



Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Instrument Development: Concept Elicitation and Cognitive Debrief Interviews Final Report

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1. 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).¹ In addition to *Staphylococcus aureus* (including MRSA), ABSSSIs are also caused by *Streptococcus pyogenes*. Acute bacterial skin and skin structure infections 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.² 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.

At the request of the Food and Drug Administration (FDA), the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium (BC) assembled a Project Team, including members from the National Institutes of Health (NIH), FDA and other key academic and industry infectious disease experts and leaders, to review historical and current data related to ABSSSI clinical trials. This review identified ABSSSI as a priority indication, and also highlighted that reliable, well-defined and clinically relevant instruments are needed to assess endpoints that measure tangible benefits for patients in clinical trials of antibacterial drugs.³

As part of this effort, the FNIH BC Project Team sought to develop a patient-reported-outcome (PRO) symptom instrument in accordance with the Food and Drug Administration guidance for patient-reported-outcome measures used to support labeling claims (FDA PRO guidance, 2009) for use in clinical trials of antibacterial interventions.⁴ The intention is that the PRO instrument will be used to identify and assess signs and symptoms related to clinically relevant endpoints for ABSSSI. A small research subteam, with members having experience treating or conducting research with ABSSSI patients and/or having experience developing and evaluating PRO measures, was also assembled.

Prior to commencing the current study, the research team reviewed the ABSSSI literature and interviewed several key clinical experts in the field to collect information about ABSSSI signs,

¹ Deleo, F.R., Otto, M., Kreiswirth, B.N., & Chambers, H.F. (2010). Community-associated methicillin-resistant *Staphylococcus aureus*. *Lancet*, 375:1557-68.

² 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).

³ Talbot GH, Powers JH, Fleming T, et al. Progress on Developing Endpoints for Registrational Clinical Trials of Community-acquired Bacterial Pneumonia and Acute Bacterial Skin and Skin Structure Infections: Update from the Biomarkers Consortium of the Foundation for the National Institutes of Health. *Clin Infect Dis.* (2012) 55(8): 1114-1121 first published online June 28, 2012.

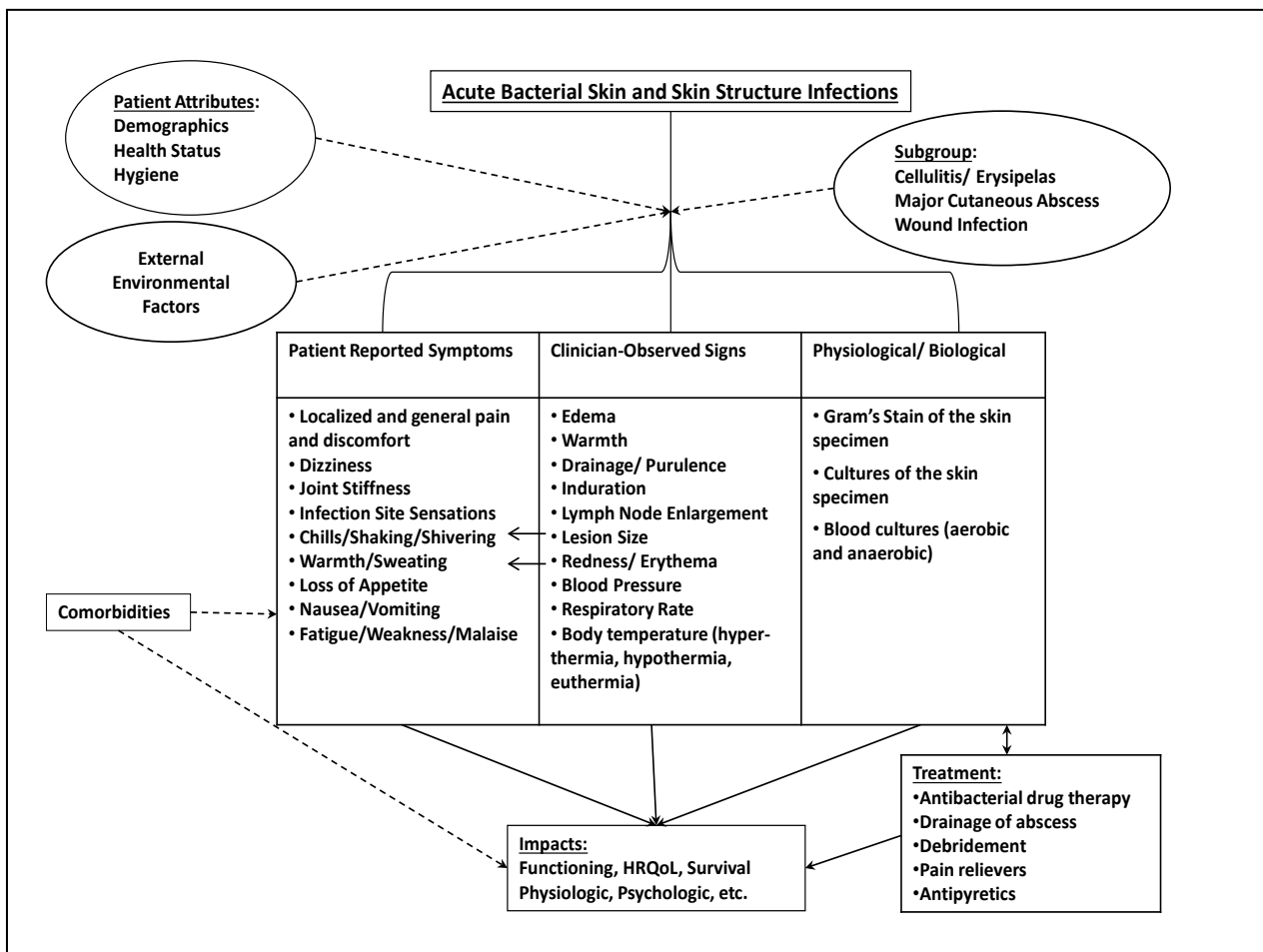
⁴ U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). (2010). Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (HFA-305). Rockville, MD.

symptoms, impacts, and treatment to help inform the development of a new patient reported outcome measure. The literature review identified a total of 14 articles that met inclusion criteria. The most frequently cited ABSSSI signs/ symptoms across all subtypes (i.e. major abscess, cellulitis, and wound infection) included increase in body temperature/ fever, redness of skin/ erythema, lesion edema, induration, pain/tenderness of the area, expansion of the lesion, demarcated lesion borders, and pus-filled drainage/ discharge. Less frequently cited signs/ symptoms/ laboratory findings included chills, nausea, enlarged local lymph nodes, hypothermia and leukocytosis. Results also confirmed that an ABSSSI-specific PRO measure had not been reported in the literature and suggested that further exploration of ABSSSI signs and symptoms was needed prior to the development of a relevant PRO measure for this patient population.

As part of the development process, nine key opinion leaders (KOLs) with expertise in the field of ABSSSI were interviewed. Across all ABSSSI subtypes, common patient-reported symptoms mentioned by KOLs were pain/ tenderness, redness of skin, and warmth/ heat in the infected area. Other symptoms included local swelling and drainage/pus. Elevated body temperature was the most frequently mentioned clinician-reported sign. Additional ABSSSI-related signs included induration, edema, erythema, and fatigue. The primary impact of ABSSSI symptoms on patients' lives mentioned included functional limitations such as physical immobility, difficulty dressing, and inability to work.

As a result of the literature review and interviews, a conceptual model (Figure 1) was developed to illustrate ABSSSI symptoms and the impact of ABSSSI symptoms on functioning. Arrows linking the concepts show the direction of influence.

FIGURE 1: ABSSSI CONCEPTUAL MODEL



This report describes the development of a new ABSSSI-specific PRO instrument building on the work previously described and aligned with regulatory guidance. The purpose of this study was to learn about patients' experience with ABSSSI and the associated symptoms, plus how these symptoms affect their lives and functioning. The information gathered in the initial concept elicitation (CE) interviews was used to develop a conceptual framework, which formed the basis of a new ABSSSI-specific PRO instrument. After the draft measure was reviewed by experts, the instructions, items, response options and recall period were assessed for clarity, relevance, comprehensiveness, and meaningfulness through patient cognitive debriefing (CD) interviews. With completion of CD interviews and required changes made to the instrument, it is now ready for psychometric evaluation. This report summarizes the objectives, methods, results, and item development from both the CE and CD stages of the current qualitative study with the end result being a content-valid PRO for patients diagnosed with ABBSSI.

2. Objectives

The purpose of this part of the ABSSSI PRO instrument development process was to conduct qualitative research on which to base the draft PRO items and to establish content validity of the new instrument. The objectives of the qualitative interviews were two-fold:

- (1) To elicit feedback from patients regarding their experience with ABSSSI and related symptomatology using CE interviews, and
- (2) To determine whether the newly developed draft items were understandable and meaningful to ABSSSI patients using CD interviews.

3. Methods

The cross-sectional, qualitative study was designed to gather information directly from patients about symptoms associated with ABSSSI, and to ensure that a newly developed PRO measure in ABSSSI would be understandable and meaningful to patients. The interviews were conducted by trained and experienced ICON PRO researchers.

3.1 Patient Selection and Recruitment

Thirty-four patients with ABSSSI in the US were recruited for the CE stage of this study, and 15 patients were recruited for the CD stage. Patients were identified by four clinical sites (California, Florida, Nevada, and Washington, D.C.). Institutional Review Board (IRB) approval was obtained prior to commencing recruitment. The sites identified consecutively eligible and interested adult patients with a confirmed diagnosis of ABSSSI including wound infection, cellulitis including erysipelas, or major abscess. An attempt was made to obtain a diverse sampling of persons in terms of gender, ethnicity, and educational level. In order to document eligibility, the sites completed a Screening and Medical History Form for each individual. Those patients who fulfilled the study selection criteria were then included in the study. Written informed consent was obtained from all participants before interviews were scheduled. The specific study inclusion/ exclusion criteria for both the CE and CD interviews are listed below:

3.1.1 Inclusion Criteria

- 18 years of age or older
- Diagnosis of an ABSSSI within the past 7 calendar days with at least one of the following:
 - Cellulitis including erysipelas
 - Defined as a skin infection with spreading areas of redness, edema, and/or induration of a **minimum** surface area of 75 cm² (e.g., length of 15 cm and width of 5 cm)
 - Major abscess
 - Defined as a skin infection with a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration of a **minimum** surface area of 75 cm² (e.g., the shortest distance of redness, edema, and/or induration extending at least 5 cm from the peripheral margin of the abscess)
 - Wound infection
 - Defined as a skin infection with purulent drainage from a wound (traumatic or surgical site) with surrounding redness, edema, and/or induration of a

minimum surface area of 75 cm² (e.g., the shortest distance of redness, edema, and/or induration extending at least 5 cm from the peripheral margin of the wound)

- At least one of the following:
 - Fever (body temperature >100.4°F)
 - Hypothermia (core body temperature <95°F)
 - White Blood Cell Count >10,000/mm³
 - >10% immature neutrophils (bands)
- Any of the following:
 - Erythema with or without induration
 - Fluctuance
 - Purulent drainage/discharge
 - Heat or localized warmth
 - Pain or tenderness to palpitation
- Willing to provide written informed consent, participate in a telephone interview for approximately 60 minutes and have the interview audio recorded
- Able to read and speak English

3.1.2 Exclusion Criteria

- ANY of the following:
 - Carbuncle
 - Folliculitis
 - Impetigo
 - Infected ulcer, such as a deep diabetic foot ulcer, an ulcer associated with peripheral vascular disease, a decubitus ulcer, or an ischemic ulcer
 - Infected major burn
 - Skin infection due to human OR animal bite
 - An infected device in place at the site of the ABSSI that will not be removed
 - Osteomyelitis
 - Septic arthritis
 - Evidence of necrotizing fasciitis or gas gangrene
 - Superinfected eczema or atopic dermatitis
- A medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the patient's ability to participate in this interview study

3.2 Study Interview Procedures

For both the CE and CD phases of the qualitative research, telephone interviews were conducted by an experienced qualitative interviewer from the ICON PRO team. Before patient participation in the telephone interview, the informed consent procedure was carried out by the clinical site coordinator. The telephone interviews took place when the patient was either at the clinical site or at their home, depending on patient preference. Although in-person interviews are generally the

preferred method of data collection, telephone interviews were the only feasible method due to the timeframe within which to interview the patient. Before audio recording was begun, patients were given the opportunity to ask questions about the study and also answered demographic and background questions (see Study Protocol submitted on December 11, 2012). Interviews lasted between 30 and 70 minutes. The interviews were audio-recorded and transcribed verbatim. The patients received \$100 as compensation for their participation.

3.2.1 Concept Elicitation Interviews

During the CE interviews, the interviewer used the Concept Elicitation Interview Guide (see Study Protocol submitted on December 11, 2012) to ask patients about their ABSSSI symptoms and how these symptoms affected their lives and functioning. The interview guide was semi-structured and contained open-ended questions, as well as specific probes. For each symptom that a patient mentioned, the interviewer probed for further details (i.e. frequency, intensity, duration). The CE interview data was used to develop a conceptual framework and to draft an ABSSSI-specific instrument, including instructions, items, responses.

3.2.3 Cognitive Debriefing Interviews

Cognitive debriefing explores the way individuals understand, mentally process and respond to items on a questionnaire (Willis, 2005). Cognitive debriefing is used to establish the content validity of a PRO instrument in terms of its clarity, relevance, and comprehensiveness of items, responses and instructions. During the CD interviews, the Cognitive Debriefing Interview Guide (see Study Protocol submitted on December 11, 2012) was used to ascertain each patient's interpretation, understanding and assessment of the ease of use of the newly developed ABSSSI-specific instrument. During the interview, patients were asked to read the instructions, each question, and the associated response options. The interviewer then used the questions and probes in the interview guide to ask patients whether the text was clear, easy to understand, and relevant to them. A "think-aloud" approach was used, which involved patients thinking aloud about what they think each question is asking them. Patients were asked to suggest alternative wording in cases where they thought the question was unclear or could be improved.

3.3 Analysis

The methodology and analysis were conducted in line with the FDA's final Guidance on PRO instrument development (2009).⁵

3.3.1 Concept Elicitation Interview Data Analysis

Thematic analysis was conducted to evaluate the information gathered during the CE interviews, according to the methodology described by Joffe and Yardley (2004).⁶ This analysis consisted of an initial reading and re-reading of the data to identify themes and concepts emerging from the data. The analysis distinguished between symptoms and impacts that were elicited spontaneously versus those that had been endorsed after probing. A qualitative analysis software tool, MaxQDA, was used

⁵ Food and Drug Administration. (2009). Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Federal Register, 74(235), 65132-65133.

⁶ Joffe, H., & Yardley, L. (2004). Content and thematic analysis. In: Research methods for clinical and health psychology. 1st ed. London: SAGE.

to facilitate the analysis process. The themes/concepts emerging from the analysis were recorded in a saturation grid, and saturation was monitored in accordance with the methods described by Kerr et al. (2010),⁷ in line with the FDA PRO guidance (2009). Saturation was achieved within the number of interviews completed for this study.

3.3.2 Conceptual Framework Development and Item Generation

The draft conceptual framework presented in the DDT Briefing Document was used as a framework in the analysis of the CE data. Its purpose was to demonstrate the relationship of items to domains and domains to total score of a PRO instrument. The qualitative interviews focused on ABSSSI symptoms and their impact. The conceptual framework was further modified to represent the areas of importance to patients as demonstrated in the qualitative data analysis.

3.3.3 Expert Review

To check the validity of the items in the draft new instrument, 3 experts in ABSSSI were consulted: Dr. Scott Overcash (Chula Vista eStudy Site); Dr. Heidi Kabler (Las Vegas eStudy Site); Dr. Larissa May (George Washington University). These experts did not overlap with the prior expert interviews described in the introduction. The 3 experts were asked to complete a survey that included questions about each item in the instrument. The purpose of this survey was to obtain information from the experts regarding which symptoms would be most important to include in the final instrument. The experts were asked to identify which symptom and functioning aspects are most relevant or most likely to be reported by patients, to comment about whether or not the items were easy to understand, and to assess if the symptoms mentioned are sensitive to change.

3.3.4 Cognitive Debriefing Interview Data Analysis

Analysis of the cognitive debrief interviews was performed on an item-by-item basis, as outlined by Willis (2005)⁸ with the goal of identifying items that presented cognitive challenges and performing an assessment of content validity. The cognitive debriefing data were analyzed using a combined approach of thematic and content analysis (Joffe & Yardley, 2004). Thematic analysis is particularly well-suited to the identification of themes and concepts which emerge from conversational data; content analysis provides a more detailed examination of participants' responses to particular questions.

An item tracking matrix was used to record patients' comments regarding each item, the response options, instructions and recall period. This matrix provided a record of any modifications occurring throughout the CD process and a transparent history of the development process overall. The item tracking matrix showed the point at which no further comments were generated in relation to each item of the new instrument.

⁷ Cicely Kerr. Saturation in qualitative PRO research. Oxford Outcomes Webinar, November 2010

⁸ Willis, G. (2005). Cognitive Interviewing: A Tool for Improving Questionnaire Design. London: SAGE.

4. Results

4.1 Concept Elicitation

4.1.1 Patient Characteristics

A total of 34 CE interviews were conducted to identify symptoms associated with ABSSEI and how these symptoms affected functioning. The patients' demographic and clinical characteristics are summarized in Table 1 below. Thirteen (38.2%) patients had major abscess, 12 (35.3%) had wound infection, and 9 (26.5%) had cellulitis. In terms of severity, the majority (79.4%) of infections were rated as moderate by clinicians. The mean age of patients was 38.8 (SD=12.2) years with a range of 20-60 years, and the majority were male. Patients were primarily Caucasian (35.3%) or Hispanic (38.2%), and the highest level of education attained was primarily high school/GED, less than high school, or some college. The employment status of the sample participants varied, with many participants who reported being unemployed or seeking work (32.3%), others in full-time or part-time employment (17.7%), some looking after home/family (14.7%), and others who were students (14.7%).

TABLE 1: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Characteristic	Distribution (N=34)
Age	
Mean (SD)	38.8 (12.2)
Range	20-60
Sex: Female	12 (35.3%)
Race/Ethnicity	
Caucasian	12 (35.3%)
Hispanic	13 (38.2%)
Black/ African American	6 (17.6%)
Other	3 (8.8%)
Education	
High School/GED	12 (35.3%)
Some college	7 (20.6%)
Associate's degree	4 (11.8%)
Did not complete high school	9 (26.5%)
Bachelor's degree	1 (2.9%)
Graduate degree	1 (2.9%)
Employment Status	
Student	5 (14.7%)
Employed full-time	4 (11.8%)
Employed part-time	2 (5.9%)
Retired	1 (2.9%)
Unemployed/seeking work	11 (32.3%)
Looking after home/family	5 (14.7%)
Temporarily unable to work	2 (5.9%)
Permanently unable to work	2 (5.9%)
Other (e.g. occasional work)	1 (2.9%)

TABLE 1: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Characteristic	Distribution (N=34)
Type of ABSSSI	
Major abscess	13 (38.2%)
Cellulitis	9 (26.5%)
Wound Infection	12 (35.3%)
Clinician Rating of Severity	
Mild	-
Moderate	27 (79.4%)
Severe	7 (20.6%)

4.1.2 Symptoms of ABSSSI

The CE interviews resulted in the spontaneous report of a wide range of symptoms (N=29) linked to ABSSSI. Report of symptoms reached saturation at interview eighteen. A saturation grid for symptoms is shown in Table 2 below. These symptoms were common across all ABSSSI subtypes. The five most frequently reported symptoms were: pain/hurt (N=32 of 34 patients, 94%), swelling (N=31 patients, 91%), pus/draining/leaking (N=27 patients, 79%), change in body temperature/fever (N=24 patients, 71%), and soreness (N=18 patients, 53%). These symptoms were reported by at least half of all patients. A further 24 symptoms were reported by participants, with varying degrees of frequency. Table 3 below shows the frequency of all spontaneously reported symptoms. A summary of findings for each of the symptoms is provided below.

TABLE 2: SATURATION GRID-SYMPTOMS

Symptoms	Patient ID's																	
	102-001	102-002	102-003	102-004	102-005	102-006	102-007	102-008	103-001	103-002	103-003	103-004	102-010	102-011	101-002	102-012	101-003	
Pain/ Hurt	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Swelling	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Change in body temp/Fever	X	X		X		X	X	X		X	X	X	X	X	X	X	X	X
Pus/ Draining/ Leaking	X	X		X	X	X	X	X		X		X	X		X	X	X	X
Throbbing	X				X	X	X			X				X		X	X	X
Hot/ Warm to touch	X	X	X	X	X	X	X				X			X		X		
Burning	X			X													X	
Soreness		X	X	X	X			X	X			X	X		X	X	X	X
Tenderness		X			X					X			X	X	X	X	X	
Hard/ Stiffness		X	X						X	X								
Nausea		X	X			X		X										
Stinging sensation		X		X														
Body weakness		X									X							
Puffiness		X				X												
Low energy			X			X									X			
Fatigue/ Tiredness				X		X	X		X	X	X		X	X				
Internal Pressure					X		X	X	X				X	X	X			
Headache					X					X		X	X	X	X			
Tightness of skin					X	X							X					
Scratchy/ Itchiness						X							X	X	X			
Chills/ Feeling cold								X		X		X						
Sweating										X		X						
No appetite								X							X			
Weight Loss								X					X					
Constant Urinating								X										
Swelling of Lymph Nodes												X						
Dizziness																		
Diarhea																		
Skin Crawling																		

Key

Green = First time code applied Yellow = Abscess Red = Cellulitis including Erysipelas Blue = Wound

Hot/ Warm to touch					X					X	X			X		X		
Burning										X			X		X			
Soreness		X	X			X		X	X		X				X	X		
Tenderness	X		X					X			X					X		

TABLE 3: FREQUENCY OF SPONTANEOUSLY REPORTED SYMPTOMS*

Symptom	Frequency (%) (N=34 patients)
Pain/ Hurt	32 (94%)
Swelling	31 (91%)
Pus/ Draining/ Leaking	27 (79%)
Change in body temp/Fever	24 (71%)
Soreness	18 (53%)
Hot/ Warm to touch	15 (44%)
Fatigue/ Tiredness	13 (38%)
Throbbing	13 (38%)
Tenderness	12 (35%)
Pressure	12 (35%)
Scratchy/ itchininess	12 (35%)
Hardness/ Stiffness	9 (26%)
Headache	7 (21%)
Burning	6 (18%)
Nausea	6 (18%)
Tightness of skin	6 (18%)
Chills/ feeling cold	6 (18%)
Sweating	6 (18%)
Low energy	5 (15%)
Dizziness	4 (12%)
Puffiness	4 (12%)
No Appetite	4 (12%)
Body Weakness	3 (9%)

*The following symptoms were each mentioned by fewer than 3 patients: weight loss (n=2), constant urinating (n=2), stinging sensation (n=2), swelling of lymph nodes (n=1), diarrhea (n=1), and skin crawling (n=1).

4.1.2.1 Pain/Hurt

Pain or hurting at the site of the infection was the most frequently reported symptom of ABSSSI, mentioned by 32 of 34 (94%) patients who participated in the CE interviews. Pain was experienced by 12 (38%) patients with abscess, 8 (25%) patients with cellulitis, and 12 (38%) patients with wound infection. Patients typically described the pain as being steady, constant, and severe at the site of the infection. Sample patient descriptions are provided below.

103-004 (abscess): "It's like a steady pain you know, like every time I take a step and then I put pressure on my leg, it makes it hurt."

101-009 (cellulitis): "But I walk on it and then the pain would start and then as soon as I sit down for a little bit, I'd try to get back up and the pain would be right back hurting again."

102-015 (wound): "...it just is like somebody just stuck you with a knife or something. That's how painful it is. If somebody bumps into it or you bump into something. It makes you want to like scream and cry at that moment."

4.1.2.2 Swelling

Thirty-one of the 34 (91%) patients reported experiencing swelling associated with their skin infection. Swelling was reported by 12 (39%) patients with abscess, 8 (26%) patients with cellulitis,

and 11 (35%) patients with wound infection. Patients typically described the swelling as a significant increase in the size of the infected area. Sample patient descriptions are provided below.

102-018 (abscess): *"I was just noticing that something was wrong because one of my arms was getting fatter than other one. A little swelling on my arm from being skinny it always is, it was just getting fat."*

104-002 (cellulitis): *"It just kind of aches and swells up now like you wouldn't believe. It was like Popeye's arm or something."*

102-015 (wound): *"Serious. Serious pus. It swelled. The bump was up here and my whole leg swelled all the way down to my ankle. It is still a little bit swollen but I know it's going to go down though."*

4.1.2.3 Change in body temperature/fever

A change in overall body temperature or fever was reported by 24 out of 34 (71%) patients. This symptom was mentioned by 12 (50%) patients with abscess, 5 patients (21%) with cellulitis, and 7 (29%) patients with wound infection. When describing the increase in body temperature or fever they had experienced, patients described the symptom in terms of feeling hot. When talking about this symptom, some patients referred to other symptoms such as having chills, feeling warm or cold, and sweating. Sample patient descriptions are provided below.

102-012 (abscess): *"I had fevers, I had chills as well. I was hot, I mean my body was literally like I was on fire, especially the area, but it was just I was cold, though, too..."*

101-009 (cellulitis): *"Then I had a headache, then I had a fever. I was sweating. My leg was hurting. I just came to the hospital..."*

102-021 (wound): *"It was like off and on. It wasn't a constant fever. It was like in the middle of the night I'd find myself hot. Man, it's hot in here. No, it's not. I'm hot. Then it would like go away and then it would come back in the middle of the night."*

4.1.2.4 Pus/ Draining/ Leaking

Pus/ draining/ leaking at the infection site was reported by 27 of 34 (79%) patients. This symptom was mentioned by 11 (41%) patients with abscess, 5 (19%) patients with cellulitis, and 11 (41%) patients with wound infection. Patients described this symptom as having a substance that was "oozing" out from their skin infection. Some patients also referred to other symptoms such as pain and pressure at the infection site that accompanied excessive pus. Sample patient descriptions are provided below.

102-006 (abscess): *"It hurts because it's too full. It hasn't popped yet. It's oozing out the puss and blood and stuff that's horrible It has been really painful..."*

102-004 (Cellulitis): *"Well, when it's still growing and ready to pop, that's when it usually will pop, and when it pop, the puss comes out and gets really, really bad."*

102-007 (wound): *"Well it started oozing out like a lot of pressure relieved it so I'm feeling a little bit better. It still hurts a little bit. Not as much as earlier this morning, but it feels a lot better now that it started oozing out."*

4.1.2.5 Soreness

Soreness at the infection site was reported by 18 of 34 (53%) patients. This symptom was mentioned by 8 (44%) patients with abscess, 3 (17%) patients with cellulitis, and 7 (39%) patients with wound

infection. When describing soreness, many patients referred to the infected area as hurting and feeling swollen. Sample patient descriptions are provided below.

102-014 (abscess): *“Very sore and it hurts and it’s puffy.”*

102-003 (cellulitis): *“My face just felt sore and I felt a little bump...”*

102-015 (wound): *“Right now, it feels like a little sore. It is sore feeling. It hurts a little bit...”*

4.1.2.6 Hot/ Warm to touch

Heat/ warmth at the infection site was reported by 15 of 34 (44%) patients. This symptom was mentioned by 5 (33%) patients with abscess, 4 (27%) patients with cellulitis, and 6 (40%) patients with wound infection. The infected site felt hot or warm to touch and the heat was described as serious. Sample patient descriptions are provided below.

102-002 (abscess): *“I also it’s like the area where it’s infected or where the abscess is, it’s like really hot to touch compared to the rest of my skin.”*

102-003 (cellulitis): *“Well, it’s hotter than the rest of me. I can feel the heat coming out of it.”*

102-018 (wound): *“Well, that’s when I knew that it was going to start getting serious because it started getting hot...”*

4.1.2.7 Fatigue/ Tiredness

Fatigue/ tiredness was experienced by 13 of 34 (38%) patients. This symptom was mentioned by 6 (46%) patients with abscess, 4 (31%) patients with cellulitis, and 3 (23%) patients with wound infection. This symptom was debilitating and interfered with daily activities. Patients reported feeling fatigued, tired, weak, and not themselves. Sample patient descriptions are provided below.

102-013 (abscess): *“...I noticed yesterday when I was out of the house just running some errands for an hour, I started feeling fatigue. I had to go back home and lay down.”*

103-003 (cellulitis): *“Just not yourself completely. I’m a big guy, 280 pounds, and I feel like a weakling kind of—my leg aren’t as strong, I get tired walking upstairs, my legs feel twice as weak—I walk a lot, I walk anywhere from 3 to 6 miles a day and I can’t do that when I have this.”*

102-007 (wound): *“I was feeling real just tired and just like I was kind of lost. It was weird. I never felt like that before.”*

4.1.2.8 Throbbing

Throbbing at the infection site was reported by 13 of 34 (38%) patients. This symptom was mentioned by 5 (38%) patients with abscess, 2 (15%) patients with cellulitis, and 6 (46%) patients with wound infection. This symptom was described as being painful and intense, and compared it to the sensation of a “heartbeat.” Sample patient descriptions are provided below.

102-008 (abscess): *“Yeah, it’s like it’s got a brain of its own, like it’s got its own heartbeat, like boom, boom, boom, boom, boom.”*

101-008 (cellulitis): *“I woke up and I said that I need to go to the hospital, you know, because it started throbbing...”*

101-003 (wound): *“I couldn’t put any weight, it was like every time I stood up, it would just throb and I’d have to lay down, so when I stood up like the pain was so intense—first it would throb like really intense like throbbing...”*

4.1.2.9 Tenderness

Tenderness at the infection site was reported by 12 of 34 (35%) patients. This symptom was mentioned by 6 (50%) patients with abscess, 2 (17%) patients with cellulitis, and 4 (33%) patients with wound infection. Tenderness at the infection site was described as sensitive and soft to the touch. Sample patient descriptions are provided below.

102-002 (abscess): "It's tender, like it's softer, like other areas are very hard to the touch and this one is like you can push into it..."

103-003 (cellulitis): "Well, I remember the first time I got it, the tenderness on the surface of my skin wasn't as bad, it was tender deeper, now the surface of my skin is really sensitive, just touching it with your hand even—it's real sensitive."

102-018 (wound): "Yeah, like very tender, you touch it and it felt like jelly, very soft to the touch."

4.1.2.10 Pressure

Pressure at the infection site was experienced by 12 of 34 (35%) patients. This symptom was mentioned by 5 (42%) patients with abscess, 3 (25%) patients with cellulitis, and 4 (33%) patients with wound infection. Patients described feeling a lot of pressure at the site of the infection and associated the pressure with pain. Sample patient descriptions are provided below.

103-001 (abscess): "It's better now because a lot of the pressure is off now that they opened it and let some of the poison out of it, I mean a lot of pressure—that's pretty much where the pain was, it was the pressure."

101-009 (cellulitis): "Before I came here, like I would lay down in the bed and when I go to get up – you go to get up and you put it down, it's like there is pressure on it like the blood rushing or something."

102-005 (wound): "When it popped, it's like it let the pressure off and it just like, some of the pain went away. Not all of it."

4.1.2.11 Scratchy/ itchiness

Scratchy/ itchiness at the infection site was reported by 12 of 34 (35%) patients. This symptom was mentioned by 5 (42%) patients with abscess, 2 (17%) patients with cellulitis, and 5 (42%) patients with wound infection. Itchiness was described as often caused by the infection site rubbing against clothes and progressively getting worse. Sample patient descriptions are provided below.

102-006 (abscess): "I feel like getting a strong bristled brush or something and like itching it with it because my fingernails don't itch it. That's how bad it itches."

103-010 (cellulitis): "Just like I said, it itched when it was rubbing against my shirt because like I said, it's right on the inside of my forearm right there by the elbow. That's where my shirts usually cut off at. And when I walk or do something it just rubs against it."

103-011 (wound): "Yeah, because first it had been three days or so and just started off a little dot. And then, it started itching, then I guess it started itching really bad."

4.1.2.12 Hardness/ Stiffness

Nine out of 34 (26%) patients experienced hardness/ stiffness at the infection site. This symptom was mentioned by 4 (44%) patients with abscess, 1 (11%) patient with cellulitis, and 4 (44%) patients with wound infection. When describing the hardness or stiffness of the infected area, several

patients referred to other symptoms such as swelling and redness. Sample patient descriptions are provided below.

103-001 (abscess): *“Well, it just starts like getting red and swelling, and then it just gets like rock hard from the poison in it...it starts off almost like a boil and it gets real stiff and then it just—it hurts, it swells, it gets real, real, real red and just real inconvenient, they’re just real sore—and I get them about every three to six months.”*

102-003 (cellulitis): *“It feels like it’s going to – it’s really hard right now...[i]t just feels like a – feels like a hard lump.”*

103-011 (wound): *“Well actually, that Friday evening when it was getting swollen it felt hard. So, it wasn’t soft. When I felt around it, it was big and swollen. But it was really hard. And now, it’s not hard, but just my sore if you go around it you can still feel it’s hard a little bit.”*

4.1.2.13 Headache

Headache was reported by 7 of 34 (21%) patients. This symptom was mentioned by 5 (71%) patients with abscess, 1 (14%) patient with cellulitis, and 1 (14%) patient with wound infection. Patients described it as “pounding” or “throbbing.” Some patients talked about their headache being accompanied by fever, sweating, and pain. Sample patient descriptions are provided below.

102-011 (abscess): *“I did have a headache, I had a pounding headache...it was—sometimes it would throb, kind of like when I would roll over when I was napping and stuff, it would just—the throbbing would wake me up, but for the most part it was just like it was just there.”*

101-009 (cellulitis): *“Then I had a headache, then I had a fever. I was sweating. My leg was hurting. I just came to the hospital at about like 11:30.”*

102-005 (wound): *“Just like a headache. That’s about it.”*

4.1.2.14 Burning

A burning sensation at the infection site was reported by 6 of 34 (18%) patients. This symptom was mentioned by 2 (33%) patients with abscess, 2 (33%) patients with cellulitis, and 2 (33%) patients with wound infection. Patients described the burning as very serious and accompanied by heat, throbbing, and stinging. Sample patient descriptions are provided below.

102-001 (abscess): *“Oh, it’s painful. Yeah. Very painful. My finger was hot, burning, and just like throbbing.”*

102-004 (cellulitis): *“It burns. It like burns. Burns and stinging sometimes and then it goes away.”*

102-020 (wound): *“Well it was very serious, maybe a little bit more...If it would’ve been a carpet not exactly like something burning you, like that. I don’t know how to explain it that much, but if it was something burning that area especially if you have those kind of cuts or something like that. If you have a cut and your pants are rubbing it burns.”*

4.1.2.15 Nausea

Six of 34 (18%) patients experienced nausea. This symptom was mentioned by 3 (50%) patients with abscess, 2 (33%) patients with cellulitis, and 1 (17%) patient with wound infection. Nausea was described by patients as constant and as an impending feeling of wanting to vomit. Sample patient descriptions are provided below.

102-008 (abscess): *“The last week was straight nausea. The last four or five days. Starting about last Wednesday I started getting and stayed nauseous.”*

101-007 (cellulitis): *“For a little bit there I was kind of nauseous. You know, I puked a couple of times.”*

102-017 (wound): *“Yeah, it was just like if you have the flu...You feel nauseated, always wanted to vomit. Yeah, I got real nausea, I drank some water and it came up, I couldn’t even hold water down.”*

4.1.2.16 Tightness of skin

Six out of 34 (18%) patients experienced tightness of the skin at the infection site. This symptom was mentioned by 2 (33%) patients with abscess, 2 (33%) patients with cellulitis, and 2 (33%) patients with wound infection. Patients described tightness as hurting and associated it with other symptoms such as pressure and swelling. Sample patient descriptions are provided below.

102-005 (abscess): *“[I]t was tight and everything and when it popped, it let a lot of pressure off it to where I could straighten my arm.”*

101-007 (cellulitis): *“It just gave me a little bit of relief because my skin is really, really tight on my arm due to the swelling.”*

102-005 (wound): *“It was real tight and when it got tight like that, it hurt. When it popped, it’s like it let the pressure off and it just like, some of the pain went away.”*

4.1.2.17 Chills/ feeling cold

Chills/ feeling cold were experienced by 6 of 34 (18%) patients. This symptom was mentioned by 4 (67%) patients with abscess and 2 (33%) patients with wound infection. When describing chills, patients mentioned other symptoms such as body weakness, lack of energy, sweating, and fever. Sample patient descriptions are provided below.

103-002 (abscess): *“I was getting on and off cold chills, but that’s about it, except for a really bad fever—and I did*

102-017 (wound): “I was feeling real weak, like I didn’t have any energy at all. I had the chills that night and I was sweating...” have a headache, but I was assuming that could be from the fever.”

4.1.2.18 Sweating

Six of 34 (18%) patients reported sweating. This symptom was mentioned by 3 (50%) patients with abscess, 1 (17%) patient with cellulitis, and 2 (33%) patients with wound infection. Patients described sweating as “real bad” and that they experienced both hot and cold sweats. Sample patient descriptions are provided below.

103-004 (abscess): *“At night when I do fall asleep, I swear that’s when I have a high fever. And it’s like really hot, really cold kind of thing. Like I’m freezing and sweating real bad. But I keep myself covered and it’s like I’m sweating a lot.”*

101-009 (cellulitis): *“I was hot, I was sweating. It had me sweating a lot. See even before I had the fever, even before I had the fever, I was still sweating. Even before I had the fever I was still sweating and I was like, why am I sweating? It’s not really even that hot.”*

102-017 (wound): *“And I had a real terrible night, like I said I couldn’t get comfortable whatsoever. And I was just sweating, I broke out in this really bad sweat.”*

4.1.2.19 Low energy

Low energy was experienced by 5 of 34 (15%) patients. This symptom was mentioned by 2 (40%) patients with abscess, 1 (20%) patient with cellulitis, and 2 (40%) patients with wound infection. When describing low energy, patients reported the constant need to sleep, feeling drained, and having no strength. Sample patient descriptions are provided below.

102-011 (abscess): *"[Y]esterday I kind of had no energy, I kept sleeping all day, kind of floated in and out, just no energy, just didn't feel good, just wanted to sleep."*

102-003 (cellulitis): *"I have been nauseated. Also nauseated, drained. The pain just like sucks the life out of me."*

102-017 (wound): *"You don't have no energy, no drive, your face is pale. You feel terrible and just the way you feel, it's just terrible. All the strength left me and I didn't have no energy at all."*

4.1.2.20 Dizziness

Dizziness was experienced by 4 of 34 (15%) patients. This symptom was mentioned by 1 (25%) patient with abscess, 1 (25%) patient with cellulitis, and 2 (50%) patients with wound infection. Patients described dizziness as the sensations of blurriness and spinning and sometimes associated the symptom with lightheadedness. Sample patient descriptions are provided below.

102-012 (abscess): *"I would get up and I would be dizzy and then I felt like I was just going to puke..."*

103-010 (cellulitis): *"Dizziness and lightheaded. Yeah, that's pretty much how I felt for the past 3-4 days."*

102-020 (wound): *"Yeah, sleepy and dizzy; like everything was blurry and spinning. And then, I'm not sure if I had a fever or what, but that's what happened that night."*

4.1.2.21 No Appetite

Lack of appetite was experienced by 4 of 34 (15%) patients. This symptom was mentioned by 2 (50%) patients with abscess and 2 (50%) patients with cellulitis. Patients described this symptom as not feeling like eating, or it being difficult to eat. It was sometimes associated with a bad taste in the mouth or their experience of pain. Sample patient descriptions are provided below.

102-008 (abscess): *"It's bad when I got the skin infection because I don't want to eat...I can't taste anything and it doesn't taste right and everything tastes so bad, it tastes terrible."*

101-007 (cellulitis): *"It's hard for me to eat...the pain kind of kills my hunger."*

4.1.2.22 Puffiness

Puffiness at the infection site was experienced by 4 of 34 (12%) patients. This symptom was mentioned by 3 (75%) patients with abscess and 1 (25%) patient with wound infection. Patients described puffiness in terms of swelling and an increase in size of the infection site. Sample patient descriptions are provided below.

102-002 (abscess): *"It was like a – like a lump kind of. Like a pillow almost. Like it was just like it puffed up..."*

102-018 (wound): *"Yeah, it just started getting puffy and stuff. It started getting puffy and fat along that area and stuff, so I knew something was wrong."*

4.1.2.23 Body weakness

Body weakness was experienced by 3 of 34 (9%) patients. This symptom was mentioned by 1 (33%) patient with abscess, 1 (33%) patient with cellulitis, and 1 (33%) patient with wound infection. When describing body weakness, patients mentioned generally feeling weak or tired and an overall sense of feeling unwell. Sample patient descriptions are provided below.

103-001 (abscess): *“My arms are more tired than they normally are.”*

103-003 (cellulitis): *“It kind of gathers the pain...and it just kind of makes your body weak.”*

102-017 (wound): *“Well, weak because of I guess the infection. I’m not feeling good at all...just deflated, just boom, weak, feeling bad.”*

4.1.2.24 Other Symptoms

Symptoms among ABSSSI patients mentioned less than 3 times (n=6) are included below. Symptoms mentioned include the following:

- Weight Loss (n=2)
- Constant Urinating (n=2)
- Stinging Sensation (n=2)
- Swelling of Lymph Nodes (n=1)
- Diarrhea (n=1)
- Skin Crawling (n=1)

4.1.3 Impact of symptoms

In addition to identifying symptoms associated with ABSSSI, the CE interviews resulted in the spontaneous report of how these symptoms impacted functioning. Symptoms negatively affected emotional functioning, social functioning, activities of daily living, physical functioning, and sleep. Table 4 below shows the frequency of all spontaneously reported impacts. Reports of the impacts on functioning reached saturation at interview three. A saturation grid for impacts is shown in Table 5 below. A summary of findings for each of the 5 impacts is also provided below.

TABLE 4: FREQUENCY OF SPONTANEOUSLY REPORTED SYMPTOM IMPACTS

Impact	Frequency (%) (N=34 patients)
Emotional functioning	31 (91%)
Social functioning	27(79%)
Activities of daily living	25 (74%)
Physical functioning	24 (71%)
Sleep	16 (47%)

TABLE 5: SATURATION GRID-SYMPTOM IMPACTS

Impacts	Patient ID's																	
	102-001	102-002	102-003	102-004	102-005	102-006	102-007	102-008	103-001	103-002	103-003	103-004	102-010	102-011	101-002	102-012	101-003	
Emotions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ADL's	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Difficulty Sleeping	X		X	X	X	X					X			X		X		
Physical functioning		X	X	X	X	X	X	X					X	X				
Social functioning			X	X		X	X		X	X	X	X	X	X	X	X	X	X
	102-013	102-014	101-007	101-008	101-009	102-015	103-010	103-011	102-016	102-017	102-018	103-013	104-002	102-019	102-020	102-021	102-022	
Emotions	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
ADL's			X	X	X	X		X	X	X			X			X		
Difficulty Sleeping		X			X			X	X	X	X	X			X			
Physical functioning			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Social functioning	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	
Key																		
Green = First time code applied			Yellow = Abscess				Red = Cellulitis including Erysipelas					Blue = Wound						

4.1.3.1 Emotions

Emotional impact of symptoms was experienced by 31 of 34 (91%) patients. This impact was mentioned by 13 patients with abscess, 8 patients with cellulitis, and 10 patients with wound infection. When describing the emotional impact of their symptoms, patients reported feelings of embarrassment, anger, depression, isolation, distress, and frustration. Sample patient descriptions are provided below.

102-002 (abscess): *“It makes me extremely self-conscious. It makes me feel embarrassed if anybody sees it. It’s just basically I feel dirty whenever I look at it and it’s nauseating because I’m already used to having track marks and now having this is just something that’s like – it’s really – it’s humiliating in a sense.”*

102-003 (cellulitis): *“The emotional toll is more because I have to stay away from everybody. So it’s physically and emotionally draining.”*

103-011 (wound): *“...It’s just another thing that I have to worry about. I make sure nothing touches my leg and stuff like that. I have to babysit my shin all day. It’s just a big thing I have to worry about.”*

4.1.3.2 Social Functioning

Impairment in social functioning was experienced by 27 of 34 (79%) patients. This was mentioned by 10 patients with abscess, 8 patients with cellulitis, and 9 patients with wound infection. Impairment was described as not leaving the house, and avoiding people and group activities. Sample patient descriptions are provided below.

102-006 (abscess): *“Not wanting to go outside down the street, you know, visit with anyone because I didn’t want to leave the house. Not that I even have people come visit me, but I didn’t feel like going and getting dressed to leave.”*

102-004 (cellulitis): *“You really can’t go out...dancing and hang with the guys because the pain is bothering you. You just want to kick back, lay down and deal with the pain.”*

102-017 (wound): *“Like I can’t go to church right now. Like I said, I can’t do none of the things, I would have to hide this and I wouldn’t know how do if someone was to come up and tap me on my arm, hey, how are you doing...”*

4.1.3.3 Physical Functioning

Impairment in physical functioning was experienced by 24 of 34 (71%) patients. This was mentioned by 5 patients with abscess, 8 patients with cellulitis, and 11 patients with wound infection. Impairment was described as a limitation in movement and bending of limbs around the site of infection, difficulty working/performing labor, and the inability to walk. Sample patient descriptions are provided below.

103-001 (abscess): *“Well, I don’t know, I mean I like to work outside and I can’t really do that because I can’t take a chance of having something get in it, like whether it be dirt or anything—even from the wind blowing.”*

101-007 (cellulitis): *“Well, for one, it limits my movement very much. I mean, I can’t bend my arm, I can’t make a fist. It is very painful. Like I said, it has a sore on the skin now, so I mean, it is really swollen. For the most part it is very, very disturbing when it comes to my limitations on movement.”*

101-003 (wound): *“I was in so much pain I could barely walk—I couldn’t walk, actually, I had to go inside in a wheelchair.”*

4.1.3.4 Activities of Daily Living

Impairment in performing activities of daily living was experienced by 25 of 34 (74%) patients. This was mentioned by 11 patients with abscess, 6 patients with cellulitis, and 8 patients with wound infection. When describing activities of daily living, patients reported difficulty with dressing themselves, eating, bathing, cooking, and showering. Sample patient descriptions are provided below.

102-001 (abscess): *“Um, yeah, actually all those things like eating, getting dressed because I’m right handed, so I use – I depend on that so much and even driving it was kind of hard to like turn the wheel because the bump was just right there, the infection.”*

104-002 (cellulitis): *“I had to have my sister dress me the morning that I went to the hospital because I just couldn’t.”*

101-003 (wound): *“I can’t go to the gym, I can’t cook, I can’t take a bath, I can’t take a shower.”*

4.1.3.5 Difficulty Sleeping

Difficulty sleeping was experienced by 16 of 34 (47%) patients. This impact was mentioned by 5 patients with abscess, 5 patients with cellulitis, and 6 patients with wound infection. Difficulty sleeping was debilitating and caused by pain at the infection site. Sample patient descriptions are provided below.

102-006 (abscess): *“I could barely sleep last night. I’m so tired. I keep closing my eyes. I didn’t get any sleep almost for two days because of staying up because when I lay on my arm, it hurts. If I lay down, it hurts.”*

103-003 (cellulitis): *“It messes with my sleep, because it does hurt when I sleep—I’m a big guy and it’s hard to sleep properly.”*

102-017 (wound): *“[I]t’s like the other day, the other night, last night for instance, I couldn’t sleep. I was in pain, it was like this hot tight throbbing and I got like fevers, chills like. I couldn’t sleep on my bed, there was no way I could get comfortable. So I had to sit up on the couch and that’s where I stayed until this morning.”*

4.1.4 Most Bothersome and Important to Treat Symptoms

Each patient was also asked to report his/her most bothersome symptoms, and the symptoms they felt were the most important to treat. Impacts of symptoms and signs of ABSSSI were also spontaneously reported. A detailed description of the results is presented in Tables 6 and 7. Overall, pain (N=27), appearance of the infection (N=10), and swelling (N=4) were the most bothersome symptoms/signs mentioned by patients. Swelling (N=12), pain (N=8), and redness (N=7) at the site of the infection were mentioned as the most important symptoms/signs to treat.

TABLE 6: PATIENTS' SELF-REPORTED MOST BOTHERSOME SYMPTOMS/SIGNS/IMPACTS*

Symptom	Frequency (%) (N=34 patients)
Pain/hurt	27 (79%)
Appearance of infection	10 (29%)
Swelling	4 (12%)
Inability to Walk	3 (9%)
Limited Mobility	3 (9%)
Low Energy	3 (9%)
Soreness	2 (6%)
Difficulty Sleeping	2 (6%)
Scarring	2 (6%)
Fever	2 (6%)
Tenderness	2 (6%)

*The following symptoms/signs/impacts were each mentioned by 1 patient: puffiness, itchiness, hardness/stiffness, pus/draining/leaking, burning, nausea, tightness of skin, and weakness.

TABLE 7: PATIENTS' SELF-REPORTED MOST IMPORTANT SYMPTOMS/SIGNS/IMPACTS TO TREAT*

Symptom	Frequency (%) (N=34 patients)
Swelling	12 (35%)
Pain/hurt	8 (24%)
Redness	7 (21%)
Fever	5 (15%)
Pus/Draining/Leaking	5 (15%)
Soreness	2 (6%)
Puffiness	2 (6%)
Limited Mobility	2 (6%)

*The following symptoms/signs/impacts were each mentioned by 1 patient: growth, pressure, hardness/stiffness, and bump

4.2 Development of the Draft Instrument Items

4.2.1 Identification of Relevant Symptoms and Impacts from CE Interviews

Following the CE interviews with patients, the wider project team was consulted to review all patient-reported symptoms, impacts, and to generate the first draft of the daily symptom diary. After close review of the symptom concepts that emerged from the CE interview data, it was decided that 19 of the 29 symptoms should be included as draft items in the symptom diary. These symptoms were common across all ABSSSI subtypes. Most of these 19 symptoms were also mentioned by patients as either most bothersome (i.e. pain/hurt, low energy, soreness, tenderness, itchiness, hardness, burning, nausea, tightness, and weakness) or most important to treat

(pain/hurt, soreness, pressure, and hardness). Overall, the symptoms were classified as either systemic or occurring at the site of the infection, as detailed below.

Systemic symptoms

- Warm/hot⁹
- Cold/chills
- Sweating
- Tiredness
- Low energy
- Weakness
- Headache
- Nausea
- Lightheadedness/Dizzy

Symptoms at the site of infection

- Pain/Hurt
- Soreness
- Warm/hot
- Throbbing
- Pressure
- Tenderness
- Itchiness
- Hardness
- Burning
- Tightness/Stretched
-

It was suggested that the remaining 10 symptoms be eliminated. Five symptoms were removed as they were deemed to be relatively uncommon or unrelated to ABSSSI (constant urinating, swelling of lymph nodes, diarrhea, stinging sensation, and skin crawling). The other five symptoms were considered inappropriate for inclusion in this diary because they were observable “signs” of ABSSSI (i.e. weight loss, swelling, pus/draining/leaking, puffiness, no appetite), instead of genuine “symptoms.”

All 5 symptom impacts reported by ABSSSI patients were considered relevant and meaningful and were included in the diary. Based on patient and expert feedback, two additional discrete symptom impacts, difficulty walking and difficulty working, were also included in the diary. This decision was made because difficulty walking was mentioned by 50% of patients (17 of 34) and was particularly relevant to patients with infections on the leg. Difficulty working was reported by 41% of patients (14 of 34) and was particularly relevant to patients in terms of interfering with their job functioning.

⁹ Although the concept of fever/change in body temperature was mentioned by over 70% of ABSSSI patients, the actual manifestations of these concepts varied across patients. Since fever produces an array of distinct and unique symptoms, the experts suggested the need to distinguish each of these symptoms in the diary, such as the experience of heat/warmth and cold/chills. Therefore, the broad symptom of fever/change in body temperature was removed.

Three out of the 7 total symptom-related impacts were also mentioned by patients as most bothersome or most important to treat.

Symptom-related Impacts

- Emotional functioning
- Social functioning
- Activities of daily living
- Physical functioning
- Difficulty sleeping
- Difficulty walking
- Difficulty working

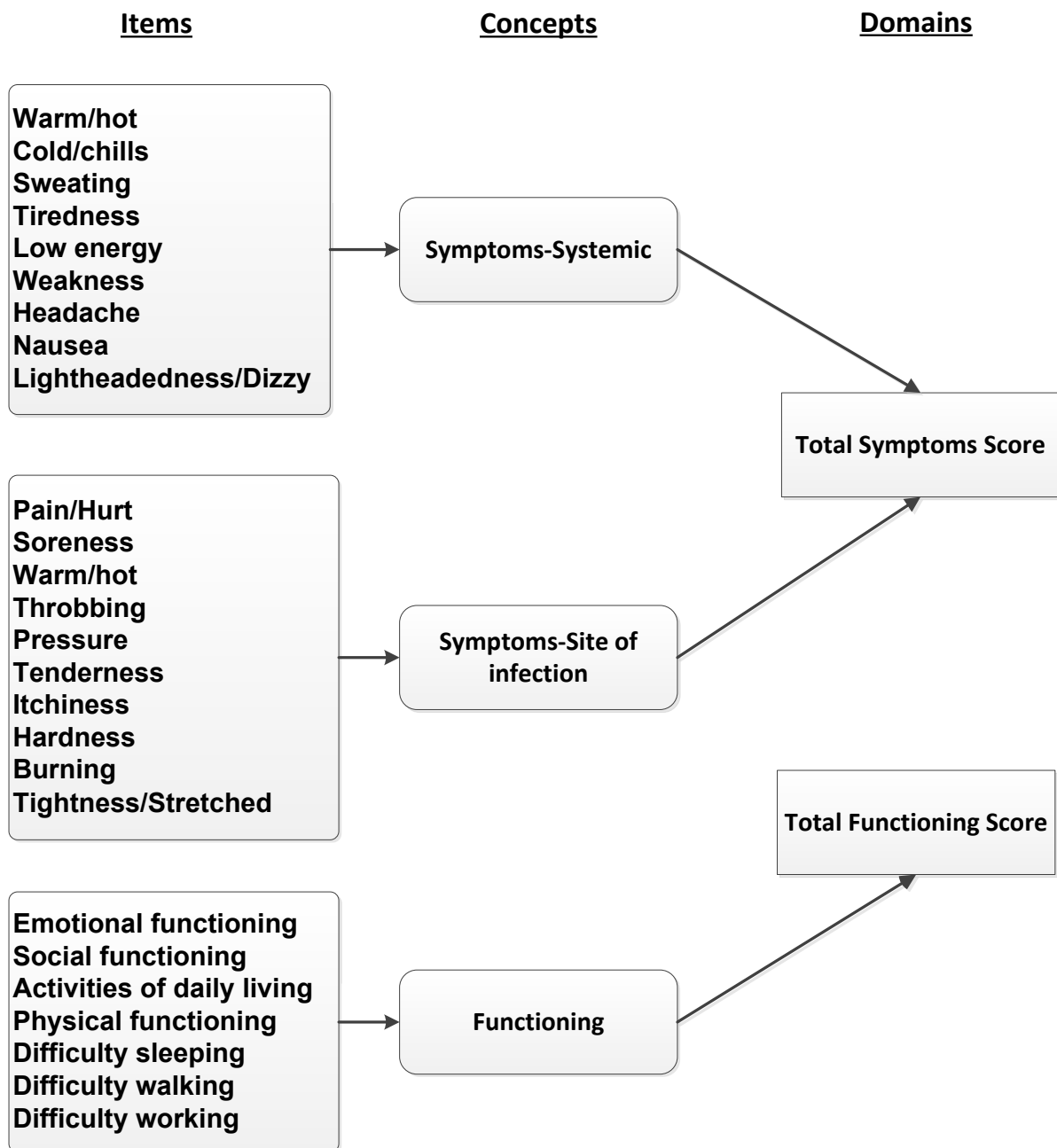
For each of the 26 concepts (symptoms and impacts) a relevant item was developed.

4.2.2 Identification of Response Options and Recall period

A 24-hour recall period was chosen due to the variability and frequency of symptoms represented by the three different ABSSSI subtypes, as reported by patients during the CE interviews. Likert scale response options of “not at all, a little bit, somewhat, quite a bit, and very much” were chosen because ABSSSI symptoms and impact were typically described in terms of varying levels of severity or degree as illustrated in the below example:

102-002 (abscess): “...Ah, yesterday morning was when it really started to hurt. It was painful over the first few days, but yesterday morning was when it was so severe that I couldn’t even move my arm.”

FIGURE 2: DRAFT CONCEPTUAL FRAMEWORK



4.2.3 Section Summary

Following a carefully documented process of item generation and expert review, a 26-item symptom and functioning diary, with each item comprised of 1 to 5 response options, was developed. In order to comply with the FDA final guidance on instrument development the instrument required further evaluation by patients using a cognitive debrief methodology; this process is detailed in the next section (Section 4.3).

4.3 Cognitive Debrief Interviews

4.3.1 Patient Characteristics

Cognitive debrief interviews were conducted with 15 additional ABSSSI patients who had not participated in the original concept elicitation interviews. The demographic information and clinical characteristics of the sample are provided in Table 1. Four (27%) patients had major abscess, 5 (33%) had wound infection, and 6 (40%) had cellulitis. In terms of severity, the majority (67%) of infections were rated as moderate by clinicians. The mean age of patients was 39.3 (SD=11.1) years old with a range of 21-53 years, and the majority were male. Patients were primarily Caucasian (67%) or Hispanic (27%), and the highest level of education attained was primarily high school/GED, some college, or did not complete high school. The employment status of the sample participants varied, with many participants who reported being employed full time (33%), unemployed or seeking work (20%), temporarily unable to work (20%), others in part-time employment (13%), retired (7%) and another who was a student (7%).

Item level changes made as a result of the cognitive interviews, along with the rationale for the revisions, are documented in the Item Tracking Matrix (Table 9).

TABLE 8: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Characteristic	Distribution (N=15)*
Age	
Mean (SD)	39.3 (11.1)
Range	21-53
Sex: Female	5 (33%)
Race/Ethnicity	
Caucasian	10 (67%)
Hispanic	4 (27%)
Black/ African American	-
Other	1 (7%)
Education	
High School/GED	7 (47%)
Some college	4 (27%)
Associate's degree	-
Did not complete high school	3 (20%)
Bachelor's degree	1 (7%)
Graduate degree	-
Employment Status	
Student	1 (7%)
Employed full-time	5 (33%)
Employed part-time	2 (13%)
Retired	1 (7%)
Unemployed/seeking work	3 (20%)
Looking after home/family	-
Temporarily unable to work	3 (20%)
Permanently unable to work	-
Other (e.g. occasional work)	-
Type of ABSSEI	
Major abscess	4 (27%)
Cellulitis	6 (40%)
Wound Infection	5 (33%)
Clinician Rating of Severity	
Mild	-
Moderate	10 (67%)
Severe	5 (33%)

*Percentages may not add up to 100% due to rounding

4.3.2 Instructions

The instructions on the ABSSSI PRO consist of two sections which ask respondents to complete the diary at the same time every day, choose one response number for each statement, record the date and time at which the respondent completes the diary, and think about how they have felt in the past week with respect to their skin infection. Patients were asked how they interpreted the instructions and if the instructions were clear and easy to understand. All of the interviewed patients (N=15) were able to correctly interpret the ABSSSI PRO instructions:

103-0014 (abscess): *"It is pretty much telling me to take the day that I am actually answering my information and time and to put a.m. or p.m. and then asking that I think about my current situation and how it made me feel."*

103-024 (cellulitis): *"It is just saying while answering the following questions, please think about your current skin infection, how you felt during the past 24 hours."*

Patients were also asked if they felt that the instructions were understandable and all patients indicated that the instructions were clear and easy to understand:

103-0014 (abscess): *"My opinion [is] to enter [the] diary every day around the same time and answer all the questions. Pretty much explaining exactly what it says."*

103-0019 (wound): *"It's very straightforward. You just use your own words to tell just how you felt. That's straightforward. That's how it's designed. I don't see anything other than that. That's perfect."*

When asked if it was helpful to include, "select only one response" after each item, 7 out of the 7 patients who were asked this question agreed that it was helpful. This question was skipped for 8 patients because it was placed as a closing question at the end of the cognitive interview guide where time was limited and interview fatigue was detected.

4.3.3 Recall Period

The recall period for the ABSSSI PRO is 24 hours. When patients were asked what time period they were considering when responding to each item, most patients who were asked this question (11/15) reported that they had followed the instructions to think about the past 24 hours:

103-017 (abscess): *"All the questions stated 'within the last 24 hours', so I was thinking within the last day."*

103-022 (wound): *"Things for me are usually more severe or I feel things more in the late evening and early morning hours. And so it was less painful once the day has been going. I am trying to think of the whole thing and give kind of a general response."*

Although patients thought the 24-hour recall period was easy to think about, some patients were thinking about the time since their skin infection was diagnosed or the time since the infection started:

102-025 (abscess): *"Maybe the last four or five days because I developed this infection on Friday"*

102-024 (cellulitis): *"From when I had the infection to now...It says during the past 24 hours, so, I mean, it has been hurting longer than that, but, so from the time that it started to now."*

103-0024 (wound): *"In the past 24 hours it's just been like a lot better. Like there's not as much pressure really. There's hardly any pain. Like it went from an 8 to a 2. Well in a lump sum I believe it should be not just taking consideration of the past 24 hours especially the fact that I've been given medications and I've undergone a little surgical process in the past 24 hours. So, it really isn't relevant I believe that whole [infection] time before that is what really matters."*

103-0023 (wound): *"Was easy to think about past 24 hours but was thinking of last week"*

Although this recall differential is important to consider, this instrument will be administered as a daily diary; therefore, the tendency for patients to consider the entire length of their infection will be reduced and the 24-hour recall will most likely be reflected. Because this cognitive interview was completed with the patient at one time only, patients were inclined to consider the entire time in which they had had the skin infection.

Two patients were thinking within the 24-hour recall period, but thought this length of time was too long as they felt their symptoms changed considerably within the 24-hour period:

103-0025 (cellulitis): *"It would be anytime, prior to getting some relief, which is the 12 hours—not the past 12 hours, but the 12 hours before that; the first 12 hours of the 24"*

103-0018 (cellulitis): *"It was half and half because I know exactly how I felt within the 24 hours the whole time, but not knowing what's going [on] like I said, the 6 hours, the 12 hours, and the 4 hours. It would have made it easier to give you more of an answer you can understand than just the whole 24 hours – it was difficult but it wasn't because I knew the answer, but didn't know which answer to give...Like just the change from 4 hours to 8 hours, I know how I felt for both, but at that time I felt sick, but at 8 hours I didn't feel sick."*

103-0026 (wound): *"It is possible to have a double sided answer because of the 24 hours."*

Patients were also asked if their responses to the questions would change if they were asked how they felt "right now". For 6 of the 19 questions, the majority of patients reported that their answer would have changed if they were asked how they felt right now. The 6 questions covered the concepts pain/hurt, feeling warm/hot, feeling cold/chills, pressure, tender when someone else touches it, and the infected area feeling hard. Many patients reported a decrease in severity in their response option when asked how they felt right now because they were seen by their doctor before or at the time of the CD interview and the skin infection was improving. For example:

103-0021 (cellulitis): *"But once I got to the clinic, it went down because I wasn't moving as much anymore."*

102-025 (abscess): *"I don't feel any pressure from it, not like how I did yesterday or earlier today before I came to the doctor."*

103-0021 (cellulitis): *"Maybe because of how I'm feeling right now. I was given some pain medication and numbing medicine."*

Overall, for the symptom questions, 11 of the 15 patients thought the 24-hour time period was easy to think about. However, of these 11 patients, 3 patients preferred to recall their experience over the past few days or week to encompass the time since the skin infection started, while 3 patients preferred to recall a more specific time within the past 24 hours. Similarly for the impact questions, 13 of the 15 patients thought the 24-hour time period was easy to think about. The same 6 patients

who preferred recalling a different time period for the symptom questions also preferred this change of time period for the functioning questions.

4.3.4 Response Options

The response options on the ABSSSI PRO consist of 5-point Likert scales ranging from “Not at all” to “Very much”. When patients were asked if they thought the response options allowed them to choose an accurate response to each items, 12 of the 15 patients stated that they were able to choose an accurate response:

103-0024 (wound): *“They are pretty clear.”*

103-0017 (abscess): *“I wanted to make sure I thought about the question and made sure that I had that if it applied to my condition. And it wasn’t really a problem to answer it.”*

103-0021 (cellulitis): *“Not at all is there is nothing bothering you with it. A little bit would be mild but it’s not distracting you from doing anything that you normally do. And, ah, somewhat, it could be a sharp pain, but it comes and goes, and quite a bit, it, um, there is discomfort, but, um, very much – it is a constant reminder of the pain.”*

Three patients reported having difficulty choosing an answer because they preferred the response choices to be more specific to their experiences. One patient stated that it was difficult to determine the difference between the response options:

103-0025 (cellulitis): *“I think ‘somewhat’ and ‘a little bit’ are pretty much the same to me. I kind of think they’re the same thing. Yeah, those too; ‘quite a ‘bit’ and ‘very much’, um, same thing. They’re pretty much the same thing to me.”*

Interviewer: “What if it just said, on a scale of 1-5? Would that have made it better?”

103-0025 (cellulitis): *“Oh yeah, that would definitely make it better. That’s easier, yeah definitely.”*

103-0016 (abscess): *“Honestly, I’m not exactly sure how I would personally word them, but it is just like usually when I see something like that it’s like a 1 to 10 scale. It’s a lot easier.”*

Two patients reported that they felt multiple choice answers limited their ability to elaborate on how they felt with respect to each symptom:

103-0024 (wound): *“I don’t think it should be multiple choice. I believe people should write down what it is I guess or—unless you know the symptoms of what they’re going through. And you could just say, select that—all that apply...You know how there’s like five options? You should maybe have another one that says, other, and then with the line that says, please explain.”*

4.3.5 Items – Summary of Responses

An in-depth summary of the results for each item of the draft ABSSSI instrument is presented in the item tracking matrix in Table 9. This table also shows the changes made to the diary after analysis of the cognitive interviews. As shown in the table, 15 items were left unchanged because all participants interpreted the concept correctly, reported it as easy to understand,

and found it relevant to their experience. These were: Item 4 (sweating), Item 5 (soreness), Item 6 (warm/hot [infected area]), Item 8 (low energy), Item 9 (weakness), Item 11 (pressure), Item 13 (itchiness), Item 15 (headache), Item 16 (burning), Item 18 (nausea), Item 21 (social functioning), Item 22 (activities of daily living), Item 23 (physical functioning), Item 25 (difficulty sleeping), Item 26 (difficulty working).

Eleven items were revised based on feedback from the patient and expert reviews.

1. Item 1, "During the past 24 hours, did the infected area hurt or feel painful?" was changed to "During the past 24 hours, did the infected area feel painful?" based on the number of patients who preferred this phrasing, who defined pain and hurt as the same concept, and felt pain was more relevant to their experience than hurt. In addition, removing "hurt" from the question removes any confusion around it being double barreled:

103-0015 (abscess): *"Hurt means pain. It relates to pain, uncomfortable pain."*

102-025 (abscess): *"It depends on how I use it. But 'hurt' - I don't really think is a strong enough word to describe like a staph infection. 'Painful' would fit better."*

103-0022 (wound): *"The infected area is sore or painful. Hurt and painful are the same thing"*

103-0018 (cellulitis): *"Pretty much the same thing as hurt...It's a little bit different. I mean, hurt is, it hurts. But painful is like, I guess the painful would describe more of the spikes, you know? That's more painful. Right now it just hurts. It's hurting. And painful when it goes up, you know? Spikes up."*

2. Item 2, "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?" to distinguish between the temperature of the body versus the site of infection temperature, as patients often confused this concept with that in question #6 while going through the interview. When asked if this phrasing is preferable, most patients agreed to add the word "body" to make the question and underlying concept clearer as well as make more relevant to their experience:

103-0025 (cellulitis): *"Yeah, that would be easier because well I mean, when you look at the question, did you feel warm, you would think, you know. I would think my whole body. But then if you're talking about my whole body, [it] didn't feel warm, but my arm did it's like, well I can't tell if they're talking about that. Then I might answer the question without knowing the question. But I would probably explain it a little bit because that's how I am."*

103-0019 (wound): *"Yeah, that would've made—that would've brought my mind to the wound. That would've brought my mind to my wound."*

103-0015 (abscess): *"Well, I might specify if we are talking physically as opposed to any other way."*

3. Item 3 was changed from "during the past 24 hours, did you feel cold or have chills?" to

“during the past 24 hours, did you have chills” because feeling cold and having chills were different concepts to patients therefore, removed any double barreled confusion. It was decided to remove cold completely and include chills because this concept was more relevant to patients and better captured the concept’s original definition:

103-0018 (cellulitis): *"Like, ah, is that different, is that cold around you, you know what I'm saying? It's not – in your body, is it cold in here? That has more to do with the temperature around you instead of what is happening to your body right now."*

103-0025 (cellulitis): *"Not really, because you can be cold and you could not be cold and have chills. You know what I mean?"*

103-0014 (abscess): *"Whenever I get the chills is when I know I'm getting sick."*

103-0022 (wound): *"If you were trying to determine if this was fever related I would leave out the feel cold, because I'm always cold. I'm pretty much not abnormal, but I associate chills more with something that happens when I run a fever."*

4. Item 7, “During the past 24 hours, did you feel tired” was changed to “During the past 24 hours, did you feel tired more than usual,” to remain consistent with language in item #4 (e.g. “sweat more than usual”) and because the phrase “more than usual” can help distinguish how one would normally feel tired in a 24 hour time period. Both experts and patients (N=2) preferred this question to include a “more than usual” qualifier:

103-0022 (wound): *"Well, I would say everybody can understand 'the past 24 hours'. I mean, not too many people stay up 24 hours at a time without feeling tired."*

Interviewer: "What if I asked you the question during the past 24 hours did you feel tired more than usual; would that have changed your answer at all?"

103-0022 (wound): *"No, but I think it's better."*

5. Item 10. The phrase “have” throbbing was changed to “feel” throbbing in item 10 to remain consistent with this language in other items:

103-0019 (wound): *"New blood going through the infected area I guess. Uh, it's, uh, it's, uh, you can like feel the—you can feel your—you can feel the pulse of your blood going through it."*

103-0015 (abscess): *"Pulsating, painful, um, spiking, getting intense, ah, felt throbbing. Intense pain."*

103-0020 (cellulitis): *"...Ah, ah, okay, the area just feels, ah, it's throbbing. Yeah, okay. But, ah, it is not hurting. It is throbbing."*

6. Item 12 was changed from “During the past 24 hours, did the infected area feel tender when you or someone else touched it?” to “During the past 24 hours, was the infected area tender to the touch?” because of the number of patients who preferred this phrasing and who spontaneously defined the concept as such:

102-024 (cellulitis): *"Tender like to the touch I guess."*

103-0022 (wound): *"Tender when someone else touches it and tender to the touch mean*

the same thing, but I think the second way is the better way to word it. Tender to touch"

Interviewer: "Does the infected area only feel tender when someone else touches it?"

102-025 (abscess): *"No, I can't really lay it flat and it tends to be very tender right now with how I place my leg."*

7. Item 14 was changed from "During the past 24 hours, did the infected area feel hard?" to "During the past 24 hours, did the infected area feel hard to the touch?" to remain consistent with the language and patient preference in item 12:

103-0019 (wound): *"The opposite of soft. It's not—the skin's not really soft when touching it. It's not squishy."*

103-0015 (abscess): *"Well, because at one point very, very hard to touch. Hard to touch...And it is still now hard to touch."*

8. Item 17 was changed from "During the past 24 hours, did the skin around the infected area feel tight or stretched?" to "During the past 24 hours, did the skin around the infected area feel tight?" because again patients thought tight and stretched were different concepts, therefore, removed any double barreled confusion. Also, patients reported "tight" more frequently than stretched during concept elicitation and cognitive interviews when asked to describe this feeling:

103-0020 (cellulitis): *"If it's tight it's like somebody is pulling it...Stretched would be more of pushing it away."*

103-0021 (cellulitis): *"Like tight, like you wouldn't be able to move it as much. Like to move my leg, it's not like too tight or restricting or too inconvenient. Same response, like with a t-shirt being stretched out. And I don't feel like it would stretch out at all...Yeah, I don't feel like it was stretched out too much."*

103-0024 (wound): *"'Tight' sounds like the opposite of 'stretched'. Isn't that the opposite of 'stretched' is tight? It's to stretch something out."*

9. Item 19 was changed from "During the past 24 hours, did you feel lightheaded or dizzy?" to "During the past 24 hours, did you feel dizzy?" because patients thought light-headedness and dizzy were different concepts therefore, this separation and deletion removed any double barreled confusion. Dizzy was also reported as more of a relevant experience to patients.

103-0024 (wound): *"Different terms, different feelings. I believe feeling 'lightheaded' is being weak. You feel like you're going to pass out. 'Dizzy', you just feel you're going to fall down."*

103-0022 (wound): *"Lightheaded is definitely more tolerable than dizzy. And I – you can be lightheaded without being dizzy."*

103-0018 (cellulitis): *"Like the dizziness, the dizzy feels like kind of a motion sickness. If I had more of a motion sickness, and that's more of a sick sickness."*

102-025 (abscess): *"Lightheaded, unbalanced. [Dizzy] is disoriented like you're—you're not like sometimes you're just there I guess."*

10. Item 20. After patient and expert feedback, item 20 “During the past 24 hours, how “down” or worried did you feel?” was divided into 2 separate questions because 12 out of the 15 patients considered down (item 20) and worried (new item #21) to be two distinct concepts, making the original item double-barrelled and confusing to answer.

103-0022 (wound): *"I think that I might separate the down and worried. Because down is more in my book associated with depression and worried is – is more of an anxiety. So I think I might separate those."*

102-025 (abscess): *"'Down' to me means maybe depressed. Yeah, so I wasn't depressed about this problem. I was just kind of worried. "*

103-0014 (abscess): *"I would say kind of similar but different because if you are feeling down, you are just maybe depressed or you're just not feeling up to it or you just don't feel good. But if you are worried, you are actually worried about something, like you are afraid something might happen or you are afraid of what is going to happen. "*

103-0025 (cellulitis): *"I don't know if 'down' and 'worried' are the same thing because I don't feel like they are really. I guess because you can be 'worried' and not be 'down'. You can be 'down', but just because of something else. Maybe you're not worried, I don't know. Maybe you're 'down' because you don't feel good, but you're not worried about it."*

103-0022 (wound): *"I think I would also – you asked the question if I felt down or worried. I think I would separate those and then I think I might ask why a person was worried, what specifically was worrying them."*

Although most of the participants felt that the symptoms included in the diary were relevant, 1 item was removed at this stage due to lack of relevancy reported by the patient and expert review panel.

11. The original item #24, “During the past 24 hours, did you have difficulty walking?” was removed because the majority of patients (8 of 15) felt this question was not relevant to their experience and 2 of the 3 experts felt the item responses would be skewed depending on the location of the ABSSSI on the patient’s body.

103-0016 (abscess): *"Because the infection is on my arm and I don't walk on my arms."*

103-0017 (abscess): *"Because it's still my arm that's infected and I'm really—and that ain't in the question. So, it's unrelated to it. It didn't cause my walking—difficulty walking. And I don't think that applies to me, so I would put 'not applicable'."*

103-0022 (wound): *"Because that has not been a symptom of my illness."*

4.3.6 General Comments on Draft instrument

Patients completed one-on-one telephone interviews while going through their responses with the interviewer. Patients were able to understand and interpret the ABSSSI PRO instrument instructions, items, response options, and recall period without any problem. When asked whether any ABSSSI symptoms and impacts they experienced were missing from the diary, 10 of the 14 patients who were asked this question mentioned that the diary captured their

experience and did not have anything to add:

102-024 (cellulitis): "No. I think that you guys have covered all the symptoms."

103-0017 (abscess): "Is it embarrassing to have your skin infection condition, but that's about it."

103-0022 (wound): "I think it's really, well, except for adding the question about discharge."

Two patients reported adding an additional emotional component question such as embarrassment or a question asking generally how one is feeling. Two patients requested to add discharge as an important symptom related to their skin infection experience. One patient was not asked this question because the patient had interview fatigue and therefore the question was skipped.

4.4 Expert Review

At least 2 of the 3 experts considered all of the 24 of the 26 concepts (19 symptoms and 7 impacts) to be relevant to patients with ABSSSI. Two symptoms, the infected area feeling itchy and having a headache, were reported by 2 of the 3 experts as not relevant and uncommon to patients who experience ABSSSI. This concept was important to the patients during CE and subsequently endorsed by the cognitive interviews, these questions were left in and will be further reviewed during the psychometric phase of the study. Two of the 3 experts neither agreed nor disagreed that some systemic symptoms: cold/chills, sweat more than usual, nauseated, and lightheaded/dizzy were relevant to patients and not commonly reported. The clinical experts noted, however, that some of the systemic symptoms are a reflection of the severity of the ABSSSI (i.e. when the condition is most severe); therefore, these items were left in as is.

Experts were also asked whether the symptoms are likely to show change over the course of a clinical trial of a new treatment for ABSSSI. Two of the 3 experts agreed that 16 of the 26 symptoms or impacts were likely to show this change. Two of the 3 experts neither agreed nor disagreed that the symptoms: sweat more than usual, feeling tired, having low energy, feeling weak, pressure in the infected area, headache, burning sensation in the infected area, nauseated, lightheaded/dizzy, and feeling "down" or worried were likely to show this change. Some of the experts reported that these symptoms are often too subjective, too changeable to be valuable, or difficult for the patients to assess. It was also recommended to remove the symptoms, 'low energy' and 'weak', as they were too similar to the symptom 'tired'. Although these recommendations are important to document, these symptoms were left in the diary because they were still considered to be important to the patients during the CE interviews and then further acknowledged by patients as important during the cognitive interviews.

Lastly, the experts were asked to list if there were any other relevant symptoms or functions relevant to patients with ABSSSI that were not included in the diary. Two of the 3 experts reported that all of the concepts were covered. Additional concepts included: drainage of the infected area, swelling, and general feelings of being unwell.

One expert recommended making minor changes to 2 items. He recommended changing the symptom “burning” to “tingling or stinging” as well as changing the item with “chills” to “shaking or shivering”. To accommodate these suggestions, interviewers documented if and when these terms were used by patients during the cognitive interviews. Because the majority of patients did not use these terms and preferred the original phrasing, the items were left as is.

No items were removed following expert review of the diary. The minor word change suggestions were considered during the cognitive debriefing testing with the ABSSSI patients.

Following item generation and expert review, a draft conceptual framework (Figure 2) was developed to illustrate the proposed items, concepts, and domains for the new ABSSSI PRO instrument.

TABLE 9: ITEM TRACKING MATRIX

Item #	Original Item and Response Options	Intended Meaning/Concept Definition	Concept ¹⁰ (General Domain)	Expert Review (n=3) ¹¹	Comments	Potential Actions	Final Item and Response Options
Instructions 1	Please fill out this diary at the same time each day. Please give only one answer for each question and answer every question. Thank you for your time.	The intention for this instruction is for participants to complete the diary at the same time each day when answering each question.	N/A	• Question not asked in guide	• No Change • Time period correct=15/15 • Interpretation=15/15 • Clear=15/15	N/A	Please fill out this diary at the same time each day. Please give only one answer for each question and answer every question. Thank you for your time.
	Please record the current date (MM/DD/YY): Please record the current time: AM / PM (circle one) While answering the following questions, please think about your current skin infection and how you felt during the past 24 hours.	The intention for this instruction is for participants to focus on the previous 24 hours only when answering each question.	N/A	• Question not asked in guide	• No Change • Time period correct=15/15 • Interpretation=15/15 • Clear=15/15	N/A	Please record the current date (MM/DD/YY): Please record the current time: AM / PM (circle one) While answering the following questions, please think about your current skin infection and how you felt during the past 24 hours.
#1	During the past 24 hours, did the infected area hurt or feel painful? (Select only one response.) <input type="checkbox"/> Not at all	Physical discomfort at the site of the infection. Described as hurting or feeling painful.	Pain/Hurt (localized symptom)	• Leave as is (n=3)	• Interpretation=15/15 • Clear=15/15 • Relevant (Yes=15)	• Suggestion to remove 'hurt' to avoid possible double barreled question. This is also based on the number of patients who preferred this phrasing, who defined pain and hurt as the same concept, and felt pain was more relevant	During the past 24 hours, did the infected area feel painful? (Select only one response.) <input type="checkbox"/> Not at all

¹⁰ These are overall general concepts of the item. Domains and sub domains will be illustrated in the conceptual framework

¹¹ These comments will be further explained and addressed in the expert review section of the final report

	<input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much				<p>to their experience than hurt.</p> <p>FINAL DECISION: remove "hurt"</p>	<input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much
#2	<p>During the past 24 hours, did you feel warm or hot? (Select only one response.)</p> <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much	<p>Feeling warm or hot in reference to general body temperature</p>	<p>Warm/Hot (systemic symptom)</p> <ul style="list-style-type: none"> • Uncommon, symptom only apparent among very severe abscesses with fever (n=2) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. 	<ul style="list-style-type: none"> • Confusion whether asking about body temperature versus infection feeling warm/hot • Needs distinction between warm and hot. Some patients felt warm but not hot. • Most patients¹² associated this concept with fever • Most patients (3/5) preferred and would have answered the question differently if question included "body" • Interpretation=13/15 • Clear=12/15 • Relevant (Yes=10; No=3; Unsure=2) 	<ul style="list-style-type: none"> • Suggestion to add "your body" to question to distinguish between body temperature and infection temperature. Patients preferred to add "body" as that was made question most relevant to their experience. <p>FINAL DECISION: add "your body"</p>	<p>During the past 24 hours, did your body feel warm or hot? (Select only one response.)</p> <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much
#3	<p>During the past 24 hours, did you feel cold or have chills? (Select only one response.)</p> <input type="checkbox"/> Not at all	<p>Feeling cold in reference to general body temperature or experiencing chills (in relation to transitioning from hot to cold or during or</p>	<p>Cold/Chills (systemic symptom)</p> <ul style="list-style-type: none"> • Uncommon, symptom only apparent among very severe abscesses with fever, suggest including "shaking chills or chills or shakiness" (n=2) • PRO team response: 	<ul style="list-style-type: none"> • Confusion whether asking about feeling physically cold versus having chills as if related to fever. • Overall, patients thought 	<ul style="list-style-type: none"> • Suggestion to remove 'feeling cold' to avoid double barreled question. It was decided that because feeling cold and chills were different concepts 	<p>During the past 24 hours, did you have chills? (Select only one response.)</p> <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit

¹² Mentioned by more than half of the patients (i.e. n≥7)

<p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>	<p>after sweating).</p>	<p>Left in as it was important to the patients during CE and subsequently endorsed by the CD. Decided to remove cold and include chills to better capture concept. Few patients spontaneously mentioned the words shiver/shake to describe this concept so decided to leave language the same.</p>	<p>feeling cold and chills were different concepts with similar symptoms (i.e. shivering). Most patients would have answered differently if question was separated into two.</p> <ul style="list-style-type: none"> • Chills was the most relevant experience between chills and feeling cold because symptom is more severe • Interpretation=14/14 • Clear=14/15 • Relevant (Yes=11; No=3; Unsure=1) 	<p>to patients, it was best to separate. Decided to keep chills instead of cold because it was more relevant to patients and because it was better at capturing the concept of fever/unwellness</p> <p>FINAL DECISION: remove "cold"</p>	<p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>
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#4

<p>During the past 24 hours, did you sweat more than usual? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>	<p>Experiencing sweating, more than usual and not due to another cause like exercise or external temperature.</p> <p>Sweating (systemic symptom)</p> <ul style="list-style-type: none"> • Uncommon, may be too subjective, overlaps with feeling of warmth so advise to remove one or the other (n=3) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. Will be reviewed during psychometric validation phase in terms of similarity to other items/concepts. 	<ul style="list-style-type: none"> • Confusion if a patients does not sweat normally or sweats a lot normally • Hard time distinguishing sweating more than usual from circumstance or due to infection • Most patients did not prefer "sweaty" to original question • Patients understand "more than usual" as "more than normal" or "more than they usually would sweat" • Interpretation=15/15 • Clear=14/15 • Relevant (Yes=9; No=5; Unsure=1) 	<ul style="list-style-type: none"> • Leave as is <p>OR</p> <ul style="list-style-type: none"> • Possible suggestion to remove "more than usual" although patients understood and didn't mind this phrase. <p>FINAL DECISION: Leave as is</p>	<p>During the past 24 hours, did you sweat more than usual? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>
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#5	During the past 24 hours, was the infected area sore? (Select only one response.)	Soreness around the site of the infection. "Sore" refers to a raw or painful area on the body.	Soreness (localized symptom)	• Leave as is (n=3)	<ul style="list-style-type: none"> • Defined as pain, uncomfortable, throbbing, hurt, inflammation, and tender. • Patients found pain and hurt to be more relevant than sore • Half of the patients feel sore and pain is the same concept and half feel they are different concepts but associated. • Interpretation=15/15 • Clear=15/15 • Relevant (Yes=14; Unsure=1) 	<ul style="list-style-type: none"> • Leave as is • Potentially will load with pain; will be evaluated in psychometric validation phase 	During the past 24 hours, was the infected area sore? (Select only one response.)
	<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much						<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much
#6	During the past 24 hours, did the infected area feel warm or hot? (Select only one response.)	Infected area feels hot or warm to the touch.	Warm/hot (localized symptom)	<ul style="list-style-type: none"> • May be too subjective and too variable to be valuable, patients may not be able to assess (n=2) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. Revised with adding "body" so patients are better able to assess symptom. 	<ul style="list-style-type: none"> • Some confusion about this question and #2. Patients misunderstand whether talking about body fever versus heat from infection area • Some define hot as burning both as fever and external sense of heat. May load with burning sensation question #16 • Confusion about whether infection feels warm/hot internally or warm/hot to the touch externally • Interpretation=14/15 • Clear=15/15 • Relevant (Yes=13; No=2) 	<ul style="list-style-type: none"> • Leave as is • With the "body" addition to #2, this question could remain as the difference is now distinguished <p>FINAL DECISION: Leave as is</p>	During the past 24 hours, did the infected area feel warm or hot? (Select only one response.)
	<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much						<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much
#7	During the past 24 hours, did you feel tired? (Select only one response.)	Feeling fatigued or tired more than usual	Tired (systemic symptom)	<ul style="list-style-type: none"> • May be too subjective (report this when not ill, can feel tired for various reasons), prefers a qualifier such as "more 	<ul style="list-style-type: none"> • Everyone gets tired at some point in 24 hours so may need something more than usual to 	<ul style="list-style-type: none"> • Leave as is <p>OR</p>	During the past 24 hours, did you feel tired more than usual? (Select only one response.)

	<p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>		<p>than usual" (n=2)</p> <p>• PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. Will be reviewed during psychometric validation phase in terms of similarity to other items/concepts. May add a qualifier – under discussion</p>	<p>distinguish (n=4)</p> <ul style="list-style-type: none"> • Interpretation=15/15 • Clear=15/15 • Relevant (Yes=12; No=3) 	<ul style="list-style-type: none"> • A possible suggestion was to add "more than usual" to be consistent with the 'sweat more than usual' question: During the past 24 hours, did you feel tired more than usual? Also this would incorporate the expert review feedback about including a qualifier. 	<p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>
#8	<p>During the past 24 hours, did you have low energy? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>	<p>Low energy or a lack of energy.</p>	<p>Low Energy (systemic symptom)</p>	<ul style="list-style-type: none"> • May be too subjective (report this when not ill, can feel low energy for various reasons), needs qualifier "more than usual" (n=2) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. Will be reviewed during psychometric validation phase in terms of similarity to other items/concepts. 	<p>• Leave as is</p> <ul style="list-style-type: none"> • Most patients thought low energy, tired, and weakness were different concepts • Most patients say there is a difference between low energy and tired. • Interpretation=13/15 • Clear=15/15 • Relevant (Yes=12; No=1; Unsure=2) 	<p>During the past 24 hours, did you have low energy? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>
#9	<p>During the past 24 hours, did you feel weak? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>	<p>Overall body weakness; a general feeling of reduced body strength.</p>	<p>Weak (systemic symptom)</p>	<ul style="list-style-type: none"> • May be too subjective, can take a long time to recover in terms of feeling weak, too similar to low energy and tired so question the value of this item (n=2) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. Will be reviewed during psychometric validation 	<ul style="list-style-type: none"> • Low energy, tired, and weakness are different concepts but similar • Most patients say there is a difference between feeling weak and tired and feeling weak and low energy • Endorsed by 3 CE interviews and KOLs as relevant in terms of severity. Endorsed by all 	<p>• Leave as is</p> <p>During the past 24 hours, did you feel weak? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>

			phase in terms of similarity to other items/concepts.	patients in CD.			
				<ul style="list-style-type: none"> • Interpretation=14/15 • Clear=15/15 • Relevant (Yes=15; No=0) 			
#10	During the past 24 hours, did you have throbbing in the infected area? (Select only one response.)	Throbbing or pulsating at the site of the infection.	Throbbing (localized symptom)	<ul style="list-style-type: none"> • May be too similar to pain/soreness (n=1) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. Will be reviewed during psychometric validation phase in terms of similarity to other items/concepts. Also only 1 expert disagreed with item's content. 	<ul style="list-style-type: none"> • Similar to pain, hurt • Interpretation=14/15 • Clear=14/15 • Relevant (Yes=12; No=3) 	<ul style="list-style-type: none"> • Leave as is <p>FINAL DECISION: change "have" to "feel"</p>	During the past 24 hours, did you feel throbbing in the infected area? (Select only one response.)
	<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much						<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much
#11	During the past 24 hours, did you feel pressure in the infected area? (Select only one response.)	Pressure at the site of the infection.	Pressure (localized symptom)	<ul style="list-style-type: none"> • Too subjective (could occur for external reasons (i.e. often times do a procedure at screening and wrap the infected area with a tight bandage thus creating pressure that is just part of the treatment, not related to the natural course of the infection) (n=2) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. 	<ul style="list-style-type: none"> • Similar to throbbing, tightness, hardness, and pain • Pain is most relevant • Interpretation=15/15 • Clear=15/15 • Relevant (Yes=14; No=0; Unsure=1) 	<ul style="list-style-type: none"> • Leave as is 	During the past 24 hours, did you feel pressure in the infected area? (Select only one response.)
	<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much						<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much
#12	During the past 24 hours, was the infected area tender when you or someone else touched	The site of the infection feeling tender or sensitive to pain when touched or	Tender (localized symptom)	<ul style="list-style-type: none"> • Leave as is (n=3) 	<ul style="list-style-type: none"> • Patients prefer "tender to the touch" because not just tender when someone else touches it 	<ul style="list-style-type: none"> • Suggestion to change to "tender to the touch" based on the number of patients who preferred this phrasing 	During the past 24 hours, was the infected area tender to the touch? (Select only one

	<p>it? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>	<p>when pressure is applied.</p>	<p>but when other things touch it as well (n=8/8). Also n=3 defined concept using this phrase.</p> <ul style="list-style-type: none"> Describe tender as sensitive pain, and sore Interpretation=14/15 Clear=14/15 Relevant (Yes=14; No=0; Unsure=1) 	<p>and who spontaneously defined the concept as such.</p> <p>FINAL DECISION: add "tender to the touch"</p>	<p>response.)</p> <p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>
<p>#13</p>	<p>During the past 24 hours, did the infected area feel itchy? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>	<p>Itching at the site of the infection. Itching is defined as an uncomfortable sensation on the skin that causes the desire to scratch.</p> <p>Itchy (localized symptom)</p> <ul style="list-style-type: none"> Leave as is, usually sign of healing, experience due to swelling (n=3) 	<ul style="list-style-type: none"> Confused about whether asking about infected area or around the infected area (n=1). Because n=1, decided not to change and highlight patient's understanding of "infected area". Interpretation=15/15 Clear=15/15 Relevant (Yes=12; No=1; Unsure=1) 	<ul style="list-style-type: none"> Leave as is 	<p>During the past 24 hours, did the infected area feel itchy? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p> <p>2 <input type="checkbox"/> A little bit</p> <p>3 <input type="checkbox"/> Somewhat</p> <p>4 <input type="checkbox"/> Quite a bit</p> <p>5 <input type="checkbox"/> Very much</p>

#14	During the past 24 hours, did the infected area feel hard? (Select only one response.)	Site of infection feels hard to touch.	Hard (localized symptom)	<ul style="list-style-type: none"> • Hard to assess and may be too subjective (n=1) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. Also only 1 expert disagreed with item's content. 	<ul style="list-style-type: none"> • Similar to tightening, tender, painful, pressure, swelling (n=1) • Interpretation=15/15 • Clear=15/15 • Relevant (Yes=15; No=0) 	<ul style="list-style-type: none"> • Leave as is FINAL DECISION: add "to the touch" 	During the past 24 hours, did the infected area feel hard to the touch? (Select only one response.)
	<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much						<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much
#15	During the past 24 hours, did you have a headache? (Select only one response.)	Experience of a headache/pain in the head.	Headache (systemic symptom)	<ul style="list-style-type: none"> • Uncommon, symptom usually only apparent among very severe patients with fever (n=3) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. 	<ul style="list-style-type: none"> • Pain, hurt, throbbing in the head • Possibly need to distinguish patients who get headaches regularly (i.e. patient mentioned not sleeping the night before so now has headache) • This is a systemic symptom that may be indicative of the general feeling of unwellness associated with any infection. • Interpretation=14/15 • Clear=15/15 • Relevant (Yes=6; No=8; Unsure=1) • Low relevancy; will be evaluated during psychometric validation 	<ul style="list-style-type: none"> • Leave as is 	During the past 24 hours, did you have a headache? (Select only one response.)
	<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much						<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit <input type="checkbox"/> 3 Somewhat <input type="checkbox"/> 4 Quite a bit <input type="checkbox"/> 5 Very much
#16	During the past 24 hours, did you feel a burning sensation in the infected area? (Select only one response.)	Burning sensation at the site of the infection	Burning Sensation (localized symptom)	<ul style="list-style-type: none"> • Associated with tingling, not relevant/likely to be reported (n=2) • PRO team response: Left in as it was important to the patients during CE and subsequently 	<ul style="list-style-type: none"> • Patients sometimes define burning as stinging so possibly add to question (3 x CE pts, 1 x CD pt). Also to distinguish between question #6 (infected area feel warm/hot) in which patients felt was similar to this 	<ul style="list-style-type: none"> • Leave as is. 	During the past 24 hours, did you feel a burning sensation in the infected area? (Select only one response.)
	<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit						<input type="checkbox"/> 1 Not at all <input type="checkbox"/> 2 A little bit

	<input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much		<p>endorsed by the CD. Tingling was not mentioned by patients in CE or CD.</p> <p>concept.</p> <ul style="list-style-type: none"> • Leave the item in as is and not to add stinging (as perceived as separate concepts). To see how the 'burning sensation' and 'did the infected area feel warm or hot' items loaded on to each other in the validation phase. • Interpretation=14/15 • Clear=14/15 • Relevant (Yes=12; No=3) 	<input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much		
#17	<p>During the past 24 hours, did the skin around the infected area feel tight or stretched? (Select only one response.)</p> <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much	<p>Skin at site of infection feels tight or stretched.</p> <p>Tight/ Stretched (localized symptom)</p>	<ul style="list-style-type: none"> • Similar to pressure, not relevant/likely to be reported (n=1). • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. Will be reviewed during psychometric validation phase in terms of similarity to other items/concepts. Also only 1 expert disagreed with item's content. 	<ul style="list-style-type: none"> • Same as hard (5/13) • Same as pressure (8/13) • Most patients say there is a difference between tight and stretched • CE data: tight was more endorsed. Tight mentioned by 6 patients versus stretched which was mentioned by 1 patient. • Interpretation=14/15 • Clear=14/15 • Relevant (Yes=13; No=0) 	<ul style="list-style-type: none"> • Suggestion to remove "stretched" to avoid double barrelled and the fact that patients thought tight and stretched were different concepts and "tight" was more commonly used by patients. • FINAL DECISION: remove "stretched" 	<p>During the past 24 hours, did the skin around the infected area feel tight? (Select only one response.)</p> <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much
#18	<p>During the past 24 hours, did you feel nauseated? (Select only one response.)</p>	<p>Feeling nausea, i.e. a queasy feeling, or the need to puke, vomit, or throw-up</p> <p>Nausea (systemic symptom)</p>	<ul style="list-style-type: none"> • Uncommon, symptom usually only apparent among very severe patients with fever, can be due to medication (n=2). 	<ul style="list-style-type: none"> • No difference between nauseated and nauseous (6/6) • Interpretation=14/15 	<ul style="list-style-type: none"> • Leave as is 	<p>During the past 24 hours, did you feel nauseated? (Select only one response.)</p> <input type="checkbox"/> Not at all

	<input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much		<ul style="list-style-type: none"> • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD 	<ul style="list-style-type: none"> • Clear=15/15 • Relevant (Yes=10; No=5) 	<input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much	
#19	<p>During the past 24 hours, did you feel lightheaded or dizzy? (Select only one response.)</p> <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much	<p>Feeling lightheaded or dizzy.</p>	<p>Lightheaded/ Dizzy (systemic symptom)</p> <ul style="list-style-type: none"> • Uncommon, symptom usually only apparent among very severe patients with fever or due to medication (n=2) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. Removed lightheaded to better capture sickness/severity aspect of concept 	<ul style="list-style-type: none"> • Lightheaded and dizziness are different concepts with similar symptoms (7/13) • Endorsed by 4 CE patients • Interpretation=14/15 • Clear=14/15 • Relevant (Yes=10; No=5) 	<ul style="list-style-type: none"> • Suggestion to remove lightheaded to avoid double barreled question and the fact that patients thought dizzy and lightheaded were different concepts. "Dizzy" was more relevant to patients. <p>FINAL DECISION: remove "lightheaded"</p>	<p>During the past 24 hours, did you feel dizzy? (Select only one response.)</p> <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much
#20	<p>During the past 24 hours, how "down" or worried did you feel? (Select only one response.)</p> <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much	<p>Emotional impact of having the skin infection. Feeling "down" (sad) or "worried" (feelings of anxiety or concern).</p>	<p>Impact on emotions (psychological)</p> <ul style="list-style-type: none"> • Uncommon, may be too subjective to be valuable or useful, needs to be assessed over a longer period of time, better to assess a patients' mood (n=2) • PRO team response: Left in as emotional impact was important to the patients during CE and subsequently endorsed by the CD. Will be reviewed during psychometric validation phase. Possible removal -- under review 	<ul style="list-style-type: none"> • Most patients felt down and worried were two distinct concepts (12/15) • Worried was more relevant among 2/3 patients) • Additional emotions experienced include: anxiety, annoyed, drained, embarrassed, anger, exhausted, depressed • Interpretation=15/15 • Clear=12/14 • Relevant (Yes=8; No=3; Unsure=1) 	<ul style="list-style-type: none"> • Item may prove to not be valuable, lean towards possible removal. Also could be perceived as eliciting a depression diagnosis. <p>FINAL DECISION: Separate into 2 items</p>	<p>During the past 24 hours, how "down" did you feel? (Select only one response.)</p> <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much
					<p>During the past 24 hours, how worried did you feel? (Select only one response.)</p> <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat	

- 4 Quite a bit
- 5 Very much

#21

During the past 24 hours, did you avoid social activities like visiting with friends or family? (Select only one response.)

- 1 Not at all
- 2 A little bit
- 3 Somewhat
- 4 Quite a bit
- 5 Very much

Avoiding or not wanting to do activities with friends and family because of the impact of the skin infection.

Impact on social activities
(impact-social)

- May be too subjective (patients likely to miss activities secondary to pain (n=1)
- **PRO team response:** Left in as it was important to the patients during CE and subsequently endorsed by the CD. Also only 1 expert disagreed with item's content.

- Additional social activities include: riding bike, dancing
- Interpretation=14/15
- Clear=15/15
- Relevant (Yes=13; No=2)

• Leave as is

During the past 24 hours, did you avoid social activities like visiting with friends or family? (Select only one response.)

- 1 Not at all
- 2 A little bit
- 3 Somewhat
- 4 Quite a bit
- 5 Very much

#22

During the past 24 hours, did you have difficulty doing your daily activities like showering, dressing, or eating? (Select only one response.)

- 1 Not at all
- 2 A little bit
- 3 Somewhat
- 4 Quite a bit
- 5 Very much

Difficulty with usual daily activities, such as showering, dressing or eating because of the impact of the skin infection.

Impact on daily activities
(impact-physical)

- Leave as is (n=3)

- Additional daily activities include: exercising, using the restroom
- Interpretation=15/15
- Clear=15/15
- Relevant (Yes=15; No=0)

• Leave as is

During the past 24 hours, did you have difficulty doing your daily activities like showering, dressing, or eating? (Select only one response.)

- 1 Not at all
- 2 A little bit
- 3 Somewhat
- 4 Quite a bit
- 5 Very much

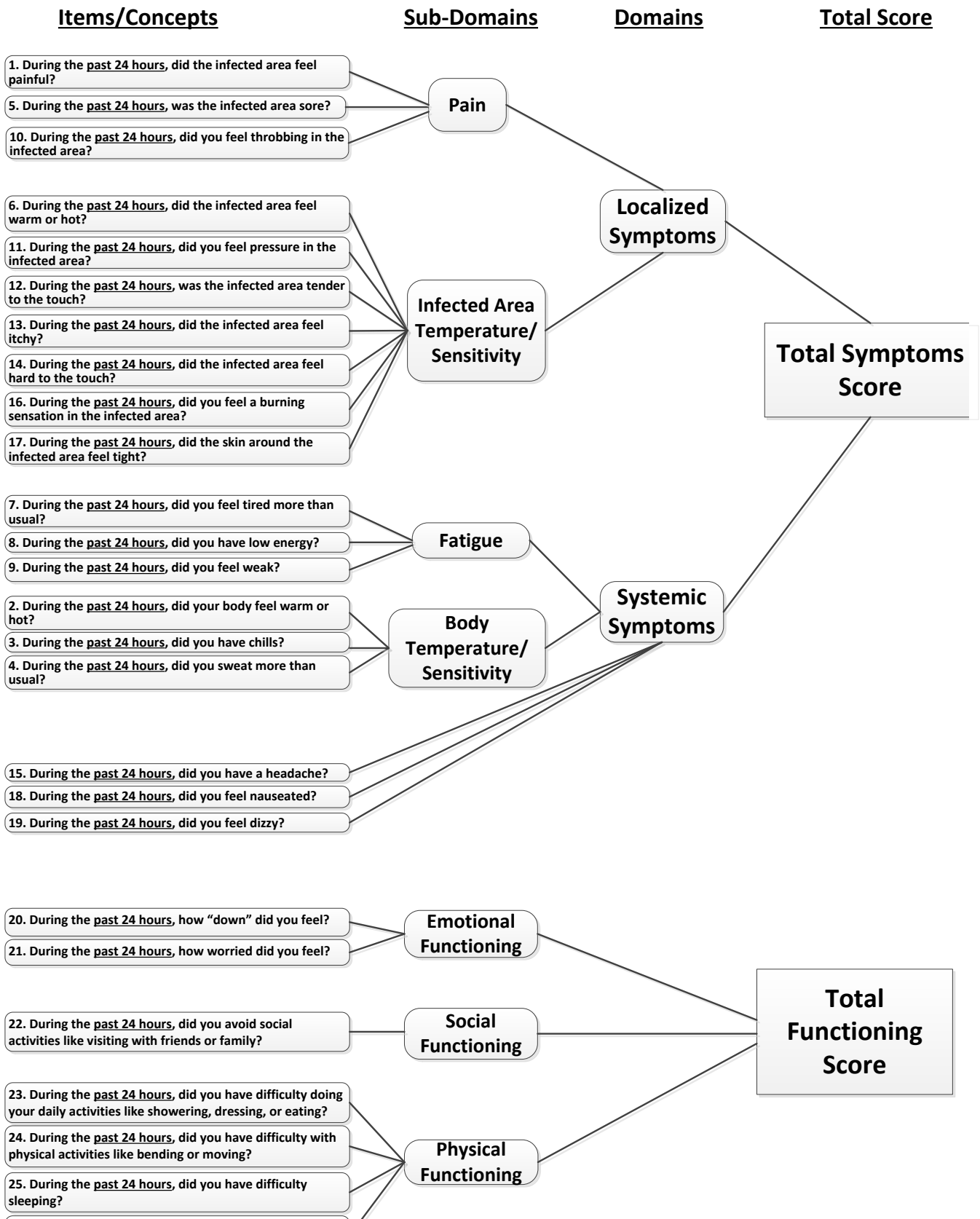
<p>#23</p>	<p>During the past 24 hours, did you have difficulty with physical activities like bending or moving? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all 2 <input type="checkbox"/> A little bit 3 <input type="checkbox"/> Somewhat 4 <input type="checkbox"/> Quite a bit 5 <input type="checkbox"/> Very much</p>	<p>Difficulty with physical activities, like bending or moving because of the impact of the skin infection.</p>	<p>Impact on physical activities (impact-physical)</p>	<ul style="list-style-type: none"> • Leave as is (n=3) 	<ul style="list-style-type: none"> • Additional physical activities inclu • de: walking, getting dressed, lifting, riding bike, exercising • Interpretation=15/15 • Clear=15/15 • Relevant (Yes=13; No=1, Unsure=1) 	<ul style="list-style-type: none"> • Leave as is <p>OR</p> <ul style="list-style-type: none"> • Suggestion was to add walking as example to incorporate the walking question since it is site of infection specific: "During the past 24 hours, did you have difficulty with physical activities like bending, moving, or walking?" • Counter: Walking may be too specific to infection site or patient's current state so may not want to include walking in physical activity question (i.e. patient can bend but cannot walk) <p>Final decision: leave as is</p>	<p>During the past 24 hours, did you have difficulty with physical activities like bending or moving? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all 2 <input type="checkbox"/> A little bit 3 <input type="checkbox"/> Somewhat 4 <input type="checkbox"/> Quite a bit 5 <input type="checkbox"/> Very much</p>
<p>#24</p>	<p>During the past 24 hours, did you have difficulty walking? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all 2 <input type="checkbox"/> A little bit 3 <input type="checkbox"/> Somewhat 4 <input type="checkbox"/> Quite a bit 5 <input type="checkbox"/> Very much</p>	<p>Inability or increased difficulty walking due to the skin infection.</p>	<p>Impact on walking (impact-physical)</p>	<ul style="list-style-type: none"> • Will be skewed based off the location of the absssi (n=2) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by some patients during CD. Still under further evaluation in terms of relevancy to patients. Possible removal – under discussion 	<ul style="list-style-type: none"> • Lack of relevance to skin infection unless infection is on the leg • Interpretation=14/15 • Clear=15/15 • Relevant (Yes=7; No=8) 	<ul style="list-style-type: none"> • Possibly remove due to low relevance <p>OR</p> <ul style="list-style-type: none"> • Incorporate walking into physical functioning question, i.e. did you have difficulty with physical activities like bending, moving, or walking. • Endorsed by 17 patients during CE interviews as a concept that was relevant to them. 	<p>Final decision: Remove item due to irrelevance</p>
<p>#25</p>	<p>During the past 24 hours, did you have difficulty sleeping? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p>	<p>Inability or increased difficulty sleeping due to the skin infection, i.e. difficulty falling asleep or remaining asleep.</p>	<p>Impact on sleep (impact-physical)</p>	<ul style="list-style-type: none"> • Leave as is (n=3) 	<ul style="list-style-type: none"> • Easy to understand and patients interpreted item correctly • Interpretation=15/15 	<ul style="list-style-type: none"> • Leave as is 	<p>During the past 24 hours, did you have difficulty sleeping? (Select only one response.)</p> <p>1 <input type="checkbox"/> Not at all</p>

	<input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much			<ul style="list-style-type: none"> • Clear=15/15 • Relevant (Yes=13; No=0; Unsure=1) 	<input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much		
#26	During the past 24 hours, did you have difficulty working? (Select only one response.) <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much	Inability or increased difficulty working or completing one's job due to the skin infection	Impact on working (impact-physical)	<ul style="list-style-type: none"> • May be too subjective (depends on type of work and where abscess is located) (n=1) • PRO team response: Left in as it was important to the patients during CE and subsequently endorsed by the CD. Still under further evaluation in terms of relevancy to patients. Also only 1 expert disagreed with item's content. Possible removal – under discussion • Question not asked in guide 	<ul style="list-style-type: none"> • Lack of relevance because most patients do not currently work – many patients stated it was relevant because they have worked before • Interpretation=13/15 • Clear=13/15 • Relevant (Yes=10; No=4; Unsure=1) 	<ul style="list-style-type: none"> • Leave as is OR • Under discussion for possible removal <p>FINAL DECISION: Leave as is</p>	During the past 24 hours, did you have difficulty working? (Select only one response.) <input type="checkbox"/> Not at all <input type="checkbox"/> A little bit <input type="checkbox"/> Somewhat <input type="checkbox"/> Quite a bit <input type="checkbox"/> Very much
	24-Hour Recall Period			<ul style="list-style-type: none"> • Question not asked in guide 	<ul style="list-style-type: none"> • Most patients thought the recall period was easy to think about • Some patients thought about since the beginning of the infection • Some patients thought about since they were seen in the clinic 	<ul style="list-style-type: none"> • Leave as is – because this is a daily diary, patients may not think about their infection as broadly as they did for these interviews 	
	Site of infection or infected area			<ul style="list-style-type: none"> • Question not asked in guide 	<ul style="list-style-type: none"> • Patients did not have trouble understanding this term. They would describe symptoms mentioned above while using the words, "infected area", "my wound", "my arm/leg", "my skin" 	<ul style="list-style-type: none"> • Leave as is 	

5. Conceptual Framework Draft

The qualitative interviews focused on ABSSSI symptoms and their impact. Following cognitive debriefing, the conceptual framework was revised to represent the item numbers, specific domains, and total symptom score. The draft conceptual framework is shown in Figure 3 below and illustrates how the draft items are related to the symptom and functioning concepts that emerged from the qualitative concept elicitation and cognitive debriefing interviews.

FIGURE 3: CONCEPTUAL FRAMEWORK MODEL



6. Conclusion

The purpose of this report was to summarize the development and evaluative work conducted to establish the content validity of the new ABSSS PRO measure. To explore content validity, 34 concept elicitation interviews were conducted with wound, cellulitis, and abscess patients to elicit key symptoms and impacts of ABSSSI. Using patients' own words from their description of their symptoms, a draft pool of items was developed and evaluated by an expert panel.

These draft items were then assessed in cognitive debriefing interviews with a new sample of 15 patients with ABSSSI. The results illustrate that the new ABSSSI PRO instrument is relevant and understandable to the target patient population. Some minor revisions were made to the final set of items in order to maximize consistency, relevance and ease of understanding. All edits are documented in the item tracking matrix. These interviews underscored the relevance and importance of the 26 concepts as well as established that the ABSSSI PRO measure is interpretable and meaningful to this patient population. Patients were able to correctly interpret the instructions and items, and felt that the response options allowed them to select an accurate response to each of the statements on the ABSSSI PRO. In addition, patients felt that the 24-hour recall period was an appropriate timeframe to consider when selecting a response.

In sum, the results of the concept elicitation and cognitive debrief interviews support the content validity of the ABSSSI PRO measure. The conceptual framework has been updated and the draft instrument is now ready for psychometric testing.