

# Content Validation of a New Patient-Reported Outcome (PRO) Instrument in Hospital-Acquired Bacterial Pneumonia (HABP)

Howard K<sup>1</sup>, Saretsky TL<sup>1</sup>, Clifford S<sup>1</sup>, Cho M<sup>1</sup>, Wang H<sup>1</sup>, Hoffmann SC<sup>2</sup>, Talbot GH<sup>3</sup>, Powers JH<sup>4</sup>, FNIH Biomarkers Consortium HABP VABP Project Team<sup>2</sup>

## Introduction

- Reliable, well-defined and clinically relevant endpoints that measure tangible benefits for patients are needed in clinical trials of antibacterial drugs for hospital-acquired bacterial pneumonia (HABP).<sup>1</sup>
- Certain endpoints currently used in HABP clinical trials (e.g., clinical response, clinical cure) are only indirect measures of treatment benefit and have not been validated.
- Currently there is no HABP PRO instrument to capture additional symptoms of how patients feel and function.
- Building on work with our previously developed community-acquired bacterial pneumonia (CABP) PRO instrument (See PIN 84, ISPOR 2015)<sup>2</sup> and in partnership with the Food and Drug Administration (FDA), the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium and ICON plc are developing clinically relevant instruments that measure tangible benefits for patients in clinical trials of antibacterial drugs.<sup>3</sup>

## Purpose

- The goal of this study was to explore HABP symptoms and impacts as reported directly by patients, and to ensure a newly developed PRO measure in HABP was understandable and meaningful, using methods in accordance with FDA PRO Guidance (2009).<sup>4</sup>
- The proposed HABP PRO has been submitted for consideration as a qualified instrument through the FDA's drug development tool (DDT) qualification program.

## Methods

- A comprehensive literature review and interviews with five US and European clinical experts informed the development of a concept elicitation (CE) interview guide and a disease model exploring patients' experience with symptoms of HABP.
- Qualitative interviews with patients were conducted by telephone within 10 days of HABP diagnosis. After 8 CE interviews, no new pneumonia concepts had emerged and concepts endorsed by HABP patients were similar to concepts reported by patients in our previous CABP study.<sup>2</sup>
- Evidence supported combined CE and cognitive debriefing (CD) interviews using items from our previously developed CABP PRO instrument due to the overlap of symptoms and impacts between the two patient populations.
- Eleven combined CE/CD interviews were conducted to further elicit HABP related concepts and assess item readability, relevance, comprehensiveness, and content validity of the original CABP PRO items with the HABP patient population.
- Demographics for all 19 patients are presented below in [Table 1](#).

**Table 1. Patient Demographics**

Characteristics	Distribution (N=19)
<b>Age</b>	
Mean (SD)	62 (11.8)
Range	41 – 84
<b>Sex</b>	
Female	9 (47%)
Male	10 (53%)
<b>Race/Ethnicity</b>	
Caucasian	8 (42%)
Black/ African American	11 (58%)
<b>Education</b>	
Did not complete high school	3 (16%)
High School/GED*	10 (53%)
Some college	4 (21%)
Bachelor's degree	1 (5%)
Graduate degree	1 (5%)
<b>Employment Status</b>	
Employed part-time	1 (5%)
Retired	8 (42%)
Temporarily unable to work	3 (16%)
Permanently unable to work	6 (32%)
Unemployed seeking work	1 (5%)

\*GED=General Educational Development

**Figure 2. Sample HABP PRO items**

**HOSPITAL-ACQUIRED PNEUMONIA DAILY SYMPTOM DIARY INSTRUCTIONS:**  
Please fill out this diary at the same time each day. Please give only one answer for each question and answer every question.

While answering the following questions, please think about your **pneumonia** and how you felt during the **past 24 hours**.

**During the past 24 hours, did you have shortness of breath? (Select only one response.)**

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

**During the past 24 hours, did you feel warm or hot? (Select only one response.)**

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

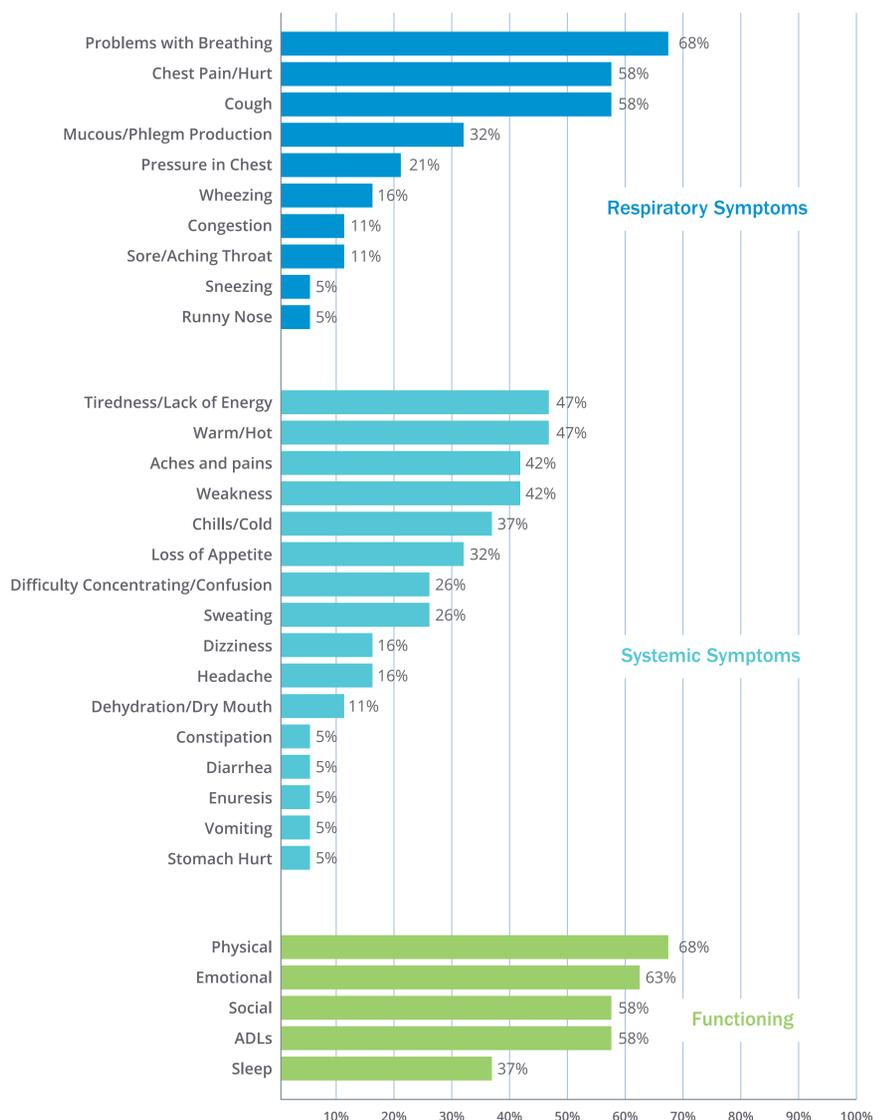
**During the past 24 hours, did you have difficulty doing your daily activities like showering, dressing, or eating? (Select only one response.)**

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

## Results

- Consistent with previously reported findings (See PIN 53, ISPOR 2016),<sup>5</sup> the most common spontaneously reported symptoms in the final HABP sample (N=19) were problems with breathing (N=13), cough (N=11), and chest pain/hurt (N=11). Approximately half of the patients also experienced tiredness/lack of energy and elevated body temperature (e.g. warm/hot).
- The most common spontaneously reported symptom impacts remained physical functioning (e.g. walking) (N=13), emotional functioning (N=12) activities of daily living (N=11), and social functioning (N=12). [Figure 1](#) below shows the frequency of all spontaneously reported symptoms and impacts.
- Symptoms frequently reported by both the current HABP patient sample and CABP patients interviewed in our previous PRO study included problems with breathing, chest pain/hurt, warm/hot, and cough. The impact frequently reported by both patient groups included physical functioning. [Table 2](#) shows example quotes from HABP patients and corresponding quotes from CABP patients to illustrate symptom overlap between the two types of pneumonia.
- Combined CE/CD interviews conducted with HABP patients and expert review confirmed the items in the draft pneumonia PRO were understandable, relevant, comprehensive, and interpreted as intended. [Figure 2](#) shows a sample of the HABP PRO items.

**Figure 1. Frequency of Symptoms and Impacts in HABP (N=19)**



**Table 2. Example HABP and CABP patient reported quotes that illustrate symptom overlap between the two types of pneumonia**

Concept	Pneumonia Type	Patient Quote
Cough	HABP	"I have a terrible cough. I'm coughing all the time, and that bothers me." <b>Patient 103-004</b>
	CABP	"You just keep coughing. You keep coughing... About three nights before I came in I started coughing and I was coughing all night." <b>Patient 203-005</b>
Aches and Pains	HABP	"It's a very awful feeling. It starts in your body and just works itself through your upper body all the way to your head, and you have pain, sharp pain. My pain was on my left side, and it was so severe that they had to keep on giving me morphine to keep the pain from coming." <b>Patient 103-005</b>
	CABP	"It started around Sunday. I had a sharp pain underneath my right shoulder. My whole entire body, but especially my back right up underneath my shoulder on the right side was sharp. It hurt. I was moaning and crying, just feeling like something was happening to me." <b>Patient 203-016</b>
Physical Functioning	HABP	"Right, such as getting up, going, exercising. That's over with. It's not gonna let you do it. Can't take the pain. The pain is too great. All you can do is get back in bed..." <b>Patient 105-138</b>
	CABP	"It hurt a little bit and then I got real dizzy. I could not walk. I could not stand." <b>Patient 201-001</b>

## Conclusions

- The final HABP conceptual framework represented the item numbers, specific domains, and total symptom score, based on our previous CABP work.<sup>2</sup>
- The qualitative data supports the use of items from the CABP PRO instrument in HABP patients. This suggests the use of a unified PRO instrument that can be used to aid the evaluation of new bacterial treatments for both HABP and CABP.
- Pending FDA review of content validity, the unified pneumonia PRO instrument is now ready for psychometric validation and scoring confirmation.
- The ultimate goal is a FDA qualified pneumonia PRO instrument that can be used in multiple settings such as drug development programs (for purposes of supporting medical product approval and labeling claims for antibiotic agents), epidemiological studies, and natural history studies.