affect medical treatment. This study was carried out with Dr. Sergo Vashakidze, a collaborator for this proposal.

63

Where do I put Preliminary Data?

- Where it makes the most sense
- NIH grant proposals used to have a dedicated section for Preliminary Studies – not anymore
- If your innovative preliminary data are driving the aims, use your preliminary data in **Innovation**
- If your exciting, highly relevant finding is driving the aims, show these findings in **Significance**
- Otherwise, preliminary data typically support methods, feasibility of the approach in your hands, and directly support the hypotheses → **Approach**

64

APPROACH : Recommendations for Organization

- Many acceptable outline formats
- Study the examples I've provided
- Must be very concise – there is not a lot of room for lengthy research plans
- What are reviewers looking for?
  - Preliminary studies pertinent to this application
  - Overall strategy, methodology and analyses
  - Potential problems, alternative strategies and benchmarks for success

65

Approach

Specific Aim 1. (restate here exactly as in Spec Aims page)
Design
Preliminary Data to Support Aim 1. (if this is the best place)
Methods for Aim 1.
- *any previous work to support innovation in methods*

Data Collection and Management Plan
Analytic Plan
Potential Pitfalls/Alternative Strategies
Benchmarks for Success = anticipated outcomes = how do you know if you've achieved your goals?

66

Clinical or Patient-focused Approach

1. **Study Overview and Experimental Design**
2. **Specific Aim 1.** (*restate exactly from Specific Aims*)
   - 2a. Hypothesis
   - 2b. Rationale
3. **Patient/Participant Recruitment**
   - Test Participant Overview.
   - Inclusion/Exclusion Criteria.
   - Control Participant Overview.
   - Consent Procedures.
   - Limitations.

67

Clinical/Patient Focused (cont.)

4. **Data Collection Procedures**
5. **Biological Samples**
6. **Intervention/Treatment Trial**
7. **Power Calculations and Sample Size**
8. **Data Analysis and Statistical Methods**
9. **Expected Outcomes/Alternative Considerations ****
10. **Potential Pitfalls and Limitations ****

*** It is especially impressive that the candidate has critically discussed the alternative approaches and potential pitfalls to the experimental approach.*

68

Rigor and Reproducibility including Sex as a Biological Variable (SABV)

- Required discussion of this issue in all NIH grants including the KL2/K12

69

Remind reader that this is a K award proposal

- Throughout *Research Strategy*, you can "personalize" (use first person)
- Refer to mentors, collaborators, etc. by name
- Remind reader where new, career-enhancing experience will be gained
- Use a subheader: New Training or Training Opportunity for each aim (possibly – if it is warranted)
  - Remind reader where you will train to learn skills, have new responsibilities – they have read the candidate section but they could use a reminder.
- Link procedures to relevant work you've done in the past
- *Convince reviewer that proposed work can be completed in the allotted time requested and for the budget described*

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Grant Writing Basics

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Terms/phrases to avoid

Expressions with no clear limits	Words of personal judgment	Causal colorful language	Use with caution as transitions but never as fillers
a lot	assuredly	agree to disagree	in effect
fairly	beautiful	bottom line	indeed
really	luckily	brute force	basically
slightly	obviously	few and far between	in terms of
sort of	sadly	okay	it goes without saying
	fortuitous	sketchy	
	intriguing	tip of the iceberg	

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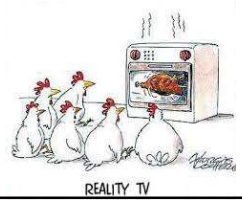
Can you deconstruct a paragraph?

Distracting	Useful
• Tangent – material that is not directly related	•Opening/introductory statement or lead statement
• Digression – going off in a different direction than the topic	•Factual support •Examples of the focal point
• Fluff/filler e.g., As part of this research, we plan to fulfill our mission of recruiting the maximum number of patients possible.	•Supporting data/findings e.g., We will enroll 10 patients per week which will be feasible based on the current census of more than 100 emergency room visits/week.
• Vague	•Implications of the facts presented
• Emotional/Jargon/Colloquial	•Transition
• Passive/indirect	•Summary statement
• Redundant	•Header/Subheader

73

The Reality Show: Summary Sheets (aka 'pink sheets')



74

Learning from Summary Sheet comments

- **Reviewers can be:**
  - fair and supportive of your research and your career
  - very generous with comments and suggestions for your project
  - overly picky about your science
  - have an ax to grind
  - harsh and inappropriate
- **Your job is to be:**
  - professional and courteous
  - an excellent writer
  - create no distractions in the document (no typos, careless errors, inconsistencies, omissions)
  - let the debate center around the science

75

Candidate

Productivity Issues (i.e., publications):

…… *This candidate's productivity is rather modest.*
…… *The candidate's publications have been largely restricted to book chapters and review articles.*

- Authorship in peer reviewed journals (and at least >1 first authorship in science related to your field) demonstrates your dedication to an academic career in research and your track record to date.
- Make your biosketch crystal clear – your goals, your skills, your desire to have a career in academic research
  - What should I do if I have relatively few published papers?
    - Include a training goal for beefing up your writing productivity!

76

Candidate

The applicant's passion for both research and HIV-related research, specifically looking at the bone disease complications of HIV disease and therapy have been consistent throughout her short career.

Training plan by year, as explained in a table is very clear and is feasible.

77

Candidate

Proposal has numerous typographical errors and errors in figures which suggests that mentor involvement in the proposal development was not optimal.

78

Mentor

While the candidate will convene a highly skilled advisory group, this does not substitute for needs of mentorship in transfusion medicine and in single cell analytic methods.

- The mentoring must speak directly to the research proposed as well as the career path of the candidate. Be sure the role of the mentor is described as one who will assist/train you in the nuts and bolts of the challenge/training areas, not only provide a resource for the larger theoretical scientific area.
- Beware of being misconstrued that your training will occur simply by 'geographic proximity mentoring'.
- **DANGER**: Big name person vs. actual description of hands-on mentoring.

79

Mentor

I am concerned that Dr. Gross has been listed to meet with the candidate on a monthly basis to provide a mini-course in endothelial dysfunction and circulating EPC activity in the IFCA lab. This is not mentioned in Dr. Gross' supporting letter of the candidate.

- Consistency between what you state the mentor will be doing and what the mentor states he/she will be doing is crucial.
- Many of these reviewers are mentors and sensitive to this issue.
- Inconsistencies mean sloppiness, lack of communication, lack of proof-reading.

80

Mentor

…… Primary mentors have excellent history of previous mentoring junior faculty and the co-mentor is federally funded

…… Incredibly strong mentorship with a very specific plan from his primary mentors.

…… Primary mentor is clearly enthusiastic about his mentorship role and has partnered with the candidate's previous mentor for a strong approach.

81

Career Development Plan

….. The applicant's career development plan is weakened by an under-specified long-term goal. What is his main career objective? The reason that it is important to specify the long-term career objectives is that it may modify the ideal career development plan.

- Explicitly state your long-term career aspirations – "*My long term goal is to have an academic career as an independently funded neuropathologist specializing in cellular models of axonal degeneration and therapy development for neurodegenerative diseases.*"
- Be bold - think 5 -10 years out from now.
- Exude confidence - this is the best job anyone could ever have.

82

Career Development Plan

….. What hands-on research experience will actually be provided?

- What NEW skills will you have at the end of this CDA?
- Where along the research timeline will you acquire these NEW skills and WHO will teach them to you?
- You may want to repeat this information in different sections of the proposal.

83

Career Development Plan

This is the best career development plan I've ever read!

84

Letters of Support

….. *The chair's letter does not explicitly state that the applicant will devote 75% of her time to the project.*

→ Redundancy on these points is GOOD.

85

Specific Aims

Descriptive vs. mechanistic focus

- Are there hypotheses that truly advance our understanding of the field? Is this clear and well-stated in the Specific Aims section?
- Descriptive work must be well-justified for what it will yield going forward. What are the next steps after discovery?

…… *The experiments as designed would not yield information as to molecular mediators or points of potential intervention that could drive further explorations.*

…… *The highly descriptive nature of the proposed outcomes is a weakness.*

86

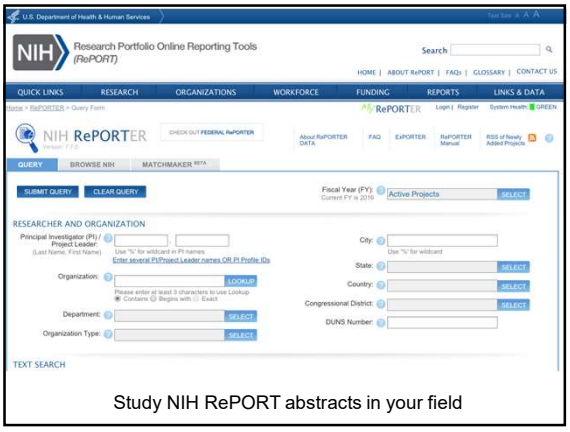
Human Subjects

- Why are you proposing the population you've chosen?
- Is this the best organism for this research question and have you defended this adequately?
- What is the relevance of your chosen samples/subjects to state of the research - why might you be omitting children, omitting males or females, omitting elderly?
- What is the availability and likelihood of getting data from these subjects, tissue, animals, etc.?
- Do you need to present a power calculation to justify sample size, or are you proposing a small (underpowered) pilot study to establish feasibility?

87

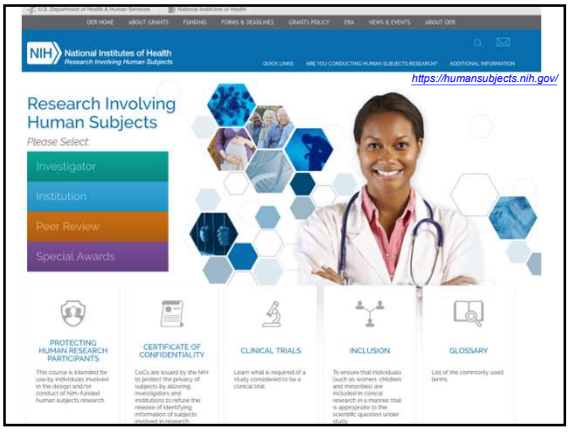
For Grant Writing

88



Study NIH RePORT abstracts in your field

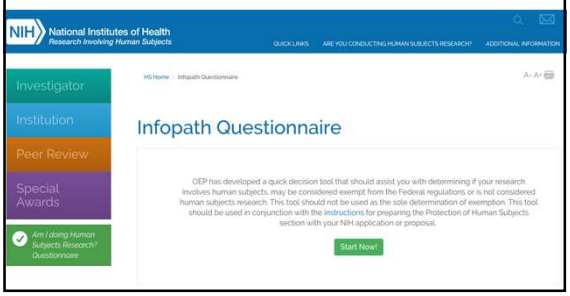
89



90

NIH RESOURCES posted on Dropbox

https://humansubjects.nih.gov/clinical-trials
https://humansubjects.nih.gov/questionnaire
http://grants.nih.gov/grants/funding/424/SupplementalInstructions.pdf



91

https://humansubjects.nih.gov/sites/hs/public_files/preparing_the_human_subjects_section_0.pdf

92

Excellent NIH Grant Writing Resource

https://grants.nih.gov/grants/oer.htm

93

https://grants.nih.gov/grants/plain_language.htm

Review: Plain Language in the NIH Applications: Before and After Examples

94

- ✓ Think critically
- ✓ Complete all sections carefully - avoid careless errors
- ✓ Have others read your work - ask for critical comments not just a cursory review
- ✓ Get feedback on the research plan from experts
- ✓ Review the Mentor's section carefully
- ✓ Build in time to reflect on your own product; read your own work "at an arm's length" (preferably on paper)

95

96