Writing Grant Applications

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One Page Summary - Components of Typical Grant Proposal

A. Specific Aims What do you intend to do? [1 page]

1. One paragraph summary of the overall study; purpose, methods, expected outcomes
2. State your hypotheses to be tested – OR - state the research questions to be answered
3. In the aims, state how you will test this hypothesis or answer these questions. What are you going to do to produce the data that will answer the research question/hypothesis?

B. Background & Significance Why is this work important?

Summarize theory and research outcomes leading to the present proposal.

- Clearly define the knowledge gap you will address in this project **(Attack The Gap)**
- Why is this "gap" important to study?
- What will a better understanding of this knowledge gap allow us to do in the future? (benefit)

Discuss the work of other investigators even-handedly, acknowledging important contributions that paved the way for your proposed investigation, as well as identifying limitations in the knowledge base produced by these studies (e.g., aspects of the issue/problem that have not yet been explored)

C. Preliminary Studies What has already been done by your research team?

Describe projects your team has completed that are directly related to this study and which set the stage (e.g., are logical preliminary steps) for this current proposal.

- Describe your published findings. Do not just append copies of articles.
- Graphically display key preliminary data, but also explain these data in the narrative.

D. Research Design and Methods How are you going to do the work?

Begin section D with a project overview. Help the reviewer understand your overall approach to this project by starting section D with an overview that explains the research questions and the design of your study. If appropriate, describe and visualize the conceptual model that communicates the underlying "logic" of how you organized the study and how you propose to conduct the project.

Use the specific aims as the organizing structure for the remainder of section D.

Aim	*Methods*	*Data Collection & Analysis*
Aim # 1	Methods for aim # 1	Data collection & analysis for aim # 1
Aim # 2	Methods for aim # 2	Data collection & analysis for aim # 2
Aim # 3	Methods for aim # 3	Data collection & analysis for aim # 3

Writing Grant Applications

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► Narrative Components of Typical Grant Application

Section	Questions to answer
Description (abstract)	What is the overall purpose & methodology?
Research Plan	
A. Specific aims	What do you intend to do? (what are your objectives?)
B. Background & significance	* Why is the work important? * What "knowledge gap" does project address? * What is innovative/unique about your project?
C. Preliminary studies	What has already been done **by your team**?
D. Research design & methods	* What is the underlying model/concept? * How are you going to do the work? **W W H W W**
Budget justification	* What personnel are needed & why? * How much time will personnel devote? * What supplies/equipment are needed & why?

Who? What? How? When? Where?

Warm-Up Exercise: Write 3 "red flags" (problems, warning signals) that may lead reviewers to question the merit of a grant application.

► Examples of usually fatal red flags

- Unclear project description (abstract) and/or specific aims (objectives)
- Hypothesis not meaningful, significant or timely
- Lack of underlying conceptual framework/model (or poorly articulated model)
- PI lacks expertise or experience in the topic area
- Methods are not state-of-the-art
- Inappropriate research design or statistical methods

What annoys reviewers?

A few items on my list

- Moving targets … "detail drift" …. sliding precision
- SAT – vagueness; camouflaged writing (SAT = Stop And Think)
- Unsupported assertions, contentions & observations (show me the evidence!)
- Surprises – "Oh BTW, we're also going to implement …"
- Disappearing components – "Oh, never mind …"

When writing your grant application, remember .....

- **Some reviewers will not read your application completely**
- **Some reviewers will only read the abstract & specific aims**
- **Many reviewers will not be familiar with your area of research**
- **No reviewer will understand the project as well as you do**
- **Reviewers will misinterpret/forget proposal elements**

But you will not be there to resolve confusion, answer questions and fill in missing details.

When writing your grant application, remember .....

You are competing for the reviewer's Attention. Do not assume that you have the reviewer's attention. You have to earn it!

► PHS 398 Application (NIH)

The PHS 398 is the most commonly used application for Public Health Service grants including solicited RFA's and RFP's and also for unsolicited grant applications initiated by independent investigators.

RFA (request for application) = agency solicits applications to study a specific issue or problem

RFP (request for proposal) = agency solicits proposals to perform specified tasks (contract)

► Narrative Components of Grant Applications

Section	Questions to answer
Description (abstract)	What is the overall purpose & methodology?
Research Plan	
A. Specific aims	What do you intend to do? (what are your objectives?)
B. Background & significance	* Why is the work important? * What "knowledge gap" does project address? * What is innovative/unique about your project?
C. Preliminary studies	What has already been done **by your team**?
D. Research design & methods	* What is the underlying model/concept? * How are you going to do the work? **W W H W W**
Budget justification	* What personnel are needed & why? * How much time will personnel devote? * What supplies/equipment are needed & why?

Acceptable Fonts for Grant Applications

At least 11 point

- **Arial / Helvetica**
- **Palatino Linotype**
- **Georgia**

How Many Words Fit into the Typical "Abstract" Box?

Fonts: Arial 11, Georgia 11, Palatino Linotype 11

Natural fall headers: 375 words Left margin headers: 350

Abstract = 200 - 400 word executive summary of the entire project

Abstract) should answer six questions:

1.) What **problem** will be addressed?

2.) What is the **purpose** of the project?

3.) What **research question(s)** will the project answer? / What **hypothesis** will be tested?

4.) What **methods/tests** will be used to answer questions / test the hypothesis?

5.) What **outcomes** will be measured?

6.) What is the potential **benefit / impact** of the project?

► Guidelines for Writing the Abstract

❖ **Clearly describe an unknown or problem that needs to be investigated / solved**

- **For RFA/RFP, do not waste words telling reviewers things they already know**
- **Provide adequate description of methods (W W H W W)**
- **Clearly state outcomes to be measured.** ***Name "names"***
- **Don't leave unanswered questions in the minds of reviewers.** Avoid S-A-T (stop & think)

► Guidelines for Use of Words in the Abstract

360 words

	Response to RFA		Unsolicited	
	%	Words	%	Words
* Problem / need	20%	72	40%	144
* Hypothesis/aims	10%	36	10%	36
* Methods & outcomes	60%	216	40%	144
* Benefit	10%	36	10%	36
	---	---	---	---
	Total: 100%	360	100%	360

► Critique this Abstract (application is in response to an RFA) 374 words

Problem: Alcoholism is a significant health problem for 45 million people in the U.S. Its precipitating role in domestic violence, DWI fatalities, criminal behavior and secondary illnesses is well documented and continues to increase. 10-15% of patients seen by Family Physicians nationwide are uncontrolled alcoholics, and the rate is substantially higher in South Texas where alcoholism is a major source of morbidity and mortality in all age groups. Yet the training of physicians in alcoholism is often deficient, limited to a few lectures or frustrating encounters with end-stage alcoholics. Presently, there is no educational model for providing Family Physicians with skills needed to diagnose and intervene with alcohol-dependent patients. **Purpose:** We will implement a community-based continuing education program (CBCEP) to provide Family Physicians in rural South Texas, a 90,000 square mile region with high alcohol-related morbidity and mortality, with skills to detect patients at risk for alcohol abuse, and refer them to treatment programs. **Methods:** The investigators have conducted successful CBCEP's for rural physicians. The expertise acquired form these programs will be applied to this project. We will use a questionnaire to identify the needs of practitioners in regard to alcoholism and identify individuals willing to participate in the protocol. After analysis of results, an educational intervention will be implemented for 35 Family Physicians in rural South Texas with five components: interactive seminars, case management exercises, a skills lab where physicians work with simulated patients (SPs) to learn the CAGE and Substance Abuse Risk Identification (SARI) diagnostic tools, in-office consultation by substance abuse specialists, and case-based teleconference seminars conducted by addictionologists. Thirty-five physicians will serve as controls and will receive an educational program on dementia as a participation incentive which is identical in format to the alcoholism education. **Outcomes:** We will audit patient charts in both groups to document alcoholism diagnosis and referal rates before and after the CBCEP. Recovering alcoholics in 12 step programs, after training, will be introduced into the subject's practices as surreptitious patient evaluators (SPEs) to determine how frequently the CAGE and SARI are used when physicians encounter symptoms and behaviors from the SPE that indicate a patient at-risk for alcohol abuse. **Benefit:** If successful, this program can be a prototype for CBCEP for other types of substance abuse problems.

► **Write your critique here**

Strengths	Red Flags (things that concern you)

► **Red Flags – Description (Abstract)**

- **<u>Fails</u> to "tell the whole story" of the proposal (leaves the reviewer guessing)**
- **If responding to RFA = "belabors the obvious" with too much background information.**
- **Inadequate text devoted to methodology (W W H W W)**
- **Lack of eye-directing "headers" within text**
- **Not reviewer-friendly: less than 11 point font; squeezed margins; long sentences (e.g., more than 30 word/sentence average**

Pages 9 – 11: Examples of Abstracts with Reviewer-Friendly Formatting

Examples of Abstracts with Reviewer-Friendly Formatting

Title: Cost-Effectiveness of Domestic Violence Interventions [Natural fall headers]

Problem: One in five women between the ages of 18 and 45 who seek care in primary care medical settings experience domestic violence. There are numerous guidelines from national medical associations that promote routine screening and intervention, and there is great public interest in this topic. But there is little evidence on how effectively care meets the needs of women experiencing domestic violence. This has led the U.S. Preventive Services Task Force to conclude that there is insufficient information to either recommend or to oppose universal screening for domestic violence in medical settings. **Purpose:** The project goals are to: (1) investigate the effectiveness of domestic violence intervention components, (2) establish a methodology to define outcome measures for domestic violence interventions that incorporate patient, community, and expert viewpoints, (3) explore the feasibility of monitoring these outcomes measures in this population with a longitudinal cohort study, (4) based on outcomes of the first three goals, create a methodology for a cost-benefit analysis of domestic violence interventions. **Research Question:** What intervention model and study design are most successful for investigating domestic violence interventions in primary care? **Methods:** The overall design consists of several methodologies, integrated to conduct a cost-effective analysis of domestic violence interventions in primary care. These are: (1) a pretest-posttest, quasi-experimental investigation of six components of a domestic violence intervention, (2) an expert consensus conference to define patient outcome measures, (3) pilot test of the feasibility of administering outcome measures, (4) a descriptive cohort study of women receiving domestic violence services, including qualitative interviews and (5) the development of a cost-effectiveness methodology. **Outcomes:** Patient outcome measures are: (1) domestic violence severity, (2) psychological sequelae, (3) quality of life, and (4) correlates of wellbeing, (5) health care utilization and (6) costs. Process measures will determine whether abused women received appropriate care according to the intervention protocol. **Benefit:** This study will provide essential, timely information to guide the medical community on how best respond to develop domestic violence interventions and investigations on cost-effectiveness of domestic violence interventions in primary care. Based on this information and other work underway by our research team, solid recommendations can be made.

359 words

[Flush left headers]

Title: INFORM: **I**nformation **N**eeds **FOR M**igrant Health

Abstract

Problem: America's 5 million migrant workers and their families are more likely to suffer from both communicable and non-communicable diseases than the general population. Migrants seek care both within and across the U.S.-Mexico border. Accordingly, providers in community and migrant health centers report frequent problems obtaining clinical information that is vital to the care of migrants. This in turn may lead to otherwise avoidable medical errors. This phenomena and its extent is largely unexplored. Attempts to solve this dilemma have not been informed by valid data about the frequency or the nature of such missing information.
Purpose: The goal of this study is to describe the phenomena and determine predictors of missing information in the care of migrants.
Research Questions: This exploratory study is organized around three research questions**:** (1) How often do U.S. clinicians caring for migrants require clinical information that is unavailable? (2) What types of information are missing in these encounters and how serious is this missing information? (3) What patient and practice characteristics predict higher levels of missing information?
Methods: We will conduct a simultaneous survey of 1000 consecutive provider / patient encounters in 28 federally funded community / migrant health centers in rural Colorado. Enrolled providers will receive an INFORM card to record details about 20 encounters. A brief pilot will be conducted to determine major categories of missing information such as medications, medical/social history and immunization. The INFORM card will include a check list of these categories of missing information, Likert-scale rankings of the clinical importance of that information, and room for elaboration. The card will also include questions about the patient's conditions, medications, and reason(s) for visit. It will include a space to record a unique identifier linked to a patient survey. This patient survey will obtain data about conditions, medications, and reason(s) for visit, frequency and location of other health care visits, and demographics. Finally, practice and provider characteristics will be collected.
Outcomes: We will describe the frequency, types, and severity of missing information. We will use regression analyses to determine patient, provider, and practice predictors of critical missing information.
Benefits: This will be the first detailed description of missing information in the care of migrants. The outcomes will provide information to policy makers and researchers which will guide future interventions to enhance health services for migrant workers.

384 words

Abstract for educational development grant [Natural fall headers]

Problem: Hispanic children experience asthma with equal frequency (8-10%) as the general population but have greater morbidity. Several models to increase patient self-management and enhance providers' adherence to asthma care guidelines have failed to improve patient morbidity, physician adherence to guidelines or health care resource utilization. **Purpose:** The goal is to evaluate an intervention for Hispanic children with asthma that combines both physician education and patient education components within one intervention. **Hypothesis:** An asthma education intervention that provides both physician and patient education components will produce better outcomes for patients' morbidity and family quality of life in comparison to previous studies that had either physician or patient education, but not both. **Methods-physicians:** Pediatric residents will participate in an intervention including case conferences, skill seminars, role modeling by attendings, pocket cards depicting asthma management algorithms, computer-based asthma management simulations and computer-based asthma knowledge self-tests. **Outcomes - physicians:** The outcomes of the physician education will be measured by asthma knowledge tests, chart audit, and computer-based patient simulations administered pre and post intervention. **Methods-patients:** 160 Hispanic children with asthma, ages 6-15 years, receiving care in the continuity clinic, will be enrolled. A research associate will interview parents and children separately using standardized questionnaires to obtain data about health beliefs and behaviors, asthma knowledge/attitudes, functional morbidity, acculturation, and sociodemographic factors. A research nurse will perform spirometry on each subject. Medical records and school attendance logs will provide additional information. Patients will be randomized into treatment and control groups. The treatment group will learn asthma self-management, use of inhalers and peak flow meters and peak flow charting. Patients/parents will participate in four educational modules conducted by a bi-lingual nurse educator. and view videotapes that provide peer role modeling by showing Hispanic children performing asthma self-management tasks. Patients will review asthma management skills with a research nurse at appointments 6, 12 and 24 months following enrollment. **Outcomes-patients:** Longitudinal data will be obtained by interview, medical record review and spirometry at the 6, 12 and 24 month visits. Intervention and control groups will be compared for: morbidity (ER visits, hospitalizations, school days missed), quality of life (Stein's Impact on Family Scale and Functional Status Measure), asthma knowledge/beliefs and pulmonary function (FEV_1). **Benefit:** The outcomes of this study can inform the development of educational programs in outpatient clinics serving Hispanic children with asthma.

385 Words

Benefits Sentence (Last Sentence)

- **Reviewers want to know: What will we learn or "GET" if we conduct this project?**
- **The benefits sentence should be directly linked to the GAP (problem) statement.**
- **Don't start the sentence with "if successful"**

Which Benefits Statement is More Effective?

- If successful, this project has the potential to enhance our knowledge of strategies to provide more effective outpatient asthma education.
- This analysis provides a unique opportunity to simultaneously examine medical, prenatal care and healthcare access risk factors for LBW which will guide development of a targeted intervention to improve LBW outcomes among African-Americans.

Examples of Benefits / Impact Statements that Communicate a "GET"

- Findings from this study will provide effective methods for tailoring interventions aimed at improving adherence to diabetes treatment and prevention guidelines in primary care practices.
- This project will provide valuable information about the impact on children when their parents lose health insurance coverage.

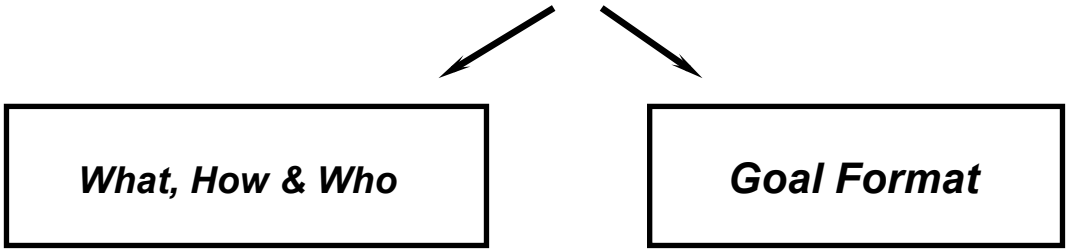
Very Important: Avoid Detail Drift Between Abstract & the Methods Section

- Review protocol details in the abstract & the methods section carefully.
- The "who, what, when, where & how" details should be exactly the same in the abstract as they are in the methods section.

Specific Aims

What will you do to test the hypothesis or answer the research questions that you propose to study?

Two Strategies For Writing Specific Aims



What task will be performed?

How will this task be accomplished?

Who are the subjects?

Describe the goal

Components of a specific aim using the "what, how & who" format:

What? (the task) **How?** (outcomes, including comparisons & time) **Who?** (what populations?)

Assess the impact of an evening home visit (EHV) program conducted by internal medicine resident – RN teams by comparing ED visits and hospitalizations 12 months prior to the intervention to the 12 month intervention period among elderly patients enrolled and not enrolled in EHV.

Breakdown of aim statement:

[What] Assess the impact of an evening home visit (EHV) program conducted by internal medicine resident – RN teams

[How] by comparing ED visits and hospitalizations 12 months prior to the intervention to the 12 month intervention period

[Who] among elderly patients enrolled and not enrolled in EHV.

Components of a specific aim using the "goal" format:

Determine if an evening home visit program by internal medicine resident – RN teams decreases ED visits and hospitalizations by home-bound elderly individuals.

Determine what? … if an evening home visit program by resident – RN teams decreases ED visits and hospitalizations

In what population? … home-bound elderly individuals.

Example of Layout for Specific Aims Page; PHS 398 Format

A. Specific Aims

A.1 Project overview

Acute otitis media (AOM) is one of the most common indications for antibiotic prescriptions in the outpatient setting. The benefit of antibiotics is limited to a slight decrease in the duration of symptoms. In Europe, an approach called watchful waiting is utilized instead of routine antibiotic therapy. Under watchful waiting, antibiotics are withheld unless symptoms persist for several days. It is unclear which approach is the most cost-effective. To explore this issue, we will perform a cost-effective analysis of watchful waiting versus antibiotic therapy.

A.2. Research questions

1. What is the cost-effectiveness of watchful waiting compared to antibiotic therapy for AOM?
2. What is the cost of antibiotic-resistant *Streptococcus pneumoniae* when AOM is routinely treated with antibiotics?

To investigate these research questions, we will complete the following tasks. **[Bridge sentence]**

A.3. Specific aims:

AIM 1: Develop a decision analysis model using efficacy-of-treatment probabilities from the AHRQ Evidence Report that outlines the management options and their range of outcomes for AOM if: 1.) managed by watchful waiting or 2.) treated with antibiotics.

AIM 2: Calculate utilities from the Quality of Well-Being Index (QWB) and compute quality adjusted life years (QALYs) to produce outcomes for the decision analysis in AIM 1.

The QWB combines measures of symptoms and functioning to provide a numerical point-in-time expression of well being, ranging from 0 for death to 1.0 for asymptomatic optimum functioning. To develop utility estimates, clinical experts will use the QWB to designate categories of health state for children with AOM. Quality adjusted life years will be calculated based on time in each health state.

AIM 3: Perform a cost-utility analysis of watchful waiting compared with antibiotic treatment using the outcomes from the decision analysis model developed in AIM 1 and AIM 2 and cost-of-therapy estimates obtained from the literature.

AIM 4: Estimate costs of antibiotic-resistance *Streptococcus pneumoniae* attributable to antibiotic treatment for AOM. Repeat the AIM 3 cost-utility analysis with this estimate to determine effect of antibiotic-resistant *S. pneumo* on cost-to-utility ratio.

Examples of Aims Associated with Hypotheses

Aim 1:
Longitudinally analyze health insurance coverage among children whose parents lost coverage after the OHP policy changes compared with children whose parents maintained health insurance coverage.

Hypothesis 1:
A higher percentage of children whose parents lost coverage after OHP policy changes will be uninsured compared with children whose parents maintained health coverage.
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SPECIFIC AIM 1. Describe maternal medical, social, prenatal care and behavioral risk factors for LBW among Black and White women delivering in Massachusetts and within a national military healthcare system.
Maternal risk factors will be described using Massachusetts Birth Certificate Data and a National Military Database (M2). The traditional risk factors for LBW will be examined in order to better understand the study populations, with an added focus on maternal hypertension. We will examine the traditional risk factors for LBW, based on previous studies in the literature and clinical experience, to fully understand the maternal characteristics of the study population.

Implementation of aim 1 will allow us to investigate four associated hypotheses that explore how traditional risk factors differ among the Black and White women and their differential impact on LBW outcomes.

Hypothesis 1.a Black women will have increased rates of chronic hypertension compared to White women.

Hypothesis 1.b Black women will demonstrate decreased level of maternal education, decreased rates of marriage, and increased rates of extreme ranges of maternal age (less than 19 years of age and greater than 35 years of age) compared to White women.

Hypothesis 1.c Among women delivering in Massachusetts, Black women will demonstrate increased receipt of prenatal care services from community health centers and increased government funded prenatal care, compared to White women.

Hypothesis 1.d There will be no significant differences in tobacco use rates between Black women and White women

SPECIFIC AIM 2. Calculate the differential contribution of hypertension to LBW, among Black and White women.
Using two large data sets, Massachusetts Birth Certificate Data and a national Military Database (M2), the association of chronic hypertension and LBW among the entire study population will be studied, while controlling for medical, social, prenatal care, and behavioral variables known to be associated with LBW outcomes. We will then examine the risk of LBW for those women with chronic hypertension alone and stratify by ethnicity to determine if there is a differential impact of hypertension on birth outcomes for Black and White women.

Hypothesis 2.a Black women with a diagnosis of chronic hypertension, will have a risk of LBW birth that is more than twice the risk of LBW births for Black women without chronic hypertension. For white women, the contribution of hypertension to the risk of LBW births will not prove as strong, indicating effect modification by ethnicity. This differential risk will hold true both in Massachusetts and within the military healthcare system, a population characterized by universal healthcare access, and might help to explain a portion of the existing racial disparity in LBW outcomes.

► Compare the specific aims sections which follow (A & B) and indicate which you would prefer if you were a reviewer.

Example A – Specific Aims

a. Specific Aims

Gametes, despite their highly differentiated and post-mitotic state, can arguably be considered penultimate stem cells because the successful fusion of male and female gametes will result in the development of an entirely new organism, including germ cells. Because of the biological importance of germline DNA in directing the development of the next generation, it seems reasonable to speculate that germline DNA is stringently protected. Indeed, our laboratory and others have shown a lower spontaneous mutant frequency in a lacI transgene recovered from spermatogenic cells compared to the frequency observed for age-matched somatic tissues and cells (Walter et al., 1998, Winn et al., 2000; Kohler et al. 1991). Because mutant frequency is intimately linked with DNA repair activity, the ability of germ cells to repair DNA damage is expected to play a major role in germline mutant frequencies. Although there are several DNA repair pathways, the base excision repair (BER) pathway is responsible for ameliorating a large portion of spontaneous DNA damage (Lindahl, 2000). Using a double-stranded oligonucleotide containing a defined lesion and nuclear extracts from mouse spermatogenic cells, we have shown that BER activity is greater in spermatogenic cell nuclear extracts than in somatic tissue or cell extracts (Intano et al., 2001; 2002). While these in vitro repair data are consistent with the lower spontaneous mutant frequency detected in germ cells, they do not begin to address repair activity on more complex chromatin structures such as that found in live cells. There are clear examples that access to DNA is impacted by chromatin structure. Our goal is to begin to examine the more biologically relevant consequences of chromatin structure on the efficacy of BER. At present there is a paucity of information on this subject for somatic cells and even less is known for spermatogenic cell types. We are applying for an R21 to facilitate extending our analysis of BER for spermatogenic cell types into the effects of nucleosomes on BER activity in nuclear extracts prepared from spermatogenic cell types. It is our immediate goal to acquire the reagents and establish the methodologies necessary for these experiments and to apply them toward understanding how BER is impacted. The specific aims are: 1) To compare in vitro base excision repair activity toward a defined lesion in double-stranded oligonucleotide and covalently closed circular DNA substrates.
2) To examine in vitro base excision repair activity toward a defined lesion in a covalently closed circular DNA substrate and to the same substrate organized into a nucleosome. 3) To quantify in vitro base excision repair activity on substrates configured into a nucleosome using extracts from defined spermatogenic cell types. The overall hypothesis is that nucleosomes impact BER activity relative to repair activity on DNA not associated with histones.

A. Specific Aims

A.1 Overview: A relationship exists between genomic integrity and health span as demonstrated by the increased prevalence of cancer and it's associated genomic instability at older ages. Organisms have multiple pathways and mechanisms to guard and maintain genomic integrity. The base excision repair (BER) pathway is one such pathway. It responds to a large fraction of spontaneous and induced DNA damage. Two major BER subpathways have been described. DNA polymerase-beta (β-pol) can function in both and is the major polymerase for one subpathway. BER activity declines with age and is associated with decreased β-pol activity in brain, liver and testis. The decline in β-pol activity and BER correlates with increased steady-state DNA damage. However, the spontaneous mutant frequency is not elevated in brain of old mice while the spontaneous mutant frequency is elevated in liver. Therefore, it is possible that the decrease in β-pol that appears to occur normally during aging may be protective in some adult tissues. Male germ cells obtained from young adult heterozygous β-pol (β-pol+/-) mice display an elevated spontaneous mutant frequency, but a lower spontaneous mutant frequency in liver compared to wildtype mice. These phenomena suggest that BER and β-pol are important for maintaining genetic integrity during aging and that change in β-pol activity can have differential effects among tissues. Recently, a tetracycline regulated mouse model of β-pol overexpression was shown to develop cataracts prematurely which suggests that overly abundant β-pol can impact health span negatively. In comparison, mice null for β-pol die in utero or in the early neonatal period suggesting that changes in β-pol activity are required embryonically and that alterations in β-pol abundance may have different consequences at different stages of life.

A.2. Project goal and hypothesis: The goal is to examine the relationship between β-pol abundance and activity to genomic stability and health span relative to age. Hypothesis: Modulation of β-pol activity and abundance will have differential effects on genomic stability and health span among tissues relative to age.

A.3 Specific Aims:

1. Determine the effects of modulating β-pol abundance on genomic integrity in prepuberal, young adult, middle-aged and old mice.

Hypothesis: Modulated β-pol abundance will impact genomic integrity differently in different tissues relative to age. Methods: Mice with altered β-pol abundance ranging from robust over expression to approximately a 50% reduction will be examined for β-pol activity, BER activity, spontaneous levels of oxidized guanine in DNA, and spontaneous mutant frequencies in a *lacI* transgene will be examined at prepuberal, young adult, middle-aged and old time points.

2. Determine the effects of modulating β-pol abundance on health span and stress response in young adult and old mice.

Hypothesis: Modulated β-pol abundance will impact health span and ability to respond to acute genotoxic stressors. Based on preliminary data, we expect that in some tissues, over expression of the DNA repair enzyme β-pol will have detrimental effects, while in other tissues, over expression of β-pol will be protective. Methods: Longevity and pathology cross-sectional studies will performed on appropriate lines of mice either over expressing or under expressing β-pol. Mice at different ages and with modulated β-pol abundance will be challenged with an acute stressor to determine if they have enhanced, reduced or unchanged resistance to stressors.

3. Examine the effects of modulating β-pol abundance on replicative senescence and the ability of select primary cell lines to respond to acute stress.

Hypotheses: Defined primary cell cultures will display similar phenotypes as the tissue from which they were prepared. We will also test the hypothesis that altered β-pol abundance will impact replicative lifespan and resistance to acute stressors. Methods: Enriched/purified cell types will be prepared from mice with altered β-pol abundance. Subsequently, when appropriate, replicative lifespan and ability to respond to stressors will be tested and compared to the responses obtained for intact mice of matched

age as the donor for the primary cells.

► Background and Significance (Section B – Research Plan)

Questions to answer:

Why is this work important?

What "knowledge gap" will this project help fill? What is the GAP?

What is unique about our approach? (What makes your project "stand-out?")

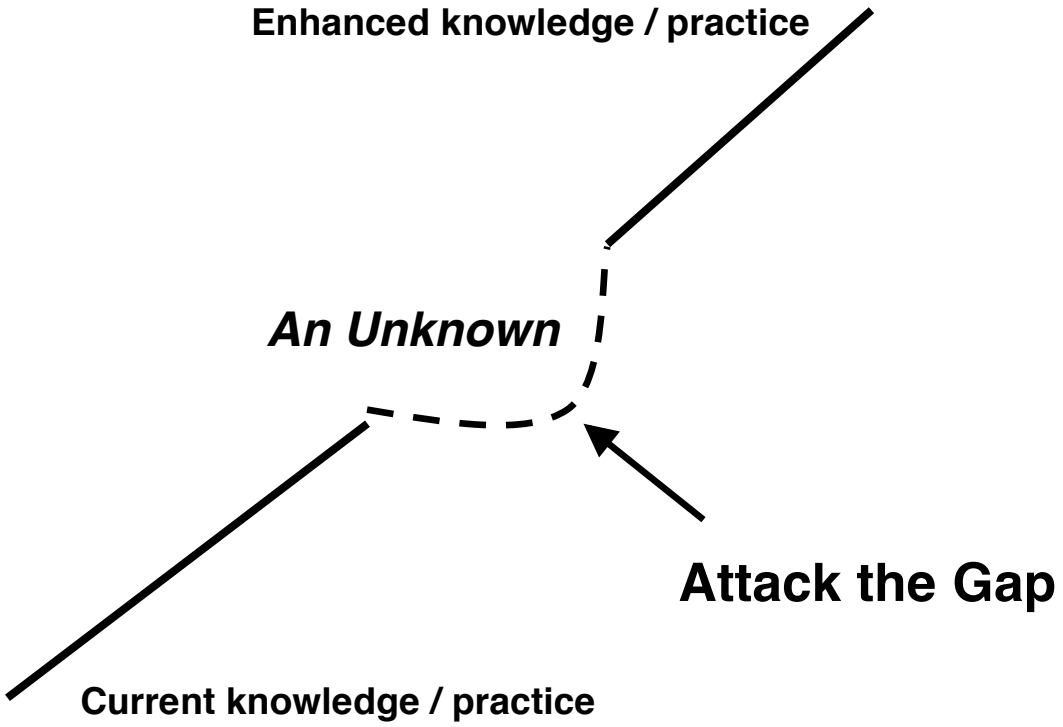
So what? Who cares … and why should they care about your project? What is the GRAB?

What is the deliverable? (i.e., what is the product or outcome?) What is the GET?

Write this section of your proposal with the Triple G" Formula

Grab Gap GET

Writing Strategy – Your "pitch" to the reviewer



Background & Significance Section

Start With A "Attack the Gap" First Paragraph

⇒ **1st Sentence: Gap Sentence** **What is the unknown?**

Several Examples ⇓

The etiology of Meniere's disease is unknown.

Despite being one of the most detectable of cancers, the mortality rate for oral cancer is 53%. Strategies to increase early detection of have not been successful.

Seventy percent of postmenopausal women at risk for osteoporotic fractures are not diagnosed despite availability of accurate screening tests.

The influence of cultural context upon the decision-making of urban low-income African-American women about infant feeding has not been studied.

⇒ **2nd - 4th Sentences: Why is it important to study this problem? [GRAB]**

Describe societal consequence: % households affected, morbidity & mortality, $$ costs, resource consumption, missed school/work days, etc.

⇒ **5th Sentence: "GET" sentence**

What will reviewers "get" from this application?

This project will develop a testable, conceptual model of how low-income African-American mothers in District of Columbia made infant feeding decisions. We will use qualitative methods and a collaborative partnership with the women in the community to develop this model.

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► **2nd paragraph = Begin review of pertinent literature**

Start this paragraph with "signpost" sentences (road map sentence)

Example of a signpost sentences:

Our understanding of the factors that influence infant feeding decisions among low-income African-American mothers is based on only three cross-sectional studies conducted in the 1980s with small samples of subjects. These studies will be reviewed in the next section, followed by a discussion of questions that were not answered by these studies

Reviewer- Focusing

Section titles (headers) in the B & S section should be complete sentences that communicate the key concept (take-away message) of that section.

Example of reviewer – focusing:

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B. Background and Significance

It is not known if depression treatment leads to improved metabolic control in patients with diabetes. Major depressive disorder is present in at least 20% of diabetic patients, and is associated with poor treatment adherence and with an increased risk of diabetes complications. Cross-sectional studies have linked depression with poor glycemic control. There are no prospective studies testing the effect of improved depressive symptoms on metabolic control. We will conduct a randomized, controlled trial to evaluate the metabolic results of treatment-related improvement of depression among adult patients with diabetes in primary care.

B.1. Depression is associated with poor diabetes outcomes

One in three people with diabetes has depression at a level that impairs functioning and quality of life, adherence to medical treatment, and glycemic control.[1] Depressive symptom severity is associated with poorer diet and medication regimen adherence, functional impairment, and higher health care costs in diabetic patients[2] and it increases the morbidity and mortality of cardiovascular disease,[3] the leading killer of patients with diabetes.

B.1.1. It is not known if improvement in depressive symptoms results in better diabetes outcomes.

Only three published studies have examined the association of depression improvement with glycemic control. No studies have evaluated outcomes of equivalent importance to cardiovascular risk in diabetes (blood pressure and lipids). The methodology and outcomes of these three studies are presented in table 2.

Table 2: Several interventions have been implemented to improve glycemic control by treating depression - Summary of outcomes

Study	Methods	Participants	**Intervention**	**Outcomes**
Lustman 1997	RCT	68 DM pts w/ new diagnosis of depression	Nortriptyline vs. placebo	At 8 weeks: Remission in 40% HbA1c unchanged despite hyperglycemic effect of nortriptyline
Lustman 2000	RCT	60 DM pts w/ new diagnosis of depression	Fluoxetine vs. placebo	At 8 weeks: Depression improvement 67% vs. 37% Remission 48% vs. 26% HbA1c better (trend)
Lustman 1998	RCT	51 referred DM-2 pts with depression	CBT (weekly x 10) vs. control [both groups got DM education]	At 6 months (n=42): Remission 70% vs. 33% HbA1c -0.7% vs. +0.9% Responders vs. persistent: HbA1c –1.0% vs. +1.7%

Close Strong With A "Significance" Paragraph

Goals:

- **Remind reviewers of the "gap" (what is knowledge is missing?)**
- **Help reviewers answer the question: "What is unique about this project?"**

Example of a "Significance" paragraph

==========

B. 6 Project Significance

This study is unique in that no previous investigation has documented the rates of hospice utilization by minority groups compared to non-Hispanic Anglos in a study population for which detailed social and demographic data are available. There have been only three published studies, all involving small numbers of upper middle class African-Americans, that investigated hospice utilization among minority populations. No published information is available to describe hospice utilization patterns among Hispanic/Latinos, Native Americans or Asian Americans. There have been no studies comparing the factors associated with end-of-life hospice care between non-Hispanic Anglos and minorities. For example: what is the effect of racial concordance between provider and patient on hospice use? To address this lack of information about hospice decision-making among minority populations, our research team will analyze hospice use among an ethnically diverse urban population in three large cities and evaluate the effect of racial concordance between provider and patient on hospice use.

► **Red Flags - Background & Significance**

Does the investigator: ("No" = red flag!)

- **Attack the gap?** Did the grant writer convince you that an important knowledge gap exists? **YES NO**
- Begin the B & S section with an "attack the gap" paragraph? **YES NO**
- Use reviewer-focusing section titles? **YES NO**
- Demonstrate real familiarity with the literature without being encyclopedic or devoting too much attention to general background literature? **YES NO**
- Demonstrate that this project offers a new & different (innovative) approach? **YES NO**

Read the background & significance section on pages 33 - 35.

Complete the critique worksheet below.

Background and Significance

Identify the strengths and weaknesses (red flags) of the Background and Significance section.
Note: The reference list is <u>not</u> included in the material to be reviewed.

Strengths - Aspects of the background & significance section that <u>impressed you as a reviewer</u>

Weaknesses (Red Flags) – What aspects of this section <u>concerned you as a reviewer</u>

► Preliminary Studies - New Application

Question: What has been done already by your research team?

This section helps convince reviewers that you ...

- Have experience with the experimental techniques you propose to use
- Can design well-controlled experiments (based on design/outcomes of your pilot studies)
- Can present your results in a clear and objective manner

Your goals as a writer ...

- **Convince** reviewers the proposed hypothesis is valid and testable by showing preliminary data that naturally "leads" to the next question (which you will attempt to answer).
- **Prove** you (PI) have appropriate training and experience to conduct the project.
- **Demonstrate** you have a **team** (co-investigators & support) capable of accomplishing project tasks.
- **Answer** feasibility questions by presenting pilot data that indicates project is **"do-able."**

Presentation of pilot data:

- Present pilot data in a professional manner - use charts/graphs and provide statistical analyses.
- Present only pilot results directly relevant to the experiments proposed in this application.
- Be objective and candid - don't overstate outcomes or make unsupported claims.
- **Getting ready:** Publish results of preliminary projects.

► Preliminary Studies – Writing Tips

Use a book-end structure:

Overview paragraph:

- Summarize pilot studies & other pertinent past work
- Describe key team members and past collaboration of the team
- Identify significant and pertinent publications
- State that experience gained from preliminary work will enhance current project

Identify each preliminary project by name. Write a one paragraph description of each preliminary study (see example on next page). List publications description of preliminary studies.

Conclusion paragraph: Describe how preliminary work has prepared team for this project

EXAMPLE – PRELIMINARY STUDIES FORMAT & CITATION DISPLAY

C. PRELIMINARY STUDIES

Overview

The preliminary studies described below demonstrate the expertise and experience of this interdisciplinary research team and its ability to carry out the proposed scope of work. The research is led by an experienced health sciences researcher and includes co-investigators from informatics, oncology, family medicine, nursing, public health, health services, and journalism. The team has conducted research in five areas that are pertinent to the proposed study: (1) the role of the patient in healthcare decision-making, self-care and patient practice variation; (2) healthcare consumer guides and organizational performance reports in hospital care and managed care; (3) breast cancer and other chronic illness management; (4) clinical oncology; and (5) patient and employer use of information.

C.1. Patient Practice Variation. (D. Longo, Hospital Research and Educational Trust, 1990-1992.) This paper established the initial conceptual underpinnings of the theory that has guided much of Dr. Longo's work in understanding the vital role played by patients in their own health and healthcare, especially as it relates to chronic problems such as smoking and cancer, and other areas in which the patient plays the primary role, such as pre-natal care. The theory of "patient practice variation" is presented as the patient analogue to Wennberg's concept of "physician practice variation" and is applicable to how breast cancer patients make decisions about their healthcare options.

Longo DR. Patient practice variation: a call for research. Medical Care 1993;31(5 Suppl):YS81-85.

C.2. Consumer Reports in Health Care: Do they make a difference in patient care? (D. Longo, et al.)

This study, published in *JAMA,* is one of the few studies to evaluate the impact of consumer guides on the quality of patient care. It found that within one year of the Missouri obstetric report, of the hospitals that did not have a car seat program, formal transfer agreements, or nurse educators for breast feeding prior to the report, approximately 50% either instituted or planned to institute these services. Hospitals in competitive markets that did not offer one of these services at the time of the report were more likely to institute a service or were about twice as likely to consider improving service. Clinical outcome indicators, ultrasound rates, Caesarean delivery rates, and rates of vaginal delivery after Caesarean all improved in the expected directions.

Longo DR, Land G, Schramm W, Fraas J, Hoskins B, Howell V. Consumer reports in healthcare: do they make a difference in patient care? Journal of the American Medical Association 1997;278(19):1579-1584.

C.3. On the Nature, Process and Modes of Hospice Care Delivery. (D. Longo, PI; Health Care Financing Administration (HCFA) $346,907, 1982.)

This project evaluated the quality of care of hospices throughout the US to determine the extent to which hospices were able to meet national standards established by the JCAHO hospice accreditation program and HCFA reimbursement participation conditions. Among other factors, this national evaluation investigated issues of patient self-determination. The study methods included on-site data collection as well as the fielding of survey instruments by mail. The study resulted in revised JCAHO hospice standards and HCFA requirements for hospice care.

Enck RE, Longo DR, Warren M. Do not resuscitate (DNR) policies in healthcare organizations with emphasis on hospice. Proceedings of the Annual Meeting of the American Society of Clinical Oncology, 1987;6:263.

Enck RE, Longo DR, Warren M, McCann BA. DNR policies in healthcare organizations with an emphasis on hospice. Am J Hosp Care 1988;5(6):39-42.

Read the preliminary studies section on pages 36 - 38.

Complete the critique worksheet below

Preliminary Studies Section

Strengths - Aspects of the preliminary studies section that <u>impressed you as a reviewer</u>

Weaknesses (Red Flags) – What aspects of this section <u>concern you as a reviewer</u>?

► Red Flags - Preliminary Studies (New Application)

Does the investigator ... NO = Red Flag

- Use a book-end writing structure? **YES NO**
- Present preliminary studies and results pertinent to the proposed hypothesis? **YES NO**
- Document team members have training/experience relevant to project? **YES NO**
- Show evidence of competence for procedures described in protocol? **YES NO**
- Provide a description of preliminary studies (vs. appending reprints without explanation? **YES NO**

► Research Design & Methods

Questions: What is the underlying model, theory, concept? How do you plan to do the work?

Your goals as a writer ...

Demonstrate that your intervention/methodology is based on a recognized model (e.g., what is the underlying framework for what you propose to do?)

Communicate your conceptualization of the project's experimental design. This is your chance to share your unique insight into the problem and show the sophistication of your approach.

Describe how you will design & conduct experiments for each specific aim.

Show your depth of planning by explaining:

* rationale for each experiment (discuss why it is an appropriate test for the specific aim)
* how you will conduct each experiment (level of specificity: see next page)
* how you will analyze the data
* your plans for revising the study design, if needed, as results are obtained

Help reviewers link tests and analyses to hypotheses/questions and specific aims; **CCC communication of the underlying "logic" of your research plan**

► **Writing Outline for Research Design & Methods Section [Example: pgs 39-48]**

- **Overview of project design**

  * One paragraph synopsis of the entire study design (150 words; mini-abstract)

  * Conceptual model (if appropriate; see below)

  * State research questions and/or hypotheses

  * **If very complex, help the reviewers by displaying the overall study design in a table**

- **Describe procedures / methods to accomplish each specific aim**

Aim	Methods	Data Collection & Analysis
Aim # 1	Methods for aim # 1	Data collection & analysis for aim # 1
Aim # 2	Methods for aim # 2	Data collection & analysis for aim # 2
Aim # 3	Methods for aim # 3	Data collection & analysis for aim # 3

- **Provide a workplan / timeline table**
- **Provide a "limitations" section**
- **Provide a "wrap-up" summary at the end of the section**

Reasons for using a model in a grant application:

- Provide rationale/framework for the structure of your study (E.g., why do you propose to conduct the project this way?)
- Help reviewers understand the "context" for the project.
- Interventions - E.g., efforts to change provider behavior or change system outcomes; efforts to educate students or provide patient education with different methods. What are the underlying assumptions or theories for the intervention you propose to implement?
- Provide a classification or analysis system to categorize subject behaviors/actions
- Provide a mechanism to interpret or explain the outcomes
- Help explain or understand variability among subjects or treatments (E.g., the big picture "WHY" question; why did we get these results?)

Bullet-Proofing

Overview: Make a list of everything a reviewer could possibly criticize about your project. Write an answer (response) to the most important criticisms that you anticipate.

- Stress innovations (what is unique and different about your approach?)
- Identify alternative approaches and discuss their limitations for your study (justify why you selected method A versus method B or method C)
- Identify recognized limitations of your procedures & methods
- Identify likely problems and describe how you will cope

Provide key details that will help reviewers evaluate decision points:

- Sequence, duration, frequency and redundancy of data collection (measurements)
- Critical details such as exposure times, temperature, concentrations, equipment, instruments
- Subject sampling (inclusion/exclusion criteria, number of subjects, randomization process)
- Statistical tests and analyses
- Data management - collection, entry, editing, storage, retrieval and security
- Workplan (display & describe project timetable within the methods section)

Example of a "Data Management" Sub-section

D.4. Data Management System

D4.1. Overview of data management system

The data management system includes the following operational components for handling the data: collection, entry, editing, monitoring, storage, and retrieval. The Data Management Unit for this study will consist of Ms. Therese Jayne, M.S. who will serve as the data manager supported by a full-time research data management assistant from the UAHSC Biostatistics Center in years 2, 3 and 4 who will be 75% in year 5 of the project. A programmer analyst, at 20% time, will be recruited for years 2, 3 and 4 and will work under the supervision of the data manager.

D.4.2. Data collection

Weekly computer generated schedules, data collection forms, and data recording forms will assure that correct data are obtained at designated times from the appropriate patient. The data collection forms will be tailored to the specific requirements of each visit and designed to facilitate accurate, complete, and error-free data collection. The data collection forms will contain the pre-printed patient I.D. number. A bilingual member of the Data Management Unit will contact the patient the day prior to their scheduled visit to confirm appointments and thereby minimize missed visits. Data collected by interview, record review, and pulmonary function studies will be maintained by the Research Associate. Data sheets will be reviewed for accuracy and completeness by the Principal Investigator prior to transmission to the Data Management Unit.

D.4.3. Data entry and editing

After data are collected and checked for completeness, they will be transferred into buffer data files (disk files) using Key Entry III. Verification by blanking the screen followed by reentry of key fields will be used to minimize entry errors. These functions will be performed by trained data entry personnel in the Biostatistics Center under the supervision of Ms. Jayne. After correction of entry errors, verification and validation will be performed on IBM-AT or compatible microcomputers using in-house developed edit programs. Any missing data or unusual values will be brought immediately to the attention of the Principal Investigator so that data may be corrected.

D.4.4. Monitoring, storage, retrieval and security

The Research Nurse and the Principal Investigator will work closely with the Data Management Unit to insure consistency in collection of patient interview data, patient training, and record review. Pulmonary function studies will be monitored by the Principal Investigator and Dr. Clyde Parsons. Long-term accessible storage will be on computer disks with backup provided by optical disk. At completion of data collection, the hard copy files will be microfilmed for long term storage. The hard copies are destroyed after verifying completeness and readability of the microfilm. The original microfilm will be stored in a safe deposit box off campus and a copy will be retained by the Data Management Unit on-site within the UAHSC Biostatistics Center. The investigators will be provided printed data summaries as requested. Data will be periodically summarized to monitor data collection for completeness, accuracy, and possible changes over time. Data will be retrieved for statistical analysis only with approval by the principle investigator. Access to data files is limited to the Data Management Unit personnel. Only the data manager (Ms. Jayne) and statistician (Dr. Montgomery) will have access to grouping codes.

► Red Flags - Research Design and Methods ("No" = red flag!)

- Does the research plan pass the "G – U – T Test?" **YES NO**

  G = Is an important knowledge **gap** identified?
  U = Is this a **unique** approach?
  T = Is a strong research **team** available to conduct the study?

- Is a model proposed to serve as the framework (logic) for the project? **YES NO**

- Is the overall project/study design displayed in a table? **YES NO**

- Are aims, methods, data collection and analysis linked together? **YES NO**

Aim	Methods	Data Collection & Analysis
Aim # 1	Methods for aim # 1	Data collection & analysis for aim # 1
Aim # 2	Methods for aim # 2	Data collection & analysis for aim # 2
Aim # 3	Methods for aim # 3	Data collection & analysis for aim # 3

- Are significant "decision points" answered in the methods section? **YES NO**

- Are details on human research protocols presented including gender, racial & ethnic composition of study populations and selection rationale? Are similar details provided for animal studies? **YES NO**

- Is a timeline presented and discussed? Does it appear to be realistic? **YES NO**

- Are alternative experimental designs discussed? **YES NO**

- Are potential limitations & sources of data contamination acknowledged? Are solutions proposed? **YES NO**

► Red Flags - Statistical Analysis ("No" = red flag!)

Is the statistical analysis ....

- Linked to the hypothesis and each aim? - OR - Is it a "fishing trip?" **YES NO**

- Described with enough precision to allow an appraisal of its merits? **YES NO**

- Appropriate for the hypothesis & nature of the data to be collected? **YES NO**

- Sophisticated enough to provide data needed to answer research questions? **YES NO**

- Are methods described for establishing the sample size requirements needed to detect statistically significant differences between groups? **YES NO**

Examples of Sections From Grant Applications

The examples on pages 32 – 49 are from several "successful" grant applications that were funded.

In some cases the names of project personnel have been obscured or changed to protect the confidentiality of the project participants.

All of the examples are displayed in this workbook with permission of the investigators and are presented for educational purposes only.

Example of "Specific Aims" For R01 Application

A. Specific Aims

A.1. Project Overview: Coordinated asthma management educational interventions for pediatric residents and Hispanic patients, ages 6 – 15, will be implemented in an outpatient pediatric clinic. Both interventions will be multi-dimensional and learner-centered, based on established behavioral change models for providers and patients. Outcome measures will include 5 functional status indicators, pulmonary function, quality of life and assessment of parents' health care beliefs and childrens' and parents' asthma knowledge, audit of physicians' management of children with asthma, and assessment of physicians' asthma knowledge.

A.2. Overall hypothesis to be tested: An asthma education intervention that provides both physician and patient education components will produce better outcomes for patients' morbidity and family quality of life in comparison to previous studies that had either physician or patient education, but not both.

A.3. Specific aims: To assess the effectiveness of the asthma education programs for pediatric residents and Hispanic patients, we will:

- **Aim 1:** Measure physician knowledge of asthma and asthma management strategies pre & post-intervention by case-based tests and computer-based patient simulations.
- **Aim 2:** Measure management of asthmatic patients via chart audit pre and post intervention.
- **Aim 3:** Measure functional morbidity, clinical (physiologic) and quality of life outcomes at baseline (enrollment) and at 6, 12 & 24 months post-intervention in treatment (receive patient education) and control groups (do not receive patient education).

A.3.1. Summary of functional morbidity and quality of life outcomes and measurements for aim 3

Outcomes	**Measurement method**
Functional status (morbidity)	
3.a. Yearly school days missed for asthma	School attendance records
3.b. Weekly ave & total annual impaired days	Patient medical record; parent report
3.c. Yearly number of emergency room visits	Patient medical record; parent report
3.d. Yearly number of hospitalizations	Patient medical record; parent report
3.e. Daily health & functional status	Functional Status Measure II
Physiologic outcomes	
3.f. Pulmonary function	Spirometry: FVC, FEV_1, $FEV_{25-75\%}$
Quality of life & health belief/knowledge	
3.g. Quality of life indicators:	Impact on Family (IOF); Functional Status Measure II (FSMII)
3.h. Patient/parent health care beliefs, health practices, asthma knowledge/attitudes & knowledge of household asthma triggers	Arizona Asthma Questionnaire

Example: B & S Section From R01 Application

B. Background and Significance

B.1. Overview: Depression is one of the most common disorders seen in primary care

Unrecognized and under treated depression results in significant personal, family and societal costs. Because of these costs, substantial attention has been focused on improving recognition and treatment. In spite of the magnitude of the problem and efforts to improve depression treatment, there is still a critical gap in the research literature in that few studies have investigated what actually occurs during the initial depression treatment negotiation encounter. To address this gap in our understanding, this study will focus on the negotiation that occurs within the physician and patient relationship. As an outcome of the proposed investigation, we expect to develop a better understanding of the patient and physician variables that influence the treatment negotiation and how communication problems between the physician and patient interfere with optimal treatment. The research proposed in this application is significant because the understanding achieved will provide a new lens through which to focus future interventions to improve depression treatment negotiation. As an outcome of these studies, physicians will have a better understanding of how to the patient/physician relationship can be enhanced in order to facilitate proper depression treatment negotiation. In this way, compliance is likely to improve and depression treatments will be more effective. This in turn will decrease the negative personal, family, and social consequences of depression.

B.2. Background

B.2.1 Depression causes economic, illness, societal and family burdens

Depression is one of the world's most common mental health problems. [19] Depression costs the United States between $30 to $50 billion in lost productivity and direct medical costs per year. [20-21] Health services costs are 50-100% greater for depressed patients than comparable patients without the disorder. These increased costs are due to higher medical utilization, not specialty mental health care. [22-23] Furthermore, examples of additional costs associated with depression include impaired concentration, failure to advance in education and vocational endeavors, increased substance abuse, impaired or lost relationships and finally suicide. [24-25]

B.2.2 Primary care physicians are major players in identifying depression

Reliable estimates suggest that depressive symptoms are present in nearly 70% of patients who visit primary care providers, with 4.8-8.6% of those patients suffering from major depression. [26-27] Numerous studies have shown that depression is under-diagnosed and often under-treated. Researchers have identified barriers to implementing the guidelines for treating depression. Nutting et. al emphasize the need for new and innovative strategies to: 1) increase patient acceptance of the diagnosis and treatment plan and 2) identify the barriers that exist within the provider-patient system that compromise quality care and thus increase patient morbidity and mortality. [28-30]

B.2.3 There are numerous barriers to effective treatment of depression

Several issues and barriers decrease positive outcomes in depression treatment including underdiagnosis, lack of patient adherence to planned treatment, substandard treatment and physician/patient barriers. *Underdiagnosis* is a commonly found problem in the treatment of depression. The U.S. Preventive Services Task Force (2002) reported that depression is undetected in up to 50 percent of all cases in primary care. Numerous studies have identified the benefits of depression screening and ways to

improve screening methods.[31] One of the recommendations is global screening for depression. [32-34]

Once individuals are screened and treated, a*dherence* to the treatment plan or patient compliance is another issue that has been studied. Self-discontinuance of antidepressant therapy is a common cause of treatment failure. Twenty-five to thirty percent of primary care patients who are treated with antidepressant medication discontinue treatment within one month, and forty to fifty percent within three months. [35-36] *Substandard treatment,* either through inadequate medication dosing and/or prematurely discontinuing treatment, has also been found to influence outcomes. [37-38] Only 19% of individuals with depression who were treated by their primary care physicians received treatment concordant with current recommended guidelines. [37, 40]

Nutting et. al. suggest that several *barriers* may reduce the likelihood that primary care physicians will use treatment strategies other than medication. [28-29] Some of these barriers relate to patients, their knowledge and attitudes about their mental health problems, and their beliefs about the best choices for treatment . Other barriers include lack of insurance coverage and the stigma associated with depression. [41] Finally, characteristics of the physician, such as treatment philosophy and practice style, have also been found to influence the outcome of an encounter where patients' emotional distress is present. [42]

In spite of the identification of the difficulties described above, proper depression treatment is cost effective and improves patient quality of life. [43-45] For these reasons, it is essential to identify and then improve the initial intervention of depression treatment. This study will investigate the issues that occur during the initial treatment encounter including issues that contribute to adequate diagnosis, adherence, and treatment.

B.2.4 Patient preferences play a key role in management of depression

One possible way to improve clinical outcomes during the initial encounter is to focus on the interaction between the physician and patient during the negotiation of depression treatment. An area that is currently being investigated is *patient preferences* in depression treatment. Since there are a number of antidepressant and psychotherapies that are efficacious, increased compliance with therapy may be achieved by matching the type of treatment with the patient's preferences. [46-47] Brody et. al. investigated patient attitudes, health beliefs, and expectations and found that patients are willing to share their preferences if they are allowed and/or encouraged to discuss their emotional distress. [48] Using a similar quantitative survey methodology, Dwight-Johnson et.al. found that many patients do not receive the treatment they prefer. [36, 49] For example, they found that depressed patients who preferred counseling but do not get it, are likely to go without treatment entirely.

Qualitative methodologies have been used to understand the physician - patient encounters through the eyes of the participants. Cooper-Patrick used focus groups to identify patient attitudes, preferences, and differences based upon race.[50] They found that patient preferences are important for physicians to explore and that most patients had expectation that were not met. This and other studies used a case report design to investigate depression treatment in general. The proposed study will look at physician and patient behavior based upon specific depression encounters.

B.2.5 Effective provider-patient communication is key to patient satisfaction

A recent study found that patients are usually satisfied with the competency of care but feel that communication is lacking. [51] Patients stated that they were not encouraged to ask questions, not asked their opinions about ailment and treatment, and were not given advice on lifestyle changes that could possibly affect their health. Thus, it appears that the communication that occurs within the provider/patient relationship is extremely important. Communication difficulties within the patient encounter have often focused upon difficulties with the physician. Current beliefs stress the

need for improved communication between the physician AND the patient and that difficulties lie within the relationship. [52-53]

B.2.6 Relational theory provides a framework for studying communication issues that exist between the physician/patient

This proposed study seeks to better understand the relationship and communication issues that exist between the physician/patient. The theoretical framework that is best suited for this inquiry is relational theory. This theory purports that interpersonal relationship patterns emerge through communication, and that the relationship is continually negotiated and defined within the relationship, not unilaterally based upon personal qualities and/or social role prescription. [54-56]

Relational theory explains that:

1) relationships are always connected to communication and cannot be separated from it;
2) the nature of the relationship is defined by the communication between its members;
3) relationships are usually defined implicitly rather than explicitly;
4) relationships develop over time through a negotiation process between those involved [55]

According to this theory, the relationship is maintained by the communication that occurs between individuals and that negotiation is a key component to building the relationship. Therefore, relational theory is believed to be an excellent theoretical framework for investigating the difficulties that occur within the encounter between a physician and a person with depression because it is believed that improved negotiation and positive relationships will improve the therapeutic outcome for these patients.

B.2.7 Significance of exploring the research question: What occurs during the patient - physician encounter that influences the initial negotiation of the treatment plan?

The research on physician barriers to diagnosis and treatment and studies of patient preferences by Brody (1997), Cooper-Patrick (1997), Schulberg (1998), and Dwight-Johnson (2001) provide the groundwork for this current project. These studies establish the important role that physician and patient preferences, attitudes and experiences play in the management of depression. Relational theory will provide a template for the investigation of the physician/patient encounter. For these reasons, the proposed study was devised to fill the current gap in our understanding of how patient-physician interactions influence the treatment of depression. It uses a three-pronged data gathering strategy: 1) direct observation of the encounter 2) follow-up interview with the physician and 3) follow-up interview with the patient. Through this methodology, we will explore what occurs during the encounter and how patient and physician characteristics influence the initial negotiation of the treatment plan. This information can then be used to develop interventions to improve the identification and treatment of depression. This, in turn, can increase patient safety by addressing a problem that contributes to significant morbidity, mortality and economic consequences.

Example of A "Preliminary Studies" Section From R01 Application

C. Preliminary Studies

C.1. Overview – preliminary studies by the research team

The research team has conducted five preliminary studies and published interim or final outcomes for these projects. Abstracts describing the results of these preliminary studies appear in the appendices. Experience gained from implementing the study design and using the techniques and instruments in these preliminary projects will enhance the management of the currently proposed project and reduce the start-up time needed for instrument development and training of personnel. Research team members for the proposed project have collaborated on aspects of all of these projects and in the process have developed strong working relationships. Members of the research team have also conducted seven professional development programs at state and national meetings about techniques we have developed to investigate health issues in low income rural children.

C.2. Preliminary Study # 1: Medication Compliance in Acutely Ill Children with Asthma (Completed)

The principal investigator, Dr. Angela T. Morales, in conjunction with current co-investigators Naranjo and Montgomery, conducted a study of factors associated with medication compliance in 111 acutely ill low income asthmatic children in four rural communities near Flagstaff, Arizona.[47] This 1994 study was funded for $5,000 by the Flagstaff Regional Medical Education Fund which supports community-based health care and educational research activities. Forty-six (41%) of the enrolled subjects were Hispanic. The data included direct measurement of serum theophylline and information obtained by interviews with the parent/caretaker of the child. The main factors associated with compliance in the Hispanic patients were type of primary care provider, whether the patient had difficulty keeping appointments, and the relationship of the caretaker to the patient. Dr. Morales has published two abstracts describing aspects of this project and a manuscript is in preparation for submission to the Archives of Pediatric and Adolescent Medicine. Additionally, Drs. Morales and Naranjo were invited to conduct workshops on clinical research techniques employed in this project at state and county medical association meetings in September and October of 1994.

C.3. Preliminary Study # 2: Asthma Treatment Compliance in Acutely Ill Children from Rural Communities in Southern Arizona (In progress)

In October, 1994, Dr. Morales received funding ($11,000) from the UAHSC Institutional Research Grant Program (IRGP) to conduct an asthma treatment compliance study in the communities of Bisbee and Douglas, Arizona. Thirty-three of the 47 enrolled subjects are Hispanic. Data collection for this project will be completed in March, 1996 and the results will provide useful information and direction for the presently proposed study. Drs. Parsons and Montgomery are co-investigators. A preliminary abstract was presented at the Arizona State Medical Association Primary Care Meeting in 1995 and an abstract, describing study methodology and interim results, has been accepted for presentation at the 1995 AHEC National Meeting in Las Vegas, Nevada. Drs. Parsons, Morales and Montgomery will also conduct a workshop at the AHEC meeting on research techniques for study of health status issues among rural Hispanic children.

C.4. Preliminary Study # 3: Morbidity in Mexican-American Children with Asthma in Tubac and Nogales, Arizona (In progress)

In January, 1995, Drs. Morales, Parsons, Naranjo and Montgomery received funding from the Tucson Area Health Education Center (TAHEC) for a two year study (funding through August 1996) to conduct a longitudinal descriptive study of factors predictive of functional morbidity in Mexican-American children with asthma living in two border communities south of Tucson (Tubac and Nogales) compared to a similar group of non-Hispanic Caucasian children with asthma from the same communities. To date, 46 Hispanic children have been enrolled. A standardized questionnaire, known as the "Arizona Asthma Questionnaire" AAQ; (developed and pilot-tested by the investigators) is being used to obtain information about health beliefs and reported health behavior, knowledge and attitudes about asthma, functional morbidity, acculturation, and socio-demographic factors. Additional information is being obtained by spirometry and review of medical records. Longitudinal data will be collected at 6 and 12 months to compare the two ethnic groups and identify factors predictive of functional morbidity in Mexican-American children with asthma. This study will also provide important baseline information about morbidity in Hispanic children with asthma and provide a basis for the interventions to be developed in the proposed study.

C.5. Preliminary Study # 4: Care providers and patient's asthma knowledge and attitudes and perceived needs for asthma educational programs (Completed)

In May, 1995, ten focus group interviews were conducted with members of the target population by members of our research team (Morales, Herrara, Huerta, Santos) at Pima-Kino Community Hospital in Tucson, Arizona (site of the presently proposed study). The purpose of these focus group sessions was to obtain information about asthma knowledge and attitudes and identify perceived needs for educational programs from the parents / primary care providers of children with asthma, and where possible because of age, to obtain the same information from the children. Participants included 31 parents and 13 grandparents of Hispanic children with asthma (total n = 44) and their children
(n = 57) who are followed in the Allergy Clinic and the Pediatric Outpatient Clinic at Pima-Kino Community Hospital. Participants were taken to a conference room in groups of 4-8 where the principal investigator and other members of our research team, working in pairs, asked the group questions about asthma. The results of the focus group show that parents feel that asthma is the
"worst thing that could happen to their child" and they live in constant fear that their child can suddenly stop breathing. Although the participants were aware of some of the symptoms of asthma, they were less knowledgeable about what they could do to help prevent asthma attacks from occurring.
Parents and children were both interested in learning what causes asthma, how it can be prevented and what medications can do. Focus groups will continue to be used to help the investigators develop culturally appropriate and relevant patient education materials for the target audience. One of the co-investigators, Lydia Serda, DPH, has extensive experience in focus group techniques, and has published papers on the technique. Dr. Morales has prepared and submitted an abstract on the findings of this study that has been accepted for the 1996 Society of Teachers in Family Medicine Meeting. She has also been invited to present the results of this study to three health care professional education groups in the Tucson including the primary care physicians research group, the county clinical nurse practitioners board and the community nursing association.

C.6. Preliminary Study # 5: Validation of the Arizona Asthma Questionnaire (In progress)

An important component of the TAHEC study is to establish the reliability and validity of both the Spanish and English versions of the Arizona Asthma Questionnaire (AAQ) and other questionnaires that will be used in the presently proposed study and to determine the comparability of the Spanish and English versions. Elizabeth Herrara, Ph.D, evaluation specialist, is coordinating this effort during the TAHEC project and will coordinate instrument development, use and assessment in the presently proposed study. Our research team has received supplemental funding in the amount of $4,000 each from the Southwest Asthma Foundation and UAHSC Institutional Research Grant Program

(IRGP) to pursue validity testing of these instruments. To determine the reliability of instruments that can be scored in a right/wrong fashion (such as the knowledge section of the Arizona Asthma Questionnaire), a KR-20 coefficient alpha was computed on all English baseline questionnaires and all Spanish baseline questionnaires with at least 15 subjects in each group.

Preliminary analysis of this subset of the total study population found a solid .76 correlation coefficient. Reliability of Likert scales were computed in a similar manner for both total questionnaire scores and subscales and preliminary results indicate good reliability in the .65 to .85 range. Categorical and open-ended responses were assessed for consistency by correlating information from baseline with information collected at a two week interval for both English and Spanish-speaking subjects. To assess the comparability of the Spanish and English questionnaires, a group of 30 bilingual subjects are currently being administered both questionnaires in a counterbalanced order and in blocks of 15 with a testing interval of 2 weeks. KR-20 coefficient alphas will be computed separately for each block in a manner similar to that already described. Preliminary data is currently being analyzed for this comparability test.

Validity testing will also include determinations of face validity, construct validity, and criterion-related validity. Face validity of the AAQ that will be employed in the proposed study is now being assessed during pilot testing in the TAHEC study under Dr. Herrara's supervision. Construct validity will be assessed by correlating instruments or subscales which measure similar constructs. For example, scores on the Functional Status Measure II (FSMII) will be compared with parent-reported severity of asthma from the AAQ. Criterion-related validity will be determined by comparing scores on a given instrument with other objective measures. For example, scores on the FSMII will be compared with standard measures of morbidity obtained from chart review and the AAQ (e.g. # ER visits, hospitalizations, and school days absent). Dr. Herrara presented a workshop on these validation techniques at the 1996 state primary care research meeting in Mesa.

C.7. Summary – Preliminary Studies

In summary, the Flagstaff medication compliance study (Preliminary project # 1), the UAHSC/IRGP-supported study (preliminary project # 2) and TAHEC-supported study (preliminary project # 3) will provide baseline information concerning patient morbidity and medical care problems prior to the implementation of either physician or patient interventions, and help us identify barriers to optimal care and barriers to effectiveness of educational efforts. Preliminary study # 4 (Pima-Kino Community Hospital focus groups) provided important information from the patient's and parents/primary care providers perspectives about topics, issues and skills to emphasize in an asthma education program. These preliminary studies will be help the investigators design relevant educational programs for use by physicians and patients. Preliminary study # 5, supported by the Southwest Asthma Foundation and UAHSC Institutional Research Grant Program, will produce assessment questionnaires that have been pilot-tested in Spanish and English with members of the target population.

Example of Research Design & Methods Section

D. Research Design and Methods

D.1. Overview of research study

Depression is highly prevalent among patients with diabetes, and is associated with poor glycemic control. It is not known if depression treatment leads to improved metabolic control in patients with diabetes. We will implement a practice-based program of Enhanced Care for depression in a low-income community clinic. In Enhanced Care, practice-based nurse care managers provide patient education, identify and address barriers to depression care, and monitor patients' response to depression treatment. Enhanced Care has been shown to be effective in general medical populations seen in primary care but has not been tested among diabetic patients. Fifty-four diabetic patients with significant depression on two-stage screening will be randomized to either Enhanced (EC) or Usual Care (UC) for depression. Six months after treatment initiation subjects will be classified as "improved" or "not improved" on the basis of a reassessment of depressive symptoms. We will then compare post-treatment changes in metabolic control among "improved" subjects against "not improved" subjects.

Wing et al. have described a conceptual model for the relationship between depression, adherence, and outcomes.[58] An adaptation of this model is shown in Figure 1.

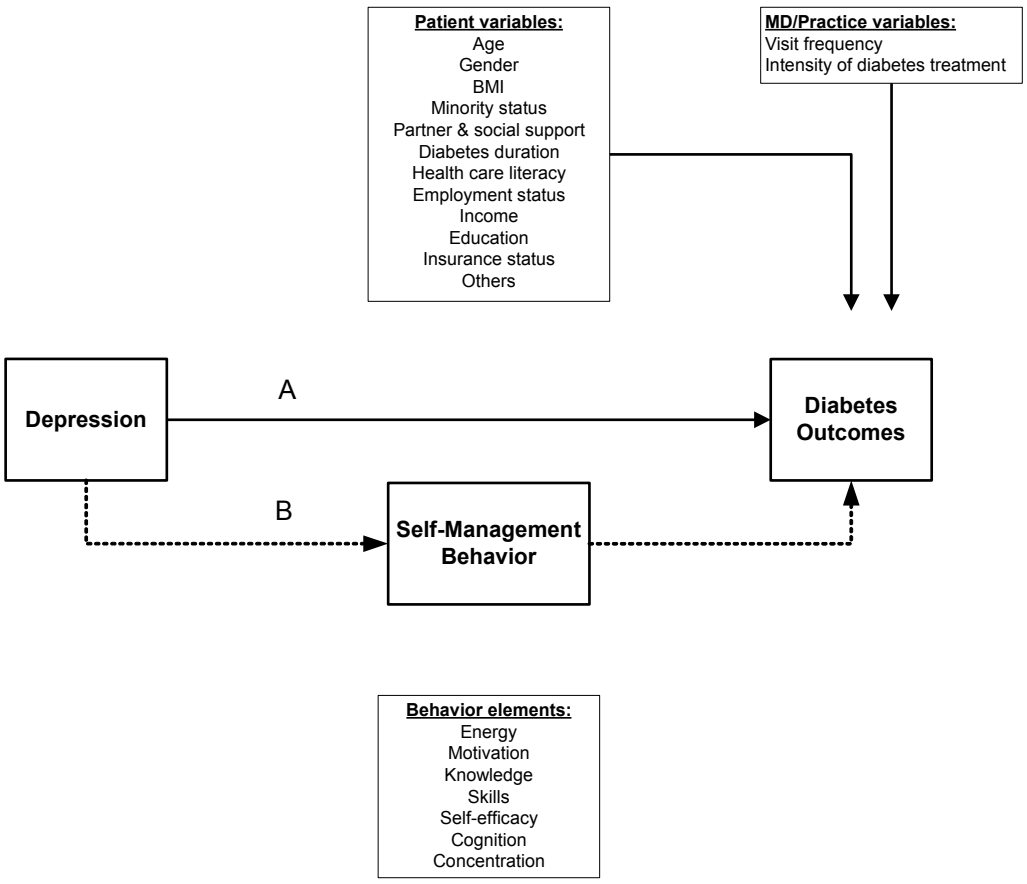


Figure 1: Conceptual Model of the relationship between depression, self-management behavior, and outcomes.

It is clear that depression leads to poor adherence to medical treatment, with over three-fold relative risk,[59] but no current evidence supports the hypothesis that adherence mediates the relationship between depression and outcomes.[58] Our study is focused on pathway A in Figure 1. To date the association of depression with diabetes outcomes is known only as a negative effect—depression worsens diabetes outcomes. We intend to test the hypothesis that improved depressive symptoms are associated with improved diabetes outcomes. Other significant determinants of metabolic control, listed in **Figure 1** as **Patient variables** and **MD/Practice variables**, will be examined as covariants in our outcomes analysis.

Our test requires a cohort of diabetic patients with demonstrable improvement in depression. Enhanced Care--care team redesign with systematic screening, identification, monitoring, and follow-up for depression--has been shown to be effective among general medical patients in primary care settings.[34, 39, 53]

D.1.1 Research Questions:

1. Does effective treatment of depression improve metabolic control in patients with diabetes?
2. How effective is Enhanced Care for depression among patients with diabetes?

The overall study design is summarized in **Table 2** below which identifies the data to be collected for aims 1 and 2 and the corresponding measurement instruments and analysis methods.

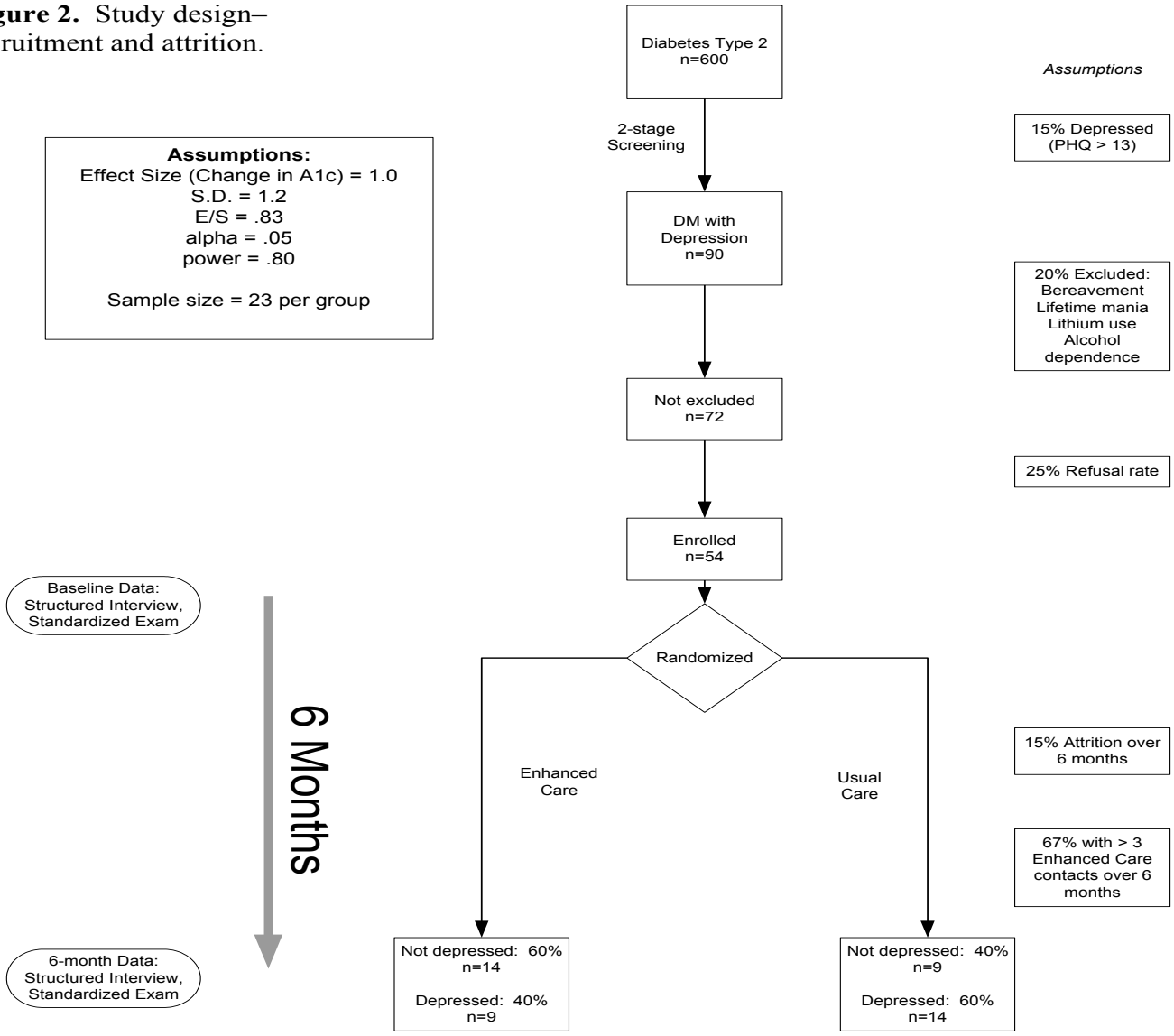
Table 2: Summary of data collection, measurement instruments and analysis for aims 1 and 2

Aims	Data to be collected	Measure instruments & analysis
Aim 1: Assess the effectiveness of Enhanced Care for depression in diabetes by comparing depression improvement after 6 months of Enhanced Care against Usual Care.	Depression severity at index visit and at 6 months	Center for Epidemiologic Studies Depression Scale (CES-D)—structured interview Intention-to-treat analysis—proportion "improved" in EC vs. UC
Aim 2: Assess the impact of depression treatment on metabolic control by comparing changes in glycemic control (HbA1c), blood pressure, and lipid profiles among subjects with and without significant improvement in depressive symptoms 6 months after initiation of treatment.	Depression severity at index visit and at 6 months Metabolic control at index visit and at 6 months	Center for Epidemiologic Studies Depression Scale (CES-D)—structured interview Diabetes Quality Improvement Project (DQIP) Index—Integrates HbA1c, BP, LDL—standardized examination Analyze correlation between 6-month change in DQIP with 6-month change in CES-D

D.1.2 Study Design – Subjects

The anticipated flow of subjects through the study is presented in Figure 2, with our assumptions listed on the right side of the figure. A power calculation demonstrating the adequacy of projected sample sizes appears in section D.6. Cross-sectional studies have consistently found major depressive disorder in over 20% of diabetic patients in clinic settings, with a two-fold risk of depression when compared with a general medical population in any setting.[1] We will screen 600 diabetic patients over 6 months to identify 120 depressed patients. This appears feasible, as the study site cares for over 900 patients with diabetes, who average 4.6 visits per year. In the QuEST study of Enhanced Care for depression, Rost and colleagues excluded 18% of second-stage positive patients for bereavement, bipolar illness, or alcohol dependence.[53] Using the same exclusion criteria, we project a 20% exclusion rate. We project a refusal rate of 25% among doubly-screened patients eligible for study inclusion. The multi-site QuEST study had a recruitment rate of 73%. 90% completed 6-month follow-up, but we project a conservative 15% attrition rate. In the QuEST trial, over 70% of Enhanced Care patients had more than 3 contacts with the nurse care manager; we are projecting a more conservative 67%.

Figure 2. Study design–recruitment and attrition.



Aim 1: EC (n=23) vs UC (n=23)
Aim 2: Not Depressed (n=23) vs. Depressed (n=23)

D.2 Methodology for the Enhanced Care for Depression Intervention

Our primary goal in implementing Enhanced Care for depression is to increase the number of patients whose depression improves within the study period. Enhanced Care has been shown to be effective in general medical populations seen in primary care. The design and conduct of Enhanced Care has been fully described elsewhere (Appendix).[53] We will adapt this intervention to a community clinic setting, and measure its effectiveness in a diabetic population.

D.2.1 Patient Recruitment

Patient Care Setting and Patient Characteristics
The Family Practice Center (FPC) operates in two adjacent buildings on the main campus of XXXX Medical Center of XXXXXXX in XXXXXXX. The FPC is the largest community clinic providing comprehensive primary care in our region. FPC patients reflect the rich ethnic diversity of XXXXXX and are socially vulnerable in ways common to populations seeking medical care in "safety-net" community clinics. Most FPC patients live at or below the federal poverty guideline. Health insurance and a "medical home" are tenuous for these individuals. In addition, language and cultural barriers often limit access to health information, education and health care.

Our Diabetes Registry currently contains 616 patients, 53% of whom are women. Half are 45-64 years old; 22% are under 45, and 28% are over 65. There is essentially no commercial insurance available to FPC patients: 68% of Registry patients have MediCal, while 27% have Medicare and 5% have no insurance. More than a quarter (26%) of our patients are Latino; 10% are Asian, and 8% are African-American. Our study sample will reflect these characteristics; children under 18 will not be eligible, but women and minority-identified patients will be enrolled.

Patient Selection
Trained administrative staff will recruit a cohort of 54 eligible patients over 4 to 6 months. Patients will be eligible to participate in the study if they have Type 2 Diabetes Mellitus and meet study criteria for depression on 2-stage screening at clinic visits.

D.2.2 Enhanced Care Implementation

Index Visit
Administrative staff will place a note on the front of the consenting patient's chart. The trained Nurse Care Manager will record subjects' baseline height, weight, and blood pressure on a number-coded data entry form, and will arrange for laboratory determination of HA1c and fasting lipids. The note will also ask the doctor to evaluate the depression diagnosis, give the patient a copy of the AHCPR Patient Guide to Depression, and ask the patient to return in 1 week to meet with the nurse and see the physician again.

Follow-up Visits—Enhanced Care
Patients will be randomized to either *Enhanced Care* or Usual Care in the week between the Index Visit and the first Follow-up Visit (see Enrollment Interview, below). *Enhanced Care* patients will be scheduled for nurse Follow-up Visits according to the nursing log returned to the Nurse Care Manager after the Enrollment Interview. Usual Care patients will not have Follow-up Visits with the nurse.

At the 1-week visit, the Nurse Care Manager will assess and record the patient's current PHQ-9 score for depression, evaluate the patient's treatment preferences, and address identified barriers to care by negotiating that patients complete a small assignment to increase or maintain their readiness to engage in active treatment. She will note the patient's treatment preferences for physician review before his/her visit with the patient the same day. The nurse will also give the patient written information on his/her preferred treatment, the assignment they had agreed upon, and the time/place of their next nurse contact.

Following this initial contact, nurses will use a similar protocol to guide telephone or face-to-face discussion with patients once a week for the next 5 weeks with the option of extending the protocol for 2 additional weeks, or a total of 8 weeks.

D.2.3 Data collection procedures – Aims 1 and 2

Study data collection will be separated from clinical care in order to minimize the burden on the clinic and to reduce bias by blinding study outcome assessment from the clinical care team. Data will be collected from each subject in the structured Enrollment and Outcome Interviews.

Enrollment Interview
Within one week of the Index Visit, subjects will complete a structured interview with the Research Assistant. Each subject will complete the Center for Epidemiologic Studies Depression Scale (CES-D) and the Summary of Diabetes Self-Care Activities (SDSCA) questionnaire. The Research Assistant will be prepared to help patients with low health literacy. The structured interview will also collect information on patient demographics, co-morbidities, and depression course. Variables of interest include:

- Demographics (age, gender, minority status, partner & social support);
- Socioeconomic status (education, employment status, household income, insurance status);
- Health status (diabetes duration and complications, co-morbidities, depression recurrence);
- Physician/practice variables (visit frequency in prior 6 months).

Subjects will then be randomly assigned to either Enhanced Care (EC) or Usual Care (UC). After randomization, the Research Assistant will record the baseline height, weight, and blood pressure recorded at the Index Visit by the Nurse Care Manager. In both the enrollment and outcome interviews, the Research Assistant's structured answer forms will be dated and number coded for anonymity. The Research Assistant will be blinded to clinical findings (height, weight, blood pressure, HA1c, lipids) until after randomization.

Outcome Interview
The Research Assistant will conduct the outcome interview 6 months after the index visit. Each subject will complete the Center for Epidemiologic Studies Depression Scale (CES-D) and the Summary of Diabetes Self-Care Activities (SDSCA) questionnaire. This structured interview will also collect information on 6-month visit frequency and diabetes treatment intensity. Subjects will be asked to report frequency of antidepressant medication use over the preceding 6 months. An independent auditor, blinded to results of the Outcome Interview, will review nursing logs and medical records for 6-month outcomes (PHQ score, HbA1c, blood pressure, height/weight, and lipids).

D.3 Outcomes and data analysis for Aim 1

Aims	Data to be collected	Measure instruments & analysis
Aim 1: Assess the effectiveness of Enhanced Care for depression in diabetes by comparing depression improvement after 6 months of Enhanced Care against Usual Care.	Depression severity at index visit and at 6 months	Center for Epidemiologic Studies Depression Scale (CES-D)—structured interview Intention-to-treat analysis - proportion improved in EC vs. UC

D.3.1 Overview of research design for Aim 1

Aim 1 is a test of the effectiveness of Enhanced Care for depression in patients with diabetes. Aim 1 compares depression outcomes in Enhanced Care against Usual Care; Aim 2 will compare diabetes outcomes in "improved" against "not improved".

D.3.2 Outcome measures for Aim 1

Timing: We will measure subjects' change in depression severity at 6 months. Most patients responding to antidepressant treatment do so within 6 to 8 weeks of treatment initiation. We intend to measure the effectiveness of Enhanced Care in the acute phase of depression treatment, and outcomes collection at 6 months will allow us to use prior studies of depression care for planning and comparison. Baseline depression severity will be determined as part of the Enrollment Interview.

Type: Depression severity will be measured with the Center for Epidemiologic Studies Depression Scale (CES-D). The primary outcome for Aim 1 is the proportion of patients achieving depression *remission*, defined as a CES-D score < 15, at 6 months. We will also measure the proportion of patients with *significant improvement* of depression, defined as at least 50% reduction from baseline in CES-D score at 6 months.

Method: Depression severity will be measured in structured interviews conducted by the trained Research Assistant. Patient preference will determine whether these Enrollment and Outcomes Interviews take place in person or by telephone. Telephone interviews would be expected to reduce patient burden and reduce study attrition, minimizing problems related to incomplete data. Telephone assessment has been found reliable and valid.[32, 33, 54, 60]

D.3.3 Statistical analysis for Aim 1

Proportion of patients in *remission* (CES-D < 15) at 6 months will be compared in subjects randomized to Enhanced Care (EC) versus those in Usual Care (UC) using chi-squared test of homogeneity. This procedure will be repeated comparing proportions with *significant improvement* (CES-D < 50% baseline) at 6 months in EC vs. UC.

D.4 Outcomes and data analysis for Aim 2

Aim	Data to be collected	Measure instruments & analysis
Aim 2: Assess the impact of depression treatment on metabolic control by comparing changes in glycemic control (HbA1c), blood pressure, and lipid profiles among subjects with and without significant improvement in depressive symptoms 6 months after initiation of treatment.	Depression severity at index visit and at 6 months	Center for Epidemiologic Studies Depression Scale (CES-D)—structured interview
	Metabolic control at index visit and at 6 months	Diabetes Quality Improvement Project (DQIP) Index—Integrates HbA1c, BP, LDL—standardized examination
		Analyze correlation between 6-month change in DQIP with 6-month change in CES-D

D.4.1 Overview of research design for Aim 2

We will randomize 54 diabetic patients with depression to Enhanced Care or Usual Care. After 6 months we will compare metabolic changes in patients with and without significant improvement in depression severity. We expect a remission rate of 40% in the Usual Care group, and 60% in the Enhanced Care group (see section **D.5** for rationale). This would yield a sample size at 6 months affording 80% power (at the 0.05 significance level) to detect a significant improvement (HbA1c difference of 1.0) in glycemic control. Randomization is necessary because it would be difficult to interpret positive findings in the study without a control group.

D.4.2 Outcome measures for Aim 2

Timing: In order to collect our outcome data in the most favorable treatment window, we will measure HbA1c outcome 6 months after the index visit. It may take 6-8 weeks to achieve treatment response in depression. HbA1c values reflect glycemic control over the 120-day lifespan of red blood cells, with 75% of the measured HbA1c value due to glycemic control over the preceding 60 days. Even if metabolic improvement requires several months of post-treatment behavior change, HbA1c measurement at 6 months is likely to show any effect of depression remission on glycemic control. The risk of depression relapse (over 35% by 12 months in primary care settings[61]) argues against outcome measurement beyond 6 months.

Type: We will use glycosylated hemoglobin (HbA1c) as our primary measure of metabolic control, the dependent variable in Aim 2. However, while glycemic control as measured by HbA1c is an objective and clinically important outcome, it is important to recognize that Type II diabetes, resulting from insulin resistance, is essentially a disease of accelerated atherosclerosis. Diabetes is a "holistic" disease; it is insufficient to judge treatment effectiveness only on glycemic control. Thoughtful investigators[62] have highlighted the need for reports of clinical trials' wider effects. The Diabetes Quality Improvement Project (DQIP) has published a "quality improvement" set[63] that can be an appropriate, objective measure of metabolic control in diabetic patients; four significant, objective clinical findings [HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), and low-density lipoprotein (LDL-C)] are stratified. We will assign weights to each DQIP stratum and report the summed, weighted scores (a continuous variable) as an index of metabolic control (DQIP) incorporating glycemic, blood pressure, and lipid management (Appendix).

Method: Height, weight, and blood pressure will be measured by protocol in clinical examination. HbA1c and blood lipids will be assessed in routine clinical laboratory determination.

D.4.3 Statistical analysis for Aim 2

Six month changes in glycemic control (HbA1c) will be correlated with 6-month change in depression severity (CES-D) by means of ANCOVA. Covariates will be baseline depression severity and baseline HbA1c. This procedure will be repeated substituting a broader measure of metabolic control (DQIP, which integrates HbA1c, BP, and LDL) for HbA1c. Potential confounding variables will be measured at enrollment (**Figure 1**). When differences between groups achieve statistical significance, variables will be analyzed as covariants in ANCOVA.

D.5 Sample size and power for a test of the null hypothesis

Our assumptions and projections of study attrition can be found in **Figure 2** and section **D.1.2**. One goal of the proposed study is to test the null hypothesis that there is no difference between the mean change in glycemic control of subjects with and without depression remission at 6 months. The criterion for significance (alpha) has been set at 0.05. The test is 2-tailed, which means that an effect in either direction will be interpreted. We based our expectations of depression remission on published 6-month outcomes of similar depression interventions in general medical populations. Simon et al. observed an odds ratio of 2.0, corresponding to a remission rate of 70% in the treatment group and 35% in controls.[33] Rost and colleagues found a 74% response rate in the intervention group, while controls had a 41% rate.[54] Lustman, studying diabetic patients with depression, observed treatment response rates of 67-70% in treatment compared to 33-37% in controls.[10, 11] The projected improvement rates of 60% in Enhanced Care and 40% in Usual Care are conservative.

A second goal is to estimate the mean difference between the two populations. On average, a study of this design would enable us to report the mean difference with a precision (95% confidence interval) of plus/minus 0.67 points. For example, an observed difference of 1.0 would be reported with a 95% confidence interval of 0.33 to 1.67. The precision estimated here is the median precision. Precision will vary as a function of the observed standard deviation (as well as sample size) and in any single study will be wider or narrower than this example.

Effect Size (Change in HbA1c) = 1.0

S.D. = 1.2
E/S = .83
Alpha = .05
Power = .80

Sample size = 23 per group

Our sample size calculations are based on the primary goal, evaluating the effect of depression improvement on metabolic control. In general, depression is associated with a 1.8% increase in HbA1c (i.e. 9.8% vs. 8%) compared to non-depressed diabetics.[3] An improvement of 1.0% would be clinically significant.[64] This effect was selected as the smallest effect whose detection would be important and reasonable to anticipate in this field of research. Without prior studies to guide us, we have estimated a common within-group standard deviation of 1.2. It is unlikely that the range of patients' 6-month change in HbA1c would exceed 5.0% in either direction. We used a two-tailed alpha in the sample size calculation.

D.6 Workplan

As shown in the project timeline on the following page (Table 3), we propose a two-year program (with a total budget of $100,000). The Enhanced Care intervention will be undertaken in the first year of the project. Physicians and nurses working at the study site will have initial training early in the year, with reinforcement immediately after enrollment begins. We plan to enroll 10 – 12 depressed patients per month over a 6-month period. Collection of outcome data will extend into the second quarter of Year 2. Data analysis and manuscript preparation will follow collection of both baseline (for cross-sectional) and outcome (for intervention effect) data.

Table 3: Project Work Plan

Project Activities	Pre-	Year 1						Year 2					
		Apr-May	Jun-Jul	Aug-Sep	Oct-Nov	Dec-Jan	Feb-Mar	Apr-May	Jun-Jul	Aug-Sep	Oct-Nov	Dec-Jan	Feb-Mar
Project organization													
MD Training													
Nurse Training													
Staff Training													
Data collection procedures													
EC Enrollment													
EC Implementation													
Baseline data													
Outcome data													
Data Analysis													
Write and submit													

D.7 Limitations and potential barriers

The following paragraphs describe potential limitations and barriers that could be encountered during implementation of this study and our strategies to avoid these problems or alternative approaches.

Because our study randomizes by patient, not practice, there is a risk of contamination if physicians apply elements of the Enhanced Care intervention to patients in the Usual Care group. This could narrow any difference between the study groups for Aim 2. However, Roy-Byrne and colleagues recently reviewed previous depression effectiveness research and found "no evidence of a spillover effect whereby usual care patients benefited from the intervention, probably because the intervention was more focused on the patient and the care process than on provider factors."[65] Our intervention shares this emphasis on the care process; physicians are insulated from the intervention. In summary, we believe that referral bias is not likely to be a significant problem, since our design strategy calls for screening of all diabetic patients for depression.

The Enhanced Care intervention may directly influence diabetes care. It is possible that some patients in the Enhanced Care arm will elect not to accept specific treatment for depression, and that the content of their weekly telephone conversations with the nurse care manager might devolve to discussions about diabetes care. This would tend to increase the likelihood of improved metabolic control while decreasing the likelihood of improved depression severity and confounding the outcome of Aim 2. We will manage this risk with specific training of the nurse care manager and by using a structured, scripted telephone protocol.

There may be initial group differences despite randomization. There may be differences in attrition rates, with fewer dropouts among the Enhanced Care cohort having weekly telephone contact with the clinic in the first 6-8 weeks of the 6-month study. Recruitment in the clinic setting may select for sicker patients, but use of the diabetes registry to recall patients without recent clinic visits will reduce this risk and should provide a more representative study sample.

Our results may not be generalizable beyond the low-income community clinic setting. However, the multi-ethnic study population strengthens the external validity of the study. Researchers have described the need for adapting and testing new care models for depression in the care of economically disadvantaged populations.[8] Scott et al. noted the failure of a practice-based approach to improving depression in an economically deprived and ethnically diverse population (the intervention succeeded in a better-resourced clinic experienced in the chronic care model).[46]

Implementation of this intervention in a residency training program may limit external validity of our findings. However, feasibility of the intervention is maximized by the close affiliation of the investigators, which allows greater control and ease of implementation.[66] Moreover, this intervention is focused on the care system rather than the physician.

There is no formal diagnostic interview to serve as a "gold standard" for the diagnosis of depression, and our primary outcome—depression remission--is an "arbitrary" cutpoint on the continuous CESD depression severity scale. There is potential risk of invalid findings if the cutpoint is unstable, or if there is regression to the mean over the course of the study. Randomization reduces the latter risk. Our use of a secondary depression outcome—improvement, defined as a 50% reduction in CESD severity—helps to minimize the effect of an "arbitrary" criterion for remission.

D.8. Summary – benefits from project implementation and future research

Depression is highly prevalent among patients with diabetes, and is associated with poor glycemic control, but it is not known if depression treatment leads to improved metabolic control in patients with diabetes. This is the knowledge gap that we will address in this project. The core research questions that shape the study design for this project have not been explored in previous research: (1) Does effective treatment of depression improve metabolic control in patients with diabetes? and (2) How effective is Enhanced Care (EC) for depression among patients with diabetes? To explore these questions, we will implement a practice-based program of Enhanced Care for depression in a

low-income community clinic. Nurse care managers will provide patient education, identify and address barriers to depression care, and monitor patients' response to depression treatment. This project will provide two tangible outcomes that will provide a foundation for future research: (1) and assessment of the degree to which EC improves the effectiveness of depression treatment and improves glycemic control, and (2) an assessment by the investigators and the nurse care managers of the components of the EC model that are most and least effective. The lessons learned by the research team during project implementation in this R03 "proof of concept" pilot project will guide development of an expanded examination of the EC model in a wider variety of community health clinics and with a larger sample.

► Budget and Budget Justification

General guidelines:

- The planning & detail evident in the budget communicates much about likely project management.
- Extend internal consistency to the budget. Make sure there is appropriate budget allocations for each experiment. Use a checklist to make sure you have covered all expense items.
- Follow budget directions precisely. Have budget checked by Grants Management.
- **Justify everything** - Do not assume that any expenses will be obvious to a reviewer

Personnel
- ☛ Less than 20% for key personnel raises concern about commitment to project.
- ☛ Don't request more than 50% for the PI, or less than 30% (if a new investigator)

Personnel justifications
- ☛ Percent effort on project
- ☛ Role - summarize primary project tasks
- ☛ Pertinent experience and expertise

Equipment & Supplies
- ☛ Fully justify expenditures for "deluxe" equipment models
- ☛ Determine exact prices from vendors (keep records)
- ☛ Don't request supplies in year one for an experiment that will be done later

Travel
- ☛ Don't exceed $$ limits per trip
- ☛ Request travel for one person to one meeting per year

Renovation
- ☛ **FORGET IT!**

Consultants
- ☛ Fully justify role and time commitment
- ☛ Be cautious about consulting time "away" from the project site

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

9/1/96	8/31/97

PERSONNEL (Applicant organization only)		TYPE APPT. (months)	% Effort ON PROJ	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED (omit cents)		
NAME	ROLE ON PROJECT				SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Angela Morales, M.D.	Principle Investigator	12	30	108,011	32,403	8,425	40,828
Clyde Parsons, M.D.	Co-investigator	12	15	116,267	17,440	4,534	21,974
Stan Montgomery, Ph.D.	Co-I	12	10	64,455	6,445	1,676	8,121
Elizabeth Herrara, Ph.D.	Co-I	12	50	63,555	31,775	8,262	40,037
Archie Dennis, Ed.D.	Co-I	12	10	73,876	7, 388	1,921	9,309
Lydia Naranjo, D.PH.	Co-I	12	10	69,217	6,922	2,007	8,929
Therese Jayne, M.S.	Co-I	12	10	73,804	7,380	2,140	9,520
To Be Named	Admin Assis	12	10	19,766	1,977	573	2,550
To Be Named	Ed Media Specialist	12	50	37,564	18,782	5,447	24,229
				Subtotals	130,512	34,985	165,497

CONSULTANT COSTS: Dr. Wallace Alvarez 12 consult days @ $500.00/day = $6,000 6 trips @ $1,000/trip = $6,000	12,000
EQUIPMENT (*Itemize*) Power Macintosh 9600 Computer	8,793
SUPPLIES (*Itemize by category*) * Office supplies @ $ 600.00 * Data management supplies @ 770.00 (50 computer disks @ 9.95 = 475.00; 1 optical disk @ 45.00 and supplies for questionnaire duplication @ 250.00)	1,370
TRAVEL Domestic 2 day meeting in Washington D.C. X 2 investigators = 2 X 1,800 = 3,600	3,600
PATIENT CARE COSTS — INPATIENT	
PATIENT CARE COSTS — OUTPATIENT	
ALTERATIONS AND RENOVATIONS (*Itemize by category*)	
OTHER EXPENSES (*Itemize by category*) * Graphic design and typesetting for print educational materials 10,000 * Videotape production for patient education component 28,000 * Computer/software programming for physician education 2,000	40,000
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD	231,260
TOTAL <u>DIRECT</u> COSTS FOR INITIAL BUDGET PERIOD (Item 71, Face Page)	**$231,260**

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY / TOTALS		INITIAL BUDGET PERIOD (FROM PAGE 4)	ADDITIONAL YEARS OF SUPPORT REQUESTED			
			2nd	3rd	4th	5th
PERSONNEL: Salary and fringe benefits Applicant organization only		165,497	*277,242	260,603	268,421	270,575
CONSULTANT COSTS		12,000	6,000	6,000	6,000	6,000
EQUIPMENT		8,793	5,200	4,784	-	-
SUPPLIES		1,370	1,717	2,072	1,930	1,172
TRAVEL		3,600	3,600	3,600	3,600	3,600
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT	-	*400	1,680	1,280	640
ALTERATIONS AND RENOVATIONS		-	*8,500	-	-	-
OTHER EXPENSES		40,000	35,765	-	-	*2,228
SUBTOTAL DIRECT COSTS		237,260	329,924	278,739	281,231	289,975
CONSORTIUM/ CONTRACTUAL COSTS						
TOTAL DIRECT COSTS		231,260	338,424	278,739	281,231	289,975

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD (ITEM 8A)——	$1,419,629

JUSTIFICATION (Use continuation pages if necessary):

From Budget for Initial Period: Describe the specific functions of the personnel, collaborators, and consultants and identify individuals with appointments that are less than full time for specific period of the year, including VA appointments.

For All Years: Explain and justify purchase of major equipment, unusual supplies request, patient care costs, alterations and renovations, tuition remission, and donor/volunteer costs.

From Budget for Entire Period: Identify with an asterisk (*) on this page and justify any significant increase or decrease in any category over the initial budget period. Describe any change in effort of personnel.

For Competing Continuation Applications: Justify any significant increases or decreases in any category over the current level of support.

EXAMPLE OF A BUDGET JUSTIFICATION FROM A 1995 GRANT APPLICATION

Personnel

Angela T. Morales, M.D. will devote 30% of her time to the project as the project director and principal investigator. Dr. Morales will be responsible for the overall coordination of project activities. She will directly supervise the research nurse and research associate and will coordinate regular meetings of the interdisciplinary research team. With other team members, she will develop the educational materials to be used in the physician and patient education interventions.
Dr. Morales brings to the project a strong background in General Pediatrics and training/experience in clinical research studies in the area of asthma, medication compliance, and medical education. Following residency training at the University of Colorado Medical Center, Dr. Morales completed a two year Robert Wood Johnson Foundation Fellowship in General Pediatrics at Michael Reese Medical Center in Chicago. During this fellowship, Dr. Morales completed a study of factors associated with medication compliance in acutely ill asthmatic children living in Cook County public housing.[26] Dr. Morales is currently an Assistant Professor of Pediatrics at the UAHSC and is actively involved in teaching as well as clinical research. In March, 1993, she was appointed Director of the Children's Wellness Center (CWC), the residents' continuity clinic and proposed site for this study. As CWC director, Dr. Morales is responsible for the effective functioning of the clinic and for coordination of the teaching activities in General Pediatrics. She has access to detailed diagnostic and demographic data which are collected on each clinic patient and will make use of this information to facilitate patient recruitment, to coordinate program activities, and to facilitate maintenance of the study population. Dr. Morales is the principal investigator on two current studies of morbidity in Mexican-American Children with asthma funded by the Tucson Area Health Education Center (TAHEC) and the UAHSC Institutional Research Grants Program which are described in the Preliminary Studies section.

Clyde Parsons, M.D., MPH is Assistant Professor of Pediatrics and a member of the Division of Pulmonary Diseases. He will devote 15% time to the project as co-investigator and pulmonary specialist. He will collaborate with Drs. Morales, Herrara, and Dennis to develop the physician education program and supporting materials including the pocket cards. He and Dr. Morales will be primarily responsible for the delivery of the physician intervention. Dr. Parsons will personally train and monitor the performance of the research nurse to insure that spirometric measurements are performed according to ATS recommendations and will provide guidance in the analysis of spirometry data. Dr. Parsons will provide advice and assistance in ensuring that questionnaires and chart review forms are clinically relevant and complete. Dr. Parsons received his M.D. degree from Emory University, were he was elected AOA. Following completion of residency training in general pediatrics at the UAHSC, he spent five years as a general pediatrician at United States Public Health Service Clinics located in Gonado and Nogales, Arizona. He completed a Pulmonary Research Fellowship at the University of New Mexicio and joined the faculty of UAHSC in July, 1987. Since 1989, he has worked one day a week at the Cobre Valley Community Hospital in Claypool, Arizona as a consulting pediatric pulmonologist and spends three weeks each summer in the same capacity at the Navajo Nation Health Foundation Hospital in Fort Defiance, Arizona. As a consequence of this clinical experiences, Dr. Parsons is quite familiar with the health care needs of Hispanic children and other minorities in the Southwestern United States.

Stanley R. Montgomery, Ph.D. Assistant Director, Center for Biostatistics, UAHSC, will provide support and advice in data collection and analysis. He will devote 10% time to the project as co-investigator and statistician.. Dr. Montgomery has already provided invaluable assistance in the

development of the research plan and in determining appropriate means of data collection as well as in calculating the appropriate sample size based upon the measurement instruments to be used. He will be responsible for insuring the quality/completeness of data and for coordinating the final data analysis. Dr. Montgomery was appointed to the Biostatistics Center following completion of a doctoral degree in statistics from Arizona State University in 1987. As is evident in the attached biographical sketch, Dr. Montgomery has been a co-investigator in numerous clinical studies including several which have examined cross-cultural aspects of health care. He brings to the project expertise in non-parametrics and statistical methodology and the demonstrated ability to function effectively as a member of an interdisciplinary team.

Elizabeth Herrara, Ph.D. is an Instructor in the Department of Pediatrics at UAHSC. She will devote 50% time to the project as co-investigator and evaluation coordinator. She will be responsible for determining the reliability and validity of the instruments to be used in this study as well as developing an evaluation of the patient education package. With the other investigators, she will be involved in the data analysis. Dr. Herrara received her doctoral degree in educational measurement from the University of Arizona in December, 1994. For the past five years, she served as the senior research associate and then as the program evaluator for a Pediatric HIV clinical research study in the Department of Pediatrics at UAHSC. Dr. Herrara has been actively involved in the development and evaluation of the instruments to be used in this study

Archie Dennis, Ed.D. is a Senior Associate in the Center for Health Professions Education at the UAHSC and is an associate professor at the University of Arizona School of Educational Policy and Research. He will devote 10% of his time as co-investigator and physician education coordinator. He will play a major role in the development and evaluation of the physician education component, including the computer-based asthma knowledge pre/post-tests and ICBMs, and also assist with the patient education component, assuming major responsibility for design and production of the videotapes. He will supervise the 50% time educational media specialist who will do software programming for the computer-based tests and patient management simulations in the physician education intervention. Dr. Dennis earned his Ed.D. from Michigan State University in 1971. He has been a medical education consultant at the University of Washington Medical School (1971-76), the University of Tennessee Medical School (1976-85) and at UAHSC since 1986. He has directed bilingual patient education programs for the American Dietetic Association, the American Heart Association and the Tennessee Kidney Foundation.

Lydia Naranjo, DPH. is a Certified Health Education Specialist for the Tucson Area Health Education Center and an adjunct faculty member for the School of Public Health at the UAHSC. She will work with Drs. Morales, Parsons and Alvarez in creating culturally relevant and appropriate materials for the patient education program and will assist training the nurse educator in the delivery of the patient education program. Dr. Naranjo received her doctorate in public health from the University of Houston in 1993. Dr. Naranjo will contribute 10% of her time as co-investigator and patient education coordinator.

Therese Jayne, M.S. is a Data Management Specialist, Center for Biostatistics, UAHSC, and will coordinate data management for this project. Ms. Jayne will devote 10% of her time as co-investigator and data manager. Her areas of expertise are computer-based data management systems and data quality control for collaborative, multidisciplinary research projects. She has directed data management, quality control, and sample scheduling for numerous large-scale studies. She is currently directing the data management for a multicenter study of determinants of atherosclerosis in youth, in which data from 13 clinical sites are sent to UAHSC for data entry, management, and statistical analysis.

Dalia Huerta, R.N. will be the full-time bilingual research associate years 2 - 5 of the project, and will be primarily responsible for patient recruitment and enrollment as well as for scheduling return visits. She will be responsible for coordination of daily study activities. Ms. Huerta will interview all patients and their parents at enrollment and at 6, 12, 18, and 24 months. She will be responsible for coordination of all data collection including interview data, spirometry, medical record reviews and school attendance records. She will be responsible for the maintenance of logbooks, questionnaires, and data sheets and for transmission of data to the data management group. The research associate will, to the extent possible, be unaware of the hypotheses of this study.

Yvonne Santos, R.N., M.S. will be the full-time bilingual nurse educator in years 2 - 5 of the project and will be responsible for the coordination and implementation of the patient educational intervention She will schedule each family for the appropriate educational modules and will insure that they view the correct videotapes and receive the appropriate written materials, which she will review with them. Ms. Santos also will be responsible for medical record review, using an abstraction form. Finally, she will perform spirometry on all patients at enrollment and at each of the follow-up visits.

The project secretary will be hired on a 10% basis and will provide secretarial support for the project. She will be responsible for assisting with data collection forms and for obtaining medical records. She will assist the research associate and research nurse in scheduling return visits and will type all study reports and manuscripts.

The educational media specialist (50% for years 1 and 2) is critical to the development of the physician educational intervention which includes several computer-based tests and patient simulations. This individual will provide computer software programming support during development of these materials under the supervision of Dr. Dennis.

NOTE: Fringe benefits have been calculated using the current UAHSC institutional rate (26%). Salary increases have been calculated at a rate of three percent per year.

Consultant Costs

Wallace Alvarez, Ph.D., will serve as consultant to this project. Dr. Alvarez is Professor and Director of the Center for Health Promotion and Research, School of Public Health, University of Miami Medical Center. He has extensive experience in the development of intervention programs for chronically ill children and their families. He has specific experience in interventions for children with pulmonary diseases. Dr. Alvarez will serve as consultant in the development of patient education materials to ensure that materials are based upon principles of social learning theory, that the format is age-appropriate, and that important content elements are included. In year one of the project, and each succeeding year, Dr. Alvarez will conduct a 2-3 hour teleconference seminar for patients/parents and a 3-4 hour seminar for residents, fellows and attending physicians. He will consult a total of twelve (12) days in the first year at $500/day ($6,000). This includes three (3) days for preparation and delivery of the long distance teleconference seminars, three days for review and editing of patient education materials and six days consultation at the project site in Tucson. Travel expenses for the six planning trips to Tucson will be $1,000/trip = $6,000.

Patient expenses

Calculations for patient expenses have been made on the basis of the proposed workplan (see research plan, item 11). We plan to enroll 160 patients over an 11 month period, beginning in the second year of the study. This should result in a final study population of approximately 120 patients, allowing for a 25-30% dropout rate. Each patient will have four follow-up visits for data collection at 6, 12, 18, and 24 months after enrollment. Intervention group patients will participate in an additional four (4)

clinic visits during which they receive the educational intervention. Patients will receive $10.00 per clinic trip for travel expenses. We estimate that the distribution of data collection visits will be as follows:

Year 1:	no enrollment		
Year 2:	50% of enrollment= 80	no follow-up	total= 80
Year 3:	50% of enrollment= 80	40% followup=256	total= 336
Year 4:		40% followup=256	total= 256
Year 5:		20% followup=128	total= 128

Year 1

Equipment

$8793 is budgeted for the purchase of a Power Macintosh 9600 computer, color monitor and appropriate software packages. This computer is necessary to handle entry and data management for this project. This equipment will be housed with the Data Management Group in the Biostatistics Center at UAHSC. The purchase of the computer in the first year will result in savings throughout the project in the following ways: port charges to the mainframe computers of $720.00 ($9.00/month for 60 months); connect time charges of $3125.00 (a conservative estimate of 25 hours/week connect time to do programming, data entry, editing, and retrieval times 50 weeks times 5 years), storage charges of $2540.00 (based on previous project having 50 patients collected with similar questionnaires and adjusted for time of project and patient number differences). This would result in a total savings for these three items alone of $6385.00. This savings represents a difference of $2743.00 over the price of the machine. This calculation does not include any CPU time charges. However, these should be considerably reduced because many of the preliminary analysis and data summaries can also be accomplished on the microcomputer. Funds have been budgeted for data management and equipment in the first year of study so that programs can be set up and ready for patient enrollment in Year 2.

Supplies:

A total of $1,370 is budgeted for supplies as follows:

$600 is budgeted for expendable supplies including computer paper and floppy disks for the physician education computer, duplication costs, and general office supplies for the study.

$770 is budgeted for supplies to be used in data management and data analysis (computer diskettes (50@9.50 =475.00), optical disk for data storage (1 @ 45.00), office supplies (folders & stationary for patient kits; 50@ 0.40 = 20.00) and 2F form printing =230.00. Long-term accessible data storage will be on high-density computer disks with backup provided by optical disk. This system will result in savings of port charges and storage charges for the mainframe computer and will also allow easy access to the data for data analysis. $230 is budgeted for supplies necessary to print computer generated schedules, data collection forms, and data recording forms. The data collection forms will contain the pre-printed patient I.D. number. Pilot data forms will be generated in year one.

Travel: One (1) 2 day meeting in Washington, D.C. to meet with other investigators. Airfare + per diem for two days for Dr. Morales and Dr. Parsons = $1,800 x 2 = $3,600

Other Expenses:

$40,000 is budgeted for design, production of educational materials as follows:

$10,000 for graphic design and typesetting of educational materials for patient and families. This includes development and production of English and Spanish versions of all materials to accompany each videotape and printing costs.

$28,000 in the first year for production of 4 of the 8 educational videotapes for patient education programs (2 English and 2 Spanish). Costs include pilot-testing, translation, narration, studio & location production, and post-production editing. These videotapes are an integral part of the patient education component and will facilitate acquisition of self-management skills.

$2,000 for development of four computer-based patient simulations for residents. This includes programming costs and field-testing.

Years 2-5

Personnel: Additional personnel costs in years 2-5 are salaries for a full-time research associate, and a full-time research nurse. The full-time bilingual research associate will be primarily responsible for patient recruitment and enrollment as well as for scheduling return visits. She will be responsible for coordination of daily study activities. She will personally interview all patients and their parents at enrollment and at follow-up visits. The research associate will be responsible for coordination of all data collection including that obtained by interview, by spirometry, by medical record review and from school attendance records. She will be responsible for the maintenance of logbooks, questionnaires, and data sheets and for transmission of data to the data management group. $31,306 is budgeted for salary (base + fringe) for the research associate for years 2 - 5.

The full-time research nurse will be responsible for the coordination and implementation of the patient intervention package. She will schedule each family for the appropriate intervention modules and will insure that they are able to view the correct tapes and receive the appropriate written materials, which she will review with them. The research nurse will be responsible for medical record review, using an abstract form. Finally, she will perform spirometry on all patients at enrollment and at each of the follow-up visits. $45,200 is budgeted for salary (base + fringe) for the research nurse for years 2 - 5.

$8,664 is budgeted for salary (base plus fringe) for a programmer analyst at 20% effort for years 2-5. He/she will develop programs for data entry, for schedules and reports, and for data analysis. He/she will be a member of the Data Management Unit and supervised by the Data Manager. $21,610 is budgeted for the Research Data Management Assistant III (100% effort). He/she will transfer all data from questionnaires and forms into buffer data files and verify accuracy. She/he will perform all data entry and prepare reports. She/he will be a member of the Data Management Unit and will be supervised by the Data Manager. The Data Management Assistant will be hired at 100% effort for years 2, 3, and 4 and at 75% effort during year 5 of the project.

Consultant: In years 2-5, Wallace Alvarez, Ph.D. will provide six days of consultation annually at $3,000 per year (6 X $500.00). Travel will be $3,000 per year (3 trips Miami - Tucson at $1,000 per)

Equipment: $4900 is budgeted in year 2 for a Collins spirometer and $300 for calibration syringe. $3584 is budgeted in year 3 for an IBM microcomputer with a 80 MB hard drive. An AT-compatible computer is necessary to interface with the Collins spirometer to collect spirometry data and to generate flow volume loops and calculate % predicted values. Without this computer, we will be unable to collect/store data to generate complete flow volume loops and access these data for analysis. This hardware will allow us to generate full sets of spirometry data for enrolled patients. No AT-compatible equipment is available at the Pima-Kino Community Hospital where spirometry will be

performed. Data can thereby be stored on floppy disks for transmission to the Data Management Group. $1,200 is also budgeted in year 3 for the Informix software package. This package converts data generated by the Collins spirometer to ASCII files so that it can be analyzed using available statistical packages.

Supplies: $1,717 is budgeted for supplies in year 2 as follows: $800 for office supplies and spirometer supplies (nose clips, tubes, paper, floppy disks). $917 for supplies for the Data Management Unit including $504 for microcomputer diskettes, $95 for two optical disks, and $318 for printing forms, questionnaires, reports, and schedules.

Travel: $3,600 is budgeted for years 2-5 for a trip to Washington, D.C. at $1800 x 2 investigators.

Patient care costs: $400.00 is budgeted in year 2 for reimbursement for patient travel expenses @ 80 data collection visits x $5/visit. In year 3, $1,680 is budgeted for 336 patient trips. In year 4, $1,280 is budgeted for 256 patients trips. In year 5, $ 640 is budgeted for 128 patient trips.

Alteration and renovation: $8,500 is budgeted as follows in year 2 for renovation of space in the CWC at Pima-Kino Community Hospital to serve as the patient education room and the spirometry testing/records room for this project. $5, 500 is for renovation of a 11 X 13 foyer into the patient education room. Access to a patient education room is critical to the project. Renovation will consist of installing walls and a door, hanging a false ceiling with suitable lighting, carpeting, painting, installation of a built-in videocassette player/monitor and furnishing with tables and chairs. $3,000 is for conversion of a 10 X 9 vending room adjacent to the CWC into a spirometry testing room and secure storage space for educational materials, questionnaires and medical records. Renovation will consist of re-carpeting, painting, installation of storage cabinets and furnishing with tables and chairs.

Other Year 2 Expenses:

$35,000 for design, production and field-testing of education materials:

* $6,000 for graphic design and typesetting materials
* $28,000 for videotape production (4 tapes x $7,000)
* $1,000 for field-testing of physician computer programs

$765.00 for office and computer expenses as follows:

* $65 for installation of a telephone for the research associate and the research nurse.
* $600 for mainframe computer charges for 2 hrs of CPU time at $300/hr for prelim data analysis.
* $100 for postage for patient reminders.

Year 5

$2,228 is budgeted under "other expenses" including $1,428 for four hours of CPU time at $357/hr, $50 for postage and $750 for microfilming data forms (10,000 documents at $.075 each).

Template for Writing Personnel Justifications

- **Name, degree, current title** (e.g., Nancy Smith, PhD; Associate Professor, Microbiology)
- **Identify department, school , university**
- **% time devoted to the proposed project**
- **Identify job title on this project** (e.g., Director – Data Management)
- **Describe key tasks this person will perform**
- **Identify any supervision responsibilities**
- **Describe pertinent training and prior work experiences**

► Red Flags - Budget **("Yes" = Red Flag!)**

Note: Red flags pertain to grant submitted by <u>new investigator</u> without established record.

- Annual first year direct costs exceed the category norm for new PI's.
- PI has insufficient time committed to the project. For a new investigator, less than 30% time may be a red flag.
- Budget includes "out of line" requests such as:

  - more than one research assistant
  - a clerical position
  - more than one technician or post-doctoral fellow
  - paid consultants without clear roles or services
  - "deluxe model" equipment requests
  - extensive travel
  - alterations or renovations of facilities

- Co-investigators are listed as non-salaried contributors (may be viewed as "window-dressing").
- Special or unusual requests for personnel that are not explained in the budget justification.
- Lack of supporting documentation that institution has staff & facilities to implement project.
- Contractual or consortium relationships are not documented by letters of agreement.

► References

Cook TD, Campbell DT. *Quasi-emperimentation: Design and Analysis Issues for Field Settings*. Chicago, Illinois: Rand McNally, 1979.

Cooper H. *Synthesizing Research: A Guide for Literature Reviews* (3rd Edition). Thousand Oaks, CA: Sage Publications. 1998.

Cuca JM and McLoughlin WJ: Why clinical research grant applications fare poorly in review and how to recover. *Cancer Investigation*, 5(1): 55-58, 1987.

Day RA. *How to Write and Publish a Scientific Paper*. 5th ed. Phoenix, AZ: Oryx Press. 1998.

Hendricson WD. Writing clear, compelling and convincing grant applications. In Blessing D. (ed.) *Physician Assistant's Guide to Research and Medical Literature*, 2nd ed. Philadelphia, PA: F.A. Davis Company. 2005. Chapter 16.

Hulley SB & Cummings SR. *Designing Clinical Research: An Epidemiological Approach* (2nd ed.) Baltimore: Williams and Wilkins. 2001.

Huth EJ. *Writing and Publishing in Medicine*. (3rd edition). Baltimore: Williams & Wilkins, 1990.

Kundel HL, Walsh C. Preparing a research grant application budget. *Investigative Radiology* 1993; 28(Supp-2): S13 - S16.

Martin PA. Writing a useful literature review for a quantitative research project. *Applied Nurs Research* 1997; 10(3): 159-162.

Milne R, Chambers L. Assessing the scientific quality of review articles. *J Epidemiol & Comm. Health*. 1993; 47(3): 169-170.

Ogden TE, Goldberg IA. *Research proposals - a Guide to Success* (2nd edition). New York: Raven Press, 1995.

Reif-Lehrer, L. *Writing a Successful Grant Application* (2nd. edition). Boston: Jones and Bartlett Publishers, 1989.

Reif-Lehrer, L. *Grant Application Writer's Handbook*. Boston: Jones and Bartlett Publishers, 1995.

Romm FJ. Practical grantmanship: the application process in health care research. *Fam Med* 1991; 23(5): 382-386.

Rosa A, Eschholz P. *The Writer's Brief Handbook*. 3rd ed. Boston: Allyn and Bacon. 1999

Rush AJ, Gullion CM, Prein RF. A curbstone consult to applicants for National Institute of Mental Health grant support. *Psychopharm Bulletin* 1996; 32(3): 311-320.

Schwartz SM, Friedman ME. *A Guide to NIH Grant Programs*. New York: Oxford University Press, 1992.

Spencer CM, Arbon B. *Foundations of Writing: Developing Research and Academic Writing Skills*. Lincolnwood, Il: National Textbook Company. 1997.

Wilkinson J, Wilkinson C. How to conduct a literature review. *Nursing Standard*. 1995; 10 (9): 28-30.

Summary of Red Flags – All Sections

► Project Description (abstract):

- Fails to "tell the whole story" of the proposal (leaves the reviewer guessing)
- If responding to RFA = "belabors the obvious" with too much background information
- Inadequate narrative devoted to methodology
- Lack of eye-directing "headers" within text
- Not reviewer-friendly: less than 11 point font; squeezed margins; long sentences (e.g., more than 30 word per sentence average)

► Specific Aims

- Too many aims; project looks overly ambitious or poorly planned
- Aims statements are difficult to understand; lack clarity
- Aims not integrated with each other (e.g., looks like a "grab-bag" of unrelated projects).
- Aims not clearly linked to the hypothesis or research question.

► Background & Significance **"No" = red flag!**

Does the investigator:

- **Attack the gap?** Did the grant writer convince you that an important knowledge gap exists? **YES NO**
- Begin the B & S section with an "attack the gap" paragraph? **YES NO**
- Use reviewer-focusing section titles? **YES NO**
- Demonstrate real familiarity with the literature without being encyclopedic or devoting too much attention to general background literature? **YES NO**
- Demonstrate that this project offers a new & different (innovative) approach? **YES NO**

► Preliminary Studies "No" = red flag!

Does the investigator ...

- Use a book-end writing structure? **YES NO**
- Present preliminary studies and results pertinent to the proposed hypothesis? **YES NO**
- Document team members have training/experience relevant to project? **YES NO**
- Show evidence of competence for procedures described in protocol? **YES NO**
- Provide a description of preliminary studies (vs. appending reprints without explanation? **YES NO**

► Research Design and Methods No" = red flag!

- Does the research plan pass the "G – U – T Test?" **YES NO**

  G = Is an important knowledge **gap** identified?
  U = Is this a **unique** approach?
  T = Is a strong research **team** available to conduct the study?

- Is a model proposed to serve as the underlying framework for the project? **YES NO**
- Is the overall project/study design displayed in a graphic? **YES NO**
- Are aims, methods, data collection and analysis linked together? **YES NO**
- Are significant "decision points" answered in the methods section? **YES NO**
- Is a graphic timeline presented and discussed? Does it appear to be realistic? **YES NO**
- Are alternative experimental designs discussed? **YES NO**
- Are potential limitations & sources of data contamination acknowledged? **YES NO**

► Red Flags - Statistical Analysis "No" = red flag!

Is the statistical analysis ....

- Linked to the hypothesis and each aim? - OR - Is it a "fishing trip?" **YES NO**
- Described with enough precision to allow an appraisal of its merits? **YES NO**
- Appropriate for the hypothesis & nature of the data to be collected? **YES NO**
- Sophisticated enough to provide data needed to answer research questions? **YES NO**
- Are methods described for establishing the sample size requirements needed to detect statistically significant differences between groups? **YES NO**

► **Budget & Justification** **"Yes" = red flag!** **For new investigator without established record.**

- Annual first year direct costs exceed the category norm for new PI's. **YES NO**
- PI has insufficient time committed to the project. **YES NO**
- Budget includes "out of line" requests such as: (examples) **YES NO**

  - more than one research assistant
  - a full-time clerical position
  - more than one technician or post-doctoral fellow
  - paid consultants without clear roles or services
  - "deluxe model" equipment requests
  - extensive travel
  - alterations or renovations of facilities

- Co-investigators are listed as non-salaried contributors (may be viewed as "window-dressing"). **YES NO**
- Special or unusual requests for personnel that are not explained in the budget justification. **YES NO**
- Lack of supporting documentation that institution has staff & facilities to implement project. **YES NO**
- Contractual or consortium relationships are not documented by letters of agreement. **YES NO**

C-A-C-T-U-S: Pre-submission Assessment of Grant Application

This rating scale is designed to help grant application writers assess the likely "reviewer appeal" of their proposal in these areas: **CCC** (clear, compelling and convincing writing style that builds a case for the merits of the project), **access to subjects and resources** (feasibility of project), **control over study environment** (logistical management of project), **Team** (Is a strong research team available that has a track record of previous and successful collaboration?), uniqueness (What is new and different about this project?) and **"sizzle factor"** (E.g., curb appeal – What is the overall first impression formed by the application? Is it likely to stand out from other applications and grab the reviewer's attention?)

CACTUS Scale		**Low**			**High**
		1	**2**	**3**	**4**
C	**CCC** = Does the application communicate a **C**lear, **C**ompelling & **C**onvincing case for why this proposal is needed?	**1**	**2**	**3**	**4**
A	**Access to subjects & resources** Difficulty of enrollment & likelihood of maintaining study groups; access to facilities, equipment and support personnel; access to consultants.	**1**	**2**	**3**	**4**
C	**Control of subjects & study environment** Logistical feasibility of the project; ability to maintain the protocol over time.	**1**	**2**	**3**	**4**
T	**Team** Strengths & limitations of the principle participants; strength of pilot projects. Has team worked together before?	**1**	**2**	**3**	**4**
U	**Unique** Is this proposal unique, different and innovative?	**1**	**2**	**3**	**4**
S	**Sizzle** factor (curb appeal) What is exciting about this project?	**1**	**2**	**3**	**4**

Total Score (1-24): ☐

Comments:

Clear, Compelling & Convincing

Access

Control

Team

Unique

Sizzle factor

Good Luck!