Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000009: Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)
Full Qualification Package

1.0 OVERVIEW OF *NSCLC-SAQ* FOR QUALIFICATION FOR EXPLORATORY USE

1.1 Introduction and Overview

Lung cancer (characterized by the uncontrolled growth of abnormal cells in one or both of the lungs) is one of the most common cancers. More than 200,000 new cases of lung cancer (non-small cell and small cell combined) are estimated to be diagnosed in the United States (US) in 2017. Lung cancer is also the leading cause of cancer-related mortality in the US, with more than 150,000 deaths annually (Siegel et al. 2017). While there are more than a dozen different kinds of lung cancer, the two main types are non-small cell (NSCLC) and small cell (SCLC). Together, these two account for over 95% of all lung cancers (Howlader et al. 2013). Approximately 75-80% of lung cancers are of the non-small cell type (Rivera et al. 2013).

Depending on the stage of the cancer and other factors, treatment options aimed at tumor reduction for people with NSCLC can include: surgery, radiofrequency ablation, radiation therapy, chemotherapy, targeted therapies, and immunotherapy. Palliative treatments are often used to help with symptoms. In many cases, more than one type of treatment is used. As novel therapies continue to be developed, the ability to reliably and validly measure symptom improvement from the patient's perspective becomes imperative.

The PRO Consortium's Non-Small Cell Lung Cancer (NSCLC) Working Group at the Critical Path Institute embarked on the development and qualification of a new patient-reported outcome (PRO) questionnaire to assess key symptoms of NSCLC as an endpoint measure in clinical trials, referred to as the *Non-Small Cell Lung Cancer Symptom Assessment Questionnaire* (*NSCLC-SAQ*). The development of this new measure has followed the recommendations outlined in the Food and Drug Administration's (FDA) guidance for industry titled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" [hereafter called the PRO Guidance] (US Food and Drug Administration 2009) and subsequently-published good research practices for measure development (Patrick et al. 2007, Rothman et al. 2009, Patrick et al. 2011a-b).

This document summarizes key details from the development process for the *NSCLC-SAQ*, the evidence for content validity, details from its early quantitative testing, and descriptions of its subsequent refinement. The intent of this document is to submit the *NSCLC-SAQ* for qualification as an exploratory endpoint measure in clinical trials for advanced NSCLC.

1.1.1 Clinical trial setting

Early-stage NSCLC is often asymptomatic or left undetected due to similar symptoms experienced by those with comorbid diseases (e.g., asthma, chronic obstructive pulmonary disease [COPD]) (Ironmonger et al. 2015). However, the degree of impairment that is

experienced by patients with NSCLC is often impacted by the severity of their disease-related symptoms. Therefore, accurate assessment and monitoring of these symptoms is an essential component when evaluating NSCLC treatment benefit in clinical studies (Masters et al. 2015).

The *NSCLC-SAQ* is designed to be used as a secondary endpoint measure to assess self-reported symptom severity alongside other endpoints in advanced NSCLC clinical trials. The intent is to use results from the *NSCLC-SAQ* to evaluate treatment benefit in clinical trials for NSCLC therapies and potentially communicate this treatment benefit in the product label.

1.1.2 Limitations of existing instruments

In developing the *NSCLC-SAQ*, the NSCLC Working Group considered the appropriateness and relevance of frequently measured NSCLC pulmonary and non-pulmonary symptoms. A literature review of patient-centered symptom experiences was conducted to help inform the identification of the content that should be covered in existing instruments and a search and review of potential existing instruments was conducted.

The review identified existing PRO measures that capture disease-related symptoms, including the *European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; Lung Cancer (EORTC QLQ-LC13* (Bergman et al. 1994), *Functional Assessment of Cancer Therapy Lung Cancer (FACT-L)* (Cella et al. 1995), *Lung Cancer Symptom Scale (LCSS)* (Hollen et al. 1993), and *M.D. Anderson Symptom Assessment Inventory – Lung Cancer (MDASI-LC)* (Mendoza et al. 2011). Despite each of these measures being rigorously tested and widely used, the development history, content, and comprehensiveness of these tools with respect to documenting symptom concepts that have been specifically elicited from first-hand accounts of the patients' experiences with NSCLC may not necessarily satisfy the expectations of the FDA PRO Guidance (US Food and Drug Administration 2009), and none have been qualified. Therefore, the PRO Consortium, with consultation from FDA advisors, identified the need for a well-defined and reliable PRO measure to assess NSCLC symptoms and provide the evidence necessary for US drug labeling. Thus, the *NSCLC-SAQ* was developed with extensive patient input to ensure that symptoms most relevant to patients were included in the measure.

1.1.3 Brief Description of the *NSCLC-SAQ*

The *NSCLC-SAQ* is a newly developed measure with seven items assessing five symptom concepts of NSCLC: cough, pain, dyspnea, fatigue, and appetite (see Figure 1). The recall period is one week (worded as "over the last 7 days"). Respondents respond to each of the seven items using a five-point verbal rating scale from either "No <symptom> at All" to "Very severe <symptom>" or from "Never to Always," depending on the item's question structure relative to either intensity or frequency. In the early development stages, it was first drafted using paper-and-pencil format. It was then programmed for tablet administration and cognitively evaluated for equivalence between the two formats. The tablet version was then used in a quantitative pilot study to complete the development and establish the initial measurement properties.

These cardinal symptoms are supported by the literature, by the expert panel clinicians, and by the patient interviews, and they are the key symptoms agreed with the FDA as important to assess and monitor during the patient experience in a clinical study for advanced NSCLC.

1.2 Concept of interest for meaningful treatment benefit

The *NSCLC-SAQ* assesses patient-reported symptom severity associated with NSCLC and is intended to be used as a secondary endpoint in clinical trials of NSCLC. The target population includes adults (aged 18 and older) diagnosed with advanced (Stage IIIB/IV) NSCLC. The *NSCLC-SAQ* has been developed in a patient sample including both males and females with varying values across age, race, education, marital status, and Eastern Cooperative Oncology Group (ECOG) performance status.

More specific labeling will be defined by the clinical trial sponsor in discussion with the FDA. As agreed in previous correspondence with the FDA, potential language for targeted claims might include improvement (fewer symptoms, less severity) as well as delay in time to worsening.

1.3 Context of Use

The *NSCLC-SAQ* assesses changes in symptom severity for patients (age 18 years or older) who have been diagnosed with and are being treated for advanced NSCLC. Because the symptom experience associated with NSCLC is slow to show meaningful change, the *NSCLC-SAQ* measure asks patients to report on the status of their symptom severity over the past seven days.

At the request of FDA, the characteristics of the study population participating in the development of the *NSCLC-SAQ* were slightly broader than those commonly used in clinical treatment trials for NSCLC. Participants were included with Stage I-II cancers as well as late stage (III, IV) cancer to assure that the new PRO measure would be able to retain relevance to those participants who might improve or might be diagnosed at earlier stages. Other eligibility criteria for participants reflected common entry criteria for clinical trials testing treatments for NSCLC, including ECOG performance status of 0 to 2, a mix of treatment naïve and treated histories, a limited number with comorbid COPD, and exclusion for confounding variables such as a past history of a personality, bipolar, schizophrenic or other psychotic disorder or confounding mental condition such as retardation or dementia. Participants were also excluded if they were deemed to be a significant risk for suicide or had evidence of drug or alcohol abuse.

The intent is to use results from the *NSCLC-SAQ* to evaluate treatment benefit in clinical trials for NSCLC therapies and potentially communicate this treatment effect in the product label. Other clinical measures or biomarkers may serve as the source of primary endpoints with the *NSCLC-SAQ* as a measure of symptom severity. In instances where the *NSCLC-SAQ* is employed to derive a secondary endpoint, the clinical trial would need to succeed on the primary endpoint before success could be attained on the secondary endpoint relating to patient-reported symptom severity.

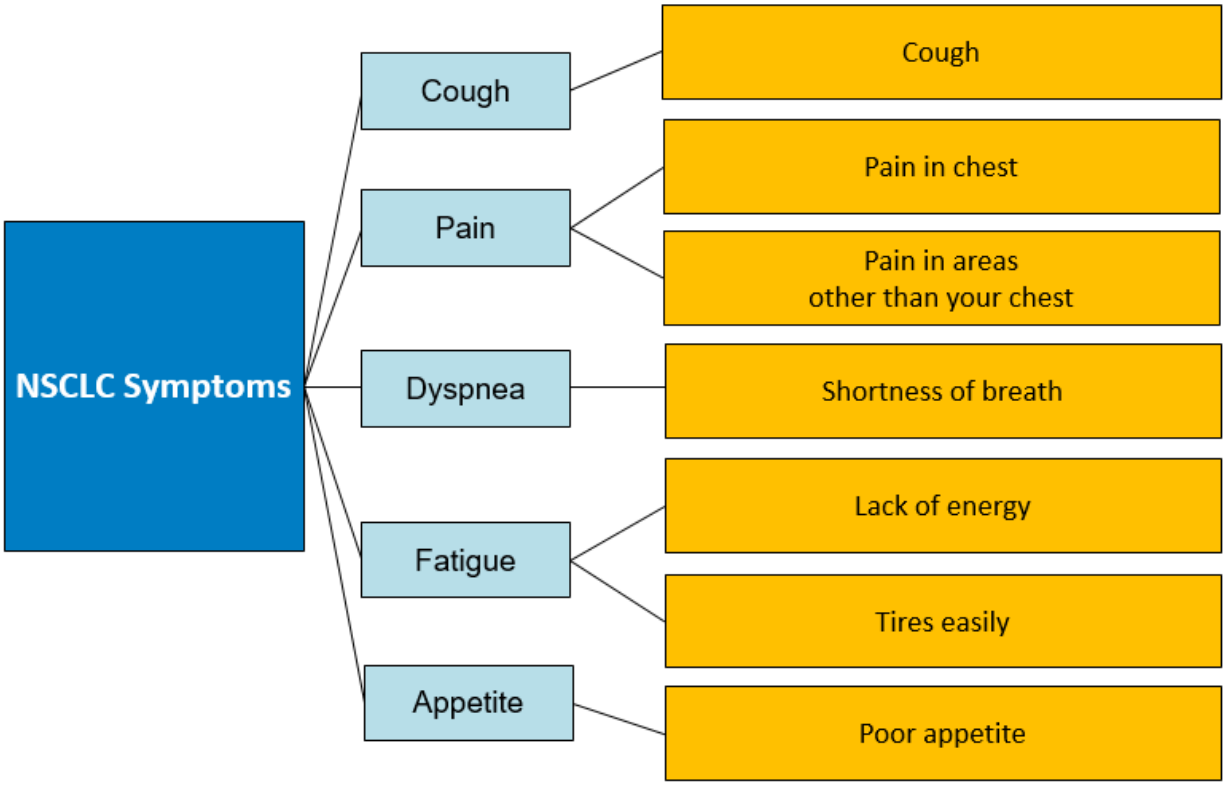
It is expected that the resulting endpoint (change in symptom severity) may be used as a secondary endpoint to support labeling claims from data produced in randomized controlled clinical trials where an experimental treatment for NSCLC is being tested.

The specific endpoint selection, positioning, and measurement approach would be determined by the study sponsor in concert with the appropriate regulatory review agencies.

1.4 *NSCLC-SAQ* conceptual framework

The final seven items of the *NSCLC-SAQ* address five different symptom concepts that are key to assess for the treatment of NSCLC: cough (one item), pain (two items), dyspnea (one item), fatigue (two items), and appetite (one item). Figure 1 provides an overview of the relationship of the seven items and five key symptom concepts of the *NSCLC-SAQ*.

Figure 1: Conceptual Framework for the *NSCLC-SAQ*



1.5 Critical Details Describing the *NSCLC-SAQ*

1.5.1 Reporter: The *Non-Small Cell Lung Cancer Symptom Assessment Questionnaire* (*NSCLC-SAQ*) is a patient-perceived report of their lung cancer symptom experience.

1.5.2 Item Content: The *NSCLC-SAQ* consists of seven items assessing symptoms of NSCLC (i.e., coughing, pain, dyspnea, fatigue, and reduced appetite) (see Table 2). The recall period is one week (worded as "over the last 7 days"). Patients respond to each of the seven items using a five-point verbal rating scale from either "No <symptom> at All" to "Very severe <symptom>" or from "Never to Always," depending on the item's question structure relative to either intensity or frequency.

Table 2: Item Content for the *NSCLC-SAQ*

Domain	Item
Cough	1. How would you rate your coughing at its worst…?
Pain	2. How would you rate the worst pain in your chest…?
	3. How would you rate the worst pain in areas other than your chest…?
Dyspnea	4. How often did you feel short of breath during usual activities…?
Fatigue	5. How often did you have low energy…?
	6. How often did you tire easily…?
Appetite	7. How often did you have a poor appetite over the last 7 days?

1.5.3 Mode of Administration: While the *NSCLC-SAQ* has been designed specifically for patient self-report, it is possible that in the case of very ill patients, a care provider might need to read the questions verbatim and capture the patient's response on the electronic device or paper-based format.

1.5.4 Data Collection Method: The *NSCLC-SAQ* has been designed for electronic data collection on a tablet to be completed directly by the patient. The *NSCLC-SAQ* was initially developed using a paper-and-pencil format, and was later programmed for tablet administration and cognitively evaluated for equivalence between the two formats. The tablet version was used to complete the development and establish the initial measurement properties. Therefore, it is possible, if necessary, to use a paper-and-pencil version of the *NSCLC-SAQ*, since it was developed, cognitively tested with patients in its early development and shown to be equivalent in terms of patient comprehension to the tablet version, so the measurement properties should be comparable.

1.6 Overview of the Developmental Status of the *NSCLC-SAQ*

To date, the development of the *NSCLC-SAQ* has included:

- Completion of systematic reviews of the NSCLC literature and existing PRO measures
- The formation of an expert panel of clinical and methodological experts to provide advice during the development process
- Completion of qualitative concept elicitation interviews conducted to identify the NSCLC symptom-related concepts that are most important and relevant to the patients' experience
- A formal item-generation process in which evidence from the concept elicitation interviews, systematic literature reviews, and expert input was used to develop the content of the *NSCLC-SAQ*
- Qualitative cognitive interviews with participants with NSCLC to evaluate and refine the draft measure, including item reduction
- A translatability assessment, conducted concurrently with the early cognitive interview process

- An electronic implementation assessment (by the Electronic Patient-Reported Outcome [ePRO] Consortium's Instrument Migration Subcommittee) to assess the viability for implementation of the PRO measure on all available and appropriate electronic platforms
- Programming for tablet-based data collection and cognitive interviews to assess conceptual equivalence between the paper and electronic formats
- Quantitative testing to further evaluate the measurement properties of the *NSCLC-SAQ* that involved development of a provisional scoring approach and an assessment of item and scale performance prior to submission to the FDA for qualification of the *NSCLC-SAQ* for use as an exploratory endpoint measure in clinical trials.

All key documents from each of these stages have been provided to the FDA Qualification Review Team (QRT), and five separate consultation and advice exchanges have occurred. At each key stage of this process, input was obtained from the NSCLC Working Group. C-Path scientists, scientific advisors (independent clinical experts), and representatives of FDA's Center for Drug Evaluation and Research (CDER) via the formal Drug Development Tool Qualification Program (US Food and Drug Administration 2014).

1.7 Description of involvement of external expertise, scientific communities or other agencies

Initially, two external clinical experts and two methodological experts were engaged in the study and participated at key points with the development team. They reviewed the literature review, instrument review summary, and study protocol. Their comments were incorporated into the study design and were addressed by revisions to the study protocol before it was finalized. These external experts took part in the item generation process and assisted with the decisions on important concepts to select for assessment of patients being treated for NSCLC. Following the item generation meeting, two additional clinical experts were added to the team and participated in all subsequent review tasks (Table 3).

The Expert Panel reviewed the final content of the *NSCLC-SAQ* before it went to the field for cognitive interviews. Following revisions made by the team based on the cognitive interview and translatability assessment results, a teleconference was held with the Expert Panel to review and discuss the preliminary measure, its design and its contents. A summary of the steps that had been undertaken, the main results, and rationale for changes was provided as a pre-read document along with the preliminary measure.

Table 3: List of Consultants on the Expert Panel

Name	Title and Affiliation
(1) Richard Gralla, MD	Albert Einstein College of Medicine Bronx, New York
(1) Suresh Ramalingham, MD	Emory University Atlanta, Georgia
(1) David Cella, PhD	Northwestern University Evanston, Illinois
(1) Donald L. Patrick, PhD, MSPH	University of Washington Seattle, Washington
(2) Ethan Basch, MD	University of North Carolina at Chapel Hill Chapel Hill, North Carolina
(2) Shirish Gadgeel, MD	Karmanos Cancer Center Detroit, Michigan

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