NCI Clinical Assay Development Program

Application Instructions

Fiscal Year 2013

National Cancer Institute

Table of Contents

I. Helpful Information

A. Receiving emails from the CADP and proposalCENTRAL

To ensure that all email correspondence is delivered correctly and is not treated as spam by email programs, please place the following domains into the safelist/whitelist:

mail.nih.gov
nci.gov
altum.com

B. Contacts

1. **CADP contact information:** Questions related to all aspects of the NCI Clinical Assay Development Program EXCEPT submission procedures should be directed to Steve Marroulis. Submit questions as early as possible. Response times will vary depending upon the volume of inquiries.

Email: NCI_CADPinfo@mail.nih.gov

2. **proposalCENTRAL Customer Support:** Questions related to the submission of the application or other documents through the proposalCENTRAL system should be directed to the proposalCENTRAL customer support hotline, which is available Monday through Friday from 8:30 a.m. to 5:00 p.m. ET.

Phone: 800 875 2562 or +1 703 964 5840
Email: pcsupport@altum.com

C. Application

The application is at the proposalCENTRAL website where potential applicants must first register at https://proposalcentral.altum.com/ and then login. Once successfully logged in applicants should open the Grantmaker tab and search for **NCI - Clinical Assay Development Program.** Once you have opened the first window in the CADP website, please follow the instructions and begin the application by inserting a title and then creating an applicant profile. Be sure to save the application frequently – every 10-15 minutes – so that the system will retain the information as it is entered. Entering and saving the information on the Title Section initiates the application file. Do not worry, you will have plenty of opportunity to review and correct before you submit the application.

II. Submission Process

Submission requires that all application components be uploaded as PDF files and submitted through proposalCENTRAL by the deadline identified on the CADP website (http://cadp.cancer.gov). Material submitted after the deadline will not be forwarded for processing.

Start the submission process early! The proposalCENTRAL system has a number of required steps that must be completed before submissions will be accepted. Make sure to allow adequate time for completion of all application steps by the deadline.

Each application submission must include the completed proposalCENTRAL application package of forms and attachments associated with the Clinical Assay Development Program (CADP) in proposalCENTRAL (proposalcentral.altum.gov).

Submit applications **at least 72 hours before the application submission deadline** to allow time for proposalCENTRAL validation of the application and, if necessary, resubmission prior to the deadline.

A compatible version of Adobe Reader must be used to view, complete, and submit the proposalCENTRAL application package. To download the latest version of Adobe Reader, go to http://get.adobe.com/reader/

The application consists of the following components that must be uploaded:

- **Abstract**
- **Intended Use and Clinical Context of Use**
- **Background and Rationale Form**
- **Assay Status and Services Requested Form**
- **Plan for Further Development of the Assay Form**
- **NIH Biographical Sketch Form**
- **Supporting Documentation**
- **Technical Feasibility Form (optional)**

Each application form must be saved as an individual PDF file in accordance with the formatting guidelines listed in Appendix 2.

After creating the title section in proposalCENTRAL, please go to **Section 2) Download Templates and Instructions** and follow the directions to download all the appropriate forms. These forms include the Background and Rationale, the Assay Status and Services Requested, the Plan for Further Development of the Assay, the NIH Biosketch, and the optional Technical Feasibility form. Most of these forms are in Microsoft Word format that need to be converted to Portable Document Format (PDF) format before being uploaded to the proposalCENTRAL site.

In **Section 7) Key Categories**, please choose from the dropdown lists ONE disease site and intended use for your assay. If you do not see an appropriate choice in the lists provided you may choose “other” and

explain with a short answer. Each application must address a single intended use in a single disease setting.

III. Instructions for Completing Each Form

A. Abstract (2500 character maximum)

Please prepare an abstract in language suitable for a general audience of no more than 2500 characters that briefly and succinctly describes the intended use of the assay and its clinical context with specific disease state, the analyte, the platform(s) used to measure the analyte, and the services requested from the Clinical Assay Development Program. Please prepare this offline and then copy and paste into the abstract box in **Section 8) Abstract** on the proposalCENTRAL site according to the formatting instructions located there.

B. Intended Use and Clinical Context of Use (4000 character maximum)

Please prepare a summary in technical language suitable for the appropriate experts. How will the assay be used for clinical decision-making such as determining choice of therapy, change of therapy, etc.? There should be a single, defined clinical use with a description of the clinical context and disease state in which the diagnostic is intended to be used. Many assays may have additional uses beyond the stated single clinical use, but please focus your request on the one area of greatest clinical need and the services that are needed to prepare the assay for this clinical application. Please prepare this offline and then copy and paste into the intended use box in **Section 8** on the proposalCENTRAL site according to the formatting instructions located there.

Below the narrative boxes in **Section 8** is a list of technical platforms and another list of analytes. Please choose as many items from each list as apply to your assay. If your assay involves a platform or analyte not listed, please choose "other" and specify in the appropriate box above.

C. Background and Rationale (2 page maximum)

Please see http://www.cancerdiagnosis.nci.nih.gov/scientificPrograms/pacct/assay_standards.htm for definitions of terms used in this application form.

1. **Introduction:** Provide a brief description of the current state of the assay and summarize the preliminary data that support your expectation that it will have clinical utility. Be sure to define the cancer, state of disease and other components of the clinical context in which the assay will be used, focusing on the area of greatest clinical need. Describe data generated to date, related literature or a sound hypothesis that correlates the assay result (biomarker) with clinical outcome or a clinical action to support the further development

(detailed data and/or literature review can be supplied as appendices within the supporting documentation). If other assays exist for this clinical use, explain why this assay is unique and needed.

2. **Biomarker Association with Clinical Measures:** How well does the assay/marker associate a pharmacologic/biological effect of a drug or a disease state to a known therapeutic outcome, e.g., response, DFS, overall survival? If the marker is the drug target provide any information related to target positive response rate and possible mechanisms of drug resistance.
3. **Services Requested:** Describe the services that are requested from CADP. Refer to the CADP website for a list of available services but define what is specifically requested for your assay in order to prepare it for clinical application.

D. Assay Status and Services Requested (4 page maximum)

Please provide enough details to allow evaluation of the current status of analytical and clinical performance of the assay in human specimens. These specimens may include xenografts or other preclinical models but should provide some evidence of the prevalence of the marker in the intended clinical subset as well as the function of that marker within its intended use. You may use the optional Technical Feasibility Form to provide more detailed evidence about the analytical performance of the marker. To include standard operating procedures and additional information about assay parameters, please upload these separately as part of the Supporting Documentation (this can include publications that have used the assay).

Note: if data are not available, please insert N/A for Not Available.

1. **Assay Details**
    a. Specify the types of specimens intended for use with the assay (e.g. FFPET slide mounted sections, FFPET curls, fresh frozen tissue, serum or plasma). Describe further details about the specimen if known (e.g. tumor cell content/cellularity, number of sections needed for the assay, any known information relating to assay performance and specimen pre-analytic parameters)
    b. Identify the analyte(s) being measured
    c. Describe the assay type & platform (Examples of type: ELISA, immunohistochemistry, qPCR, etc.; Examples of platform: Luminex 200, AQUA, ABI Prism SNaPshot, etc.). Provide any information on other acceptable platforms or any unacceptable platforms for use in upcoming clinical studies.
    d. Assay components (i.e., reagents, calibrators or controls)

2. **Analytical Performance of the Assay**
    a. Describe the analytical sensitivity, specificity and precision/reproducibility you envision is necessary to serve the intended clinical use. Precision/reproducibility can be reported as inter-assay and intra-assay Coefficient of Variance of replicates, or as inter-operator and inter-instrument and inter-lab precision. It is

not necessary that the current assay meet these expectations. Please upload pdfs of manuscripts in **Section 9** if they describe the performance of the assay in the types of human samples in which the assay will be used.

b. Services requested. Select as many services as you think you may need.

3. **Clinical Performance of the Assay**

   a. **Endpoint:** Describe how good the assay needs to be for its intended clinical use and what specific clinical outcome or endpoint will be measured in conjunction with assay results, such as tumor response by RECIST criteria, time to progression, disease free survival, overall survival, etc. Please consider the risk to the patient of a false positive or negative result of the assay. For example, if the assay is to assign therapy in a trial what harm may occur to a patient if the assay is incorrect, either a false positive that causes the patient to be treated when s/he should not be or a false negative when the patient may not receive a therapy that could help them.

   b. **Clinical Sensitivity**: State what percentage of persons who have a given condition (based on clinical outcomes or endpoints) who are identified by the assay as positive for the condition should be. (True positive rate)

   c. **Clinical Specificity**: Describe what percentage of persons who do not have a given condition (based on clinical outcomes or endpoints) who are identified by the assay as negative for the condition should be. (True negative rate)

   d. **Precision/reproducibility**: Describe the acceptable range of assay results for replicate samples in the intended clinical context to support use in that context.

E. Plan for Further Development of the Assay (2 page maximum)

What will be done with the assay after CADP completes its work on the assay?

1. **Clinical Development Plan**
   Describe how this assay will be developed for widespread clinical use. Will the clinical utility of the assay be further assessed? Is it intended to be provided by a central service laboratory, or as SOPs for individual laboratory-developed tests and performed at multiple sites? Will it be submitted for approval or clearance to the FDA?

2. **Clinical Trial Plans**
   If this assay is intended to be used in a clinical trial, please indicate what clinical trial this assay is intended to support and state the anticipated trial start date (year and quarter). List the specific individual(s) and laboratory(ies) being considered for conducting the assay(s) for the clinical trial. Please indicate if help identifying a laboratory to perform the test for the trial is needed. Note: Assays used for clinical decision-making must be performed in a CLIA-certified facility and may need a pre-IDE review by the FDA if the diagnostic is integral to the trial.

3. **Clinical Utility**
   Provide details on the plan for confirming analytical and clinical performance and for testing the clinical utility of the assay. Indicate whether sufficient samples exist and are readily available for these studies or whether a source of samples will also be required to optimize the assay. If specific clinical trial specimens are required, please discuss with Cancer Diagnosis Program personnel.

4. **Intellectual Property Considerations**
   What is the status of the Intellectual Property associated with the marker and its assay? Applicants must be able to provide rights to any materials or techniques necessary to develop the assay. List any material transfer agreements or other intellectual property agreements that are already in place. Attach agreements as supplements in the supporting documentation.

F. NIH Biographical Sketch PHS 398/2590 (4 page maximum)

Please enter the information required by the proposalCentral online form as well as the standard NIH Biosketch whose modified instructions follow below. In addition, as with standard NIH applications, all Key Personnel should append their NIH Biosketch according to the instructions that follow. An eRA Commons User Name may be provided, but is not required.

1. Personal Statement: Briefly describe why your experience and qualifications make you particularly well-suited for your role (e.g., PD/PI, statistician, consultant, laboratorian) in the project that is the subject of the application.

2. Positions and Honors: List in chronological order previous positions, concluding with the present position. List any honors. Include present membership on any Federal Government public advisory committee.

3. Selected Peer-reviewed Publications: Please limit the list of selected peer-reviewed publications or manuscripts in press to no more than 15. Do not include manuscripts submitted or in preparation. You may choose to include selected publications based on timeliness, importance to the field, and/or relevance to the proposed research.

4. Research Support: List both selected ongoing and completed research projects for the past three years (Federal or non-Federally-supported). Begin with the projects that are most relevant to the research proposed in the application. Briefly indicate the overall goals of the projects and your responsibilities as a key person identified on the Biographical Sketch. Do not include the number of person months or direct costs.

G. Supporting Documentation (50 page maximum)

Combine and attach as a **single PDF file named "Support.pdf."** Please include current assay standard operating procedures, assay validation results to date, appendices and any

other information requested. Upload this single file to the proposalCENTRAL site as described in **Section 9) Proposal Narrative and Other Attachments**.

IV. Completion of the Application Process

Once all the forms have been prepared offline, please go back to the proposalCentral CADP site and follow the online instructions for completing the remaining sections. Please remember to save your application frequently as you work so that data entered are incorporated into the application. If any questions arise about the application and/or use of proposalCentral, please do not hesitate to contact the information sources listed in Section I above.

V. Suggestions for Online Interaction with the proposalCENTRAL Application

In **Section 3**, before other users (key personnel, institutional officials, etc.) may be enabled to access the application, the PI/Applicant must register each person in the proposalCENTRAL system. This requires that the applicant has the relevant information needed and the applicant should at least go through this section and its subparts in order to do appropriate registration if the applicant needs to grant access to other individuals as the application is created.

In **Section 4**, the applicant needs to click on the "Edit Professional Profile" and answer the straightforward questions before moving on to another section. In addition, the applicant should upload his/her NIH Biosketch form as a separate attachment. However, the NIH Biosketches for the Key Personnel need to be uploaded as part of the Support.pdf file.

In **Section 5**, the applicant needs to enter the appropriate information for the institution and the institution's point of contact. Since this is not a grant, the applicant may submit this application directly through proposalCentral; a Sponsoring Official need not be appointed unless the applicant's institution requires such action. However, it is both appropriate and the applicant's responsibility to ensure that the appropriate officials at the local institution are informed that the application for clinical assay development is being submitted.

In **Section 6**, if a Key Person is already in the proposalCentral system, inputting the email address is enough to add the person to the application. However, if the person is not in the system, then the applicant would be wise to gather the appropriate address and contact information ahead of time as well as to notify the person that they will be contacted by e-mail to confirm or enter their contact information. The system notifies the Key Person that a profile is needed and may send reminders until the profile is entered to the system's satisfaction.

In **Section 7** choose **ONE** disease site and **ONE** intended clinical use for your assay. Even if you envision your assay having additional uses beyond the stated single clinical use, please focus your request on the one area of greatest clinical need and the services that are needed to prepare the assay for this clinical application.

In **Section 8**, please enter the Abstract and the description of Intended Use and Clinical Context. Please observe the stated limits on the number and types of characters that may be entered into each space. Use the pick lists to indicate the technical platform(s) and analyte(s) your assay uses. There is no need to explain these further here unless they are not on the lists.

In **Section 9**, please upload the required documents as part of the Support.pdf. Please do not upload these instructions as one of the forms. For the Supporting Documentation please construct a single PDF file titled “Support.pdf” of no more than 50 pages in the following order:

biosketches of key personnel

assay validation results

standard operating procedures

appendices of any other information requested

APPENDIX 1 Eligibility Information

Eligible Investigators: Includes all individuals, regardless of ethnicity, nationality, or citizenship status, who are employed by, or affiliated with, an eligible organization.

Eligible Organizations: Eligible organizations include for-profit, nonprofit, public, and private organizations, such as universities, colleges, hospitals, laboratories, and small businesses.

Government Agencies: Local, state, and Federal Government agencies are eligible to the extent that proposals do not overlap with their fully funded intramural programs. Federal agencies are expected to explain how their proposals do not overlap with their intramural programs.

APPENDIX 2 Formatting Guidelines

All pre-application and application documents should be clear and legible and conform to the formatting guidelines described below. The font size, spacing, page size, and margins may differ between the word processing, PDF, and printed versions. These guidelines apply to the document properties of the electronic version of the PDF file(s) as viewed on a computer screen.

• **Document Format:** All attachments must be in PDF.

• **Font Size:** 12 point or larger.

• **Font Type:** Times New Roman is strongly recommended.

• **Spacing:** No more than six lines of type within a vertical inch (2.54 cm).

• **Page Size:** Must be no larger than 8.5 inches x 11.0 inches (21.59 cm x 27.94 cm).

• **Margins:** At least 0.5 inch (1.27 cm) in all directions.

• **Print Area:** 7.5 inches x 10.0 inches (19.05 cm x 25.40 cm).

• **Color, High-Resolution, and Multimedia Objects:** Documents may include color, high-resolution, or multimedia objects (e.g., MPEG, WAV, or AVI files) embedded in the PDF files; however, these objects should not exceed 15 seconds in length and a size of 10 MB. Photographs and illustrations must be submitted in JPEG format; bit map or TIFF formats are not allowed.

• **Scanning Resolution:** 100 to 150 dots per inch.

• **Internet URLs:** URLs directing reviewers to websites containing additional information about the proposed research are not allowed in the application or its components. Inclusion of such URLs may be perceived as an attempt to gain an unfair competitive advantage. Links to publications referenced in the application are encouraged.

• **Language:** English.

• **Headers and Footers:** Should not be used. Pre-existing headers and footers on required forms are allowed and should be retained.

• **Page Numbering:** Should not be used.

• **Recommended Attachment Size:** Each attachment should not exceed 20 MB.

APPENDIX 3 Definitions

Markers or Diagnostics:

- Integral markers are required for the trial to proceed (e.g., patient eligibility, assignment to treatment, stratification, risk classifier or medical decision-making - often requires performance in a CLIA laboratory and may require a pre-IDE review by the FDA).
- Integrated markers are performed on all or a statistical subset of patients but are not used for medical decision-making.
- Research markers are all other assays and commonly referred to as correlative research.

Types of Sensitivity or Specificity

Analytical Sensitivity is how often the test is positive when the analyte is present (true positivity).

Analytical Specificity is how often the test is negative when the analyte is absent (true negativity).

Clinical Sensitivity is how often the clinical endpoint is present or reached when the test is positive.

Clinical Specificity is how often the clinical endpoint is absent or not reached when the test is negative.