An Evidence-Based Guide to Writing Grant Proposals for Clinical Research

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The competition for funds to conduct clinical research is intense, and only a minority of grant proposals receive funding. In particular, funding for patient-oriented research lags behind that allocated for basic science research. Grant writing is a skill of fundamental importance to the clinical researcher, and conducting high-quality clinical research requires funds received through successful grant proposals. This article provides recommendations for the grant-writing process for clinical researchers. On the basis of observations from a National Institutes of Health study section, we describe types and sources of grant funds, provide key recommendations regarding the process of grant writing, and highlight the sections of grants that are frequently scrutinized and critiqued. We also provide specific recommendations to help grant writers improve the quality of areas commonly cited as deficient. Application of this systematic approach will make the task more manageable for anyone who writes grants.

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High-quality clinical research is essential to understanding disease and improving health care. Each research proposal should provide the potential to add to the existing body of knowledge, to advance understanding, and to alleviate human disease and suffering. However, converting the proposal into reality requires grant funding. In this era of budget cuts and deficits, obtaining peer-reviewed research funds has become ever more competitive. The overall rate of funding of new R01 applications by the National Institutes of Health (NIH) in 2003 was only 24.1% (of the 18 733 applications to all institutes, 4521 were awarded grants) (1). Obtaining funding for patient-oriented research may pose a particularly difficult challenge (2). In 2001, while the success rates for principal investigators with MD and PhD degrees were similar (35% and 31%, respectively), far fewer awards were made to MDs (2839) than to PhDs (6137) (3). The scientific director of the National Institute of Child Health and Human Development stated, "The number of physicians participating in patient-oriented research has fallen over the past decade for a number of reasons, while disease-oriented research, as informed by cell and molecular biology, has been on the ascendancy. A major issue . . . is the recent and dramatic decline in patient-oriented research, i.e., research that requires interaction between a physician-investigator and a patient" (4). Given this climate, understanding the essentials of grant writing is of fundamental importance to the academic clinical researcher—for career development and for advancement of clinical research projects and programs.

Writing a grant proposal forces the investigator to create, define, and refine the research project. In fact, the time spent to fully conceptualize and synthesize the proposal will enhance the investigator's ability to conduct a better study and will provide the framework for future reports of the work. The proposal should be innovative and exciting, and its conceptualization stimulates the investigator to develop a logical sequence for future activities. This article provides guidance on the grant-writing process for new clinical researchers, describes the most common critiques and comments on grant applications during peer review, and provides recommendations based on this evidence. While some principles may apply to basic science grants, this article is primarily intended for clinical researchers carrying out patient-oriented research. This article is not intended to provide instruction on conducting clinical research. More detailed information on conducting clinical research (5–8) is available elsewhere.

Background Information on Grants

Types of Grants

In general, grants are of 2 major types: project and career development grants. Project grants generally support a specific research project and usually include only a small proportion of the principal investigator's salary, typically about 20% to 25% (but sometimes as much as 35% to 40%). These can be small grants for pilot work or preliminary studies, or larger grants, such as for investigator-initiated projects. Career development grants (9) generally provide mostly salary support (75% to 100%) and relatively little project support. Examples of these include NIH K awards and foundation-based career development awards.

Funding Sources

Many sources are available to help with locating information on grants for clinical research (**Table 1**). One of the most useful is the NIH Office of Extramural Research home page, which outlines all NIH grant mechanisms (http://grants.nih.gov/grants/oer.htm). The NIH

See also:

Web-Only
Appendices
Appendix Figure
Appendix Tables
Conversion of figures and tables into slides

Guide Archive (http://grants.nih.gov/grants/guide/index.html) provides NIH program announcements and requests for applications. Researchers can establish customizable searches for grant information in specific areas of interest on the Web sites of the Community of Science (http://fundingopps.cos.com/), Grantsnet (http://www.grantsnet.org/), or the Illinois Researcher Information Service (IRIS) (www.library.uiuc.edu/iris/). Information on foundation grants can be found on the Web site of the Foundation Center (http://fdncenter.org/), an independent nonprofit organization that provides comprehensive, up-to-date information on foundations and corporate giving programs. Other valuable sources of grant information are institutional grants or development offices, research mentors and other experienced investigators, and foundation files or resource libraries.

Understand the Reviewers' Perspective

The reviewers are probably successful, busy clinical researchers who will be reviewing the grant in time "borrowed" from other activities. Assume that the reviewers are intelligent, are savvy about research, have a broad fund of scientific knowledge, but perhaps have little in-depth experience in your area of interest. While the reviewers are probably committed to being thorough and fair, it is important to remember that they will often not be in your exact field and will be reviewing your grant in a few hours at the most. Given these circumstances, the urgency of focus, conciseness, conceptual clarity, and transparent language becomes apparent. The grant writer must help the busy reviewer understand the project by making its significance crystal clear, avoiding jargon and topic-specific abbreviations or terminology, and not expecting reviewers to search references. The proposal should be completely self-contained. The quality of the review, however, may vary depending on the experience and skill of your assigned reviewers in research, mentoring, and the grant-review process. Examining the NIH Review Criteria can be helpful (10, 11). See Appendix 1 (available at www.annals.org) for more information on the NIH review process.

Seek Guidance from the Program Officer or Grants Administrator

Contact the program officer or grants administrator (if available) for the grant before and during the grant-writing process as questions arise. Their guidance can be invaluable in this process. However, their encouragement does not represent endorsement by the review committee.

Review Successful Grant Applications

If successfully funded grant applications are available for the particular funding mechanism, these can serve as useful models for the application. For NIH grants, information on funded grants (including principal investigator and abstract) can be obtained from the CRISP (Computer Retrieval of Information on Scientific Projects) database (http://crisp.cit.nih.gov/). Knowing what studies are being conducted can help you identify unanswered questions, avoid duplication, and gauge the priorities of the funding agency. Obtain a full grant proposal by contacting the principal investigator directly or the NIH under the Freedom of Information Act (FOIA). For information, contact the NIH Freedom of Information Office Coordinator for the appropriate NIH Institute (www.nih.gov/icd/od/foia/coord.htm) or the NIH Freedom of Information Office (301-496-5633). There will be a processing and copying fee. For foundation grants, contact the foundation for a listing of recently funded grants, and then contact the principal investigators directly.

Table 1. **Clinical Research Funding Sources for New Investigators***

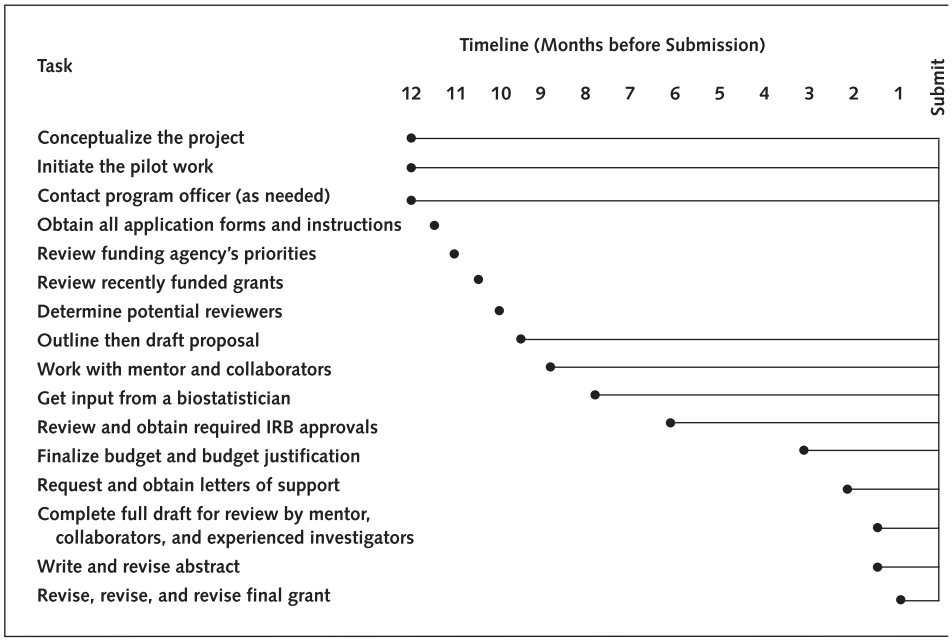
Source	Details about Funding Mechanism
NIH/AHRQ	K08 (Mentored Clinical Scientist Development Award) K23 (Mentored Patient-Oriented Research Career Development Award) R01 (Investigator Initiated Research Grant) R03 (Small Grant) R21 (Exploratory/Developmental Research Grant) Other federal funding sources include: CDC, CMS, VA
Foundations/national organizations	Specific to clinical or research area, such as Alzheimer's Association, American Cancer Society, American Diabetes Association, March of Dimes Offer career, project, pilot grants
Industry/pharmaceutical companies	Some unrestricted educational or research grants Grants may be linked to specific drug or product
Local/community/intramural	Local or community foundations, local organizations, hospital auxiliaries Source for small research projects, clinical demonstration projects, quality improvement initiatives, service delivery enhancements Intramural programs (e.g., pilot grants from Center grants, such as General Clinical Research Center, Older Americans Independence Center, Diabetes Center)

* AHRQ = Agency for Healthcare Research and Quality; CDC = Centers for Disease Control and Prevention; CMS = Centers for Medicare & Medicaid Services; NIH = National Institutes of Health; VA = Department of Veterans Affairs.

Know Your Audience

Find out in advance as much as possible about the potential reviewers. For the NIH, the membership of study sections (Integrated Review Groups) is available on the Centers for Scientific Review Web site (www.csr.nih.gov/committees/rosterindex.asp). Search the literature to determine the potential reviewers' areas of expertise. The Web sites of foundations, or their staff, may provide the composition of review committees. In these organizations, trustees or board members and foundation staff may also review the grant, so it is imperative that key sections and significance be understandable to lay reviewers.

Figure 1. **Grant-writing timeline: example 1.**



Stress the Significance

The importance of the proposed study should be communicated clearly and should be readily apparent to someone outside the field. Present the burden of the problem in quantitative terms, and demonstrate the impact of the proposed research on the field. The grant writer needs to convey why this research is important—innovative, incremental knowledge or paradigm shift—and its implications.

Follow All the Rules

Obtain and follow all of the guidelines exactly. Grant proposals that do not meet guidelines are commonly returned without review. Even if they proceed through the review process, the score may be adversely affected. Determine the requirements for documentation of Institutional Review Board (IRB) approval because these vary by funding agency and mechanism. Most applications involving human participants require a description of the proposed methods for their protection. Some grants allow the investigator to provide evidence of IRB approval after peer review has been completed but before funding is awarded. Determine the procedures of the specific funding agency to which you are applying. Follow all instructions regarding font size (characters per inch and lines per vertical inch), margins, format, and content. Grammatical and typographical errors annoy reviewers and convey a sense of carelessness that does not reflect favorably on the skills of the grant writer. Indicate the principal investigator's name and grant number on every page, and number each page. Do not expect any flexibility about submission dates.

Get Advice and Input from a Biostatistician

Input on the methods and analyses from an experienced biostatistician will enhance the success of your proposal. Seek advice early on for input about study design, data analysis plans, and sample size calculations.

Allow Enough Time for Prereview and Revision

Set yourself an internal deadline for completing the application 4 to 6 weeks before the actual deadline to allow time for prereview by mentors and colleagues, as well as by an experienced investigator outside of your field. Give colleagues at least 2 weeks for their review. Allowing enough time to revise the proposal in response to this feedback before submission will maximize the chances for success. It is important that you prepare the application carefully and convincingly. A high-quality product is more important than meeting a funding deadline, particularly when the application could be submitted for a future funding cycle or a different funding mechanism. In addition, allow ample time to refine budgets and subcontracts, and to obtain letters of support. See **Figure 1** for a proposed timeline for tasks related to grant preparation.

Write the Abstract Carefully

The abstract should distill the essential elements of the research project into short, concise, and clear statements. The abstract will guide the assignment of a grant to a particular study section and is generally the first portion of the grant that reviewers read. Therefore, the abstract must engage the reviewers' interest immediately and sustain their interest throughout. The abstract should highlight the nature of the problem, the need for the research, the hypoth-

esis to be tested, the methods to be used, and the significance and unique features of the research. It is good practice to write the abstract early and revise it throughout the process instead of writing it just before the grant is submitted.

Avoid Use of Appendices

Never put any vital information into appendices. The grant should stand alone, and appendices should only provide supporting materials. The reviewers may not receive or read the appendices.

Major Review Issues Identified in NIH Grant Proposals

Study Approach

To base our recommendations on evidence from the actual grant review process, we examined the review sheets (formerly called "pink sheets") from 66 R01 applications submitted to 1 clinical research study section. This informal study was intended to describe the representative types of problems commonly raised in NIH review of grants for patient-oriented research. We categorized major areas of critique raised by reviewers on each of the grants (**Appendix Table 1**, available at www.annals.org). This study was not intended to comprehensively or systematically examine the NIH review process or to thoroughly describe the grant-writing process. More detailed information on grant-writing can be found elsewhere (12–21).

Results

See **Appendix Table 1** (www.annals.org) for the major review issues identified in 66 NIH applications by grant section. In general, from the reviewers' perspective, the most important sections of the grant are specific aims/hypotheses, methods, and preliminary work. Thus, these sections should receive the appropriate amount of time and space in the grant-writing process.

Specific Aims/Hypotheses

This is the most important section of the grant. Common critiques from reviewers are that the specific aims and hypotheses are poorly focused, underdeveloped, or overly ambitious (**Appendix Table 1** at www.annals.org). Grant writers should spend considerable time and energy on fully conceptualizing and articulating the key elements of the research questions and hypotheses. We advise getting careful input from mentors, colleagues, and collaborators to refine this section. Begin the section with a concise, accurate synopsis of the research (study design, sample size, study groups, and primary outcomes) so that reviewers can tell what is planned in the research proposal; no additions or surprises should appear later. Follow the synopsis with clearly worded primary and secondary aims and related hypotheses. They should be focused, clearly conceptualized, and feasible. See Appendix 2 and Appendix 3 for examples (Appendix 3 is available at www.annals.org).

Background and Significance

This section justifies and builds the case for the project, but it is important to focus on the proposed specific aims and highlight the need for the proposed study. This section puts the project into context by providing essential background information for the content area, showing how the proposed project builds on previous work, and identifying gaps in previous knowledge. Common critiques from reviewers are that this section did not justify the need for the study, provided too much extraneous background information, or overstated the significance of the study (see **Appendix Table 1** at www.annals.org). After reviewing the literature for pertinent areas, the grant writer should strive for balance in setting the context for the grant. For each background area presented, it is important to show exactly how the background directly links with the proposed project. This section should naturally progress from the description of the current state of knowledge to the gap that the proposed research will fill. The following types of closing sentences on the paragraphs can be helpful to guide the reviewer:

"Thus, these studies demonstrate the importance of this area [elaborate here]"

"These studies provide the important background for this study in. . ."

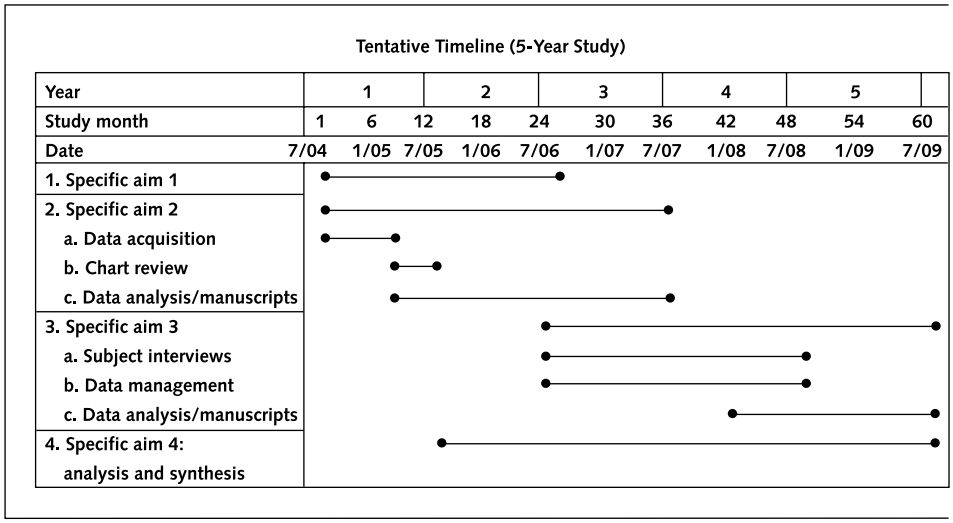
"The proposed project will build on this previous work [or address limitations in the previous work by]. . ."

For each area covered, explicitly state the relationship to the proposed project. Avoid the common mistake of making this section too long; be sure to leave adequate room for a fully developed Methods section. Having a "Significance" paragraph at the end of the Background section can help to frame the current status of the work in the field and explain how the proposed project will make a contribution. Specify in strong but realistic terms how the proposed project will contribute to the field. Use this section to justify the study and the methods used. Make the case for the proposed project, but be careful not to overstate its significance.

Preliminary Studies and Pilot Work

Reviewers are particularly interested in detailed description of preliminary or pilot work that is directly linked to the proposed study. Common critiques from reviewers are that preliminary or pilot work was lacking, was inadequately described, or lacked clear linkage to the proposed study. This section should summarize the principal investigator's (or co-investigators') previous work related to the proposed project. The principal investigator (or co-investigators) on the grant should be an author on the studies presented, and the references should be provided (manuscripts or abstracts). This section allows the investigator to convince the reviewers that 1) he or she has the expertise and experience to carry out this work, 2) the work is feasible, and 3) suitable groundwork has been done. This

Figure 2. **Grant-writing timeline: example 2.**



section shows the reviewer that the investigator knows how to do research; shows the thoughtfulness, rigor, and preparation needed for the study; and gives important preliminary data for the proposed project. This important section warrants space and detail. For each preliminary or pilot study indicated, present the specific objectives, methods, results (with brief description and data), and significance (provide direct linkage with the proposed study—one quarter to one half a single-spaced page for each) (for examples, see Appendix 3 at www.annals.org).

Indicate which studies provided experience with the proposed methods (for example, design, intervention, assessment instruments, and enrollment strategies) in the current study, even if they are on a different topic. Pilot work to assure availability of study participants is key. The presentation of pilot data on a proposed intervention strategy—its feasibility, reproducibility, and standardization—is crucial here. This is one section where "more is better," as long as the contributions and linkage to the proposed project are clear.

General Issues

Reviewers often raise issues on the layout and formatting of the grant, such as comments about typographical errors, small font sizes, formats that were difficult to read, excessive use of topic-specific jargon or abbreviations, and information presented in the wrong sections (for example, background information in the Methods section, new aims in the Analysis section).

Reviewers are unlikely to be convinced that the principal investigator is a good researcher if the grant is sloppily written or poorly laid out. Give time and attention to proofreading and making the grant easy to read. Provide spaces between paragraphs and between sections. Address study limitations thoroughly and realistically. For revised grants, the reviewers will focus on the degree of responsiveness to previous critiques. Provide an itemized, cordial, thoughtful response to each reviewer comment.

Methods

This section represents the heart of the grant, and all of the grants reviewed had comments on the Methods section (**Appendix Table 1** at www.annals.org). The most common general issue is that the methods were underdeveloped. We recommend that grant writers devote at least 50% of the page allowance of the grant to methods, with particular attention to the specific issues raised in the following paragraphs.

Design and Setting. Describe the study design in detail. If randomization is involved, describe the procedure. Describe the method for blinding of participant allocation to treatment groups. If applicable for observational studies, describe how you will select case-patients and controls. Will you enroll a representative sample of the target population? If not, will there be any potential biases? How will you handle them? Describe the setting or settings in enough detail so that reviewers can understand how this setting would compare or extrapolate to other study settings.

Study Sample: Inclusion Criteria. The major purpose of this section is to carefully describe and justify the choice of the study sample. Common critiques from reviewers are that the study sample is potentially biased or nonrepresentative, or that the inclusion criteria are poorly described or not well-justified. We advise addressing any potential biases and assuring that these will not invalidate the study results. The NIH requires inclusion of women, minorities, and children; grant writers must justify the exclusion of these populations.

Study Sample: Exclusion Criteria. Exclusion of partici-

Table 2. **Checklist for the Grant-Writing Process**

Section and Topic	Questions To Address
Specific aims/hypotheses	Are the aims well focused and fully conceptualized? Are the hypotheses clearly articulated? Do the aims appear balanced—not overly ambitious or unrealistic?
Background/significance	Is the significance/importance of the work evident? Is the work innovative? Does it contribute substantially to previous work in the field? Is the need for the study (or all aspects of the study) well-justified? Is the significance overstated? Is there extraneous information?
Preliminary/pilot studies	Are preliminary studies well described and their contributions to the proposed project clear? Is there sufficient pilot work? Is availability of subjects assured? Are enrollment and/or intervention procedures tested and feasible?
Methods	
Study sample	Are inclusion and exclusion criteria fully described and well-justified? Are the reasons for selecting this sample clear, not merely convenience? Are there important potential biases in the sample selection? Are there too many exclusions that are not well justified, or are important exclusions overlooked? Are there postenrollment exclusions that could potentially bias the sample? Is availability of adequate numbers of participants from the sampling frame assured? Are there enough participants in the setting to do this study as described?
Data collection/procedures	Are procedures well-described? Are there quality assurance measures for data collectors? Is there adequate description of study instruments/measures? Are standardized, validated measures used? Are there concerns about validity or reliability of data collection methods? Are all important study variables described and collected? Are there extraneous variables that are never used in subsequent analyses?
Outcome	Is the outcome adequately described, defined, and specified? Are the validity, reliability, and performance characteristics of the outcome measure provided? Are the outcome data collected by researchers who are blinded to the study hypotheses and study group assignment?
Intervention (if applicable)	Does the intervention appear potent (that is, is it likely to be effective as described) Is the intervention well-described—can you understand what was done, or is it a "black box"? Is the protocol standardized so that it is likely to be reproducible in other settings? Is the intervention administered by a separate individual/group not involved in outcome assessment? Is there blinded administration of the intervention protocol (e.g., double-blinding of drug trial)? Is there randomization to study groups? Is there likely to be potential bias in the way the patients were allocated to treatment groups or received the intervention? Will adherence to the intervention be monitored? Will the effects of nonadherence be considered? Are safety issues regarding the intervention addressed? Is an appropriate control group selected? Are issues of contamination or co-interventions in the control group addressed?
Data analysis	Have you consulted a biostatistician? Are the analytic approach and structure of analyses adequately described? Will an intention-to-treat approach be used? Is there adequate attention to potential confounders? Are there sample size or power calculations? Are attrition rates/losses provided? Do they appear realistic/justified? Do anticipated losses threaten the validity of the study? How will missing data and nonresponses be handled in analyses?
Summary	Are the strengths and weaknesses of the grant presented? How do the weaknesses affect the validity or interpretation of the study results? Are potentially fatal flaws unaddressed? Are the implications of the work discussed?

pants may be required for feasibility or safety reasons, but the grant writer should remember that any exclusion will make the study less generalizable. Common critiques are that the reasons for exclusion were not well justified, that the exclusions would result in important bias in the sample, or that in some cases important exclusions were overlooked. We advise that each exclusion criterion be well-justified. Address any important potential biases, and assure that these will not invalidate the study results or their applicability to more general samples.

Availability of Participants. A common critique from reviewers is that the availability of participants for the proposed study is not assured. Provide data and assurance that adequate numbers of patients will be available for the study in the proposed setting, given the inclusion and exclusion criteria. The strongest evidence is pilot work in the pro-

posed study population (even early descriptive work); if this is not possible, provide data from previous related studies.

Data Collection/Procedures. This section assures quality in the data collection procedures. Common critiques by reviewers are inadequate description of the proposed study instruments or variables and concerns about validity or reliability of the data collection methods. We advise describing all study procedures and instruments. A tabular format can help provide information on standardized and validated instruments, including references and performance characteristics, such as sensitivity, specificity, and reliability statistics. Describe all study variables (that is, measurements or data elements), and indicate how each variable will be used in subsequent analyses. List and define all variables; tabular formats can be useful (for examples, see **Appendix Tables 2** and **3**, available at www.annals.org). Be inclusive, but do not include any variables that will not be used in the analyses. Outline the screening and enrollment procedures, along with subsequent assessment and follow-up procedures. Elucidate the interviewer training and standardization or reliability assessments, as well as ongoing procedures for quality assurance of data collection.

Outcomes. This section provides a detailed description, including the operational definition and specification, of each study outcome. Common critiques by reviewers include concerns about the lack of or inadequate blinding of outcome assessment, inadequate description or specification of the outcome measure, or concerns about validity or reliability of the outcome. The grant writer must fully define the outcome or outcomes and describe the performance characteristics of the measures used for each outcome. Ideally, the outcomes should be assessed by trained research staff who are not involved in the intervention (if applicable) and who are blinded to the study hypotheses and to the intervention status of the participants. Describe how blinding will be achieved and maintained; address any potential threats to maintaining blinding. Describe how equal surveillance for outcomes will be assured in all study groups (that is, that the outcomes will be equally likely to be detected in all study groups). The study should be adequately powered to evaluate all of the primary outcomes in the study.

Intervention/Controls (If Applicable). This section should comprehensively describe the intervention strategy and how it will be implemented. Common critiques by reviewers are that grant proposals poorly describe the intervention, present an unstandardized intervention or one of questionable potency, do not adequately describe plans to monitor adherence, and do not address contamination or co-intervention in the control group. Another common reviewer concern is that inadequate randomization procedures or unblinded administration of the intervention may lead to potential bias in allocation to the intervention. We advise the grant writer to describe the intervention strategy and standardized protocols in sufficient detail so that the intervention is not a "black box" and might be replicated in other settings. Describe the interventionists, their proficiency, and any training required. Give details on how you will track adherence to interventions. Detail the quality assurance methods for the interventionists. Report how you will monitor potential sources of contamination or co-intervention in the control group during the study.

Data Analysis/Sample Size Calculations. This section describes all data analysis issues, including data management procedures, analytic approach, and sample size/power calculations. Common critiques by reviewers are insufficient description of the analytic approach, lack of an intention-to-treat analytic strategy, inadequate control for potential confounders, insufficient description of the handling of missing data, and not enough consideration of attrition. We advise early and ongoing involvement of a biostatistician in the grant-writing process to ensure statistical input in the study design, data management, analysis, and sample size calculations. Working with the biostatistician, the grant writer should fully describe data management and quality assurance procedures, such as double entry of data, error and validity checks, and training of staff who will handle data management procedures. Lay out proposed analyses here for each specific aim or hypothesis. Specify the outcome variable and the independent variables and covariables to be examined in each analysis. Laying out the framework for the analyses is of paramount importance; however, use caution in specifying only one statistical approach, since locking oneself into a particular statistical method (for example, logistic regression) may raise concerns. Discuss alternate strategies considered and why you decided on your approach. Carefully address how nonresponses and missing data will be handled in analyses.

Work with a biostatistician to provide relevant sample size and power calculations for primary outcomes applying best estimates for effect sizes from pilot work or previous studies. Estimate realistic attrition rates, and account for these in the calculations.

Advantages and Limitations of Current Approach

Realistically assess the strengths and weaknesses of the proposed project. State how you will address the limitations, and assure reviewers that the limitations will not invalidate the study results.

Tentative Timetable

A timetable for the proposed study is invaluable for reviewers to understand the study procedures and duration. Many graphical or tabular formats are available. For examples, see **Figure 2** and the **Appendix Figure** (the **Appendix Figure** is available at www.annals.org).

Summary and Conclusions

Table 2 summarizes key questions to address in any grant proposal. This summary was based on the evidence

and recommendations in this article and can assist you with writing future grants. Following this approach will ensure that you have addressed key areas of concern from the reviewers' point of view. We based our recommendations directly on primary evidence (reviewers' comments) gathered from an NIH Study Section; thus, we provide a real-world representation of review issues. While results of only 1 study section are represented, a sizable number of grants were included and the comments capture critical issues that have been stressed in other reports (14–21).

We believe that application of this systematic approach to grant-writing may help to make the task less onerous and more enjoyable for new clinical investigators, and for all persons embarking on writing grants.

Appendix 2: Example of Specific Aims Section

(Note: Appendix 1 is available at www.annals.org.)

The following is an example of a specific aims section. The principal investigator gave permission for inclusion of this example.

Delirium, or acute confusional state, is a common, serious, and potentially preventable problem for hospitalized older patients. Our previous study, the Delirium Prevention Trial which involved 852 patients, documented the effectiveness of a multicomponent targeted intervention strategy (MTI) for substantially reducing the risk of development of delirium during hospitalization, compared with usual care (UC). The overall objectives of the current renewal application are to extend the analyses of the Delirium Prevention Trial to examine cost-effectiveness, secondary short-term and long-term outcomes, and effects of adherence on intervention effectiveness. These investigations will more fully establish the effectiveness of our intervention strategy, including its overall cost-effectiveness and the lasting nature of the benefits.

A.1. Specific Aim 1

To examine the cost-effectiveness of the multicomponent targeted intervention (MTI) strategy for delirium prevention compared with usual care (UC). This aim involves the following sub-aims:

1. To measure the direct health care costs of the MTI strategy, as compared with UC.

2. To perform a net cost analysis for health care costs for the MTI strategy for short-term (hospitalization and one-month follow-up) and long-term (six-month and twelve-month follow-up) periods.

3. To estimate cost-effectiveness ratios of MTI compared with UC.

The associated hypotheses are:

Hypothesis 1a: In the short term, the MTI strategy may result in increased costs compared with the usual care group because of the costs associated with the intervention itself.

Hypothesis 1b: In the long term, the MTI strategy will prove cost-effective since the intervention is effective and long-term cost-savings from reduction of delirium and its associated sequelae (e.g., institutionalization, rehospitalization, and increased use of home care) will offset—in whole or part—the costs of the intervention.

A.2. Specific Aim 2

To examine the effectiveness of the intervention strategy in the Delirium Prevention Trial relative to usual care on improving secondary outcomes in short-term (hospitalization and one-month follow-up) and in six-month and one-year follow-up, including functional status, cognitive status, depression, subjective health rating, independent living ability, mortality, and health care utilization (i.e., rehospitalization, emergency department visits, physician visits, formal home health care, rehabilitation stay, and nursing home placement).

Hypothesis 2: The intervention strategy will result in improved short-term and long-term secondary outcomes compared with usual care.

A.3. Specific Aim 3

To measure the impact of level of adherence on effectiveness of the interventions in the Delirium Prevention Trial.

Hypothesis 3: The effectiveness of the intervention strategy will increase as the level of adherence with the interventions increases.

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References

1. Office of Reports and Analysis. NIH competing research grant applications, fiscal years 1970-2003. Bethesda: Office of Extramural Research, National Institutes of Health. Accessed at http://grants.nih.gov/grants/award/success/rpgbyacttype7003.xls on 23 July 2004.

2. **Kotchen TA, Lindquist T, Malik K, Ehrenfeld E.** NIH peer review of grant applications for clinical research. JAMA. 2004;291:836-43. [PMID: 14970062]

3. Office of Reports and Analysis. NIH support for M.D.'s and Ph.D.'s: NIH Competing research project applications and success rate by degree. Bethesda, MD: Office of Extramural Research, National Institutes of Health. Accessed at www.nih.gov/grants/award/trends/mdsphds7001.htm on 23 July 2004.

4. Scientific Director's Preface. Bethesda, MD: National Institute of Child Health and Human Development, National Institutes of Health. Accessed at http://dir2.nichd.nih.gov/info/ar/a1.php3 on 23 July 2004.

5. **Feinstein AR.** Clinical Epidemiology: The Architecture of Clinical Research. Philadelphia: WB Saunders; 1985.

6. **Fletcher RH, Fletcher SW, Wagner EH.** Clinical Epidemiology: The Essentials. 3rd ed. Baltimore: Williams & Wilkins; 1996.

7. **Sackett DL, Haynes RB, Guyatt GH, Tugwell P.** Clinical Epidemiology: A Basic Science for Clinical Medicine. 2nd ed. Boston: Little, Brown; 1991.

8. **Hulley SB, Cummings SR, Browner WS, Grady D, Hearst N, Newman TB.** Designing Clinical Research. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

9. **Gill TM, McDermott MM, Ibrahim SA, Petersen LA, Doebbeling BN.** Getting funded. Career development awards for aspiring clinical investigators. J Gen Intern Med. 2004;19:472-8. [PMID: 15109347]

10. Review criteria for and rating of unsolicited research grant and other applications. NIH Guide 1997;26. Bethesda: National Institutes of Health. Accessed at http://grants.nih.gov/grants/guide/notice-files/not97-010.html on 23 July 2004.

11. NIH announces updated criteria for evaluating research grant applications. Notice No. NOT-OD-05-002, 10/12/04. Bethesda, MD: National Institutes of Health. Accessed at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-002.html on 11 November 2004.

12. **Browner WS.** Publishing and Presenting Clinical Research. Baltimore: Williams & Wilkins; 1999.

13. **McCabe LL, McCabe ER.** How To Succeed in Academics. San Diego, CA: Academic Pr; 1999:41-72.

14. **Lusk SL.** Developing an outstanding grant application. West J Nurs Res. 2004;26:367-73. [PMID: 15068558]

15. **Bordage G, Dawson B.** Experimental study design and grant writing in eight steps and 28 questions. Med Educ. 2003;37:376-85. [PMID: 12654123]

16. **Barnard J.** Keys to writing a competitive grant. J Pediatr Gastroenterol Nutr. 2002;35:107-10. [PMID: 12187283]

17. **Sandler RS.** Writing clinical research grant applications. Inflamm Bowel Dis. 2002;8:196-200. [PMID: 11979141]

18. **Throckmorton T.** Grant writing: learning to climb a professional mountain. J Perianesth Nurs. 2002;17:196-201. [PMID: 12046016]

19. **Goldblatt D.** How to get a grant funded. BMJ. 1998;317:1647-8.

20. **Schwinn DA, DeLong ER, Shafer SL.** Writing successful research proposals for medical science. Anesthesiology. 1998;88:1660-6. [PMID: 9637661]

21. **Barbieri RL, Ladd KM, Hill JA.** Ten steps to writing a research proposal [Editorial]. Fertil Steril. 1996;66:690-2. [PMID: 8893668]

Appendix 1: The NIH Review Process

Several federal NIH Web sites describe the NIH grant review process:

www.csr.nih.gov/Welcome/Grant_Application.htm, www.csr.nih.gov/REVIEW/peerrev.htm, and www.niaid.nih.gov/ncn/grants/basics/index.htm.

Briefly, on a thrice-yearly cycle the NIH Center for Scientific Review assigns received grants, roughly 16 000 per round, to an integrated review group. Within the review group each grant is assigned to a study section that typically includes 20 or more researchers. Within the study section, your grant is assigned to a primary and secondary reviewer, who thoroughly review and critique the grant on the basis of the project's significance, approach, innovation, and the strengths of the investigator and research environment. The primary and secondary reviewers of all grants for a study section present the research proposal to the integrated review group, which is followed by a 10- to 15-minute discussion by all review group members, most of whom have focused primarily on the abstract, significance, and specific aims sections. Within 6 to 8 weeks of the review you will receive a summary statement, which includes a priority score and a percentile rank. Based on the score, percentile rank, and the priorities of the institute, your grant may or may not be funded during the cycle.

Appendix 3: Grant Section Examples

Following are examples of specific aims and preliminary studies sections. **Appendix Tables 2** and **3** provide examples of study variables tables, and the **Appendix Figure** shows a sample timeline. Principal investigators gave permission for inclusion of these examples.

Specific Aims Section: Example 1

The Insulin Resistance Intervention after Stroke Trial (IRIS) is a randomized, double-blind, placebo-controlled trial that will test the hypothesis that reducing insulin resistance and its sequelae with thiazolidinedione therapy will prevent stroke and myocardial infarction (MI) among patients with a recent ischemic stroke. Eligible subjects are men and women over 44 years of age without diabetes mellitus who have insulin resistance and a recent non-disabling ischemic stroke. During 3 years of recruitment, 3136 patients will be randomly assigned to pioglitazone, a thiazolidinedione (TZD), or placebo. The specific aims are:

Primary Aim

1. To determine if pioglitazone, compared to placebo, will reduce the overall risk for fatal or non-fatal stroke or fatal or non-fatal MI among non-diabetic men and women over age 44 years with insulin resistance and a recent ischemic stroke.

> Among non-diabetics with insulin resistance, we hypothesize that pioglitazone will reduce the occurrence of any primary endpoint (fatal or non-fatal stroke or MI) within four years from 27% to 22%. The basis of this hypothesis is research showing that insulin

Appendix Table 1. **Major Review Issues in National Institutes of Health Grant Proposals (n = 66)**

Area*	Grants, *n* (%)
Specific aims/hypothesis	30 (45)
Goals overstated, overly ambitious or unrealistic	12 (18)
Poorly focused or inadequately conceptualized	10 (15)
Hypotheses not clearly articulated	8 (12)
Background/significance	24 (36)
Need for study not well justified	19 (29)
Too much background, insufficient room for methods, extraneous information	3 (5)
Overstatement of significance of study	2 (3)
Preliminary/pilot studies	33 (50)
More pilot work needed	27 (41)
Studies cited with no clear link to proposed study	4 (6)
Inadequate description of preliminary studies	2 (3)
General issues	24 (36)
Layout poor (editing/typographical/grammatical errors, inconsistencies, too-small font, omitted lines or tables, poor photocopy, difficult to read)	13 (20)
Use of jargon, abbreviations, undefined terms	3 (5)
Information presented in wrong sections	3 (5)
Limitations not adequately discussed	2 (3)
(For revision) Inadequately responsive to previous reviewers' comments	5 (8)
Methods	66 (100)
Generally underdeveloped	10 (15)
Study sample	46 (70)
Inclusion criteria	36 (54)
Flawed sample (nonrepresentative, potential bias)	24 (36)
Poorly described	12 (18)
Exclusion criteria	23 (35)
Reasons for exclusion not well justified	12 (18)
Important exclusions overlooked	7 (11)
Postenrollment exclusions (potential bias)	4 (6)
Availability of study participants not assured	4 (6)
Data collection/procedures	18 (27)
Inadequate description of study instruments or variables	9 (14)
Concerns about validity or reliability of data collection methods	5 (8)
Important variables omitted	2 (3)
Many study variables not used in analyses	2 (3)
Outcome	40 (66)
Concerns about adequate blinding of outcome assessment	24 (36)
Outcome measure inadequately described, defined, or specified	15 (23)
Concerns about validity or reliability of outcome measure	9 (14)
Intervention	16 (24)
Inadequate description of how adherence will be monitored or analyzed	9 (14)
Method of randomization not described or potential bias in selection process	5 (8)
Concerns about potency of intervention	5 (8)
Poorly described or unstandardized protocol	4 (6)
Unblinded administration of intervention	2 (3)
Concerns about unaddressed safety issues	2 (3)
Controls	7 (11)
Issue of contamination or co-intervention	4 (6)
Lack of or inadequate description of control group	3 (5)
Data analysis	42 (66)
Inadequate control for important confounders	21 (32)
Insufficient description of analytic approach	16 (24)
Intention-to-treat analytic strategy needed	7 (11)
Inadequate description of handling missing data or nonresponses	7 (11)
Sample size/power	28 (42)
Lack of or inadequate description of sample size or power calculations	17 (26)
Estimates of attrition rates not provided, too low, or require justification	13 (20)
Anticipated attrition or losses to follow-up that threaten validity of study	2 (3)

*Note: Within general topic areas, individual grants may have been categorized according to more than one issue; thus, the sum of the individual issues for the topic area may exceed 100%.

Appendix Table 2. **Study Variables Table: Example 1**

Variable*	Source of Information†	Time(s) of Assessments‡	Analyses (by Specific Aim No.)
Patient descriptors			
Demographics	INT, MR	B	1-3
Matching factors (age, gender, delirium risk)	INT, MR	B	1-3
Study group	SDAT	B	1-3
Functional status			
ADL	INT	B, 5 d, 1 mo, 6 mo, 12 mo	1-3
IADL	INT	B, 1 mo, 6, mo, 12 mo	2
Incontinence	INT	B, 1 mo, 6, mo, 12 mo	2
Cognitive status			
Delirium (CAM)	INT	B, H, 5 d, 1 mo, 6 mo, 12 mo	1-3
MMSE	INT	B, H, 5 d, 1 mo, 6 mo, 12 mo	1-3
mBDRS	INT	B, 1 mo, 6 mo, 12 mo	1-3
Other delirium risk factors			
MMSE, orientation	INT	B, 5 d	1,3
ADL impairment	INT	B, 5 d	1,3
Vision impairment	INT	B, 5 d	1,3
Hearing impairment	INT	B, 5 d	1,3
BUN/Cr ratio ≥ 18	MR	B, 5 d	1,3
Depression: GDS or proxy rating	INT	B, 5 d, 1 mo, 6 mo, 12 mo	2,3
Subjective health rating	INT	B, 5 d, 1 mo, 6 mo, 12 mo	2,3
Burden of illness			
APACHE II Score	INT, MR	B	1-3
Charlson comorbidity index	MR	B	1-3
Mortality	NDI, INT, MR	DC, 1 mo, 6 mo, 12 mo	1,2
Health care utilization and costs			
Hospital LOS	MR	DC	1,2
Hospital costs	MIS, CARE	DC	1
Rehospitalization	INT, MR, MIS, CARE	1 mo, 6 mo, 12 mo	1,2
Emergency department visits	MR, CARE	1 mo, 6 mo, 12 mo	1,2
Physician visits	INT, MR, CARE	1 mo, 6 mo, 12 mo	1,2
Formal home health care use	INT, MR, CARE	1 mo, 6 mo, 12 mo	1,2
Short-term rehabilitation stay	LTC, INT, MR, CARE	DC, 1 mo, 6 mo, 12 mo	1,2
Long-term nursing home placement	LTC, INT, MR, CARE	DC, 1 mo, 6 mo, 12 mo	1,2
Level of adherence with interventions			
Overall	IDAT	DC	3
By components	IDAT	DC	3

* ADL = activities of daily living; BUN/Cr = blood urea nitrogen: creatinine (index of dehydration); CAM = Confusion Assessment Method; GDS = short form Geriatric Depression Scale; IADL = instrumental activities of daily living; LOS = length of stay; mBDRS = modified Blessed Dementia Rating Scale; MMSE = Mini-Mental State Examination.
† CARE = Medicare database; IDAT = interventionists' data tracking system; INT = interview (patient and/or proxy); LTC = Long-Term Care Registry; MIS = hospital medical information service; MR = medical record; NDI = National Death Index; SDAT = study data tracking system.
‡ 1 mo, 6 mo, 12 mo = 1-, 6-, 12-month follow-up contacts; 5 d = 5 day (or discharge if sooner) reassessment in hospital; B = baseline; DC = at hospital discharge; H = daily throughout hospitalization.

resistance is associated with increased risk for stroke, myocardial infarction, and pathologic processes that promote vascular disease. Insulin resistance is associated with vascular endothelial dysfunction, vascular inflammation, dyslipidemia, impaired fibrinolysis, and atherosclerosis. Markers of vascular inflammation have recently been shown to be related to increased risk for stroke and heart disease. Pioglitazone markedly reduces insulin resistance and vascular inflammation. It also improves endothelial function, lipid metabolism and fibrinolysis. By these and other mechanisms we hypothesize that pioglitazone will protect patients with ischemic stroke and insulin resistance against recurrent vascular events.

Secondary Aims

1. To determine if pioglitazone, compared to placebo, will reduce the risk for recurrent stroke.

   We hypothesize that pioglitazone will reduce the occurrence of recurrent fatal or non-fatal stroke as a discrete outcome.

2. To determine if pioglitazone, compared to placebo, will reduce the risk for acute coronary syndromes (acute MI or unstable angina).

   Unstable angina is an important clinical event because it identifies individuals at high risk for MI who need urgent diagnostic and therapeutic intervention. We hypothesize that pioglitazone will reduce the overall occurrence of acute coronary syndromes.

Appendix Table 3. **Study Variables Table: Example 2***

Demographics	Ascertained-when	Ascertained-how	Purpose
Age	Admission	DOB-chart	Descriptive
Sex	Admission	Medical record	Descriptive
Race	Admission	Medical record	Descriptive
Residence	Admission	Proxy	Descriptive
Education level	Admission	Proxy	Descriptive
Proxy interview			
Modified Blessed Dementia Scale (MBDRS)	Within 48 hours of admission	Proxy-identified through proxy screening form	Confounder/effect modifier
IQCODE	Within 48 hours of admission	Proxy	Confounder/effect modifier
Family Confusion Assessment Method (CAM)-Delirium	Within 48 hours of admission	Proxy	Confounder/effect modifier
Functional status (ADL/IADL)	Within 48 hours of admission	Proxy	Confounder
Prior diagnosis of cognitive impairment (CI) or depression	Within 48 hours of admission	Proxy	Confounder
Tobacco/alcohol/drug abuse	Within 48 hours of admission	Proxy	Confounder
Hearing/vision impairment	Within 48 hours of admission	Proxy/research nurse	Confounder
DNR status/living will	Within 48 hours of admission	Proxy and medical record	Descriptive/confounder
Medical record abstraction			
Drugs on admission	On ICU Admission	Medical record	Descriptive/confounder
ICD-9 admitting diagnosis	On ICU Admission	Medical record	Descriptive/prognostic
Evidence of delirium	Daily	Medical record	Primary outcome
Daily ICU interview			
Confusion Assessment Method-ICU (CAM-ICU)	ICU daily	Patient interview	Primary outcome
Post-ICU discharge interview			
Confusion Assessment Method (CAM)	Every other day on floor	Patient interview	Primary outcome
Delirium Rating Scale (DRS)	Every other day on floor	Patient interview	Primary outcome
Patient factors			
Charlson Comorbidity Index	Admission	Medical record	Confounder
Body Mass Index	Admission	Measured by nurse	Effect modifier
APACHE II	Within 24 hours of admission	Medical record	Confounder
SOFA score	Daily	Chart review	Effect modifier
Glasgow Coma Scale	Daily	Nurse assessment	Confounder
Ramsay sedation scale	Daily	Chart review	Effect modifier
Renal function	Daily	Medical record	Effect modifier
Hepatic function	Daily	Medical record	Effect modifier
Oxygenation/ventilation (ABG)	Daily	Chart review	Effect modifier
Drug data			
IV infusions	Every 8 hours	Automated delivery pump	Risk factor of interest
IV drugs–boluses/PRN	Daily during ICU stay	Pyxis automated computer	
IV drugs–scheduled	Daily during ICU stay	Tracking	
Oral drugs	Daily during ICU stay		
ICU interventions			
Mechanical ventilation	Daily	Yes/no–medical record	Descriptive
Non-invasive ventilation	Daily	Yes/no–medical record	Descriptive
Re-intubation	Daily	Yes/no–medical record	Descriptive
Pulmonary artery catheter	Daily	Yes/no–medical record	Descriptive
Physical restraints	Daily	Yes/no–medical record	Descriptive/confounder
ICU readmission	During hospital stay	Yes/no–medical record	Descriptive
Change in DNR status	Ongoing	Medical record	Confounder
Other data collection			
ICU mortality	Ongoing	Medical record	Secondary outcome
Hospital mortality	Ongoing	Medical record	Secondary outcome
Length of ICU stay	Discharge	Medical record	Secondary outcome
Length of hospital stay	Ongoing	Medical record	Secondary outcome
Days on ventilation	Ongoing	Medical record	Secondary outcome
Institutionalization	Discharge	Medical record	Secondary outcome

* ABG = arterial blood gases; ADL = activity of daily living; APACHE = Acute Physiology and Chronic Health Evaluation; DNR = do-not-resuscitate; DOB = date of birth; IADL = instrumental activity of daily living; ICD-9 = International Classification of Diseases, Ninth Revision; ICU = intensive care unit; IV = intravenous; PRN = as-needed; SOFA = Sepsis-related Organ Failure Assessment.

3. To determine if pioglitazone, compared to placebo, is effective in preventing progression to overt diabetes among patients with cerebrovascular disease and insulin resistance.

Insulin resistance is the principal risk factor for type II diabetes. We hypothesize that pioglitazone, by sensitizing cells to insulin's action, will prevent progres-

Appendix Figure. **Grant-writing timeline: example 3.**

Study Timetable										
Project activity	7/04–12/04	1/05–6/05	7/05–12/05	1/06–6/06	7/06–12/06	1/07–6/07	7/07–12/07	1/08–6/08	7/08–12/08	1/09–6/09
Study activity										
Interrater reliability/training	X	X	X	X	X					
Database setup	XX									
Patient enrollment	XX	XXX	XXX	XXX	XXX					
Data management	XX	XXX	XXX	XXX	XXX					
Data analysis, specific aim 1					XXX	XXX				
Manuscript preparation, aim 1						X	XX			
Data analysis, specific aim 2						XX	XXX	X		
Manuscript preparation, aim 2								XXX		
Data analysis, specific aim 3								XX	XXX	X
Manuscript preparation, aim 3									X	XXX

Each X represents 2 months.

sion to diabetes, a major antecedent to adverse cerebrovascular morbidity and mortality.

4. To determine if pioglitazone, compared to placebo, will reduce the risk for all-cause mortality.

We hypothesize that pioglitazone will reduce all-cause mortality because of its potent vaso-protective effects.

Specific Aims Section: Example 2

The proposed study will test the hypothesis that the efficacy for reducing illicit drug use and improving buprenorphine adherence of physician management (PM) plus cognitive-behavior therapy (CBT) is greater than PM alone during the initial 12 weeks of maintenance treatment, and during 12 weeks of follow-up. The study will explore potential patient predictors of differential treatment response identified in early studies (early abstinence achievement, cocaine abuse or dependence, prescription opiate (versus heroin) dependence) and help identify patient subgroups for whom CBT leads to the greatest differential improvement and is most cost effective. The study will also expand upon our prior work exploring important service delivery questions regarding costs, spillover effects, and patient and staff experiences regarding benefits and problems.

The specific aims of this grant are:

1. To determine the effect of the addition of CBT to PM compared to PM alone on illicit drug use in opioid dependent patients receiving buprenorphine maintenance in a primary care office-based setting.

Hypothesis 1a is that the addition of CBT to PM will lead to decreased illicit drug use during the time CBT is provided. Hypothesis 1b is that CBT will lead to decreased illicit drug use in the 12 weeks follow-up period after completion of CBT.

2. To determine the effect of the addition of CBT to PM compared to PM alone on adherence to buprenorphine.

Hypothesis 2 is that the addition of CBT to PM will lead to greater adherence to buprenorphine.

3. To compare the cost-effectiveness of the addition of CBT to PM to PM alone.

Hypothesis 3 is that the addition of CBT to PM will demonstrate cost-effectiveness overall.

4. To conduct exploratory analyses regarding patient-treatment matching and evaluate whether some patient subgroups (e.g., lack of achievement of early abstinence, cocaine abuse or dependence, and heroin (versus prescription opiate) dependence) specifically benefit from the addition of CBT to PM.

Preliminary Studies Section: Example 1

Secondary Outcomes of Delirium: Does Delirium Contribute to Poor Hospital Outcomes? A Three-Site Epidemiologic Study*

In three prospective cohorts totaling 727 patients aged 65 years and older, delirium was found to be an important independent prognostic determinant of hospital outcomes at discharge and 3-month follow-up, including new nursing home placement, death or new nursing home placement, and functional decline—even after controlling for age, gender, dementia, illness severity, and functional status. These cohorts were observational (non-interventional), and the populations were distinct from the Delirium Prevention Trial subjects. The adjusted odds ratios for delirium associated with each secondary outcome were as follows. Delirium was a significant predictor of new nursing home placement at both hospital discharge (adjusted odds ratio (OR) for delirium = 3.0, 95% confidence interval (CI) 1.4-6.2) and at 3-month follow-up (adjusted OR = 3.0, CI 1.5-6.0). Although not a significant independent predictor of death (which was an

infrequent outcome), delirium was a significant predictor for the combined outcome of death or new nursing home placement (adjusted OR = 2.1, CI 1.1-4.0 at discharge and adjusted OR = 2.6, CI 1.4-4.5 at 3-month follow-up). Moreover, delirium was a significant independent predictor of functional decline at both hospital discharge (adjusted OR 3.0, CI 1.6-5.8) and 3-month follow-up (adjusted OR 2.7, CI 1.4-5.2).

Significance

This study documents that delirium itself serves as an important independent prognostic predictor for secondary outcomes at hospital discharge and 3-month follow-up. The Delirium Prevention Trial—with its successful reduction of delirium rates—may well improve these secondary outcomes. Thus, this preliminary study provides convincing evidence justifying the need for the proposed detailed examination of secondary short-term and long-term outcomes in the current application. The current application will allow completion of follow-up data collection (telephone interviews and medical record reviews), tracking of health care utilization data and other secondary outcomes (nursing home placement, rehospitalization), tracking of all losses to follow-up, and verification of mortality status—all of which are critical to conduct the proposed analyses.

*Cite pertinent abstracts or references for preliminary work.

Preliminary Studies Section: Example 2

The Study of Insulin Resistance after Stroke-II (SIRS-II)*

This study was a critical preliminary investigation seeking proof of the principle that TZDs would reduce insulin resistance in non-diabetic patients with cerebrovascular disease. The aim of SIRS-II was to examine the effectiveness of pioglitazone 45mg daily, compared with placebo, for improving insulin sensitivity among non-diabetic patients with insulin resistance and a recent TIA or ischemic stroke.

SIRS-II was a randomized, double-blind, placebo controlled trial. Eligible patients were recruited from SIRS-I if they had an insulin sensitivity index ≤ 2.5 and no history of New York Heart Association class III or IV heart failure (a contraindication to therapy). Consenting patients underwent a repeat oral glucose tolerance test before randomization if their prior test was over 30 days old. Patients were randomized according to a pre-printed schedule that was prepared by the investigational pharmacist at Yale-New Haven Hospital. Randomization was blocked in groups of 4 subjects to assure balanced treatment allocation. Investigators did not have access to the randomization schedule. After randomization, a research associate contacted subjects by telephone weekly for one month to supervise dose escalation, monitor for side effects, and encourage adherence. The study pill was dispensed as a 15mg tablet of pioglitazone or matching placebo. Dosage was increased by one pill weekly to a total of 3 pills per day by week three. After the first month, the telephone contact was reduced to every two weeks. At two months, blood was obtained from all subjects to monitor for liver toxicity (serum aspartate transaminase). At 3 months, all subjects underwent a repeat oral glucose tolerance test, measurement of serum aspartate transaminase, and physical examination, and treatment was stopped.

From 3/20/01-6/1/01, 20 patients were enrolled, with mean age of 67 in the placebo group (n = 10) and 66 in pioglitazone group (n = 10). As shown in **Appendix Table 4,** the insulin sensitivity index declined 0.1 units (-1%) among patients who received placebo and increased 1.1 units (62%) among patients who received pioglitazone (p = 0.0003), indicating a significant reduction in insulin resistance for pioglitazone recipients.

Appendix Table 4. **Mean Change in Insulin Sensitivity Index according to Treatment**

	Insulin Sensitivity Index				*P* Value
	Placebo (N = 10)		Pioglitazone (N = 10)		
Time of test	Mean	SD	Mean	SD	
Entry	1.8	0.5	2.1	0.6	.28
Exit	1.7	0.6	3.2	0.9	.0002
Change	−0.1	0.6	1.1	0.6	.0003
Proportional change	−1%	30%	62%	38%	.0006

Other measures of insulin sensitivity also indicated that pioglitazone had a significant effect. Fasting insulin declined 29% among patients who received pioglitazone (from 17 μU/ml to 11 μU/ml) compared with a 7% increase among patients who received placebo (from 18 μU/ml to 19 μU/ml). The homeostasis model assessment of insulin sensitivity (HOMA), an alternative measure to the Insulin Sensitivity Index, decreased 29% among patients who received pioglitazone compared with a 10% increase among placebo recipients (a lower HOMA score indicates greater insulin sensitivity). In a secondary analysis using stored blood, mean C-reactive protein declined 33% among patients who received pioglitazone compared to an increase of 10% among persons who received placebo (p = 0.06 for comparison of mean change).

Pioglitazone therapy was well tolerated. No patients were withdrawn from therapy because of side effects, and 6 out of 10 patients on active therapy said they would take their assigned treatment again if asked. All patients were interviewed every two weeks regarding specific side effects. Compared to patients on placebo, patients assigned to pioglitazone were more likely to report nausea (3 subjects compared to none) and weight gain (3 subjects compared to none). Despite the more frequent report of weight gain among subjects taking pioglitazone, actual mean weight gain was less among subjects receiving pioglitazone (-0.8 pounds) than among those receiving placebo (+2.2 pounds).

In summary, these findings demonstrate that pioglitazone is effective in reducing insulin resistance and safe for use among elderly non-diabetic patients with a recent TIA or ischemic stroke.

*Cite pertinent abstracts or references for preliminary work

Preliminary Studies Section: Example 3

Methadone Maintenance for Stabilized Patients in Primary Care*

To determine the feasibility and efficacy of office-based methadone maintenance provided by primary care physicians for

stable opioid dependent patients, we performed a randomized controlled open clinical trial in the offices of primary care internists and an opioid treatment program (OTP). Of 87 eligible patients, 47 opioid dependent patients on methadone without evidence of illicit drug use for one year and without significant untreated psychiatric comorbidity were randomized to office-based methadone maintenance from primary care physicians or usual care at an opioid treatment program. Thirteen of the twenty-two (59% CI: 38%-80%) patients in office-based care compared with 11/24 (46% CI: 26%-66%) of OTP patients had evidence of any illicit drug use by self-report, urine or hair toxicology testing during the six-month treatment period ($p = 0.37$). Ongoing illicit drug use meeting criteria for clinical instability occurred in 4/22 (18%, CI: 2%-34%) of office-based care patients compared with 5/24 (21%, CI: 5%-37%) of OTP patients ($p = 0.82$). Sixteen of the 22 (73%, CI: 54%-92%) office-based patients compared with 3/24 (13%, CI: 0%-26%) of the OTP patients felt the quality of care was excellent ($p < .001$). There were no differences over time within or between treatments in functional status, or the use of health, legal or social services. These results support the feasibility and efficacy of transferring stable methadone maintained opioid dependent patients to physician offices for continuing treatment.

Relevance

This study supports the feasibility and efficacy of opioid agonist maintenance in primary care and demonstrates our ability to conduct detailed assessments of opioid dependent patients receiving this treatment in a clinical trial. The study also points to the fragility of abstinence even among stable, methadone maintained patients and suggests the potential importance of providing patients cognitive behavioral therapy (CBT) to prevent resumption of illicit drug use.

*Cite pertinent abstracts or references for preliminary work.

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