Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000019: Skin Infection Patient-Reported Outcome Measure (SKINFECT-PRO)
February 3, 2017 Update

FDA Comment

1. Timing of assessments

a. Table 1 in the quantitative protocol indicates that the clinician global impression (CGI) will be administered only on Days 1 and Day 14 and the clinician global impression of change (CGIC) will be administered only on Day 14. We acknowledge that the duration of treatment may be variable depending on the patient's response to treatment, but we still suggest an earlier time-point to capture those patients who may respond early to treatment. The time-point should be not more than 48-72 hours post-baseline due to the potential for rescue medication use based on the results of the lesion measurement at 48-72 hours post-baseline. The 2013 *Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf), states that the primary efficacy endpoint for clinical response (percent reduction in lesion size) should be at 48 to 72 hours post-baseline. These same time points should be used for primary efficacy data collection even if only ICON clinical sites are used for the study. We strongly recommend that you follow the entry criteria, trial procedures, and timing of assessments as stipulated in this guidance.

Response from the ICON/ FNIH team

As the purpose of this study is to measure the psychometric properties of a patient-reported outcome instrument, clinician-based assessments of signs and symptoms at 48-72 hours post-baseline are not necessary to evaluate either construct validity of the PRO instrument or interpretation of scores. Data collected from the PRO instrument will provide direct evidence of how the patients feel or function at 48-72 hours and will also directly measure improvement at this time point (or at any other time point). The patient-reported variables will be key for evaluating the psychometric properties of the new PRO instrument. We are not evaluating a ClinRO nor are signs/ClinRO the reference standard for symptoms to which symptoms should be compared (FDA PRO guidance, 2009). The goal of this work is to show that the PRO can accurately and precisely evaluate patient health status on symptoms and function, not relate it to other factors like signs of disease or clinician impressions of change. However, if CGI/CGIC data are available in a clinical trial at 48-72 hours, they will be captured and used in the psychometric evaluation, where appropriate.

FDA Comment

b. The protocol states that patients must have been diagnosed with an ABSSSI within the past 7 calendar days to be eligible for the study. There remains a concern about the timing

of the baseline assessments in this study relative to the first day the patient receives treatment. Please be sure that the instrument is administered immediately upon hospitalization for baseline assessment due to the rapid timeline for symptom reduction with treatment.

Response from the ICON/ FNIH team

Eligibility based on diagnosis with the past 7 calendar days is an error. This language was left over from the qualitative protocol and has now been removed. Thank you for pointing out this error. We will ensure that the instrument is administered as closely in time as possible to treatment initiation and in any event no longer than 24 hours thereafter. To clarify the timing of assessments, we have added the following language in the inclusion criteria:

Patient is enrolled into study BEFORE treatment initiation OR no more than 24 hours AFTER treatment initiation

Patient can complete their first daily study assessments (e.g. ABSSSI PRO instrument, etc.) within 24 hours AFTER treatment initiation

FDA Comme nt

c. We note your plans to conduct this study as part of ongoing clinical trials for new treatments of ABSSSI. Please feel free to inform sponsors of these trials that CDER's final guidance on ABSSSI provides a reference to your publication on the development work of your instrument in the context of the primary efficacy endpoint based on symptom improvement and should not affect the integrity of efficacy results based on the recommended endpoint described in the guidance. Furthermore, the FDA discusses the development of this ABSSSI instrument in reference to efficacy endpoint development for antibacterial drug trials in an editorial (Toerner JG, Cox E. A collaborative model for endpoint development: advancing the science of antibacterial drug clinical trials. Clin Infect Dis 2016: Mar 1; 62 (5)). http://cid.oxfordjournals.org/content/early/2016/01/01/cid.civ1007.full).

Response from the ICON/ FNIH team

Thank you for the suggestion and we will inform sponsors as appropriate.

FDA Comme nt

d. While test-retest analysis is not absolutely critical especially for a condition such as this where treatment response is highly variable, we suggest that the timing of the test-retest occur at two different time points and be tied to study visits. The first could be at two different times during the same day to capture rapid responders and the second could be at the end of treatment day with the day for test of cure to capture those patients who are remaining.

Response from the ICON/FNIH team

As currently outlined in the protocol and SAP, Day 7 and 10 data will be used to assess test-retest reliability (change in the new ABSSSI PRO instrument among patients whose condition is considered stable on the basis of PGI/PGIC and CGI/CGIC scores). These two assessments occur well after the first 72 hours of treatment, when the most change is expected, and span a time period in which the patients' condition should be more or less stable and thus appropriate for assessing test-retest reliability.

FDA Comment

2. Patient recruitment and the patient population

a. In our response letter dated August 13, 2015, clinical setting for diary administration was discussed as being administered in both in the inpatient and outpatient settings. The protocol is unclear if both inpatient and outpatient settings will be used for patient recruitment. Please clarify the setting for administration of the diary and list a target number of patients from each setting with a minimum number of recruitment sites in each setting.

Response from the ICON/FNIH team

Specifying a target number of patient subgroups such as inpatients and outpatients is not required for psychometric evaluation as the purpose of a psychometric evaluation study is to assess the ability of a PRO to accurately and reliably measure concepts in all patients, not how subgroups may differ based on intensity and duration of symptoms or treatment effects. Selecting a formal target from each setting would place an unnecessary restriction on recruitment, especially from an IRB perspective. The data will be analyzed on the overall sample. Descriptive statistics for the study assessments will be presented for inpatients and outpatients.

FDA Comment

b. It is unclear whether all patients at a site will be given an opportunity to participate in the psychometric study at the time of randomization into the respective clinical trials. The protocol should describe methods used to minimize biased selection or convenience sampling during patient recruitment. Also, please clarify if only certain sites will be selected for this study and provide description of any site selection processes used.

Response from the ICON/FNIH team

Every effort will be made to include a full spectrum of patients who are enrolled in clinical trials, particularly in terms of severity. Treatment assignment is irrelevant for the purpose of recruiting in a psychometric evaluation study. A mix of clinical trial sites and sites independent of a clinical trial will be selected for this study to ensure a suitable sample can be recruited in an appropriate timeframe.

The protocol has been updated to describe methods used to minimize biased selection or convenience sampling. ICON will conduct training via teleconference with each site to ensure clarity, understanding, and consistent application of inclusion/exclusion criteria.

Sites will also use a patient tracking sheet to track patient recruitment, which will be monitored by the ICON team throughout the recruitment process.

FDA Comment

c. Please verify that patients older than 65 years of age are targeted for this study (as stated in the August 13, 2015 response letter) since they may not exhibit the symptom of fever. This would impact their responses to Q#2-4 of the proposed diary.

Response from the ICON/FNIH team

Every effort will be made to recruit a comparable distribution of age groups, including patients > 65 years of age. This will be monitored regularly using sociodemographic form data.

FDA Comment

d. An alternate or additional source of patients has been indicated as using ICON clinical sites. Please supplement the protocol and respective SAP for the scenario where ICON clinical sites will be used rather than or in addition to the clinical trial sites. The protocol should also describe how relevant information (e.g. baseline characteristics, clinician-ascertained objectives clinical responses, disease progression etc.) will be collected from patients recruited outside of ongoing clinical trials. As stated earlier, please refer to the guidance on specifics for the data points to be collected. If only ICON clinical sites are used, please also provide which psychometric property assessments will and will not be completed.

Response from the ICON/FNIH team

Our primary patient recruitment strategy is to conduct this PV study in conjunction with an ongoing drug development trial for ABSSSI sponsored by a pharmaceutical company. If it is not possible to recruit adequate numbers using pharmaceutical study sponsors, ICON PRO will recruit clinical sites and patients independent of a pharmaceutical clinical trial or collaborate with other investigators who may have ongoing cohort studies. These options have been described in the protocol under section 3.3, "Site and Patient Recruitment."

The collection and timing of the psychometric property assessments will be essentially identical regardless of the recruitment strategy. The only exceptions will be analyses using the CGI and CGIC. If clinical sites and patients are recruited independent of a pharmaceutical clinical trial, completion of the CGI and CGIC will be required. If pharmaceutical clinical trial patients are recruited, completion of the CGI and CGIC will be considered optional as patients in a clinical trial may not necessarily be returning to the clinical site for data collection purposes at the time the CGI/CGIC is typically administered.

FDA Comment

e. You have indicated the qualitative work had 41% IV drug users. Please indicate whether there is a cap for the number for IV drug users in the quantitative study (to prevent an over-

representation of the number of patients with abscesses). Please be sure to document IV drug user status.

Response from the ICON/FNIH team

Every effort will be made to recruit a comparable distribution of patients who have used IV drugs versus those who have not. This will be monitored regularly using data from the medical history form.

FDA Comment

f. In Appendix A of the quantitative protocol, the source of wound infection is specified. Please indicate if the data will be stratified by source of wound infection and if certain targets are being pursued for each source of the wound infection.

Response from the ICON/FNIH team

Approximately 300 patients will be recruited for this study including an equal distribution (e.g. 100) for each of the three subtypes (e.g. cellulitis including erysipelas, abscess, and wound infection (traumatic or surgical site)). Stratifying data by source of wound infection will be used for descriptive purposes only. This level of analyses is not necessary for measuring the psychometric properties of the PRO instrument. Notably, our qualitative data indicated that no differences in concepts were reported in patients across all three ABSSSI subtypes.

FDA Comment

3. Survey administration and data collection

a. The timing and collection of data and information is unclear from Table 1 of the quantitative protocol (e.g., the clinician's recording of lesion size on Days 1 and 3). Details should be provided regarding the collection of data for all endpoints of interest. Please also refer to the first point for the timing of assessments. As indicated earlier in the document, please refer to the Guidance document on assistance regarding timing and collection of data.

Response from the ICON/FNIH team

Regarding the collection of data for all endpoints of interest, details are outlined in the schedule of assessments which provides information on when clinician recording of lesion size will occur. See Table 1 on page 17.

As mentioned previously, we are not evaluating a ClinRO nor are signs/ClinRO the reference standard for symptoms to which symptoms should be compared. The goal of this work is to show that the PRO can accurately and precisely evaluate patient health status on symptoms and function, not relate it to other factors like signs of disease or clinician impressions of change. However, since we are assuming lesion size is already being collected in the clinical trial setting, these data will be recorded, if available, on Days 1 and 3, and on any subsequent days. Details are outlined in the schedule of assessments in Table 1 of the protocol.

FDA Comment

b. No information was provided on the instrument administration and data collection procedures for this study. Please provide this information in the protocol including the difference in administration between inpatient and outpatient settings if any, how the instrument will be given to the patient and returned, and details on the prevention of backfilling and prospective filling of data.

Response from the ICON/FNIH team

Electronic data capture will be the primary mode of data collection in the current study. Data will be captured electronically using an eCOA system. Patients will either use a handheld device to complete the assessments or they will be contacted by their site to complete the assessments over the telephone where the data will be inputted directly into the eCOA system via web. The study team will supply each site with electronic devices. The device is programmed to not allow backfilling and prospective filling of data. There will be no difference in administration between inpatient and outpatient settings. In the case of extenuating circumstances such as device malfunction, additional devices will be available as a back-up and patients will also have access to 24/7 support from the ePRO vendor Helpdesk personnel.

FDA Comment

c. We recommend recording time from randomization (when used in a randomized clinical trial) and time from initiation of therapy (for both randomized clinical trials and observational studies).

Response from the ICON/FNIH team

Since the goal of a PV study is to measure proposed concepts, not treatment effects (i.e. difference between test and control group), the recording of either time from randomization or time from initiation of therapy is unnecessary. We can still document these details (on the medical history form) for patients enrolled in clinical trials or through independent clinical sites, although the data will not influence the measurement properties of the PRO instrument itself.

To clarify the timing of assessments, we have added the following language in the inclusion criteria:

Patient is enrolled into study BEFORE treatment initiation OR no more than 24 hours AFTER treatment initiation

Patient can complete their first daily study assessments (e.g. ABSSSI PRO instrument, etc.) within 24 hours AFTER treatment initiation

FDA Comment

d. Please indicate the procedure regarding PRO completion for those patients who respond early to treatment (prior to the 14 day time-point).

Response from the ICON/ FNIH team

Participation in the study will be considered complete at Day 14 or at end of therapy, if earlier than Day 14. Once participants reach symptom resolution (as measured by the PGI, i.e. no symptoms), if subsequent daily diary days are not completed this will not be considered missing data.

FDA Comment

e. The instrument does not appear to include any patient identifying information, e.g. unique patient ID number for this study. Please clarify in the protocol how completed daily diaries belonging to the same patient will be determined.

Response from the ICON/ FNIH team

Electronic data capture will be the primary mode of data collection. A unique patient ID number will be assigned to each patient account and each daily dairy entry will be date and time stamped electronically.

FDA Comment

f. We acknowledge your plans to collect data related to patient withdrawal. Please describe how treatment status (e.g. whether the patient is continuing or has discontinued assigned therapy) will be tracked during this study. Also, describe any assessments planned for the end-of therapy time point.

Response from the ICON/ FNIH team

Please see response from the ICON/ FNIH team in 3d regarding plans to collect data related to patient withdrawal. Table 1 of the protocol outlines the assessments planned for the end-of therapy time point. Also, Appendix L of the protocol documents specific reasons for patient withdrawal from the study.

FDA Comment

4. Data analysis and interpretation

a. Please reconsider the order of the planned analyses as described in Figure 1 of the SAP. It might be useful to conduct the item-level analysis first, followed by the exploratory factor analysis (EFA), and lastly by the Rasch analysis.

Response from the ICON/ FNIH team

We have revised the order of the analyses in Figure 1 and in the text.

FDA Comment

b. Item-reduction and item-redundancy will be undertaken, if appropriate, following the item-level analysis. We recommend that in the SAP you carefully and thoroughly document the decision-making process surrounding item-reduction and determination of a preliminary scoring algorithm.

Response from the ICON/FNIH team

We have addressed this by documenting the decision-making processes surrounding item reduction and determination of a preliminary scoring algorithm under section 5.2 in the SAP.

FDA Comment

c. Please clarify how you will handle the ordinal nature of the data in the EFA.

Response from the ICON/FNIH team

The EFA will be performed using the polychoric correlations[1] to account for the ordinal nature of the data. This is a technique used to estimate the correlation between two ordinal variables.

FDA Comment

d. Please specify if any particular a priori subgroup analyses are being proposed. In addition to any planned subgroup analyses, we recommend that you evaluate whether the ability to detect change varies by important patient subgroups.

Response from the ICON/FNIH team

Our qualitative data indicated that no differences in concepts were reported in important patient subgroups such as inpatients/outpatients or ABSSSI subtypes. However, as recruitment permits, every effort will be made to ensure a comparable distribution of inpatients and outpatients. The data will be analyzed on the overall sample. Descriptive statistics for the study assessments will be presented for each subgroup.

FDA Comment

e. Table A of the SAP indicates that the medication data will only be captured only on Day 1. To understand the context of the symptoms expressed by the patients, the frequency and duration (including stop date) of these medications at additional points during the study should be captured. Please capture all information that would characterize the overall management and assessment of the patient at time points during treatment and at least

[1] Holgado–Tello, F. P., Chacón–Moscoso, S., Barbero–García, I., & Vila–Abad, E. (2010). Polychoric versus Pearson correlations in exploratory and confirmatory factor analysis of ordinal variables. Quality & Quantity, 44(1), 153-166.

one time point after completion of therapy. This information should be requested as part of data sharing agreements and incorporated into the data analysis plans.

Response from the ICON/FNIH team

Similar to our agreement with the FDA DDT Qualification Team on the CABP psychometric study, we will include an additional case report form in our ABSSSI study to capture information from the patient regarding the initiation of any additional interventions during the course of the follow-up period. These data will help elucidate why patients might have been feeling better and will only be analyzed descriptively (i.e. not included in the psychometric evaluation) at the end of the study.

FDA Comment

f. We recognize that you are conducting an exploratory study. However, it is important that objectivity is maintained wherever possible. For example, you can document what you did and what you found as well as pre-specify the approaches to be used. Examples (not all-inclusive) where more details could and should be added:
   i. Approach and process to be used in determining whether data are normal vs. non-normal and the types of statistical tests to be used (i.e. parametric tests vs. non-parametric tests)
   ii. Approach and process to be used for item reduction and group specification for comparisons.
   iii. The protocol mentions the use of intra-class correlation coefficients in the psychometric validation. Details should be provided regarding how the correlation was computed.

Response from the ICON/FNIH team

i. This point is addressed in sections 4.3 and 4.4 of the SAP
ii. Additional information has been added to section 5.2.1 of the SAP to address this.
iii. We now specify we will be computing a ICC [2,1] using the method outlined in Shrout and Fleiss (1979).

FDA Comment

g. We acknowledge your proposal to categorize lesion size change as follows: improvement, no change, or deterioration. It might be preferable to create categories that relate to clinically meaningful changes, e.g. improvement by X%, no meaningful change, and deterioration by Y%. Please refer to the guidance document (cited earlier in the document) for a reference as to the minimum accepted percentage change from the clinical division.

Response from the ICON/FNIH team

We are not evaluating a ClinRO nor are signs/ClinRO the reference standard for symptoms to which symptoms should be compared. The goal of this work is to show that the PRO can accurately and precisely evaluate patient health status on symptoms and function, not relate it to other factors like signs of disease or clinician impressions of change. However, if

available, lesion size will be recorded on Days 1 and 3 and used to evaluate the ability of the ABSSSI PRO instrument to detect change using categories such as improvement, no change, or deterioration.

FDA Comment

5. Scoring algorithm development

a. Please provide details in the SAP for the development of the scoring algorithm.

Response from the ICON/FNIH team

Determination of a preliminary scoring algorithm is reported in sections 5.2.2 of the SAP.

FDA Comment

b. As we discussed during our teleconference on May 11, 2015 (and in the response letter dated August 13, 2015), a total symptom score is anticipated. Please clarify and/or confirm that a modular approach will be assessed to determine scoring (i.e. only using the symptom domain without the functional domain), whether both the symptom and functional domains will be administered to the patients, and if the functional domain is being included in the psychometric property assessment.

Response from the ICON/FNIH team

This has been clarified in section 5.2.2 of the SAP. Both symptoms and functional domains will be considered. All items will be administered to patients and will be considered in the eventual scoring approach.

FDA Comment

c. Section 4.2 of the SAP states that "depending on the extent of missing data, imputation methods may be considered such as the mean of the answered items." Please provide additional details on the missing data analysis. We recommend that the studies take steps as part of their processes, including monitoring, to limit missing data as much as possible and to document the detailed reasons for missing data. In addition, the tolerance of the summary measure(s) to missing item data should be assessed and the methods used to make this determination specified in the SAP. Once the final set of items and domains have been determined, we recommend that you conduct the following analyses to assess the impact of missing data to inform the development of the scoring algorithm:

   i. At the item, domain, and total score levels: Randomly replace valid (non-missing) responses with missing responses for an increasing number of items (1 item, 2 items, 3 items, etc.) and evaluate at which point the daily score(s) becomes unstable (indicated by a large standard deviation (SD) and/or a large deviation from the original daily score computed without missing data). The definition of "large" is not commonly described in the literature, but several developers choose SD or SD change of 0.5. Instability may vary depending on which items are missing, not only on the number of items missing.

   ii. At the form and endpoint level: If multiple daily scores will comprise the endpoint, randomly replace valid (non-missing) daily scores with missing daily scores for an increasing number of days (e.g. 1 day, 2 days) and evaluate at which point the

overall/average score (per your preliminary scoring algorithm) becomes unstable (indicated by a large standard error and/or a large deviation from the original overall/average score computed without missing data).

Response from the ICON/FNIH team

Addressing and imputing missing data is part of the clinical trial, not the evaluation of a PRO instrument. The impact of missing data on study conclusions can be affected by treatment effect size and other factors that are inherent to a specific context of use and not the instrument itself. Once participants reach symptom resolution (as measured by the PGI, i.e. no symptoms), if subsequent daily diary days are not completed this will not be considered missing data, as the intention of the PV study is to frame the correct duration of symptom capture.

Overall, missing data will inherently be mitigated by using an eCOA system for data collection. The system is programmed to send reminders to patients to complete their assessments and does not allow patients to skip an item/proceed to the next screen before inputting a response option.

Additional FDA comments:

- Please describe the type of blinding used in the clinical trials from which patients will be recruited.

Response from the ICON/FNIH team

As described earlier, we will recruit patients in conjunction with an ongoing drug development trial for ABSSSI sponsored by a pharmaceutical company or recruit patients independent of a pharmaceutical clinical trial. If a clinical trial is the method of recruitment, information about patient blinding would be described later in the methods section of the final report and updated FDA briefing package.

- The ordering of the questions in the instrument provided with the quantitative study does not match the Final conceptual framework submitted as part of the qualitative study results. The ordering of the questions in the Final conceptual framework seems appropriate. Please indicate the rationale for the change in the ordering of the questions.

Response from the ICON/FNIH team

The phrasing and order of the items, as presented in the final conceptual framework (CF) submitted as part of the qualitative study results (DDT COA 000019, ABSSSI PRO Initial Briefing Package, submitted January 23, 2015), are correct. The phrasing and order of the items as shown in the ABSSSI PRO quantitative protocol (ABSSSI PRO Psychometric Evaluation Protocol, submitted November 25, 2015), were not appropriately updated. This was a mistake and the discrepancies have been rectified. The PRO items in the quantitative protocol now match up with the items in the CF.

- There might be the potential for misinterpretation of Q2, i.e "do you feel warm or hot?" This potential for misunderstanding may occur due to the contextual effect of Q1. Though not a

regulatory requirement for qualification, we encourage you to determine a patient's understanding of this question in the quantitative study as potential exit interviews. A potential alternative for this question could be "Do you feel feverish?" According to the qualitative data previously submitted, some patients have used fever to describe how they experienced the symptom.

Response from the ICON/ FNIH team

By mistake, the phrasing (and order) of the items as they appear in the ABSSSI PRO instrument included in the quantitative protocol were not updated to match the phrasing and order of the items as listed in the final conceptual framework, as explained above. Question 2 in the original PRO, "During the past 24 hours, did you feel warm or hot?" was changed to, "During the past 24 hours, did your *body* feel warm or hot?" in the final CF to help distinguish between body temperature and infection temperature. This change is likely to eliminate potential misunderstanding and the need for exit interviews.

I. Introduction

Over the past decade, the United States has experienced an epidemic of acute bacterial skin and skin structure infections (ABSSSI) caused by methicillin-resistant Staphylococcus aureus (MRSA).[5]

In addition to Staphylococcus aureus (including MRSA), ABSSSIs are also caused by Streptococcus pyogenes and are among the most common infections encountered in clinical practice.[1] Treatment of ABSSSI is challenging due to a limited number of safe and efficacious antibacterial medications, especially those administered by the oral route, and the ongoing threat of antibacterial resistance.[6] The development of new antibiotics is clearly needed, and well- designed clinical trials involving patients with ABSSSI are necessary to understand the efficacy and safety of these new antibiotic agents.

ICON Commercialisation & Outcomes (ICON) Clinical Outcomes Assessments (COA) group is collaborating with the Foundation for the National Institutes of Health Biomarkers Consortium (FNIH BC) to develop two reliable, well-defined, and clinically relevant endpoints (PRO instruments) that measure tangible patient benefits in antibacterial drug clinical trials, one in ABSSSI and the other in community-acquired bacterial pneumonia (CABP). Through a consortium-based approach, the FNIH BC ABSSSI and CABP Project Team together with ICON COA have utilized the signs and symptoms from both conditions in the published literature and results from qualitative, post-treatment interviews to create the current ABSSSI and CABP disease models and conceptual frameworks. This work informed the development of the proposed ABSSSI-specific PRO and CABP-specific PRO instruments for use in future clinical trials of antimicrobial drugs. The same team has also started working together to develop a PRO for hospital-acquired bacterial pneumonia using the same approach. The success from this collaboration for the ABSSSI and CABP work highlights the effectiveness of the consortium approach. Further collaboration between industry and academia will foster the project's impact in future clinical trials.

The FNIH BC has requested the new ABSSSI PRO and CABP PRO instruments be developed according to the FDA qualification process outlined in the FDA Qualification Process for Drug Development Tools Guidance (Qualification Process DDT Guidance, 2014). This protocol details the objectives, methods, and analysis required for ICON to demonstrate the psychometric properties of the ABSSSI PRO in line with the FDA PRO guidance, and satisfy the communication and scoping document requirements for the qualification process. Subsequently, a separate protocol will be prepared for CABP.

II. Project Objectives

The objective of this study is to evaluate the psychometric properties of the new ABSSSI PRO instrument. The psychometric properties of the ABSSSI PRO will be measured in a patient population characterized by major abscess, cellulitis (including erysipelas), and wound infection (traumatic or surgical site). This is part of a broader effort between ICON and FNIH BC to support an FDA label claim submission used in clinical trials for anti-bacterial

interventions and other studies as appropriate. The psychometric properties the study will assess include:

- Item level properties (item variability, item-total correlations, Rasch analyses)
- Domain Structure (Exploratory Factor Analysis (EFA))
- Reliability (internal consistency, test-retest)
- Construct validity (known groups/discriminant, convergent/divergent)
- Ability to detect change
- Responder definition (distribution-based, anchor-based)

References:

1. This protocol assumes that patients for the study will be recruited through a pharmaceutical study sponsor(s) as part of a clinical trial for an investigational or FDA-approved treatment for ABSSSI. If it is not possible to recruit adequate numbers using pharmaceutical study sponsors, ICON PRO will recruit clinical sites and patients independent of a pharmaceutical clinical trial or collaborate with other investigators who may have ongoing cohort studies in the target patient population.
5. Deleo, F.R., Otto, M., Kreiswirth, B.N., & Chambers, H.F. (2010). Community-associated methicillin-resistant Staphylococcus aureus. *Lancet,* 375:1557-68.
6. Foundation for the National Institutes of Health Biomarkers Consortium Project Team. (2011). Recommendations to the FDA for Interim Endpoints for Clinical Trials in Acute Bacterial Skin and Skin Structure Infections (ABSSSI Docket ID: FDA-2010-D-0433).