

How to craft the “Approach” section of an R grant application

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Overview

- Preliminary Data
- Study Design
- Sample Size and Power Analysis
- Statistical Methods
- Writing Strategies

Preliminary Data

- Primary Question: “Is there reason to believe that the study hypotheses could be true and is this research team capable of carrying out the study?”

Necessary Elements: Preliminary Data

- Strong and relevant preliminary data key for R01 grants
- Demonstrate:
 - Expertise with assays
 - Novel assays work in patients/samples to be collected
 - Support for hypotheses
- Use figures and tables where possible

Ways to Fail: Preliminary Data

- Insufficient annotation for figures/tables
- Poor data analytic techniques
- Weak support for hypotheses
- Unrealistically strong/naïve preliminary results
- Presenting needle in a haystack results
- Presenting too much preliminary data at expense of rest of the approach

Study Design

- Primary Question: “Is the design of the study appropriate to address the study aims?”

Necessary Elements: Study Design

- What is overall study design (RCT, Cohort study, Case-Control, Cross-sectional, Biomarkers)
- Describe endpoints and clarify, if necessary, how they will be quantified and their measurement scale.
- Describe study population and control groups
- Inclusion/Exclusion Criteria
- Describe all study measures with appropriate measurement process details

Additional Considerations: Study Design

- Describe existing population clearly.
 - Include relevant demographics
 - Include information on prognostic or confounding measures.
- Nothing says that this is a ready to go study better than a clearly defined population that is relevant to the study aims.

Additional Considerations

- Randomization methods for clinical trials
- Collect confounding factors
- How long will follow-up period be?
- Validity and reliability of study measures
- Subject matching?
- Validation of model building either with cross-validation or training-test designs

Ways to Fail: Study Design

- Study population or design doesn't match objectives
- Insufficient time for recruitment and follow-up.
- Lack of clarity with respect to availability of subjects
- Very uninteresting to read technical details of assays that are standard

Sample Size

- Primary Question: “Is the sample size sufficient to give the study the ability to answer the primary study questions?”

Necessary Elements: Sample Size

- Identify study endpoint(s) for all aims.
- Clearly describe sample size for each aim
- For each endpoint:
 - What is the effect of intervention or magnitude of the relationship?
 - How much variability?
 - Level of power?
 - One or two sided test?
 - What is the statistical test used to compute power?

Additional Considerations: Sample Size

- Account for study dropouts
- Account for multiple comparisons (either Bonferroni or False Discovery Rate)
- Often useful to examine sample sizes for a variety of scenarios when uncertainty exists concerning what is to be expected for an endpoint

Ways to Fail: Sample Size

- Sample size calculation does not have sufficient information for a reviewer to replicate
- Sample size calculation does not use relevant preliminary data or methods described in the statistical analysis section.
- Prediction modeling with large number of predictors relative to sample size

Bad Examples

“A previous study in this area recruited 150 subjects and found highly significant results ($p=0.014$), and therefore a similar sample size should be sufficient here.”

“Our lab usually uses 10 mice per group.”

“Sample sizes are not provided because there is no prior information on which to base them.”

“The throughput of the clinic is around 50 patients a year, of whom 10% may refuse to take part in the study. Therefore over the 2 years of the study, the sample size will be 90 patients. “

“It is estimated that for a sample size consisting of 6 animals in each trial and with a tumor volume variance from 0.1 to 1.0 cm³ – that when the difference in the population reaches 0.25, the power will reach 100%.”

Good Examples

“A sample size of 38 in each group will be sufficient to detect a difference of 5 points on the Beck scale of suicidal ideation, assuming a standard deviation of 7.7 points, a power of 80%, assuming a two sided significance level of 5% and a two sample t-test. This number has been increased to 60 per group (total of 120), to allow for a predicted drop-out from treatment of around one third. This difference of 5 points is based on our prior study in which..... ”

“A sample size of 292 babies (146 in each of the treatment and placebo groups) will be sufficient to detect a difference of 16% between groups in the sepsis rate at 14 days, with 80% power. This 16% difference represents the difference between a 50% sepsis rate in the placebo group and a 34% rate in the treatment group. This assumes a Chi-square test with a two sided 0.05 significance level. This estimated difference in sepsis rate is based on the study of Bob et al [ref] in which they observed....”

Statistical Methods

- Primary Question: “Are the statistical methods appropriate for the analysis of the data that will be collected?”

Necessary Elements: Statistical Methods

- Need methods section for each aim.
- Clearly describe analytic strategies for each endpoint.
- Methods should be appropriate for type of variable (ex. categorical, ordinal, count) and study design
- Typically includes inferential testing of endpoints and model building

Additional Considerations: Statistical Methods

- Statistical methods appropriate for sample size (ex. Fisher test vs Chi-square test)
- Include evaluation and validation strategies for regression/prediction models
- Can include model assumption checking methods
- Accounting for missing data

Ways to Fail: Statistical Methods

- Ignoring key confounders or demographic variables.
- Ignoring standard prognostic or predictive measures in models
- Describing software but not ideas/methods

Writing Strategies

- Use the resources and human subjects sections to full effect
 - Can give details of available study population and subject demographics
- Standard experimental methods can be referenced
- Long blocks of text are boring a can often get skimmed.
- Emphasize key points: bold, underline

Writing Strategies

- Graphical displays:
 - Theoretical Framework
 - Experimental Design
 - Aims flowchart
 - Patient characteristics
 - Study measures

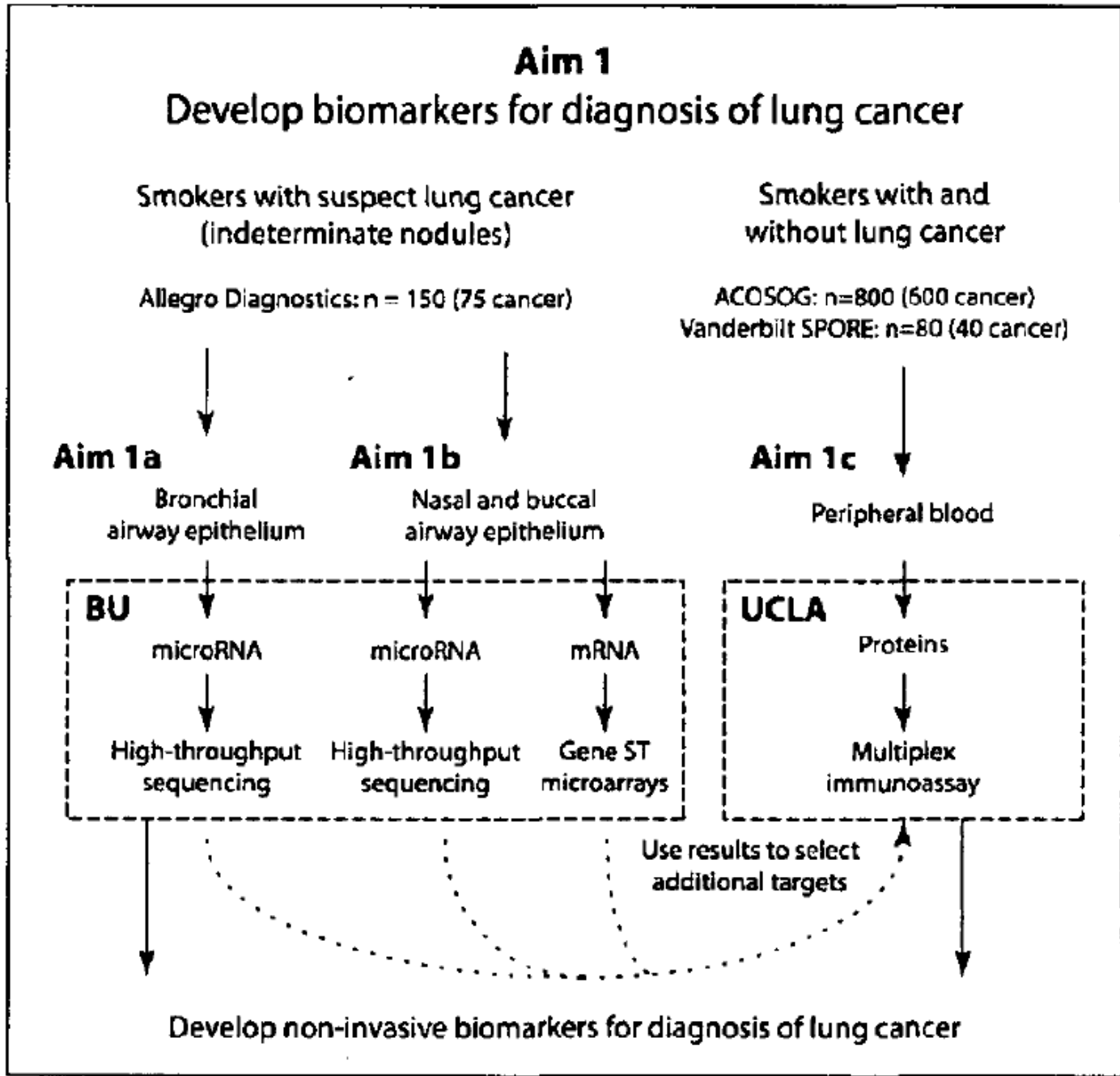


Figure 1. Overview of Aim1

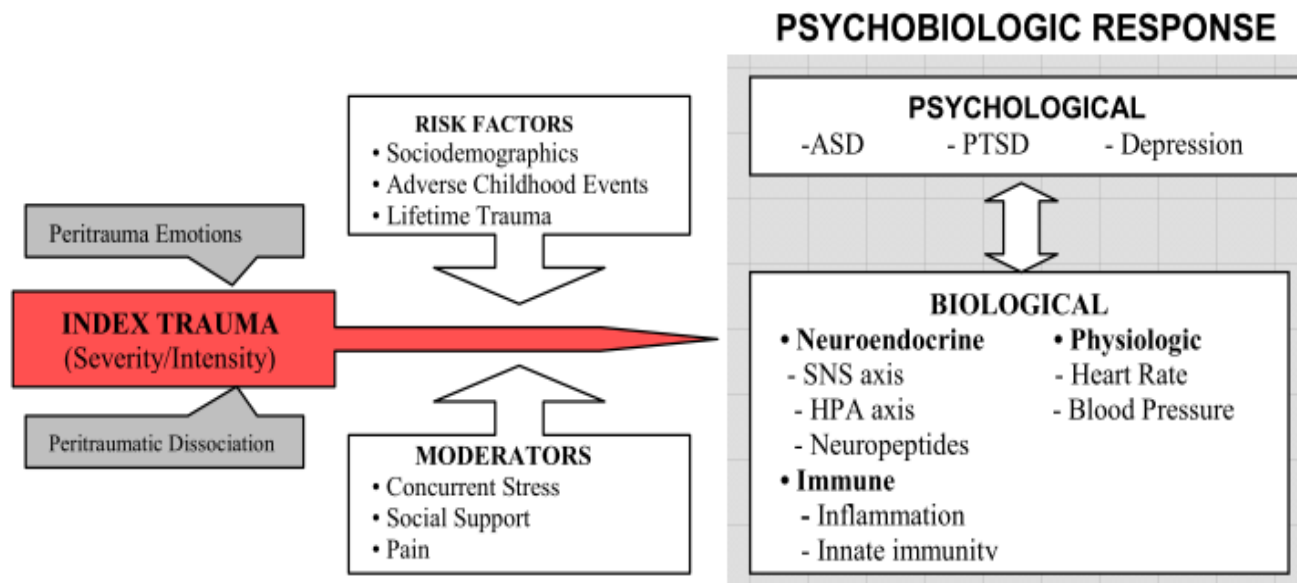


Table 1. Putative stress biomarkers and associated pathways

Biological Pathway	Salivary Biomarker	References
Sympathetic Nervous System (SNS)	<ul style="list-style-type: none"> • α-amylase (sAA) • Chromogranin A (CgA) 	Nater & Rohleder 2009; Chatterton et al. 1996; Soo-Quee Koh & Choon-Huat Koh 2007; Groschl 2008; Robles et al. 2010.
Hypothalamic-Pituitary-Adrenocortical Axis (HPA)	<ul style="list-style-type: none"> • Cortisol • Dehydroepiandrosterone (DHEA and DHEA-S) 	Hellhammer et al. 2009; Handwerker 2009; de Kloet et al. 2006; Maninger et al. 2009; Michaud et al. 2008; Assies et al. 2004; Michael et al. 2000.
Immune	<ul style="list-style-type: none"> • Immunoglobulin A (IgA) • Interleukin-1 (IL-1α) • Interleukin-6 (IL-6) • Tumor necrosis factor (TNF-α) • C-reactive protein (CRP) 	Gill et al. 2008; Segerstrom & Miller 2004; Piazza et al. 2010; Wong 2002; Singh & Rose 2009; McEwen 2007; Herbert & Cohen 1993; Zhang et al. 2009.
Neuropeptides	<ul style="list-style-type: none"> • Substance P • Melatonin 	Parris et al. 1993; Bob & Fedor-Freybergh 2008; Claustrat et al. 2005)

Table 2. Assessments and their administration schedule.

	DOMAIN	MEASURE	ASSESSMENT TIME POINT			
			Hospital Intake	+ 12 days	+ 1 month	+ 5 months
INJURY	1. INDEX TRAUMA					
	1a. Injury Severity	<i>Injury Severity Score</i>	X			
	1b. Peritraumatic Emotions	<i>Peritraumatic Distress Inventory</i> <input type="checkbox"/>	X			
	1c. Peritraumatic Dissociation	<i>RAND-Peritraumatic Dissociative Experiences Questionnaire</i> <input type="checkbox"/>	X			
MODERATORS	2. RISK FACTORS					
	2a. Sociodemographics	<i>TCU Intake Subscale</i> <input type="checkbox"/>	X			
	2b. Childhood Adversity	<i>Adverse Childhood Experiences</i> <input type="checkbox"/>	X			
	2c. Lifetime Trauma	<i>Trauma History Questionnaire</i> <input type="checkbox"/>	X			
	3. MODERATORS					
	3a. Concurrent Stress	<i>Life Experiences Survey</i> <input type="checkbox"/>		X	X	X
	3b. Perceived Social Support	<i>Social Provision Scale</i> <input type="checkbox"/>		X	X	X
	3c. Pain	<i>VRS-PI</i> <input type="checkbox"/>		X	X	X
	3d. Substance Use	<i>Substance Use Inventory</i> <input type="checkbox"/>	X		X	X
	4. Predictive Index	<i>Predictive Screening Index</i> <input type="checkbox"/>		X		
RESPONSE	5. PSYCHOLOGICAL					
	5a. Posttraumatic Stress Disorder	<i>Clinician-Administered PTSD Scale (CAPS)</i>				X
	4b. Depression	<i>Structured Clinical Interview for DSM-IV</i>				X
	6. BIOLOGICAL					
	6a. Physiological	<i>Heart Rate/Blood Pressure</i>		X	X	X
	6b. Neuroendocrine-Immune	<i>Saliva Samples</i>		X	X	X

- CAPI administered

Grant Applications Assistance

- Assistance with preparing grant applications (CTSI)
 - Study Design
 - Data Analysis Protocols
 - Sample Size and Power Analysis
 - Budgeting and Identifying Appropriate Collaborators
 - Core facilities
- Substantial lead time with opportunity for multiple iterations is necessary for high quality grant application assistance: Study Design vs Analysis sections

Final Thoughts

- Consult statistical collaborator for study design and approximate sample size some weeks in advance
- Most successful proposals require multiple iterations of research design sections