Clinical Trial of Topical Thalidomide for Aphthous Stomatitis in Patients with HIV/AIDS
RFP: NIDCR-DR-04-15

PROJECT DESCRIPTION AND RATIONALE

Thalidomide given orally (PO) is effective for aphthous ulcers in HIV+ as well as immunocompetent patients. However, its utility has been limited by a spectrum of adverse effects. The combination of lack of tolerability for PO thalidomide, its teratogenicity, and reported increases in viral load have raised concerns regarding use of this drug in HIV-infected patients. Given the growing numbers of patients with HIV infection and the absence of other effective treatments for these painful and debilitating ulcerations, the need exists to develop alternative treatment strategies. Topical drug administration is a strategy for enhancing absorption at the anatomical target site while lowering plasma drug concentrations, hence decreasing the potential for toxicity.

When given PO, thalidomide takes four to six weeks to reach sufficient tissue concentrations to promote ulcer healing. However, efficacy for healing and pain reduction has been demonstrated for 20 mg topical thalidomide in a mean of 17 days, with minimal systemic absorption and adverse effects, suggesting that topical administration produces high local tissue concentrations which cannot be achieved with PO administration without dose-limiting adverse effects. Topical thalidomide may be an effective alternative to PO thalidomide treatment for aphthous ulcers in patients with HIV infection, without the side effect liability. Successful demonstration of a therapeutic effect and/or reduced toxicity will provide a basis for the further development of this route of administration for the treatment of painful aphthous ulcers associated with HIV infection. Moreover, demonstration of a therapeutic effect or reduced toxicity may provide a basis for the further development of this formulation for the treatment of immune-related mucosal ulcers of other idiopathic ulcerative conditions.

Well-designed clinical studies are needed to increase the understanding of the pathogenesis of aphthous ulcers and their impact on oral and general health. Therefore, the NIDCR proposes a phase II/III multi-center clinical trial for the treatment of aphthous ulcers in HIV/AIDS using a topical thalidomide formulation.

ARTICLE C.1. STATEMENT OF WORK FOR SOLICITATION PURPOSES (AND RELATED RFP SECTIONS AND ARTICLES)

a. Background Information

Infection with HIV results in progressive immune dysfunction characterized by opportunistic infections, malignancies, impaired wound healing, and idiopathic cutaneous and mucosal lesions. The oral cavity is a common site for these mucosal lesions. Since the introduction of combination therapy for HIV, a decrease in

opportunistic oral infections, such as candidiasis, oral hairy leukoplakia, and HSV has been noted, and is attributed to lower viral load and higher numbers of CD4+ cells. Although the prevalence of infectious oral manifestations has been reduced, specific reductions in aphthae have not been formally reported. National surveillance data from the CDC indicates that the decline in HIV incidence noted in the 1990's has slowed. The increased incidence of HIV combined with the decline in deaths due to AIDS translates into a higher AIDS prevalence. These data, combined with the lack of prophylaxis for HIV infection and its progression to AIDS, has contributed to the prediction that the numbers of persons living with HIV/AIDS will continue to increase over the next several years.

Data from the oral health component of the HIV Cost and Services Utilization Survey reveal that a large proportion of respondents reported experiencing oral lesions, with 38 percent describing their lesion as a "painful ulcer." Studies of prevalence in clinical populations report aphthous ulceration in 15 to 31 percent of HIV-infected patients. Hence, recurrent aphthous ulcers are a frequent oral manifestation in HIV-infected patients, causing substantial morbidity in the form of oral pain. Oral pain leads to a decrease in food intake and associated weight loss, as well as diminished quality of life. There are no satisfactory therapies or accepted standards of care associated with aphthous ulceration in HIV seropositive (+) patients.

A phase I/II dose-finding study conducted in the NIDCR Division of Intramural Research randomly assigned subjects to receive 0 (placebo vehicle), 5, 10, or 20 mg of thalidomide ointment using a double-blind, randomized, placebo-controlled design. The primary endpoint of healing was defined as an 80 percent decrease from baseline size using methodology developed by NIAID's AIDS Clinical Trial Group. Blood samples were obtained 5 minutes prior to ointment placement (baseline), and at 5 minutes, 1, 2, and 4 hours after placement. Plasma was stored at -80^{o}C until batched analysis for thalidomide by HPLC with UV detection on blinded, coded samples. Probability of ulcer healing was highest for the 20 mg dose (87.5 percent), and a positive trend for dose response was observed. The mean time to ulcer healing was 17 days for the 20 mg group versus 23 days for those healing in the placebo group, and there were more unhealed ulcers (60 percent) in the placebo group compared to the other groups. A dose response pattern was also observed for pain relief, with the most significant reduction observed for the 20 mg dose. Adverse events were similarly distributed between treated and placebo groups and no subjects discontinued the study medication secondary to adverse effects, nor were any dose reductions necessary. Drug concentrations for the placebo, 5, and 10 mg doses were either undetectable or below the level of quantification, while the 20 mg dose was detectable at 5 minutes post-application, highest at 1 hour post-application, and decreased, but remained detectable at a little over 0.1 mg/mL over the course of the remaining observation period of four hours. This dose-finding study was supportive of further testing of a 20 mg dose and indicates that topical thalidomide may be safe and effective.

b. Project Objective

The purpose of the present study is to assess the efficacy and safety of a novel topical thalidomide formulation for healing of aphthous ulcers associated with HIV/AIDS in a Phase II/III clinical trial of 160 subjects as outlined in the appended protocol (Attachment 1). The predicted outcome is that a topical route of administration for thalidomide will result in lesion healing and diminution of pain, without the adverse effects inherent in the higher systemic (PO) dose.

c. Detailed Description of the Technical Requirements

Independently, and not as an agent of the Government, the Contractor shall furnish all other necessary services, qualified personnel, equipment, facilities, and material, not otherwise provided by the Government, to assess the efficacy and safety of a novel topical thalidomide formulation for healing aphthous ulcers associated with HIV/AIDS.

Specifically, the Contractor shall carry out the following:

PHASE 1. Planning Phase (3 months)

1. Establish a Data Coordinating Center (DCC or Coordinating Center) capable of conducting all aspects of a multi-center clinical trial for the treatment of aphthous stomatitis in patients with HIV/AIDS, using a topical formulation of thalidomide. The Coordinating Center shall have overall responsibility for the operation of the clinical trial.

[NOTE TO OFFEROR: The Coordinating Center must demonstrate past success as a coordinating center with knowledge and expertise in regulatory requirements such as HIPAA, GCP, FDA (specifically IND), and human subject protections, including practices of quality control and quality assurance, training of data collection staff at clinical sites, data and safety monitoring procedures, and IRB policies and procedures. The Coordinating Center must demonstrate the capacity for data capture, handling, and secure transmittal using appropriate clinical trial level software.]

2. Submit to the Government Project Officer a plan for clinical site selection, site monitoring, and site closure by the end of the 2nd month after award of the contract.

3. Develop a statement of work for the clinical sites, in collaboration with the Project Officer.

PHASE 2. Site Selection and Materials Preparation (6 months)

1. Identify up to 10 clinical sites capable of recruiting study subjects 18 years of age or older with HIV infection or AIDS who are experiencing painful oral lesions. Clinical sites identified must be capable of recruiting approximately 10 - 12 patients per year for up to two years, with each

subject evaluated weekly and followed up to four weeks beyond study entry (refer to Attachment 1).

Selection criteria for clinical sites shall include:

- Demonstration of sufficient enrollment capacity, including description of recruitment strategy, patient catchment area, and flow.
- Description of regional and local population race/ethnicity and expected enrollee profile.
- Appropriate medical support for patients with HIV/AIDS.
- Appropriate pharmacy facilities for receipt, storage, allocation and documentation of drug supply.
- Demonstration of capacity to participate in oral health studies, including clinical and lab facilities equipment and instrumentation*, specimen and data handling capabilities, and appropriate study personnel.
- Demonstrate past experience as a successful clinical site for other studies/trials.

[Note to Offeror: Coordinating Center shall demonstrate experience with selection of clinical sites. The Coordination Center with the Project Officer will develop selection criteria for clinical sites. *Clinical Sites must furnish and maintain equipment and instruments necessary for the standardized conduct of the study including intraoral examination and documentation devices e.g., intraoral camera.]

2. Begin process of site selection by the end of the 3rd contract month, and complete site selection by the end of 6th contract month.

   - The DCC in collaboration with the Project Officer and the Contracting Officer will develop a generic subcontract as a template, and will work with the clinical sites to approve and implement. The Contracting Officer will review all draft subcontracts and provide formal approval.
   - One copy of the fully executed subcontracts with the selected clinical sites shall be submitted to the Contracting Officer and one copy, to the Project Officer, by the 9th month of the contract.

3. Using the existing NIDCR protocol, Attachment 1, which has been reviewed and approved by the NIH IRB and FDA, and in collaboration with the Government Project Officer, develop, disseminate and revise, as needed, Standard Operating Procedures that will become part of the Manual of Procedures that will include but will not be limited to:

   ..Inclusion/exclusion criteria.
   ..Patient enrollment and closure.
   ..Data collection and verification.

..Data entry and verification.
..Safety monitoring (including flow chart and timelines).
..Analysis and reporting of all of the above.
..Protocol violations and tolerance levels.
..Training and calibration.
..Drug handling and monitoring.
..Quality control and assurance plan.
..Specimen Handling Plan.
..Dissemination Plan
..Study Forms

- A draft of the Manual of Procedures shall be submitted to the Government Project Officer by the end of the 5th month and the final document, by the end of the 7th month of the contract.

- In collaboration with the Government Project Officer, develop study and case report forms and set up a data entry system referred to under Phase 3, Conduct of Clinical Trial and Data Collection and Analysis, Task 4, Data Management and Maintenance.
- Disseminate to the clinical sites the Manual of Procedures, including the study/case report forms, protocol, and standard operating procedures by the 9th contract month.
- Train data collection/entry staff at each clinical site.

4. In collaboration with the clinical sites, develop a recruitment plan, accounting for specific resources and advantages of individual clinical sites. Submit the recruitment plan to the Government Project Officer for review and approval one month after the subcontract is approved by the Contracting Officer. The recruitment plan should include a copy of the proposed informed consent forms and all data collection instruments.

5. The government (NIH) holds the IND for the test article (drug) and will supply the drug for the study. The DCC will randomize and coordinate with the NIH pharmacy to disseminate the drug to the Clinical Sites and maintain appropriate control records.

6. The Contractor, in cooperation with the Government Project Officer, shall establish and oversee a Data and Safety Monitoring Board (DSMB) based on the guidelines for the establishment and operation of the DSMB found at http://www.nidr.nih.gov/clinicaltrials/data_safety_guidelines.asp .

7. The Coordinating Center will work with the Clinical Sites to obtain and maintain IRB approval.

- Any future revisions and changes to the protocol, statement of work, and Manual of Procedures will become a part of the contract.

- The DCC will keep on file all documentation, including IRB approved protocols from the Clinical Sites.

8. The Contractor shall start site investigator training, calibration, and recalibration with each site prior to subject enrollment at any site.

Research involving human subjects shall not be conducted under this contract at a particular site until the Contractor has provided to the Contracting Officer certification of IRB review and approval of the protocol at that site. The Contractor shall not proceed with Phase 3 below until either an OMB approval or a clinical exemption has been received and written authorization to proceed is granted by the Contracting Officer.

PHASE 3: Conduct of Clinical Trial and Data Collection and Analysis. (39 months)

Task 1: Subject Recruitment

The contractor shall provide assistance to the Clinical Sites to develop and prepare recruitment materials for the clinical trial based on protocol specifications including duplication and distribution of materials to selected target audiences. Contractor shall assure that recruitment of study population adequately represents the population-at-large and the population-at-risk.

Task 2: Data Collection, Storage and Analysis

1. The Coordinating Center shall prepare and supply the clinical sites with all study forms, copies of the study protocols and other materials; shall receive all data from study clinical sites and laboratories; and shall be responsible for the inventory and storage of these materials. Specifically, the Contractor shall:

    - Assume responsibility for the reproduction and distribution of all study forms, manuals, and other documentation.
    - Receive and store all data transmitted on the study forms or other media by the participating clinical sites and laboratories.
    - Maintain copies of any lists of shipments of data, specimens, drugs, or materials.
    - Protect against loss of study data and hold all information in confidence.

2. The Coordinating Center shall also be responsible for transmitting accurate data to the Project Officer, as required by the protocol and manual of operations and delivery schedule. The Contractor shall ensure completeness and accuracy of all data received from the clinical sites.

Task 3: Monitoring and Communications

1. The Coordinating Center shall be responsible for tracking protocol violations and shall notify the Project Officer and the Contracting Officer of such violations. Specifically the Contractor shall:

    - Implement requirements for standardization of observations, objective application of definitions, and other methods of quality control. Identify problems in adhering to the details of the various protocols and help solve these problems promptly.
    - Assign each patient for treatment based on a randomization schedule.
    - Conduct periodic training sessions for new personnel. These sessions shall review methods of collection and preparation of data.
    - Provide all logistical support for DSMB meetings and other study meetings as necessary.
    - Monitor adherence to all study protocols and update the NIDCR Project Officer and the NIDCR Clinical Director and IRB Chair of the results at regular operations committee meetings.

2. The Coordinating Center shall be responsible for overseeing the operations of the clinical sites to ensure:

    - Accurate reporting by each site of number of individuals screened, enrolled, and completed in accordance with the approved inclusion/exclusion criteria.
    - Each site is following the Manual of Procedures and all Standard Operating Procedures.
    - Initial and annual IRB approval is obtained and documentation is provided to the Coordinating Center no later than two weeks following IRB approval date.
    - Appropriate reporting of adverse events in accordance with toxicity monitoring and reporting plan.
    - Tracking, receiving, and processing of data specimens is occurring according to plan as per Task 2 and as described:
        - Specimen collection kits: The Project Officer will provide the Coordinating Center with a list and example of materials to be included in the blood collection kits as well as the main packaging material for the kits. The Coordinating Center shall purchase the supplies and assemble the kits following instructions provided by the Project Officer.
        - Instruction sheets for collection of blood: The Coordinating Center shall assist in drafting and revising the instruction sheets that will accompany the blood collection kits. The instructions will describe the procedures to be followed in obtaining the specimens and arranging for the collected

specimens to be sent to the Project Officer.
    - Sample tracking form: The Coordinating Center will develop the forms that will be used for tracking biological specimens.
    - Abstracting forms: The Coordinating Center will develop the forms that will be used to abstract information from medical records, pathology reports, and death certificates.
- Updating the information to and from the clinical sites, including changes in Standard Operating Procedures and operations, reporting and regulatory requirements, and IRB and DSMB findings.
- Written informed consent is obtained from all study subjects. Medical and research records are collected and maintained according to institutional requirements and the Manual of Procedures.
- Accurate data are transmitted to the Coordinating Center, as required by the Manual of Procedures and as per Task 2.

- Training and calibration as scheduled; including conducting site visits for quality assurance and control in collaboration with the Project Officer.
- In collaboration with the Project Officer, prepare and submit the annual FDA IND report.
- Perform data entry adhering to established clinical trials management practices.
- Quality control and standardization
    - Monitor study activities to determine whether data collection is proceeding uniformly and efficiently
    - Ascertain and report verification, discrepancy, and error rates for data collection, preparation and entry. The Project Officer may check samples of abstracting, coding, keying, or other work.
    - Institute corrective action when deviations from the protocol are found (i.e. retrain personnel)
    - Conduct other quality assurance checks as required by the Manual of Procedures
    - Monitor the performance and progress of any work done under subcontract
- Reporting and Documentation
    - Use the data management system referred to under Phase III, Task 4, Data Management and Maintenance, to monitor the status of data collection
    - Document all of the individual steps in the study and maintain the orderly arrangement of all relevant material, so that any aspect of the study can be reviewed and evaluated by the NIDCR staff at any point during its course. Included are the following:
        - Type letters, forms, and other documents necessary to conduct the study

- Duplicate materials used in the study when the original sources cannot be retained
- Maintain a filing system of all relevant materials, cross referenced to permit easy access
- Maintain a log of all decisions made during the study that pertain to study design, conduct, and analysis

3. Arrange and coordinate communications and meetings including:

- The Contractor shall respond to telephone and written inquiries.
- A one-day "kick-off" meeting within a month after the subcontracts have been executed, attended by the Project Officer, Co-Investigators, Clinic PIs and Coordinators, and the Coordinating Center.

- A two-day "mid-project" meeting during Phase 3, to review progress and to trouble shoot all procedures, attended by the Project Officer and Co-Investigators, the Coordinating Center, and Clinic PIs and Coordinators.
- A two-day "wrap-up" meeting during data analysis, to review analyses, attended by the Project Officers and Co-Investigators, the Coordinating Center and Clinic PIs and Coordinators.
- Other face-to-face meetings as needed to discuss issues related to the study.
- Conference calls as needed, between Project Officer and Co-Investigators, the Coordinating Center, and Clinical Site representatives.
- Attend and report on such meetings and communications, and take action on recommendations after approval by the Project Officer.

Task 4. Data Management and Maintenance

1. The Contractor shall establish a data management plan by the sixth month of the contract.

2. The Contractor shall possess a computer data storage system that will receive, inventory, and store all information. The Contractor shall design and implement edit systems to insure completeness, quality and uniformity of all data. Upon the effective date of this contract, the Contractor shall have, on-line and operational, computing capabilities and all other capabilities necessary to perform the Statement of Work. Specifically, the Contractor shall:

- Design and implement a data entry system. Edit systems shall be designed to insure completeness and quality of data. Outstanding data forms, incomplete forms, delinquent forms or missing reading center or laboratory data must be recognized by the system so that quality control programs can respond promptly. The Contractor shall be

responsible for training all personnel who are responsible for data entry, including personnel at Clinical Sites.

- The Contractor agrees to cooperate fully with the Project Officer and Contracting Officer, who may periodically review the Coordinating Center's performance in the development of systems for data management, data processing, and data maintenance.
- The Contractor shall provide to the Project Officer and designates access to data and data files whenever requested.

Task 5. Data Analysis

The Contractor shall prepare analyses of all data in accordance with an approved data management plan as follows:

1. Prepare detailed analyses of accumulated data for the DSMB to monitor the study for adverse and beneficial treatment effects at intervals determined by that committee and the Project Officer. These analyses shall assess positive and negative aspects of the effectiveness of any treatments under study.
2. Generate analyses as suggested by the DSMB and approved by the Project Officer. Only the Project Officer may direct the Contractor to doing work on such analyses.
3. Develop new or modified methods of analyses that meet the specific needs of the study.
4. In collaboration with the Project Officer and the study investigators, prepare analyses of study data for publication.

Task 6. Data Reporting

Publications will be prepared by the Coordinating Center in collaboration with the Clinical Sites and Project Officer. It is anticipated that all abstracts and manuscripts from this trial will be based on the complete patient data set because an insufficient number of subjects would be generated by any individual site to support secondary hypothesis or inference.

d. Level of Effort

Estimated effort for personnel is listed below:

Direct Labor (Years 1-3)	**Effort**	**Direct Labor (Year 4)**	**Effort**
Principal Investigator	15%	Principal Investigator	15%
Project Manager	100%	Project Manager	50%
Statistician	50%	Statistician	75%
Data Management	100%	Data Management	25%
Data Coordinator	100%	Data Coordinator	0%
Administrative Support	75%	Administrative Support	75%

Offerors shall ensure that the PI and all other personnel proposed will not be committed on Federal grants and contracts for more than a total of 100% of their time. If the situation arises where it is determined that a proposed individual is committed for more than 100% of his or her time, the Government will require action of the part of the offeror to adjust the time commitment.

e. Guidance for clinical center costs

For proposal preparation purposes, please budget $1,035,000 to cover the total cost of the clinical site subcontracts. Please allocate this amount over the four years accordingly to cover start-up, clinical trial operation and close-out costs.

f. List of Attachments

Attachment 1 – Protocol for clinical trial