PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM

Non-Small Cell Lung Cancer
Symptom Assessment Questionnaire (NSCLC-SAQ)
Provisional User Manual

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
CDER	Center for Drug Evaluation and Research
C-Path	Critical Path Institute
ClinRO	clinician-reported outcome
COPD	chronic obstructive pulmonary disease
ECOG	Eastern Cooperative Oncology Group
ePRO	electronic patient-reported outcome
FACT	*Functional Assessment of Cancer Therapy*
FDA	Food and Drug Administration
FLSI-17	*FACT Lung Symptom Index-17*
HRA	Health Research Associates, Inc.
ICC	intraclass correlation coefficient
IVR	interactive voice response
NSCLC	non-small cell lung cancer
NSCLC-SAQ	*Non-Small Cell Lung Cancer Symptom Assessment Questionnaire*
PGIS	Patient Global Impression of Severity
PRO	patient-reported outcome
SCLC	small cell lung cancer

1.0 BACKGROUND

1.1 Overview of the PRO Consortium

The PRO Consortium was formed in 2008 by the Critical Path Institute (C-Path) in cooperation with the U.S. Food and Drug Administration's (FDA) Center for Drug Evaluation and Research and the pharmaceutical industry. Its mission is to establish and maintain a collaborative framework with appropriate stakeholders for the qualification (US Food and Drug Administration 2014) of patient-reported outcome (PRO) measures and other clinical outcome assessment (COA) tools that will be publicly available for use in clinical trials where COA-based endpoints are used to support product labeling claims (Coons et al. 2011, Hayes et al. 2015).

The PRO Consortium's structure consists of a Coordinating Committee, subcommittees that address consortium-wide topics, and therapeutic area working groups, which focus on diseases or conditions with an unmet measurement need. The goal of these working groups is to generate and/or compile the necessary evidence to enable new or existing COA measures to be qualified by FDA for use in assessing primary or secondary clinical trial endpoints.

1.2 Overview of disease

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 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 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 lung cancer (NSCLC) and small cell lung cancer (SCLC). Together, these two account for over 90% of all lung cancers (Barzi and Pennell 2010, Howlader et al. 2013). Approximately 75-80% of lung cancers are of the non-small cell type (Rivera et al. 2013), which is comprised of three sub-types, each differing in size, shape and chemical make-up:

Squamous cell carcinoma is usually linked to smoking. It tends to be found centrally, near a bronchus, and is more common in men than women. It accounts for about 42% of smoking cancer patients, and 33% of non-smokers.
Adenocarcinoma of the lung is currently the most common type of lung cancer in lifelong non-smokers. It accounts for about 45% of non-smoking cancer patients. It is usually found in the outer region of the lung.
Large-cell lung carcinoma is a heterogeneous group of undifferentiated malignant neoplasms originating from transformed epithelial cells in the lung. It can appear in any part of the lung and tends to grow and spread quickly making it hard to treat.

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.

1.3 Purpose of the *Non-Small Cell Lung Cancer Symptom Assessment Questionnaire* (*NSCLC-SAQ)*

In response to a need for high quality clinical outcome assessment tools, the Patient-Reported Outcome (PRO) Consortium's NSCLC Working Group at the Critical Path Institute (C-Path) embarked on the development of a new PRO measure designed to assess advanced NSCLC-related symptoms that are important and relevant to the patient's experience. This measure, named the *Non-Small Cell Lung Cancer Symptom Assessment Questionnaire* (*NSCLC-SAQ*), was developed with consideration of the recommendations and scientific best practices set forth in the FDA's 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).

Many patient-reported questionnaires already exist that purport to assess health-related quality of life and cancer-related symptoms; however, their development history and comprehensiveness in capturing patients' experience with NSCLC may not be fully aligned with recommendations in the PRO Guidance. As with most conditions, the patient is the best source of valid information about the symptoms of NSCLC. The *NSCLC-SAQ* was developed with extensive patient input to ensure that disease-related symptoms most relevant to patients were included in the measure. The *NSCLC-SAQ* is intended for inclusion in clinical research alongside other endpoint measures to support the assessment of NSCLC treatment benefit.

1.4 Context of use

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

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.

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

1.5 Development and evaluation 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 computer-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.

At each 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).

1.5.1 Evidence of content validity

Content validity is important for any PRO measure, and necessary for those intended to support claims in approved medical product labeling (US Food and Drug Administration 2009, Coons et al. 2011). The content validity of PRO measures is generally established through evidence confirming the measure provides a sufficiently comprehensive assessment of concepts that are relevant and important to the target population and does so in a manner that is easily understood and consistently interpreted by respondents.

NSCLC-SAQ content was informed via a review of existing published research studies conducted in NSCLC and findings from open-ended concept elicitation interviews with a diverse sample of 51 adults. The 51 participants in the concept elicitation interviews were an average of 64.9 years old (range 46-86), 51.0% were female, and 75.0% were white (non-Hispanic). Fifty-one percent were Stage IV, 37% were Stage III, and 47% were at ECOG 1.

Saturation of concepts (the point at which no new concepts were elicited) was achieved after the third of six transcript groups (8-9 transcripts per group). Determined by the number of subject expressions, the symptom-related concepts of "Coughing," "Tiredness," "Shortness of breath," "Appetite," "Difficulty breathing," "Pain in chest" and "General pain" were most often expressed spontaneously by study participants. The most bothersome symptoms (rated on a 0 to 10 scale with 0 being "not bothersome at all" and 10 being "extremely bothersome") were "Shortness of breath" (6.9), "Tiredness" (6.8), "Pain in chest" (6.8), and "General pain" (6.6). The symptoms that participants rated as most severe (rated on 0 to 10 scale with 0 being "none" and 10 being "extremely severe") were "Breathing difficulty" (8.2), "General pain" (8.0), and "Fatigue" (8.0). Participants also described the most bothersome symptoms to be "Shortness of breath," "Coughing," and "Fatigue." Concept elicitation interview results were analyzed by NSCLC stage; concepts within the *NSCLC-SAQ* were expressed by participants in each stage. Frequency and intensity were identified by participants as the most relevant attributes to assess their NSCLC symptoms.

During an item-generation meeting, the development team (composed of the NSCLC Working Group, outcomes research scientists from Health Research Associates [HRA] and C-Path, and external expert panelists) reviewed the 43 symptom concepts identified from published literature, existing measures, and the qualitative data from the concept elicitation interviews as the basis for selection of concepts for inclusion in the PRO measure. This initial evaluation process resulted in the selection of candidate symptom concepts to be targeted for PRO measurement. During subsequent review by the development team, these targeted concepts were further reduced by removing redundant or problematic concepts, and a 9-item draft questionnaire was prepared for evaluation in cognitive interviews as well as an electronic implementation assessment and a translatability assessment.

A total of 20 adults with NSCLC participated in three waves of cognitive interviews, during which the draft items were completed and evaluated; both paper and tablet formats were evaluated in waves two and three. Over the three waves, two items were removed based on cognitive interview findings and expert panel discussions. Other changes included item wording, switching from numeric rating scales to verbal rating scales, and placing the recall statement "over the last 7 days" at the end of the items. After revisions were made, a final wave of six cognitive interviews was completed where participants found the 7-item *NSCLC-SAQ* to be relevant and comprehensive.

1.5.2 Measurement properties and psychometric evaluation

Initial measurement properties of the *NSCLC-SAQ* were assessed in a quantitative pilot study. A total of 152 participants were enrolled and all were included in the *NSCLC-SAQ* item-level analyses and convergent validity analyses while 90 participants were included in the retest analyses using data collected on Day 1 and Day 8. Subjects were 64 years of age on average, 57% were female, and 87% were white.

Of the 152 participants, 126 (83%) had Stage IV NSCLC. Time since diagnosis of NSCLC averaged 1.1 years (range 0.1-9.6). About one-third (32.9%) were treatment naïve and half (51%) had an ECOG performance status of 1 (32% were ECOG 0 and 17% ECOG 2). Sixty-five participants (43%) had a comorbid clinical diagnosis of chronic obstructive pulmonary disease

(COPD), 68% had histological evidence of adenocarcinoma, and 33% had histological evidence of squamous cell carcinoma.

Mean scores for each of the seven items of the *NSCLC-SAQ* ranged from 0.84 to 2.14 using a response scale between 0 ("Never" or "No Pain at All" or "No Coughing at All") to 4 ("Always" or "Very Severe Pain" or "Very Severe Coughing"). All items used the full range (0, 1, 2, 3, and 4) of responses. Two items (#2 "How would you rate the worst pain in your chest over the last 7 days?" and #3 "How would you rate the worst pain in areas other than your chest over the last 7 days?") had a ceiling effect of 51% and 37%, respectively. A total of 43 (28%) participants indicated "No Pain at All" for both pain items. Although items could be skipped, all items were answered and there were no missing data.

Only one pair of items had a large item-to-item correlation (r=0.84) indicating redundancy: #5 "How often did you have low energy?" and #6 "How often did you tire easily?" The two other similar items (#2 "How would you rate the worst pain in your chest?" and #3 "How would you rate the worst pain in areas other than your chest?") had a correlation of 0.46.

Rasch analyses showed that all seven items were appropriately ordered meaning that the threshold values between adjacent pairs of response options were ordered by magnitude. Each item's response categories reflect an ordered continuum from "No <symptom> at all" to "Very severe <symptom>" (items 1-3) or "Never" to "Always" (items 4-7). In other words, each response had its own probability of being adequately endorsed; the 0 response "No/Never" being independent of 1 "Mild/Rarely" which is independent of 2 "Moderate/Sometimes" and so on. The person-item distribution for the *NSCLC-SAQ* items showed that the items cover the range of severities experienced within the study sample, with no large gaps in concept coverage.

To account for conceptual overlap and to avoid over-weighting in the *NSCLC-SAQ* scoring, the scores for the following items were combined: "low energy" and "tire easily" (represented by the mean of both items), and "pain in chest" and "pain in other areas" (represented by the most severe answer of either item). This scoring approach results in five symptom scores representing each of the five concepts identified in the conceptual framework: cough, pain, dyspnea, fatigue, and appetite. When entered into an exploratory factor analysis, the five item-based scores form a single component with factor loadings exceeding 0.55.

Convergent construct validity was assessed by examining the magnitude of correlations between the *NCSLC-SAQ* items and the FACT Lung Symptom Index-17 (FLSI-17) (Yount et al. 2012) items. All associations hypothesized to have stronger correlations (>0.50) between items of the *NSCLC-SAQ* and items of the FLSI-17 were met. The *NSCLC-SAQ* total score was correlated with the FLSI-17 Disease-Related Symptoms-Physical score at 0.87 ($p<0.001$).

Construct validity of the *NSCLC-SAQ* was also supported by evidence from known groups comparisons using the Patient Global Impression of Severity (PGIS), self-reported health status, and ECOG performance status. The *NSCLC-SAQ* total score was able to differentiate between levels of: severity (not severe, mildly severe, moderately severe, very/extremely severe [$p<0.001$]), health status (excellent, very good, good, fair, poor [$p<0.001$]), and performance status (ECOG 0, ECOG 1, ECOG 2 [$p<0.001$]).

Internal consistency reliability was examined and resulted in a Cronbach's alpha estimate of 0.78, indicating adequate reliability. Test-retest reproducibility was examined using the intraclass correlation coefficient (ICC) and Pearson's product-moment correlation. These

analyses were restricted to the subset of participants whose disease remained stable during the study period as defined by having no change in responses to the Patient Global Impression of Severity (PGIS) from Day 1 to Day 8. Of the 148 participants that completed the Day 8 (retest) data collection, 90 (61%) provided the same response on the PGIS on Day 1 and Day 8. The ICC was 0.87 with a 95% confidence interval of 0.80 to 0.91 and the Pearson's *r* was also 0.87 ($p<0.001$). These reproducibility values indicated that the *NSCLC-SAQ* demonstrated good test-retest reliability in this sample.

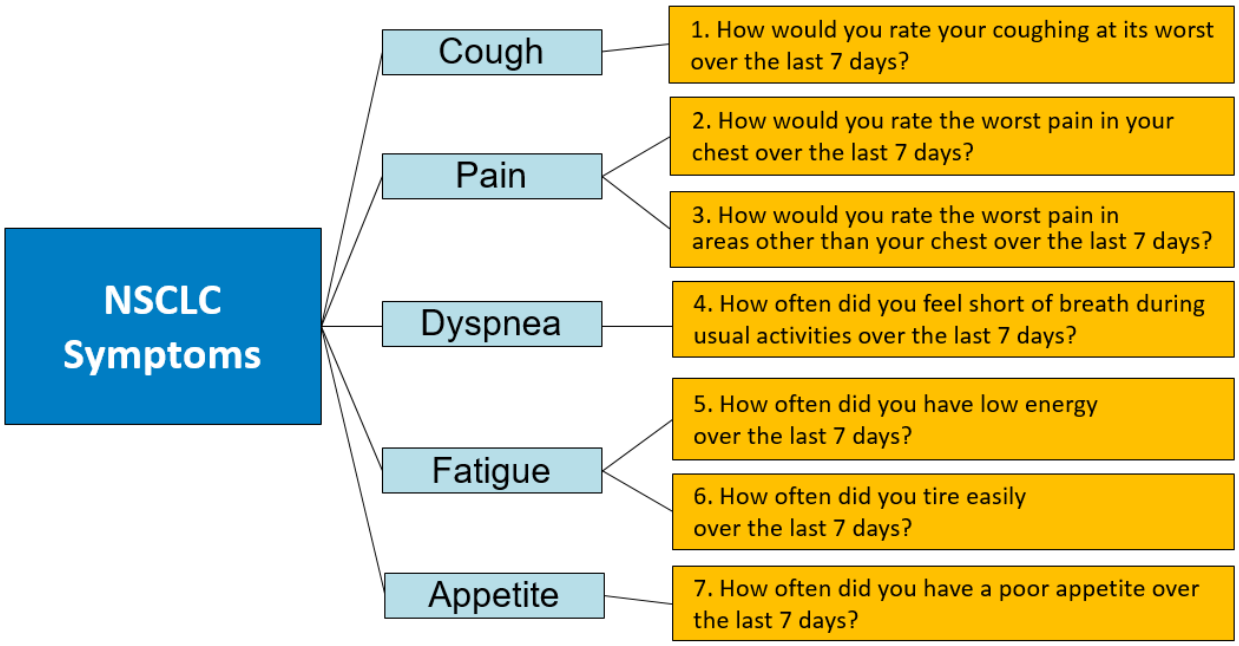
2.0 OVERVIEW OF THE *NSCLC-SAQ*

2.1 Content

The *NSCLC-SAQ* is a 7-item PRO measure (see Appendix A for ePRO version and Appendix B for paper version) designed for use in adults to assess symptoms of advanced NSCLC (Stage IIIB/IV). The *NSCLC-SAQ* has a seven-day recall period. It contains five domains and accompanying items that were identified as symptoms of NSCLC: cough (1 item), pain (2 items), dyspnea (1 item), fatigue (2 items), and appetite (1 item). The *NSCLC-SAQ* takes approximately three minutes to complete.

2.1.1 Conceptual framework

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



2.1.2 Instructions and recall period

The *NSCLC-SAQ* has been developed to present a low burden to respondents. For each of the seven items, the respondent is asked to "please choose the one response that best describes your experience over the last 7 days." Each item concludes with "…over the last 7 days" to remind the respondent to answer the question thinking about the seven days prior to providing the response.

2.1.3 Items and response options

During the item generation process, it was decided that each item's response set would be a five-level verbal rating scale. In order to better facilitate administration of one-item per screen on ePRO devices, each item carries a reference to the recall period within the item stem and displays the response options vertically under the item stem. See Appendix A for screenshots depicting the preferred layout of the item stems and response scales. Based on findings during the concept elicitation interviews, the *NSCLC-SAQ* includes items measuring the attributes of symptom intensity and frequency. Items 1, 2 and 3 are framed to assess intensity and have response options of: "No <symptom> at all," "Mild <symptom>," "Moderate <symptom>," "Severe <symptom>," and "Very Severe <symptom>." Items 4 through 7 are framed to assess frequency and have response options of: "Never," "Rarely," "Sometimes," "Often," and "Always." Subsequent qualitative and quantitative testing has confirmed the adequacy of *NSCLC-SAQ* response options in terms of respondent understanding, reliability, and validity.

2.2 Translations

2.2.1 Translation methodology

To ensure the quality and availability of translated versions of the *NSCLC-SAQ* across studies, users must follow the approved PRO Consortium Translation Process. The approved process is based on the good practice principles and recommendations for translation, cultural adaptation, and linguistic validation outlined in the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) task force reports (Wild et al. 2005; Wild et al. 2009). To build consensus around the process, firms within the translation industry were engaged in a review cycle and a consensus teleconference to arrive at the final process. The process includes the following steps: development of list of concepts, multiple forward translations, reconciliation, back-translation, back-translation evaluation and revision of reconciled forward translation, international harmonization, proofreading, cognitive interviewing, post-cognitive interview analysis and review, and final review and documentation. The PRO Consortium process includes in-country affiliate review and feedback prior to linguistic cognitive interviews whenever possible and a back-up plan to fill this role if in-country affiliates are not available.

The PRO Consortium, through our partner, FACIT.org, manages (but does not necessarily conduct) all translations of the measure and maintains the *NSCLC-SAQ* translation files for distribution.

A critical step in ensuring consistency across translations is the development of a List of Concepts (Appendix C) which is distributed to all translation firms involved in translating the

NSCLC-SAQ. The List of Concepts provides translators with the instructions, item stems, and item response options, as well as the intended meaning and interpretation of terms in the item /response options. Foreseeable translation issues and points of clarification are also outlined and possible alternative wording and synonyms are provided.

The purpose of following a formal translation process that includes linguistic validation is to obtain translated versions of the *NSCLC-SAQ* that are both conceptually equivalent to the English source version and easily understood by the target population.

2.2.2 Available translations

A list of available translations is provided on the PRO Consortium's website [INSERT LINK-TBD], and is updated as new translations become available. Translation certificates ensuring good practices in translation and cultural adaptation for each translation are available upon request. Please note that licensing fees may apply for use of existing translations.

When appropriate and feasible, a "universal" approach to translation is preferred by the PRO Consortium. A "universal" translation is intended for use in multiple countries or regions, which helps to minimize the number of translations needed for a single language. As languages are tested in additional countries or other issues arise, modifications can be made to translations based on the results of this new information. The most current versions will be distributed to licensee following execution of the license agreement providing authorization to use the measure and any of the translations available for the measure. Translations are available for *NSCLC-SAQ* only; translation of device-specific instructions for ePRO administration is the responsibility of the sponsor and ePRO vendor. See Section 2.3 for information on obtaining available translations and requesting permission to translate the *NSCLC-SAQ* into new languages, which must follow the approved translation process highlighted here

2.3 Copyright and licensing

To protect the integrity of the measure, the *NSCLC-SAQ*, including the User Manual, scoring instructions, and any portions, subsets or versions of the above, any modifications to the above, translations of the above, or derivative works based on the above (regardless of whether made by C-Path, Licensee, or others), together with all intellectual property rights contained in or related to any of the foregoing, are owned by C-Path (). The measure may not be used or altered in any way without prior written permission from C-Path. The *NSCLC-SAQ* is available for use under a formal licensing agreement. Please contact (INSERT EMAIL ADDRESS-TBD) to request permission for use or for additional information.

3.0 ADMINISTRATION PROCEDURES

3.1 Modes of data collection

The *NSCLC-SAQ* was designed with electronic self-administration in mind. The quantitative pilot study utilized a tablet-based data collection approach. Advantages over paper data collection include minimizing missing data, minimizing time and potential errors with manual data entry, providing confirmation of when data entry took place (preventing back or forward-filling of data) and implementing safeguards for avoiding missing data and missed completions (e.g., through use of reminders) (Coons et al. 2009). Given the numerous advantages of electronic over paper-based completion, the electronic modes of data collection are recommended over paper for the *NSCLC-SAQ*. Any planned use of the *NSCLC-SAQ* in modes of data collection other than the ones for which data are already available will need to be approved.

3.1.1 Paper-and-pencil forms

A US English paper and pencil format of the *NSCLC-SAQ* was used in the cognitive interviewing phase of its development. This format was evaluated by four participants in wave one and then migrated to a tablet-based data collection format, with a single-item per screen. A paper to electronic mode equivalence study was conducted to confirm cognitive equivalence between the paper and tablet formats, as described in more detail in Section 3.1.2. The paper format of the *NSCLC-SAQ* is available under a licensing agreement with C-Path should study sponsors wish to implement it in this format. The PRO Consortium recommends that a paper mode of data collection only be considered for a study design which uses site-based assessment of the *NSCLC-SAQ* at clinic visits; use of the paper format for field-based assessment (e.g., at home, work, school, or other non-clinic location) is not recommended.

3.1.2 Tablet PCs

The *NSCLC-SAQ* (Appendix A) was developed on paper and tested as a tablet-based questionnaire in the quantitative pilot study, for which it was programmed by YPrime. Prior to the quantitative pilot study, the *NSCLC-SAQ* was migrated to the tablet format, and 16 cognitive interviews were conducted in waves two and three of the cognitive interview study to evaluate modifications to the measure content as well as the success of the migration of the draft *NSCLC-SAQ* from paper to electronic (P-to-E) format. Feedback from participants during the interviews demonstrated that the understanding of the instructions, items, or response options was not affected by the mode of data collection. Therefore, the tablet version of the *NSCLC-SAQ* was shown to be cognitively equivalent to the originally developed and evaluated paper format. Evidence for usability, reliability, and validity of the tablet-based version of the *NSCLC-SAQ* has been documented through qualitative (cognitive interviews) and quantitative data analyses.

3.1.3 Web-based applications

The more widespread use of the Internet and web-based technologies by potential clinical trial participants suggests that web-based questionnaires may be a viable alternative to conventional paper-and-pencil questionnaires in research studies (Hohwu et al. 2013). The *NSCLC-SAQ* has not yet been implemented via the web. A cognitive interview-based evaluation should be sufficient to confirm equivalence among the presentation of items on a web platform and the other modes of data collection tested, since the difference in presentation between the modes is likely to be minimal. For web-based implementations, it is recommended for participants to use a larger-sized display, either a desktop screen or laptop screen, to minimize errors due to variability in *NSCLC-SAQ* display.

3.1.4 Handheld devices

The *NSCLC-SAQ* has not yet been implemented on a handheld device (e.g., smartphone). Given that the use of handheld devices will involve presenting smaller font and potentially alternate presentation styles, confirming consistent interpretation across device types via cognitive interviews is recommended.

3.1.5 Interactive voice response (IVR) systems

IVR methodology has been in widespread use for two decades for assessing patient-reported outcomes across a variety of disease states, interventions, and clinical trial designs (Corkrey & Parkinson 2002; Kobak et al. 2001; Mundt et al. 1998; Piette 2000). An auditory version of the *NSCLC-SAQ* has not yet been implemented on an IVR system. The *NSCLC-SAQ* is amenable to administration via IVR; however, a change of this magnitude would likely require equivalence testing, including both qualitative and quantitative evidence of measurement comparability (Coons et al. 2009).

3.2 General principles for *NSCLC-SAQ* completion

The general principles for completion of the *NSCLC-SAQ* are as follows:

- The *NSCLC-SAQ* should be administered electronically using a clear and simple interface on a chosen mode outlined in the protocol.
- The *NSCLC-SAQ* is designed as a PRO measure and should be completed only by the intended respondent (i.e., a person with NSCLC). Observers, including (but not limited to) clinicians and spouses/caregivers, should not complete the *NSCLC-SAQ* on behalf of the intended respondent.
- The seven *NSCLC-SAQ* items are used to calculate the *NSCLC-SAQ* Total Score (see Section 4.0).

3.3 Training

In general, no specific training is required to complete the *NSCLC-SAQ* since the instructions are self-explanatory. This may vary from case to case however depending on the age and ability of the respondent and the particular mode of data collection being used.

No difficulties have been reported among the various respondent groups who have assisted with the preliminary testing using tablet-based data collection in the studies conducted thus far. The lack of missing data attests to the acceptability of the *NSCLC-SAQ* to respondents.

3.3.1 Investigator training

Standard considerations for training of investigators and clinic staff who provide the questionnaires to the participants should include the following training:

- Proper administration of the *NSCLC-SAQ* to a respondent (including set up and log on to ePRO devices, demonstration of how to register responses and move forward in the questionnaire, and where the respondent is to end and what the procedure is for completion).

- Great care should be taken to avoid messages (verbal or otherwise) that might influence participants to respond to items in a way they feel may be acceptable to the investigator rather than according to their own feeling. Avoid introducing any bias in any interaction that could influence how a participant may respond to an item.

- Investigator should not answer questions of interpretation or clarification for *NSCLC-SAQ* items. If a respondent asks how he or she is meant to answer a particular item, the investigator/trainer should reply that the respondent should answer the question based on what he or she thinks the question is asking (and say nothing else, no further explanation, etc.) The subjective response of the respondent must be given according to what he or she perceives the item to be asking. Insertion of explanations on meaning and terms from the clinic staff is a source of bias that should be avoided.

Staff members are instructed on how to train respondents on the use of the device or other mode of data collection. With electronic PRO data collection systems, investigators are able to utilize a web-based data management system to monitor respondent compliance. Sites are instructed to contact respondents if they exhibit low compliance. The purpose of this contact is to ask if the respondent is having problems with the device or mode, and to further remind him or her to complete the measure according to the protocol assessment schedule.

A quick reference guide for study investigators should be made available and include details of preparing the device (if applicable) prior to deployment in a study. This guide includes details on how to confirm site specific settings, setting up a new respondent on the device, training the respondent on how to use the device and to complete the *NSCLC-SAQ*, transmitting/sending data and device deactivation. The reference guide for web-based or IVR modes would be tailored to the mode in question.

3.3.2 Respondent training

Respondent training procedures include a review of the questionnaire, guidance on how and when to complete it, and an opportunity to practice completing it on the data collection mode prior to submitting any data.

Study personnel should ensure that the following general information about the *NSCLC-SAQ* is provided to respondents:

- Respondents should be informed about the *NSCLC-SAQ* assessment schedule per protocol.
- Respondents should be informed that when completing the *NSCLC-SAQ*, they will be asked to reflect on the last 7 days from the day of completion.
- Respondents should be instructed to complete the *NSCLC-SAQ* on their own without the help of others and should answer the questions based on their own experience of NSCLC.
- Respondents should be instructed to be honest and as accurate as possible in their responses.
- Respondents should complete the *NSCLC-SAQ* in a quiet place and within a single time period, if possible.
- Finally, as always, please ensure confidentiality. Assure the respondents that all their responses will be kept confidential and will only be used for the purpose of the study.

If applicable, study personnel should ensure that the following information about completing the *NSCLC-SAQ* on an electronic data collection device is provided to respondents:

- The respondent should be reminded that the device should be charged at all times.
- The respondent should be taught how to use the device, including:
    - Turning the device on/off
    - Navigating the device
    - Setting a PIN code to access the device
    - Setting alarms to remind the respondent to enter data at the correct time
- The *NSCLC-SAQ* will not be available on the device outside of the stated completion time periods. If a respondent is unable to complete the *NSCLC-SAQ* during these windows, he or she cannot make it up later.
- The respondent should be shown how to access the measure in a practice setting and then should answer all 7 items in order to ensure comprehension of the *NSCLC-SAQ* and the characteristics of the specific ePRO device.
- If the respondent is required to actively send/transmit data, he or she should be informed of the process to do this and a practice run should be conducted.

- The respondent should be provided with a 24-hour helpdesk number in case of issues with data transmission or use of the device.
- The respondent should be provided with a user guide to take home with instructions on how to use the device.
- The site should monitor data upload in accordance with the study protocol and ensure missing data are within acceptable protocol defined limits.

The electronic device will include a pre-installed training module, which all respondents are instructed to work through. Through this training, any issues with the device functionality should be identified. This training module allows respondents to complete the practice version of the measure until they are sufficiently familiar with the process.

Respondents are instructed to respond to all of the items in one sitting, and to save their responses at the end. Respondents should be encouraged to respond to all items in the *NSCLC-SAQ*, but sponsors may choose to allow items to be actively skipped, so site staff should be aware of this potential option. If employed, the following standard skip language is recommended via the inclusion of electronic pop-up edit checks.

- In cases where there is a pop-up heading, the heading and message text would be as follows:

  "No response selected"

  "Do you want to continue without providing a response?"

- In cases where no pop-up heading is used, only the following message text would be shown:

  "No response selected. Do you want to continue without providing a response?"

It is recommended that respondents complete the *NSCLC-SAQ* at the same time for each assessment. An audible alarm (on tablets or handheld devices) that sounds at the appropriate time can be used to remind the respondent to complete the *NSCLC-SAQ* on the assessment date if it has not been completed. For web-based implementations, the reminder may take the form of an email or SMS text message on the due date.

Respondents should be provided with a quick reference guide, which provides instructions on: how to use the ePRO device, how to respond to the items, the time windows for completion, the alarm that will remind them to provide responses (where applicable), how to transmit their data (where appropriate), and how to report a problem with the device.

3.4 Instructions for administration by study/clinic staff

Administration of the *NSCLC-SAQ* should be in a quiet place away from the influence of others. The investigator and clinic staff should consider the reading ability required for self-completion before leaving a respondent alone to complete the questionnaire. This can be done by asking if the respondent needs assistance. Persons with low literacy or compromised eyesight should

always be provided the assistance of a clinic staff person to read the items for them and record the responses.

Before the respondent is left to complete the questionnaire on his or her own, the investigator and/or clinic staff person should be sure that the respondent is properly logged on, understands how to enter responses and move to the next item on his or her own. Respondents also need to know what they are to do next once they have completed the *NSCLC-SAQ*.

3.4.1 Interviewer administration

The *NSCLC-SAQ* was designed to be self-administered by persons with NSCLC. The quality of the data is predicated on the respondent's subjective response, with no interference or influence by others. However, self-administration is not always possible because the respondent may be too ill, unable to read the screen for some reason (e.g., vision impairment), or uncomfortable using computers or electronic data capture devices. In these extenuating cases, data collection may require the assistance of a staff person or another person with appropriate training to administer the *NSCLC-SAQ* via interview.

- If a respondent is able to read the items on his or her own but not enter his or her response, a staff person can enter the response for the respondent, but cannot question the response or attempt to influence the response in any way.
- If a respondent cannot read the items or instructions on the screen, a staff person may help him or her by reading exactly what the item on the screen says and what the response options are, but may not alter the language in any way, give explanation or further elaborate any of the text in the *NSCLC-SAQ* items.
- If a respondent does not read the language provided (e.g., English in the US) sufficiently well to be able to self-administer the *NSCLC-SAQ*, it is NOT ACCEPTABLE for any other person (family member or clinic staff) to interpret between varying languages. In this case, the *NSCLC-SAQ* cannot be completed, as the interpretation itself will be biased and outside of the accepted good practices for translation of PRO measures. A formal translation/cross-cultural adaptation process is required to develop any other language version of this standardized instrument, as described in Section 2.2.1.
- If the protocol allows interviewer administration, the mode of administration will need to be indicated in the database for each assessment so that the data from each mode of administration can be identified and analyzed separately.

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4.0 SCORING

4.1 Summary of provisional scoring instructions

The *NSCLC-SAQ* consists of seven items covering five domains: Cough, Pain, Dyspnea, Fatigue, Appetite (see Table 1). All five of these domains must be non-missing to compute a total score. Two of the domains contain 2 items: Pain and Fatigue.

PAIN: The two pain items [2. "How would you rate the worst pain in your chest over the last 7 days?" and 3. "How would you rate the worst pain in areas other than your chest over the past 7 days?"] are combined into a score by selecting the most severe response from the two items (or the single response if both items have the same score). The goal of the *NSCLC-SAQ* is to assess worst pain, wherever it manifests, hence a score will be derived by taking the most severe answer to either of the items, becoming a single "Pain" score. If one of these two items is missing, the included response (from the remaining item) is used as the "Pain" score.

FATIGUE: The two fatigue items [5. "How often did you have low energy over the last 7 days?" and 6. "How often did you tire easily over the last 7 days?"] are also combined. Given the high correlation between the two items (0.84), indicating considerable conceptual redundancy, a score will be derived by taking the mean of the two items, thus becoming a single "Fatigue" score. If one of these two items is missing, the included response (from the remaining item) is used as the "Fatigue" score.

For both "Pain" and "Fatigue" domains, if both items are missing responses, then the score would not be computed, it would remain missing.

The provisional scoring algorithm of the *NSCLC-SAQ* total score is as follows:

- **Cough Domain Score**: score of the cough item, or missing if skipped
- **Fatigue Domain Score**: if both items present, compute mean; or use score from 1 item if the other is missing; or set to missing if both are skipped
- **Pain Domain Score**: if both items present, use most severe of both; or use score from 1 item if the other is missing; or set to missing if both are skipped
- **Dyspnea Domain Score**: score of the shortness of breath item, or missing if skipped
- **Appetite Domain Score**: score of the poor appetite item, or missing if skipped
- **NSCLC-SAQ Total Score**: sum all five domain scores; if any are missing, a total score is not computed. This creates a total score ranging between 0 and 20 with higher scores indicating more severe symptomatology.

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Table 1. Scoring the *NSCLC-SAQ*

Domain	Item		Response
Cough	1. How would you rate your coughing at its worst…?		0, 1, 2, 3, 4
Pain	2. How would you rate the worst pain in your chest…?	*Create a single score by selecting the highest severity (i.e., value) on either item*	0, 1, 2, 3, 4
	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…?		0, 1, 2, 3, 4
Fatigue	5. How often did you have low energy…?	*Create a single score by calculating the mean of these 2 items*	0, 1, 2, 3, 4
	6. How often did you tire easily…?		
Appetite	7. How often did you have a poor appetite over the last 7 days?		0, 1, 2, 3, 4
NSCLC-SAQ Total Score (Sum the 5 domains)			**Range 0 to 20**

4.2 Interpretation of scores

The *NSCLC-SAQ* total score ranges between 0 and 20. Higher scores indicate more severe NSCLC-related symptomatology. Currently, the measurement properties of the *NSCLC-SAQ* have only been explored using data from a non-interventional, observational study. Given that little to no change occurred in this sample as no intervention occurred, no analyses associated with the interpretation of change on the *NSCLC-SAQ* have been conducted thus far. Proposed methods for future analyses (e.g., anchor and distribution-based methods and cumulative distribution functions) should be considered when aiming to assess the meaningfulness of within-patient change on the *NSCLC-SAQ* total score within a clinical trial.

4.3 Handling of missing data

If it is possible, try to think about how to avoid missing data before the actual data collection takes place. There are two types of missing data for PRO measures: missing data at the 'form' level and missing data at the 'item' level.

4.3.1 Form-level missing data

If a respondent does not complete the *NSCLC-SAQ*, such as due to attrition in longitudinal studies or due to forgetting to complete an individual assessment, his or her *NSCLC-SAQ* score should not be computed for that time point.

4.3.2 Item-level missing data

If data are being collected electronically, sponsors may decide to allow respondents to skip individual items within the *NSCLC-SAQ*.

If respondents are allowed to skip items, missing data at the item level may be present. Given the minimal number of items of the *NSCLC-SAQ* and the effect of missing items on the total score, if a respondent is missing **any** of the five domain scores, his or her *NSCLC-SAQ* score should not be computed. It is possible for respondents to miss one of the Pain items or one of the Fatigue items and still have a *NSCLC-SAQ* total score calculated.

5.0 *NSCLC-SAQ*-RELATED PUBLICATIONS

McCarrier KP, Atkinson TM, DeBusk KP, Liepa AM, Scanlon M, Coons SJ on behalf of the Patient-Reported Outcome Consortium, Non–Small Cell Lung Cancer Working Group. Qualitative development and content validity of the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ), a patient-reported outcome instrument. *Clin Ther*. 2016 Apr;38(4):794-810.

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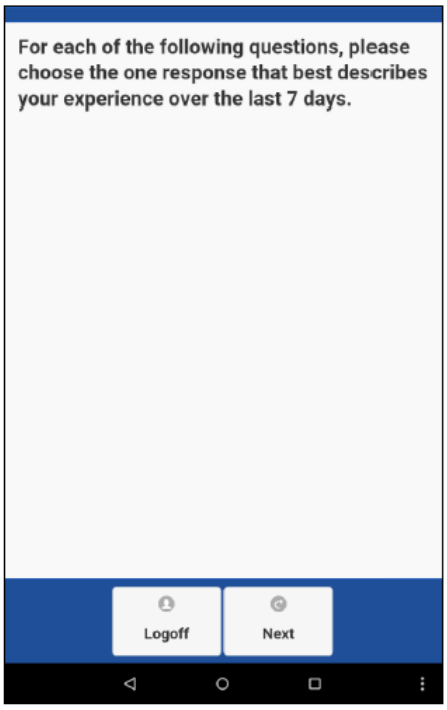
APPENDICES

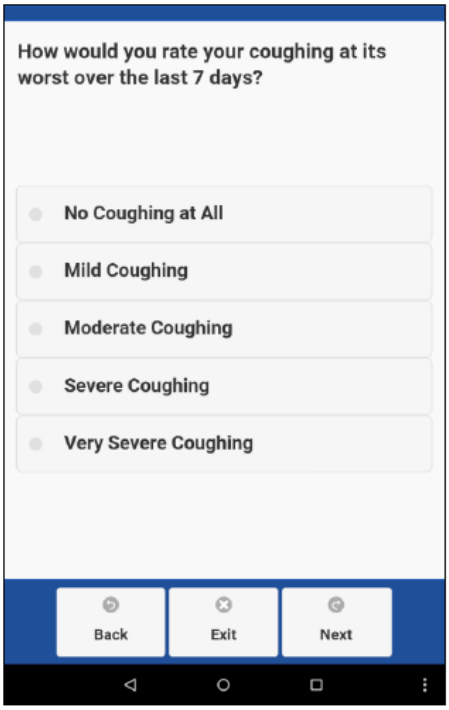
Appendix A: *NSCLC-SAQ* Screenshots of full measure (v0.1) (one item per screen)

Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (*NSCLC-SAQ*) Version 0.1
Confidential and Proprietary to Critical Path Institute

NSCLC-SAQ Instructions



NSCLC-SAQ Item 1



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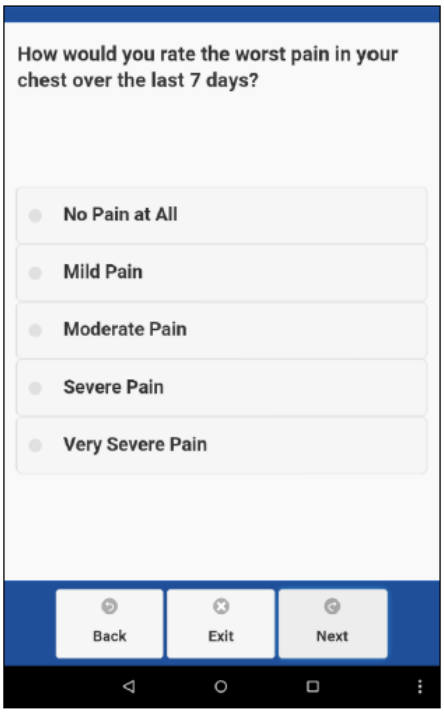
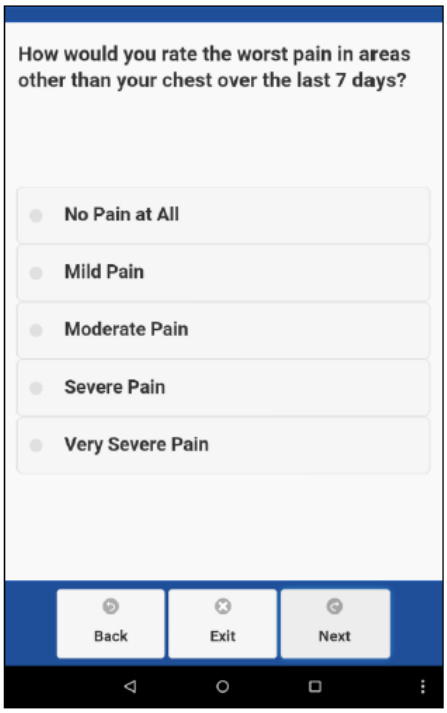
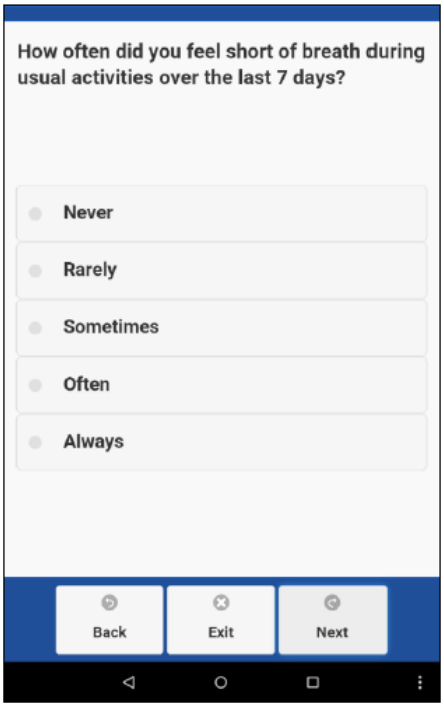


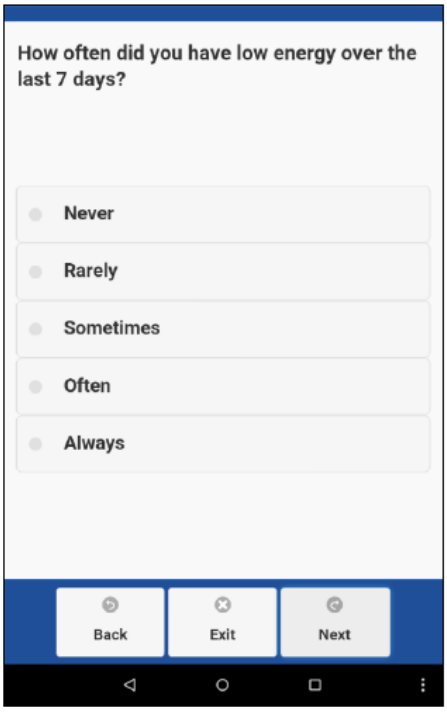
NSCLC-SAQ Item 3



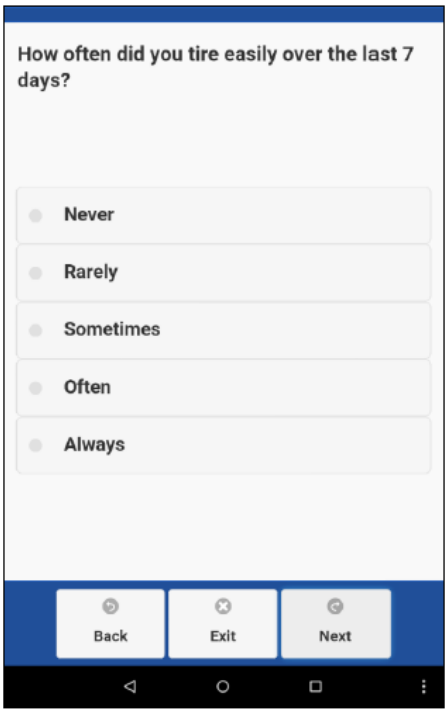
NSCLC-SAQ Item 4



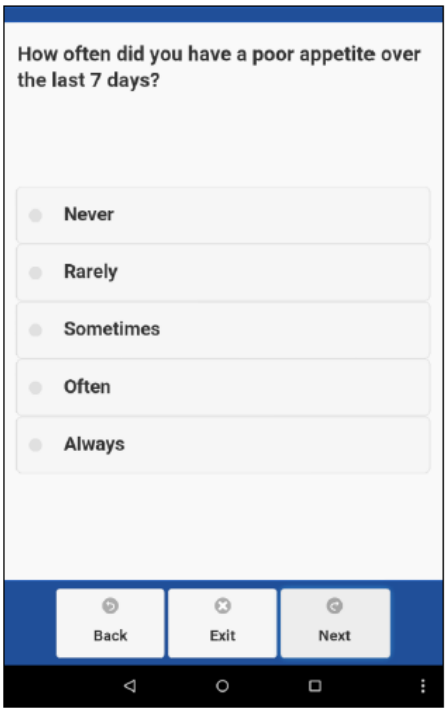
NSCLC-SAQ Item 5



NSCLC-SAQ Item 6



NSCLC-SAQ Item 7



Appendix B: *NSCLC-SAQ* Paper Version (v0.1)

Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) v0.1

For each of the following questions, please choose the one response that best describes your experience over the last 7 days.

1. How would you rate your coughing at its worst over the last 7 days?

- ☐ No Coughing at All
- ☐ Mild Coughing
- ☐ Moderate Coughing
- ☐ Severe Coughing
- ☐ Very Severe Coughing

2. How would you rate the worst pain in your chest over the last 7 days?

- ☐ No Pain at All
- ☐ Mild Pain
- ☐ Moderate Pain
- ☐ Severe Pain
- ☐ Very Severe Pain

3. How would you rate the worst pain in areas other than your chest over the last 7 days?

- ☐ No Pain at All
- ☐ Mild Pain
- ☐ Moderate Pain
- ☐ Severe Pain
- ☐ Very Severe Pain

Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) v0.1

4. How often did you feel short of breath during usual activities over the last 7 days?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

5. How often did you have low energy over the last 7 days?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

6. How often did you tire easily over the last 7 days?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

7. How often did you have a poor appetite over the last 7 days?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

Appendix C: List of Concepts

List of Concepts for the *Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)*

Note to the translator: This list of concepts is designed to provide you with detailed information about the intended concept of each item in the document. The central column contains an explanation of the key terms and ideas, and the column on the right side contains *possible* rewordings and alternatives for some key terms in English. Please note that you are in no way limited to those possibilities, they are simply provided to give you as much information about the concept of the item as is possible in English. This way, you can decide on the most appropriate wording in your language to fit that concept. Questions and comments regarding this List of Concepts are welcome at any time.

*****IMPORTANT INFORMATION ABOUT COLUMN THREE: Please keep in mind that these alternatives are simply conceptually equivalent ways to state these ideas *in English.* Our intent is that you should use this column to get a deeper understanding of the concept of that item, in order to develop the most appropriate way of phrasing the item in the target language. We do not want to imply that literal translations of these wordings/alternatives are requested; each language must be handled independently. Please always remember that for our purposes, the ideal translation is the one that matches the *concept* of the original English yet reads naturally and fluently in the target language.**

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Title ***Non-Small Cell Lung Cancer Symptom Assessment Questionnaire* (*NSCLC-SAQ*)**	This is the title of the questionnaire. The target language should utilize the most common medical terms for this condition.	The acronym of the title of the questionnaire should be retained in English as it is and should not be translated. This will facilitate the identification of the measure later when translated versions are published. If necessary, the phrase "by its English acronym" can be added with the acronym in the appendices.
Instruction Sentence 1 For each of the following questions, please choose the one response that best describes your experience over the last 7 days.	This sentence specifies that the respondent should consider only the immediate past 7 days when reporting the NSCLC symptoms. If the person is filling out the questionnaire on a Wednesday, s/he should consider the time from the previous Thursday up through the current day (one week back).	**over the last 7 days** could also be "during the previous 7 days," "during the past 7 days," "in the last 7 days," etc. **the last 7 days** should *not* be translated as "the past week"
Item 1 How would you rate your coughing at its worst over the last 7 days?	This refers to the experience of coughing during the last 7 days. It asks about the time when the coughing was at its worst, and how severe it was over that time period.	**your coughing at its worst** could also be "your worst coughing"

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Response scale for Item 1 No Coughing at All Mild Coughing Moderate Coughing Severe Coughing Very Severe Coughing	**No Coughing at All** – Indicates the respondent did not experience this symptom at all. **Mild Coughing –** Indicates a minor degree of coughing. **Moderate Coughing** – Indicates a medium degree of coughing. **Severe Coughing** – Indicates a high degree of coughing. **Very Severe Coughing –** Indicates an extremely high degree of coughing. When translating, each of the response options should increase in equal degrees, such that each option is evenly spaced as severity climbs.	**No Coughing at All** might be expressed as "no coughing" if that is more appropriate in your language. However, **No Coughing at All** should *not* be translated as just "none" or "never" or "not at all" The descriptor symptom of "coughing" must appear with each response option.
Item 2 How would you rate the worst pain in your chest over the last 7 days?	This refers to the experience of chest pain during the last 7 days. It asks about the time when the chest pain was at its worst, and how severe it was then. This pain is about pain in the lungs, the chest muscles and ribs. Note, this item is **not** referring to cardiac or heart attack pain.	**the worst pain in your chest** could also be "your chest pain at its worst" Any translation of chest pain used should *not* be something that is used colloquially to express cardiac pain or heart attack pain.
Response scale for Items 2 and 3 No Pain at All Mild Pain Moderate Pain Severe Pain Very Severe Pain	**No Pain at All** – Indicates the respondent did not experience this symptom at all. **Mild Pain –** Indicates slight pain. **Moderate Pain** – Indicates a medium level of pain. **Severe Pain** – Indicates a high level of pain. **Very Severe Pain –** Indicates an extremely high level of pain. When translating, each of the response options should increase in equal degrees, such that each option is evenly spaced as severity climbs.	**No Pain at All** might be expressed as "no pain" if that is more appropriate in your language. However, **No Pain at All** should *not* be translated as just "none" or "never" or "not at all" The descriptor symptom of "pain" must appear with each response option.

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Item 3 How would you rate the worst pain in areas other than your chest over the last 7 days?	This refers to the experience of pain, other than chest pain, during the last 7 days. It asks about the time when pain in other parts of the body was at its worst, and how severe that pain was then.	**the worst pain in areas other than your chest** could also be "pain in areas other than your chest at its worst" or "the worst pain, not in your chest,"
Item 4 How often did you feel short of breath during usual activities over the last 7 days?	This refers to how frequently the respondent experienced shortness of breath in the last 7 days. It asks about shortness of breath while performing usual, everyday activities. Feeling **short of breath** refers to difficulty breathing while performing an activity, which people often describe as having trouble "catching their breath." **Usual activities** refers to regular, day-to-day activities, like running errands, doing housework, going to work, preparing a meal, reading a book, etc.	**How often** could be "how frequently" **usual activities** could be "daily activities" or "regular activities"
Response scale for Items 4 to 7 Never Rarely Sometimes Often Always	**Never** – Indicates the respondent did not experience this symptom at all (none of the time or 0% of the time). **Rarely** – Indicates hardly ever, a little of the time, a little bit, infrequently (about 25% of the time). **Sometimes** – Indicates with some frequency but not with great regularity. This response option is the middle of the response scale (about 50% of the time). **Often** – Indicates frequently and with some regularity, most of the time (about 75% of the time). **Always** – Indicates the respondent has experienced the feeling or encountered the situation all the time (100% of the time). When translating, each of the response options should increase in equal degrees, such that each option is evenly spaced as frequency increases.	

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Item 5 How often did you have low energy over the last 7 days?	This refers to how frequently the respondent experienced low energy in the last 7 days. Having **low energy** refers to experiencing a lack of energy (can be physical or mental). It implies a feeling of fatigue. Energy is about both physical strength and mental vitality. Low energy refers to having lower energy than usual but does not mean the respondent has zero energy.	**How often** could be "how frequently" **low energy** could be "lack of energy" as long as the translated phrase does not imply zero energy
Item 6 How often did you tire easily over the last 7 days?	This refers to how frequently the respondent felt that they got tired easily in the last 7 days. To **tire easily** refers to experiencing a depletion of physical strength or energy sooner than usual. Tiring easily implies feeling tired soon after beginning an activity. This is an issue some may describe as endurance or stamina. It affects a person's ability to complete tasks that they start.	**How often** could be "how frequently" **tire easily** could be "feel tired quickly"
Item 7 How often did you have a poor appetite over the last 7 days?	This refers to how frequently the respondent had little, or small, or diminished appetite in the last 7 days. Having **poor appetite** refers to experiencing a reduced desire to eat.	**How often** could be "how frequently"