



Request For Proposals (RFP)

Project Title: Developing Endpoints for Clinical Trials of Drugs for the Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

RFP Objective: Solicit applications from organizations with experience in developing well-defined and reliable clinical trial outcome assessments

Issued by: The Foundation for the National Institutes of Health Biomarkers Consortium (FNIH BC) on **January 09, 2012**

Responses: must be received by 11:59 PM ET on **February 06, 2012**

Award will be announced by FNIH: on or before **April 02, 2012**

Eligibility: Any organization from the private and public sector is eligible to apply as long as it can meet the requirements below. It is acceptable for more than one organization to collaborate and submit a joint response.

The Biomarkers Consortium Overview: This project is overseen by the Foundation for the NIH Biomarkers Consortium (FNIH BC), a public-private partnership of government, academia, non-profit, and industry. The goals of the FNIH BC are to develop new biomarkers and strengthen the evidence for their use to help improve diagnosis, measure disease progression, guide treatment, accelerate drug development and target therapies to individuals. More information on the consortium can be found at <http://www.biomarkersconsortium.org/>. The FNIH BC Project Team releasing this RFP is one of several teams developing or managing these cross-sector, collaborative projects. This team is composed of experts from NIH, FDA, academia, non-profit organizations and the pharmaceutical industry.

Project Overview: This RFP will support the studies of the Biomarkers Consortium project, “**Developing Endpoints for Clinical Trials of Drugs for the Treatment of Acute Bacterial Skin and Skin Structure Infections and Community-Acquired Bacterial Pneumonia (Phases I and II)**.” The overall goal of this project is to develop reliable, well-defined and clinically relevant endpoints that measure tangible benefits for patients in terms of how they feel, function, and survive in clinical trials of antibacterial drugs for both CABP and ABSSSI. This is one of two planned RFPs that will support this Project. The present RFP is focused on the ABSSSI related studies only.

Additional information on this project, including a list of project team members, can be found by accessing the Project Team recommendations to the FDA for interim ABSSSI endpoints: (<http://www.regulations.gov/#!documentDetail;D=FDA-2010-D-0433-0011>).

There are significant limitations of the available information to quantitatively assess the effect of antibacterial drug treatments vs. no treatment or placebo and in comparisons between active agents. These unresolved scientific issues on endpoints for clinical trials are an impediment to the field of antibacterial drug development for ABSSSI. The lack of qualified outcome measures also impedes patient care if clinicians and patients cannot understand the similarities and differences between therapeutic agents when they are not measured in a well-defined, reproducible and clinically relevant manner.

RFP Goal: The goal of this RFP is to elicit proposals to complete the content validity (including qualitative research) phase of development for both a patient reported instrument and clinician reported outcome tool for outcome measures for use in clinical trials in ABSSSI.

Competitive applications should propose to:

- 1) Evaluate the medical literature to determine those ABSSSI signs and symptoms that are clinically relevant to the patient in measuring the course of the disease and how those signs and symptoms are related to other clinically relevant clinical trial endpoint measures (through use of endpoint models),
- 2) Design and perform qualitative research in appropriate patient and clinician groups with the disease of interest to further identify and refine those symptoms and signs,
- 3) Identify final item sets with response options, scoring rules, and a finalized conceptual framework for each instrument, and document the content validity of the final instrument including the instrument's ability to adequately measure the full range of ABSSSI severity observed in a population similar to that targeted by ABSSSI clinical trials.

Background on Outcome Measures in ABSSSI

Acute Bacterial Skin and Skin Structure Infections are common infections that include cellulitis, surgical site infections, traumatic wound infections and abscesses. These lesions are often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, among other types of bacteria. The recent epidemiological shift to a greater proportion of ABSSSI caused by methicillin-resistant *S. aureus* (MRSA) acquired in the community, approximately 59% in one recent survey (Moran, et al NEJM, 2006), has been a recent cause for concern due to limited antibacterial drugs for treatment of MRSA.

As the science of clinical trial design advanced during the late 20th and early 21st century, it became apparent that the endpoints used in previous trials for ABSSSI treatments, although perceived as clinically relevant, lacked rigorously developed measures that could be characterized as well-defined and reliable according to current standards of measurement. In addition, for non-inferiority trials, the magnitude of the therapy-related effect size for these endpoints was not readily supported by easily retrieved historical data.

During recent decades, efficacy endpoints for ABSSSI registrational studies relied on a clinical assessment of cure requiring “complete resolution of signs and symptoms” based on a combination of non-standardized, physician-based observations and comments collected from the patient by the physician as well as on the investigator’s assessment of the need for alternative antibiotic therapy. The development of quantifiable, reproducible, externally verifiable and clinically relevant endpoints to measure the efficacy of treatments for ABSSSI would improve the design of present-day non-inferiority and superiority clinical trials for these indications. Published data from the 1930s and 1940s provide historical evidence of substantial treatment effects; however, the data are incomplete, the definitions of the outcome measures and how measurements were obtained are not clear, and the data cannot be audited. Furthermore, questions exist as to whether the constancy assumption required for non-inferiority trial design can be met. Review of the endpoints used in historical trials reveals lack of clarity in the definitions of outcomes, raising questions about how previous measures relate to measures used in current clinical trials. Developing well-defined, reliable and clinically relevant measurements of outcomes would serve both drug development and public health; such endpoints could be employed in future trials.

Consequently, and at the request of FDA, FNIH BC convened a Project Team in early May, 2010 with broad participation from NIH, FDA, the academic research community (including members of the Infectious Diseases Society of America [IDSA]), and interested biopharmaceutical companies to address these issues. The group reached consensus on an initial candidate list of primary and secondary endpoints for each indication and submitted its recommendations regarding these interim or “bridge” primary endpoints -- essentially, regression of measurable lesion size as a primary bridge endpoint for ABSSSI -- to the federal docket as input to FDA’s emerging guidance for clinical trial endpoints (see <http://www.regulations.gov/#!documentDetail;D=FDA-2010-D-0433-0011>). Establishment of these endpoints and the development of standardized approaches to measurement thereof are recognized by all stakeholders as critical to support future clinical trials of antibacterial therapies. This initiative is particularly important at a time when the incidence of emerging treatment-resistant pathogens (such as MRSA and many gram-negative bacilli) is increasing, as has been highlighted by the IDSA (Boucher et al., CID, 2009). The goal of this RFP is to develop the evidence base for the content validity for patient and clinician reported outcome measures for ABSSSI

Budget: The budget for this project is \$250,000.

Submitters are urged to present the items described below under “Technical Specification Requirements” as separate budget line items.

Expectations: The response to this RFP should include the following:

1. Prior experience relevant to the work as described in this RFP
2. A listing of your organization’s approach to addressing the needs of the RFP , what components would you include, why, and how would you best address these issues.
3. A listing of what resources you would need and have available to be successful in completing the proposed studies.
4. Estimated project timeline

5. List of deliverables
6. Itemized project budget with justification

Technical Specification Requirements:

- Kick off (project initiation) meeting with this Project Team. Clarify definitions and subsets of disease to study
 - Types of skin disease (see FDA ABSSSI guidance)
 - Severity of disease
 - Inpatients and outpatients and other potential patient populations
- Literature search and gap analysis for both patient reported and clinician reported outcome measures in ABSSSI
- Letter of Intent to the FDA (DDT Guidance)
- Meeting with FDA to agree on measurement concept(s) and context of use for the new measure
- Scoping Stage Summary Document to the FDA (DDT Guidance)
- Develop protocol for development content validity of both patient and clinician reported outcome measures
- IRB submission
- Site management activities
- PRO instrument development
 - Qualitative research with US and non-US patients for each type of skin infection similar to those patients targeted for future clinical trials
 - Data analysis using an iterative approach to demonstrate saturation and content validity
 - Finalize preliminary items and initial PRO instrument content
 - Cognitive debriefing with patients to confirm content validity
- Clinician-reported outcome assessment development
 - Qualitative research with US and non-US investigators to evaluate what concepts of the diseases are relevant for measuring the course of the diseases
 - Identification of methods of measuring signs of skin infections with the best content validity and ability to implement in setting of clinical trials
- Final endpoint model explaining how all measures relate to each other
- Presentation of results to FNIH BC
- Final report
- Briefing Document to FDA
- Meeting with this group and with FDA to discuss next steps (e.g. testing of instrument properties and other populations including pediatrics)

Kick off Meeting: The meeting will allow introduction of team members from both the applicant and the FNIH project team. The meeting will entail discussion of the project goals and objectives, and a discussion of deliverables and timelines. The groups will discuss the

details that would be included in the project protocol including target concepts and populations as well as other details.

Letter of Intent to FDA: The applicant will draft a letter to FDA informing the Agency of the intent to develop outcome measures as spelled out in the FDA Guidance for Industry: Qualification Process for Drug Development Tools (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>)

Literature Search: The applicant will perform a thorough literature search of multiple databases in both English and other languages to evaluate current outcome measures for symptoms and signs in patients with ABSSSI. The applicant will evaluate current measures in the public literature as well as any unpublished data discovered from other databases. The applicant further will evaluate the development, validity, reliability and reproducibility of the outcome measures discovered in this search according to criteria outlined in the FDA Guidance for Industry: Patient-Reported Outcome Measures, Use in Medical Product Development to Support Labeling Claims) (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>). The goal of performing this literature search is to identify any significant strengths and weaknesses of current outcome measures to inform item selection and content validity for the development of conceptual endpoints models for future endpoints for this indication and to inform protocols for qualitative research in patients as described below. The applicant will prepare a scoping stage summary document for submission by FNIH to FDA in accordance with FDA Guidance for Industry: Qualification Process for Drug Development Tools (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>)

Qualitative Research: The applicant will perform qualitative interviews in subjects with ABSSSI, including subjects with a range of severity with cellulitis, erysipelas, abscess, traumatic/ surgical wound and burn infection. These interviews will provide the basis for understanding patients' perspectives to develop PRO assessment(s) of ABSSSI symptoms. The applicant should have the ability to perform patient interviews in international settings. The applicant should describe its methodology for assessing when saturation of concepts has been achieved in each subgroup of subjects. The applicant will record, transcribe and translate the interviews and evaluate the themes and concepts described by patients in the patient's own words. For ABSSSI the focus should be on both signs and symptoms of disease. The applicant will combine the information obtained from the literature search and the evidence from the qualitative interviews with data from one-one interviews conducted by the applicant with the members of the FNIH BC Project Team to develop and evaluate clinician-reported outcome assessment(s) of ABSSSI signs. . The applicant should also have the ability to perform interviews with experts from US and non-US sites with names supplied by the FNIH BC Project Team. The applicant will identify the final item sets with response options, scoring rules, and a finalized conceptual framework for the patient reported outcomes instrument. The applicant will confirm the content validity of the final patient reported outcome instrument with cognitive interviews in patients. The applicant will perform qualitative interviews with US and non-US clinicians to determine the content

validity of clinician reported outcomes assessments in various forms of ABSSSI. The applicant will document the content validity of each final instrument in a publishable format.

The applicant should have the capacity to develop the measures with the intent for future incorporation in an electronic data format. The applicant should be prepared to have the instruments reviewed for future international translation.

Identification of various methods for measuring skin infection lesions: The applicant should have the ability to explore various methods for evaluating signs of disease in various types of skin diseases, including methods used in other therapeutic areas that might be applicable in the setting of skin diseases, depending on the information obtained in the content validity phase of the project. The potential methods of testing will be discussed during the kick off meeting.

Final conceptual framework and draft instrument development: The applicant should have demonstrated ability in development of conceptual models for endpoints as spelled out in FDA Guidance for Industry: Patient-Reported Outcome Measures, Use in Medical Product Development to Support Labeling Claims) (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM193282.pdf>). The applicant should demonstrate proficiency in development of draft outcomes instruments.

Future Plans: Future plans will include the further testing of the instruments to document other measurement properties (i.e., construct validity, reliability and ability to detect change) and to gain experience with the measures to inform interpretation of data in clinical trials and to support the conclusion that the instruments are well-defined, reliable, and clinically relevant outcome measures for ABSSSI, as well as evaluation of methods of measuring signs of diseases in a clinician reported outcome measure.

Application Process: Any investigator from the public or private sector is eligible to apply in response to this RFP, including investigators who are not based within the United States. Note that FNIH does not give awards to individuals; awards are made only to institutions. Submit a response to this RFP via email to **Dr. Judy Siuciak**, The Biomarkers Consortium Scientific Program Manager, at jsiuciak@fnih.org. **Responses must be received by 11:59 PM ET on February 06, 2012.** Call 301-435-6247 with any questions about the application process, or use the e-mail address above.

Final Decision Announcement: Organizations that submit a high-caliber, focused, and detailed response to this RFP may be invited to meet via teleconference or in-person with members of the Project Team prior to the final decision. The proposal selected will be announced on or before **April 02, 2012**. As the FNIH Biomarkers Consortium is a collaborative effort to which organizations voluntarily contribute, there is no guarantee that an award will be made to one of the teams submitting an application in response to this RFP.