

# NIH Grantsmanship: Methods

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## **D. Research Design and Methods**

Describe the research design conceptual or clinical framework, procedures, and analyses to be used to accomplish the specific aims of the project. Unless addressed separately in Section i, include how the data will be collected, analyzed, and interpreted as well as the data-sharing plan as appropriate. Describe any new methodology and its advantage over existing methodologies. Describe any novel concepts, approaches, tools, or technologies for the proposed studies. Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. As part of this section, provide a tentative sequence or timetable for the project. Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be exercised.

**Although no specific number of pages is recommended for the Research Design and Methods section, be as succinct as possible. There is no requirement that all 25 pages allotted for *items A-D* be used.**

# Methods

- Purpose of the Methods Section:
  - to describe how you will carry out your specific aims.

# Methods: Organization

- As before, section headings should be d.1, d.1.1, d.2 etc.
- Divide into two parts.
  - Individual experiments should follow aims point by point (d.1.1->number of aims).
  - Methods that will be used in multiple aims (imaging techniques, assays, models...) so you don't have to repeat yourself (d.2.1->number of procedures).
- I think you should put the experiments first but some applications have the common methods first.

# Experiments

- Organize each experiment subsection as follows:
  - Specific Aim (verbatim as in the Specific Aims)
  - Hypothesis
  - Rationale (justify the experimental approach taken). More effective if short!
  - Experiment(s)
  - Methods
  - Expected Results

# Experiments

- Experiment subsection continued:
  - Statistical tests including the calculation of sample size.
    - Do you have enough statistical power to find effects if they exist?
    - Use to determine how much data to collect.
    - This is a critical section which often causes an application to fail.

# Design and Methods

- Sample Size/Power Calculations
  - Sample size. The number of patients or animals,  $n$ , required to test a null hypothesis is given by the following equation:

$$n > \left[ \frac{[Z_{2\alpha} + Z_{2\beta}] \sigma}{\delta} \right]^2$$

where  $\alpha$  is the required probability of a Type I error,  $\beta$  is the required probability of a Type II error,  $\delta$ , is the estimated difference between the means of two comparison groups, and  $\sigma$  is the estimated standard deviation of the means in each of the two comparison groups.

# Experiments

- Experiment subsection continued:
  - Limitations
  - Alternatives
    - “State what you expect to find, and then indicate what you will do if you don’t find it, i.e., if your experiment fails [but avoid the use of the word failure!]. This tells the reviewer you’ve thought long and hard about each individual experimental approach.”
    - Limitations and alternatives can go in a separate section (d.3)

# Methods

- **Discuss the limitations** of each approach you are proposing and how they may affect your results and data.
  - Call attention to potential difficulties.
  - Propose alternatives.
- **State what you'll do if results are negative**, how negative findings will also advance the field, and what you'll do next.

[http://www.niaid.nih.gov/ncn/grants/write/write\\_m3a.htm](http://www.niaid.nih.gov/ncn/grants/write/write_m3a.htm)

# Methods

- How much detail?
  - Describe in detail all methods that have not been published.
  - Give a brief overview of methods that have been fully described previously in published articles and cite references.

# Methods

- **Cite references wherever possible.** If a technique is well known, the citation is enough.
- **One caveat: do not give more information than is needed** to state your case. Reviewers will look for flaws and penalize you heavily for them. Don't give them ammunition by including anything in the application you don't plan to do.
- **If your proposal is highly innovative,** you'll need to make a very strong case for why you are challenging the existing paradigm and have data to support your innovative approach. Also read [Be Persuasive, But Be Careful of Being Too Innovative.](#)

[http://www.niaid.nih.gov/ncn/grants/write/write\\_m2.htm](http://www.niaid.nih.gov/ncn/grants/write/write_m2.htm)

# Pictures, Figures and Cartoons

- “It is super helpful to have a cartoon showing the model you are testing. Also, a cartoon for each complicated experiment is very useful. (The best score ever for me was a grant with many cartoons in Methods and just a little text around them.)”<sup>1</sup>

1. Paul Simpson, Cardiology, UCSF

Methods		
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.
Objectives	5	Specific objectives and hypotheses.
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.
Randomization		
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.

**Moher D, et al, The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials, JAMA 285: 1987, 2001**

# Design and Methods: Clinical Studies

- Overview
- Study Sample
- Data Collection Procedures
- Intervention(s)
- Outcome measure(s)
- Data Analysis/Sample Size Calculations

# Design and Methods: Clinical Studies

## (2)

- Description of subjects
  - Inclusion criteria (address biases)
  - Exclusion criteria (well justified)
  - Women, minority, and children inclusion (per NIH)
- Availability of participants.
  - Recruitment plan.
  - Pilot work showing ability to recruit.
  - Data from previous, related studies.

# Design and Methods: Clinical Studies (3)

- Data collection
  - List and define all study variables (perhaps in table)
- Procedures
  - Outline screening and enrollment procedures
  - Describe interviewer training
  - Describe quality assurance procedures

# Design and Methods: Clinical Studies (4)

- Outcome measure(s)
  - Describe or specify each outcome measure
  - Who assesses outcomes?
  - How is blinding achieved/maintained?
  - How is equal surveillance of outcomes assured for all groups?

## Design and Methods: Clinical Studies (5)

- Intervention and Controls (if any)
  - Describe the intervention in detail, including standardized protocols
  - Describe how intervention will be implemented
  - Describe the interventionists, their proficiency and training
  - Describe how adherence is monitored
  - Describe how you will monitor potential sources of “contamination” in the control group.

# Design and Methods: Clinical Studies (6)

- Data Analysis
  - Describe data management procedures
  - Describe analytic approach (intent to treat?)
  - Lay out proposed analyses for each specific aim or hypothesis
  - Discuss alternative strategies considered and why you decided on your approach
  - Discuss how you will handle confounders, missing data, and attrition

# Methods: Organization

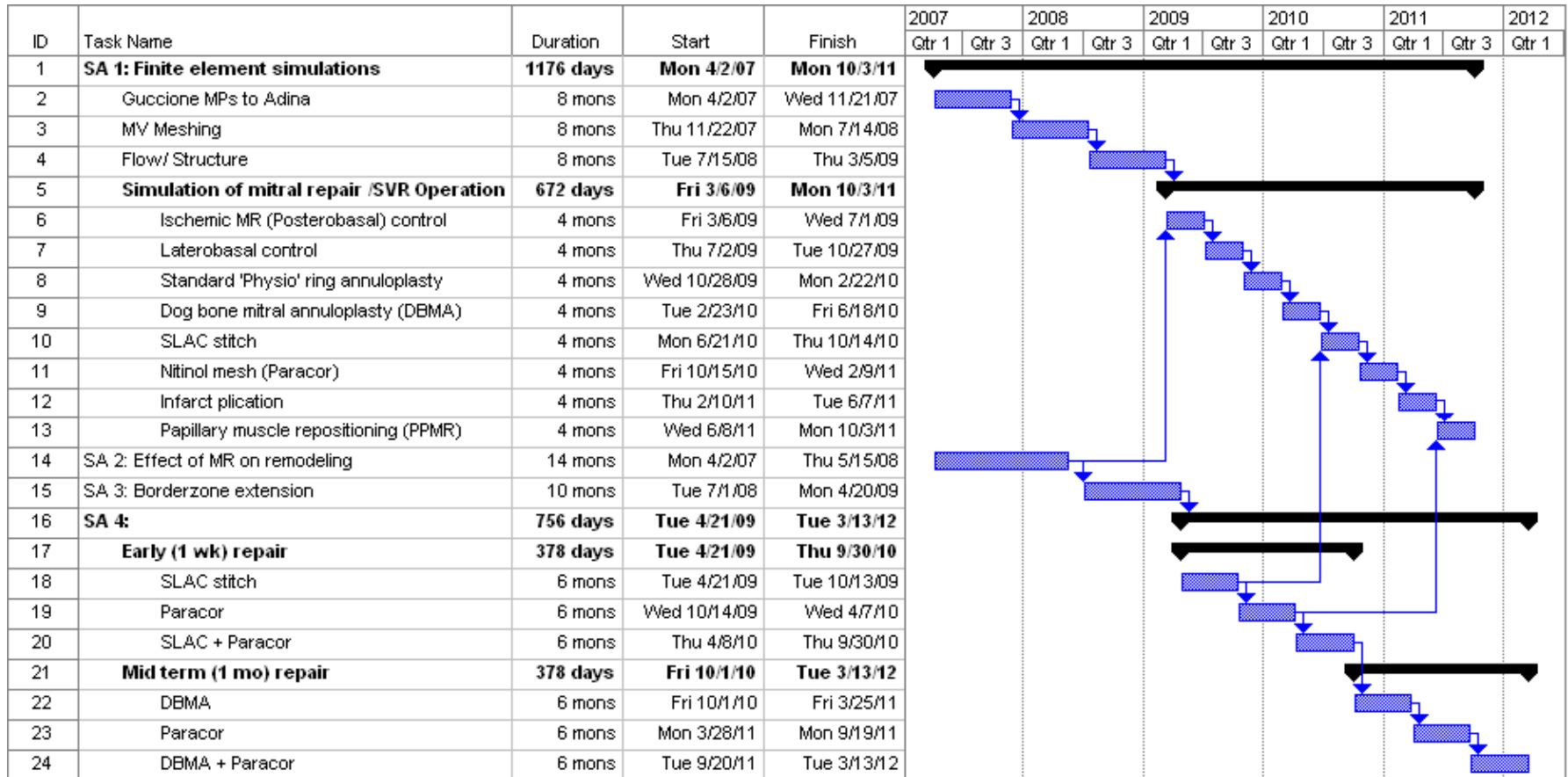
- A timeline usually goes at the end of the list of experiments.

# Simple Timeline Table

	Year 1	Year 2	Year 3	Year 4	Year 5
Course Study	X	X			
Specific Aim 1		X	X	X	
Specific Aim 2				X	X
Specific Aim 3	X	X	X		
Manuscript Submission			X	X	X

# Gantt Chart<sup>1</sup>

## d.1.6 Timetable



The project will take five years to complete, but we expect that the results will lead directly to new work that will continue beyond the time for which support is requested here. All of the computational and experimental techniques required have already been developed.

## **F. Vertebrate Animals.**

**Failure to address the following elements will result in the application being designated as incomplete and it will be grounds for the PHS either to defer the application from the peer review round or to potentially negatively affect the application's priority score.**

Under the Vertebrate Animals heading address the following five points.

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

[http://www.niaid.nih.gov/ncn/clinical/researchanimals/tutorial/answer\\_points\\_vertibrat.htm](http://www.niaid.nih.gov/ncn/clinical/researchanimals/tutorial/answer_points_vertibrat.htm)

# General Comments

- Remember to obtain letters from everyone who agrees to help out indicating that they are aware of the commitment.<sup>1</sup>

1. Kessel D, Chest 130: 296 2006

# AHA Fatal Flaws

- **Problems with experimental approach**
  - Too much unnecessary experimental detail
  - Not enough detail on approaches, especially untested ones
  - Lack of appropriate controls
  - Not directly testing hypothesis
  - Correlative or descriptive data
  - Experiments not directed towards mechanisms
  - No discussion of alternative models or hypotheses
  - No discussion of potential pitfalls
  - No discussion of interpretation of data

