PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM

Asthma Daytime Symptom Diary (ADSD) and *Asthma Nighttime Symptom Diary (ANSD)*

User Manual

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VERSION CONTROL

Version	Changes from previous and rationale for changes	Date Issued
1.0	Initial release of *ADSD* and *ANSD* User Manual	March 30, 2019

LIST OF ABBREVIATIONS

Abbreviation	Definition/Explanation
AASDS	*Adult Asthma Symptom Diary Scales*
ADSD	*Asthma Daytime Symptom Diary*
ANSD	*Asthma Nighttime Symptom Diary*
ATS	American Thoracic Society
CDER	Center for Drug Evaluation and Research
COA	clinical outcome assessment
C-Path	Critical Path Institute
DDT	drug development tool
EPR-3	Expert Panel Report 3
ERS	European Respiratory Society
ePRO	electronic patient-reported outcome
FDA	US Food and Drug Administration
FEV_1	forced expiratory volume in one second
ICC	intraclass correlation coefficient
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IVR	interactive voice response
NRS	numeric rating scale
PEF	peak expiratory flow
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PRO	patient-reported outcome

1.0 BACKGROUND

1.1 Overview of the Patient-Reported Outcome (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 (Coons et al. 2011; Hayes et al. 2015). Its mission is to establish and maintain a collaborative framework with appropriate stakeholders for the qualification 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.

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

Asthma is a chronic inflammatory respiratory disease that is characterized by periods of variable and recurring airflow obstruction (National Asthma Education and Prevention Program 2007a; National Asthma Education and Prevention Program 2007b). The airflow obstruction is caused by inflammation and airway hyperactivity and is reversible either spontaneously or with treatment (Adel et al. 1998). The clinical manifestations of asthma may include symptoms such as difficulty breathing, coughing, wheezing, chest pain, and/or chest tightness (National Asthma Education and Prevention Program 2007a; National Asthma Education and Prevention Program 2007b). The management of asthma relies on early diagnosis, implementation of effective treatment(s), and patient adherence to therapy. It is estimated that approximately 300 million people worldwide are affected by asthma, and this figure is expected to increase by 33% to 400 million by 2025 (Masoli et al. 2004).

1.3 Purpose of the *Asthma Daytime Symptom Diary (ADSD)* and *Asthma Nighttime Symptom Diary (ANSD)*

Currently there is no generally accepted gold-standard measure for the assessment of asthma symptoms and, according to Krishnan and colleagues (2012), none which had sufficient validation information to be selected as a core asthma outcome measure for use in clinical research.

In order to provide a holistic understanding of patient disease severity and asthma control in clinical research, there is a need for a standardized way of assessing patients' experience of asthma symptoms, many of which can only be known to the patients themselves and best reported via PRO measures.

To fill this measurement gap, the PRO Consortium's Asthma Working Group at C-Path developed the *Asthma Daytime Symptom Diary (ADSD)* and the *Asthma Nighttime Symptom Diary (ANSD)* to assess severity of asthma symptoms among adolescents (aged 12-17 years) and adults (aged 18+ years) diagnosed with asthma. The *ADSD* and *ANSD* were developed in accordance with the FDA PRO Guidance (US Food and Drug Administration 2009) and are

intended for inclusion in clinical research alongside measures of physiologic and clinician-reported endpoints to support the assessment of asthma treatment benefit.

1.4 Context of use

The *ADSD* and *ANSD* are intended to be used as PRO-based co-primary (e.g., along with FEV_1) or secondary endpoint measures in asthma clinical trials to assess self-reported asthma symptom severity in adolescent and adults. The *ADSD* and *ANSD* assess six symptoms which, based on extensive qualitative research with patients and consultation with clinical experts, may be considered the 'core' symptoms of asthma.

1.4.1 Target population

The target population includes adults and adolescents aged 12 and older with a clinical diagnosis of mild persistent through severe persistent asthma, with lung function impairment (i.e., forced expiratory volume in one second [FEV_1] of 45%-90% of predicted normal value), and who demonstrate reversibility consistent with American Thoracic Society (ATS)/European Respiratory Society (ERS) standards for the diagnosis of asthma (National Asthma Education and Prevention Program 2007a; National Asthma Education and Prevention Program 2007b; Reddel et al. 2009). Diagnosis of other respiratory conditions (like chronic obstructive pulmonary disease) or upper airway obstructions are excluded. The targeted patients require daily asthma controller therapy based on current asthma management guidelines (Expert Panel Report-3 [EPR-3]).

The *ADSD* and *ANSD* have been developed in a sample of participants diverse with respect to sex, ethnic and racial backgrounds, and differing levels of educational attainment. Diversity in clinical characteristics (e.g., asthma control, asthma symptom severity, exacerbations, and medication use) was also ensured during the development of the measures, meaning that the *ADSD* and *ANSD* are appropriate for use in clinical trials that have recruited persons with asthma with varied demographic and clinical backgrounds. The *ADSD* and *ANSD* have been developed and tested in US English.

1.4.2 Endpoint positioning

In regulated pharmaceutical trials, the intent is that the *ADSD* and/or *ANSD* would be used as co-primary (e.g., along with FEV_1) or secondary endpoint measures to facilitate the comparison between either treatment and placebo groups, or different treatment groups. Other clinical measures (e.g., FEV_1 or peak expiratory flow [PEF]) or clinically relevant events (e.g., exacerbations or rescue medication use) would be expected to be used to derive primary or co-primary endpoints of disease severity and asthma control alongside the *ADSD* and/or *ANSD* as measures of symptom severity. In instances where the *ADSD* and *ANSD* are employed as secondary endpoint measures, the clinical trial would need to succeed on the primary endpoint before success could be attained on *ADSD*- or *ANSD*-based secondary endpoints relating to symptom severity.

The *ADSD* and *ANSD* were designed to be able to be completed in conjunction with each other to provide a holistic assessment of daytime and nighttime asthma symptom severity. However, sponsors are not required to use both measures and may, depending on the design of a specific clinical study, decide to administer either the *ADSD* or *ANSD* independently.

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

1.4.3 Target label language

Product-specific claims and labeling language would be the responsibility of the sponsor and should be based on product attributes, study design and hypotheses, and discussions with the appropriate regulatory agencies. Using the *ADSD* and *ANSD*, product-specific claims and labeling language pertaining to the severity of symptom experience and/or the occurrence of symptom free days could be targeted, depending on sponsor-specific clinical trial aims.

1.5 Development and evaluation of the *ADSD* and *ANSD*

Figure 1 provides an overview of the process and methods involved in the development of the *ADSD* and *ANSD*, including the qualitative and quantitative research conducted to support the content validity and other measurement properties of the measures. At each stage of this process, input was obtained from the Asthma 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 (DDT) Qualification Program (US Food and Drug Administration 2014).

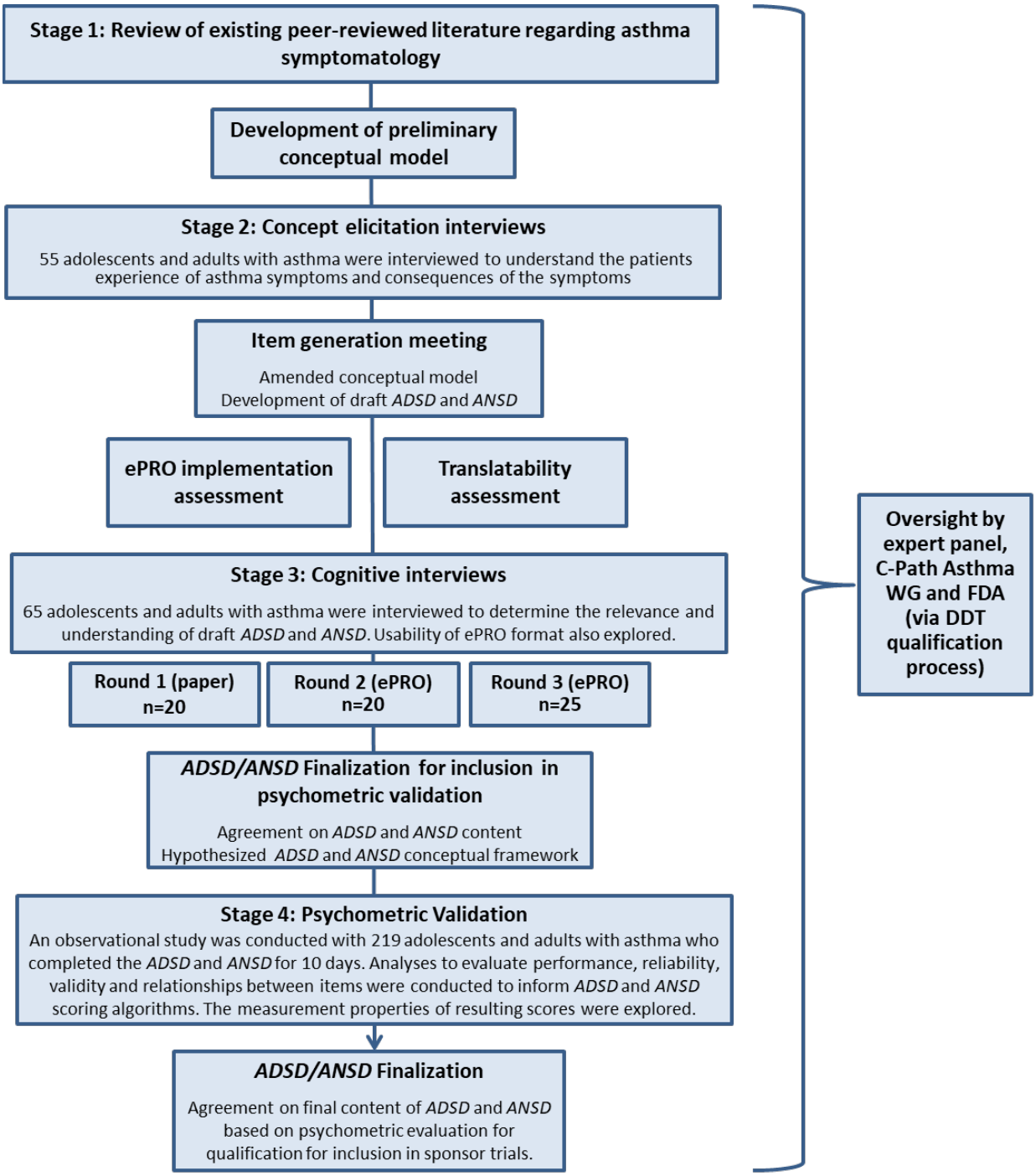

Figure 1: Overview of *ADSD* and *ANSD* development and testing

1.5.1 Evidence of content validity

Content validity is important for any PRO measure and substantial evidence of it is required for those intended to support claims in approved medical product labeling (Coons et al. 2011; US Food and Drug Administration 2009). The content validity of PRO measures is generally established through evidence confirming the measure provides a 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.

ADSD and *ANSD* content was informed via a review of existing published qualitative research studies conducted in asthma and findings from open-ended concept elicitation interviews with a diverse sample of 55 participants with asthma in the US. This sample comprised 25 adolescents (12-17 years old) and 30 adults (18+ years old) (mean: 31 years old; range: 12-76 years old). The sample was 55% (n=30) female, 18% (n=10) Hispanic or Latino, and racially diverse (White [n=25, 45 %]; Black/African American [n=17, 31%]; Multi-racial [n=5; 9%], other [n=8, 15%]). All adolescent participants were enrolled in school (12-14 years old in school grades 6-9 and 15-17 years old in grades 10-12, respectively) and adults' highest level of education ranged from some high school (n=9, 30%) to college level or higher (n=21, 70%). Differing levels of asthma control were represented in the sample as reported by participant scores on the Asthma Control Test: Well-controlled asthma (n=16, 29%), Not well-controlled asthma (n=18, 33%), and Very poorly controlled asthma (n=21, 38%). The sample included participants on a range of asthma medication steps as categorized by the EPR3 guidelines for diagnosis and management of asthma (National Asthma Education and Prevention Program 2007b): Step 1 (n=5, 9%), Step 2 (n=7, 13%), Step 3 (n=16, 29%), Steps 4-5 (n=24, 44%), and Step 6 (n=3, 5%).

From the review of the existing published literature and concept elicitation interviews, eight 'core symptoms' of asthma were identified based on the frequency with which they were spontaneously reported by research participants and their clinical relevance (as confirmed via consultation with the scientific advisors). These symptoms were broadly categorized as breathing symptoms (e.g., difficulty breathing, shortness of breath, and wheezing), chest symptoms (e.g., chest tightness, chest pressure, and chest pain), and cough symptoms (including the presence of mucus/phlegm). Subgroup analyses highlighted consistency in conceptual definitions and the terms used by participants to describe their symptoms across various socio-demographic (e.g., age, sex, ethnicity) and clinical (e.g., asthma control, asthma medication, recent exacerbation history) variables.

It was decided to operationalize the assessment of the eight core symptoms of asthma as a diary suitable for use with adults and adolescents with asthma aged 12 years or older. A twice-daily (morning and evening) diary format was chosen to minimize the impact of recall bias and to account for day-to-day variation in asthma symptoms. This format also facilitates both the calculation of symptom-free days and the assessment of changes in symptom severity over time. Draft versions of the *ADSD* and *ANSD* were developed, informed by findings from the literature review, concept elicitation interviews, input from the scientific advisors, and findings of both an electronic patient-reported outcome (ePRO) implementation assessment and translatability assessment.

Semi-structured cognitive and usability testing interviews were conducted with a second (independent) sample of 65 participants with asthma in the US to evaluate the relevance and participant understanding of draft *ADSD* and *ANSD* items, instructions, response options, and ease of *ADSD* and *ANSD* completion using an ePRO device. This sample comprised 35 adolescents (12-17 years old) and 30 adults (18+ years old) (mean: 28 years old; range: 12-69 years old). The sample was 55% (n=36) female, 19% (n=29) Hispanic or Latino, and racially diverse (White [n=25, 38%]; Black/African American [n=13, 20%]; Multi-racial [n=12, 18%] and other [n=15, 23%]). All adolescent participants were enrolled in school (12-14 years old in school grades 6-9 and 15-17 years old in grades 10-12, respectively) and adults' highest level of

education ranged from some high school (n=10, 33%) to college level or higher (n=20, 67%). Differing levels of asthma control were represented in the sample as reported by participant scores on the Asthma Control Test: Well-controlled asthma (n=20, 31%), Not well-controlled asthma (n=18, 28%), and Very poorly controlled asthma (n=27, 42%). The sample included participants on a range of asthma medication steps as categorized by the EPR3 guidelines for diagnosis and management of asthma (National Asthma Education and Prevention Program 2007b): Step 1 (n=12, 18%), Step 2 (n=8, 12%), Step 3 (n=26, 40%), Steps 4-5 (n=15, 23%), and Step 6 (n=4, 6%).

Cognitive interviews were conducted in three rounds: round 1 based on paper and pencil formats of the *ADSD* and *ANSD* (n=20) and rounds 2 (n=20) and 3 (n=25) based on ePRO formats of the *ADSD* and *ANSD*. *ADSD* and *ANSD* items and instructions were generally well understood and consistently interpreted among all socio-demographic and clinical subgroups of participants. Minor wording changes were implemented between interview rounds and tested in subsequent rounds. Conceptual coverage of the *ADSD* and *ANSD*, however, was sufficient with no additional symptoms being deemed necessary for inclusion in the *ADSD* or *ANSD*.

Exit interviews with a subset of participants (n=24) from the quantitative pilot study designed to evaluate the measurement properties of the *ADSD* and *ANSD* offered further support for the content validity of the *ADSD* and *ANSD*.

1.5.2 Measurement properties and psychometric evaluation

The performance, reliability, and validity of *ADSD* and *ANSD* items and scores were explored during an observational, quantitative pilot study among a diverse sample of 219 adolescents and adults with asthma in the US. This sample comprised 88 adolescents aged 12-14 years old, 42 adolescents aged 15-17 years old, 45 adults aged 18-45 years old and 44 adults aged 46 years or older (mean: 25.8 years old; range: 12-74 years old). The sample was 55% female (n=120), 35% (n=76) Hispanic or Latino, and racially diverse (White [n=99, 45%]; Black/African American [n=66, 30%]; Asian or Pacific Islander [n=11, 5%]; Native American or Alaskan native [n=21, 10%] and other [n=23, 11%]). All adolescent participants were enrolled in school (12-14 years old in school grades 6-9 and 15-17 years old in grades 10-12, respectively) and adults' highest level of education ranged from some high school (n=30, 34%) to college level or higher (n=58, 65%). Differing levels of asthma control were represented in the sample as reported by participant scores on the Asthma Control Test: Well-controlled asthma (n=81, 37%), Not well-controlled asthma (n=65, 30%), and Very poorly controlled asthma (n=73, 33%). The sample included participants on a range of asthma medication steps as categorized by the EPR3 guidelines for diagnosis and management of asthma (National Asthma Education and Prevention Program 2007b): Step 1 (n=60, 27%), Step 2 (n=47, 22%), Step 3 (n=44, 20%), Steps 4 (n=50, 23%), and Step 5 (n=18, 8%).

Participants in this study were asked to complete the *ADSD* and *ANSD* in an ePRO format (alongside a number of other concurrent PRO measures) for a period of 10 days. Overall, *ADSD* and *ANSD* items demonstrated strong item performance, reliability (reproducibility), and validity (in terms of ability to distinguish between known-groups and relationships with other PRO measures of related concepts).

For each item of the *ADSD* and *ANSD*, ceiling effects (instances where ≥35% of responses were at '0' or 'None,' which reflects the best possible symptom experience on the scale) were observed. Across all items, ceiling effects were higher for the *ANSD* than for the *ADSD*. Despite

the presence of these ceiling effects, participants endorsed all response categories across the 0 to 10 numeric rating scale (NRS) response continuum for the *ADSD* and *ANSD*. Selection of response options at the upper end of the response continuum (scores of 8 to 10) were infrequent (<1% of the total number of responses) for the *ADSD* and *ANSD*. No significant floor effects (i.e., endorsement of the worst health state; 10 on the NRS) were observed. The pattern of item response distributions for adolescent and adult participants was similar to that observed for the total study sample.

Item discrimination indices calculated on Day 3 and Day 10 using Patient Global Impression of Severity (PGIS) ratings revealed that participant responses to *ADSD* and *ANSD* items were able to distinguish between patients reporting severe asthma symptoms and those with moderate and mild symptoms. Empirical item curves and stacked histograms revealed that individual response categories on the 0 to 10 NRS for symptom severity on the *ADSD* and *ANSD* were distinct and participant's responses to *ADSD* and *ANSD* items were consistent with global asthma symptom severity (based on PGIS ratings). Missing data at the item (0.8%) and form (6.2%) level was low.

All items of the *ADSD* and *ANSD* demonstrated 'good' test-retest reliability (intraclass correlation coefficient [ICC]=0.71-0.94) when participants were defined as experiencing 'no change' in the severity of their asthma symptoms between Day 3 and Day 10 according to PGIS ratings. Construct validity of the *ADSD* and *ANSD* items was examined using known-groups methods. *ADSD* and *ANSD* items were able to discriminate between participant groups defined according to self-reported asthma severity, asthma control, inhaler use, nebulizer use, nighttime awakenings (*ANSD*) and activity limitations (*ADSD*). High inter-item correlations revealed some evidence of redundancy between Item 4 ('Chest pressure) and Item 5 ('Chest tightness') (0.94 on the *ADSD* and 0.95 on the *ANSD*) and Item 7 ('Cough') and Item 8 ('Mucus/phlegm) (0.85 on *ADSD*). This evidence in conjunction with data regarding item performance supported the removal of Item 4 ('Chest pressure') and Item 8 ('Mucus/phlegm') from the *ADSD* and *ANSD*.

Principal component analysis and confirmatory factor analysis supported the derivation of average scores for the 6-item versions of the *ADSD* and *ANSD* (based on an average of participant responses to individual items of the *ADSD* and *ANSD*, respectively).

Test-retest reliability was examined using the intraclass correlation coefficient (ICC) calculated using the two-way mixed effect model with absolute agreement for single measures. The *ADSD* and *ANSD* Scores demonstrated good test-retest reliability (ICC=0.86 [95% confidence interval 0.78 to 0.91] and 0.95 [95% confidence interval 0.92 to 0.97], respectively) when participants were defined as experiencing 'no change' in their asthma between Day 3 and Day 10 according to PGIS ratings. Internal consistency reliability was high for both the *ADSD* and *ANSD* (Cronbach's alpha = 0.94 and 0.95, respectively). Construct validity of the *ADSD* and *ANSD* Scores was also supported by evidence that these scores could effectively discriminate between participant groups defined according to self-reported asthma severity, asthma control, inhaler use, nebulizer use, recent exacerbations, nighttime awakenings, and activity limitations (i.e., known-groups validity). The *ADSD* and *ANSD* Scores correlated with items on the Adult Asthma Symptom Diary Scales (*AASDS*) assessing similar concepts (i.e., concurrent validity) ($r>0.50$ and $r\geq0.70$, respectively).

2.0 OVERVIEW OF THE *ADSD* AND *ANSD*

2.1 Content

The *ADSD* and *ANSD* are each 6-item PRO measures designed for use in adults and adolescents (aged 12 years and older) diagnosed with asthma to assess the self-reported severity of the core, defining symptoms of asthma. The *ADSD* is to be completed before going to bed and asks respondents to rate the severity of six asthma symptoms during the day. Conversely, the *ANSD* is to be completed upon waking and asks respondents to rate the severity of six asthma symptoms during the night. Item wording is consistent between both diaries with the only differences being references to the respective recall periods.

Screen shots of the *ADSD* and *ANSD* are displayed in APPENDIX A and APPENDIX B, respectively. The paper formats of the *ADSD* and *ANSD* are provided in APPENDIX C and APPENDIX D, respectively.

The Asthma Working Group has also developed supplementary items to provide sponsors with standardized wording for measurement of optional relevant concepts associated with asthma that are often assessed in clinical trials. See ATTACHMENT 1 for detailed information regarding these supplementary items which are not included in the *ADSD or ANSD*.

2.1.1 Conceptual framework

Conceptual frameworks for the *ADSD* and *ANSD* are presented in Figure 2.

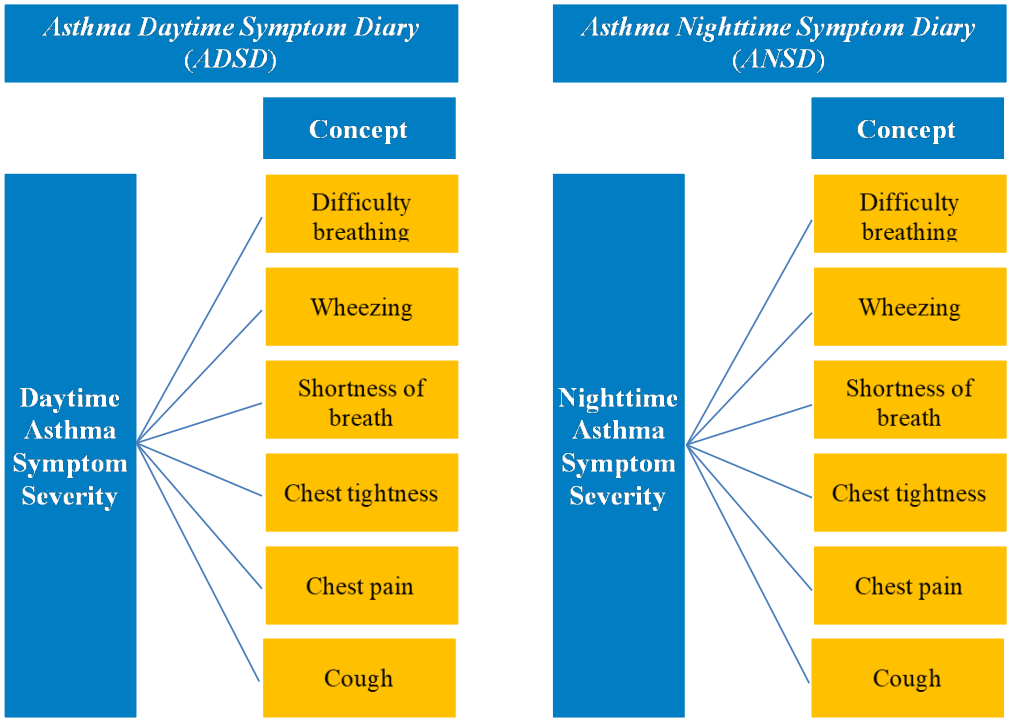

Figure 2. *ADSD* and *ANSD* conceptual frameworks

2.1.2 Instructions and recall period

Assessing asthma symptoms twice daily using the *ADSD* (completed in the evening) and *ANSD* (completed in the morning) is possible to account for the variability in symptom occurrence (daytime vs. nighttime); however, it is not required. The *ADSD* instructs respondents to complete the diary *"every night before you go to bed"* and to "*answer each question by thinking about your asthma symptoms today, from when you got up this morning until now"* (see Figure 3). The *ANSD* instructs respondents to complete the diary *"every morning when you get up"* and to *"answer each question by thinking about your asthma symptoms last night from when you went to bed until now"* (see Figure 3).

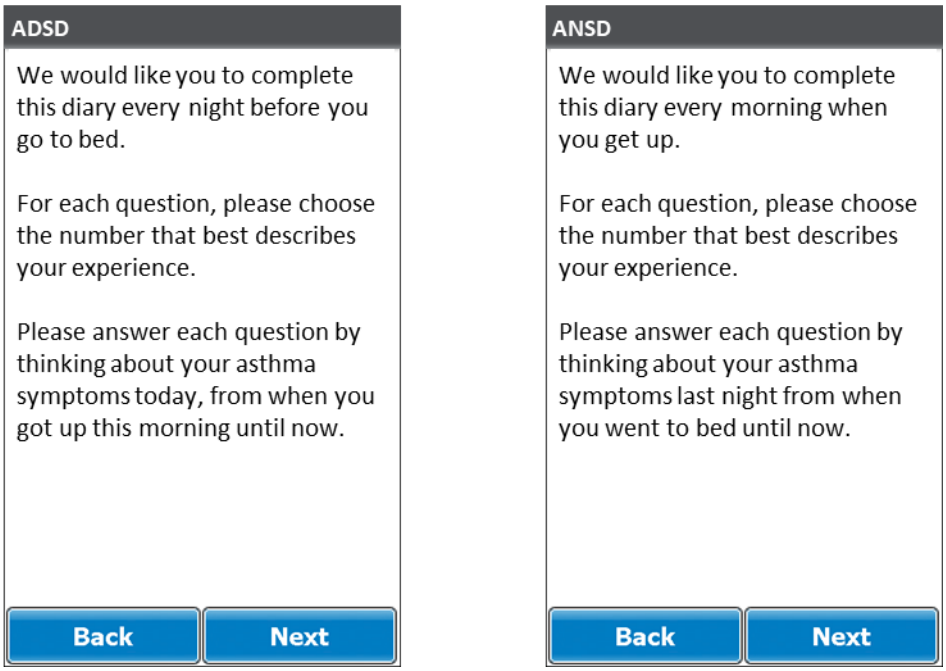

Figure 3. *ADSD* and *ANSD* Instructions (Screen shots)

2.1.3 Items and response options

The *ADSD* and *ANSD* ask respondents to rate the severity of their asthma symptoms at their worst using a 0 to 10 NRS ranging from "none" to "as bad as you can imagine" (see Figure 4). Ratings on a 0 to 10 scale were used spontaneously by participants during the concept elicitation interviews and have the advantage of offering greater gradation of response options (promoting responsiveness/sensitivity to change). The NRS can also be universally applied cross-culturally and across languages. The *ADSD* and *ANSD* ask respondents to rate each individual symptom at its 'worst' as this is most representative of the burden experienced by respondents. Subsequent qualitative testing of the *ADSD* and *ANSD* response options during the cognitive interviews demonstrated that the 0 to 10 NRS was well understood, consistently interpreted by participants, and deemed appropriate for the assessment of asthma symptom severity/intensity. Subsequent quantitative testing has further confirmed the adequacy of *ADSD* and *ANSD* response options in terms of the full endorsement of the response options, test-retest reliability, and construct validity.

The *ADSD* and *ANSD* response options are intended to be presented in a portrait format, appearing horizontally across the screen with one item per screen. Qualitative testing of both portrait and landscape orientations demonstrated equivalence with regards to respondent understanding and response selection. Users may therefore select the orientation most appropriate for their intended use, as the landscape orientation was preferred by a number of participants in the qualitative research while portrait is often the default available by technology providers.

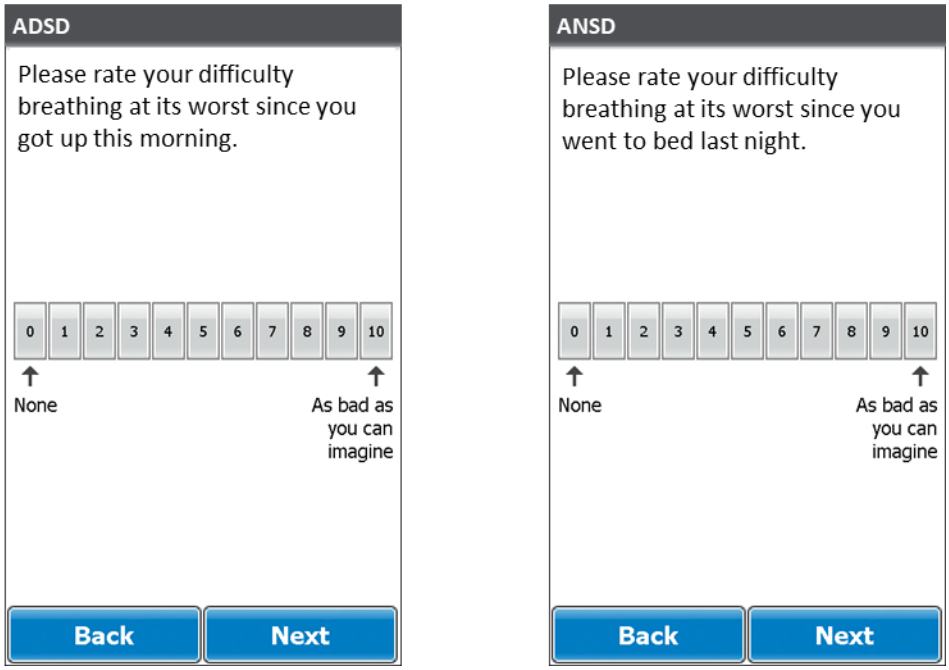

Figure 4. *ADSD* and *ANSD* example items (Screen shots)

2.2 Translations

2.2.1 Translation methodology

To ensure the quality and availability of translated versions of the *ADSD* and *ANSD* across studies, users must follow the approved PRO Consortium Translation Process (Eremenco et al. 2018) if the translations needed are not available. The approved process is based on the good practice principles and recommendations for translation, cultural adaptation, and linguistic validation outlined in the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force reports (Wild et al. 2005; Wild et al. 2009). To reach consensus on the process, firms within the translation industry were engaged in a consensus development initiative that resulted in the final process. The process includes the following steps: development of item definition tables, 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 its partner, FACIT.org, manages (but does not necessarily conduct) all translations of the measures and maintains the *ADSD* and *ANSD* translation files for distribution.

A critical step in ensuring consistency across translations is the development of item definition tables (Appendix E) which are distributed to all translation firms involved in translating the *ADSD* and *ANSD*. The item definition tables provide 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 *ADSD* and *ANSD* that are both conceptually equivalent to the English source versions and easily understood by the target population.

2.2.2 Available translations

A list of available translations for the *ADSD* and *ANSD* 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 the 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 the *ADSD* and *ANSD* only; translation of mode-specific instructions for electronic data collection 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 *ADSD* and *ANSD* into new languages, which must follow the approved translation process addressed above.

2.3 Copyright and licensing

3.0 ADMINISTRATION PROCEDURES

3.1 Modes of data collection

The *ADSD* and *ANSD* were designed with electronic self-administration in mind. The quantitative pilot study utilized an electronic handheld device (i.e., smartphone) 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, electronic modes of data collection are recommended over paper for the *ADSD* and *ANSD*. Any planned use of the *ADSD* and *ANSD* via modes of data collection other than the ones for which data are already available will need to be approved. Evidence from a small sample of the target population should be provided that demonstrates respondents are interpreting and responding to each item the same way regardless of the data collection mode.

3.1.1 Paper and pencil forms

US English paper and pencil formats of the *ADSD* and *ANSD* were developed and tested during cognitive interviews designed to evaluate the respondent understanding and interpretation of the *ADSD* and *ANSD* (round 1 only). This paper and pencil formats of the *ADSD* and *ANSD* are available under a licensing agreement with C-Path should study sponsors wish to implement the *ADSD* or *ANSD* in this format. However, the measurement properties of paper formats of the *ADSD* and *ANSD* have not been evaluated and due to concerns regarding data quality and integrity (e.g., the potential for missing data and back or forward-filling of data), administration in paper format is not recommended.

3.1.2 Handheld devices

The *ADSD* and *ANSD* were developed and migrated to an electronic handheld device format in accordance with industry best practices (Critical Path Institute ePRO Consortium 2014a; Critical Path Institute ePRO Consortium 2014b; Critical Path Institute ePRO Consortium 2014c). Usability, reliability, and validity of the *ADSD* and *ANSD* have subsequently been explored extensively through qualitative (i.e., cognitive interviews and exit interviews) and quantitative research (i.e., quantitative pilot study).

3.1.3 Tablet devices

The *ADSD* and *ANSD* have not yet been implemented on tablet platforms. Given that the use of tablet devices will involve presenting larger font and potentially alternate presentation styles, ensuring consistency across devices via cognitive interviews is recommended.

3.1.4 Web-based applications

The *ADSD* and *ANSD* have not yet been implemented on web-based platforms. A cognitive interview-based evaluation should be sufficient to confirm comparability 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 (Coons et al. 2009). 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 *ADSD* and *ANSD* display.

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 and Parkinson 2002; Kobak et al. 2001; Piette 2000). It has major advantages in the automation and standardization of data collection in clinical trials (Mundt et al. 1998). Auditory formats of the *ADSD* and *ANSD* have not yet been implemented on an IVR system. The *ADSD* and *ANSD* are 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 PRO measure completion

The general principles for completion of the *ADSD* and *ANSD* are as follows:

- The *ADSD* and *ANSD* should be administered electronically on a chosen mode outlined in the protocol.
- The six items of the *ADSD* should be completed every evening between 7pm and 1am for the duration of the study period outlined in the protocol.
- The six items of the *ANSD* should be completed every morning between 6am and 12pm for the duration of the study period outlined in the protocol.
- The *ADSD* and *ANSD* are designed as PRO measures and should be completed only by the intended respondent (i.e., a person with asthma). Observers, including (but not limited to) clinicians and spouses/parents/caregivers should not complete the *ADSD or ANSD* on behalf of the intended respondent.
- The six *ADSD* items are used to calculate an *ADSD* Score and the six *ANSD* items are used to calculate a separate *ANSD* Score (see section 4.0).

3.3 Training

In general, no specific training is required to complete the *ADSD* or the *ANSD* 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. Training for mode-specific interactions with the device is the responsibility of the sponsor and ePRO vendor (e.g., logging into the device, navigating to the *ADSD* and *ANSD*).

No difficulties have been reported among the various respondent groups who have assisted with the preliminary testing using handheld-based data collection in the studies conducted thus far. The minimal missing data attests to the acceptability of the *ADSD* and *ANSD* to respondents.

3.3.1 Investigator training

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

- Proper completion of the *ADSD* and *ANSD* (including set up and log on to ePRO devices, demonstration of how to register responses and move forward in each measure, 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 respondents 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 respondent may respond to an item.
- Investigator should not answer questions of interpretation or clarification for *ADSD* or *ANSD* 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 item 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.

Further training for investigators focuses on the use of the device itself, including a review of the equipment and procedures for enrolling a respondent onto the ePRO device. Investigators are instructed to set a reminder alarm at the respondent's preferred time if the technology allows, assisting in reminding the respondent to complete the daily entries (see section 3.3.2).

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. This has previously been defined as missing two consecutive diary windows. 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 of a study. This guide includes details on confirming site-specific settings, setting up a new respondent on the device, training the respondent on how to use the device and to complete the *ADSD* and/or *ANSD*, 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 *ADSD* and *ANSD* and guidance on how and when to complete the diaries. Assuming completion via electronic device, respondents would also be provided with an opportunity to practice completing the diaries on the electronic data collection mode prior to submitting any data.

Study personnel should ensure that the following general information about the *ADSD* and *ANSD* is provided to respondents:

- Respondents should be informed that the *ADSD* is to be completed every evening between 7pm and 1am.
- Respondents should be informed that when completing the *ADSD*, they will be asked to reflect on the time period "since you woke up this morning."
- Respondents should be informed that the *ANSD* is to be completed every morning between 6am and 12pm.
- Respondents should be informed that when completing the *ANSD*, they will be asked to reflect on the time period "since you went to bed last night."
- Respondents should be instructed to complete the *ADSD* and/or *ANSD* on their own without the help of others and should answer the questions based on their own experience of asthma.
- Respondents should be instructed to be honest and as accurate as possible in their responses.
- Respondents should complete the *ADSD* and/or *ANSD* in a quiet place and within a single time period, if possible.
- Finally, respondents should be assured that their identity will be kept confidential and their answers will only be used for scientific purposes.

Study personnel should ensure that the following information about completing the *ADSD* and/or *ANSD* on an electronic 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 to access the device
    - Setting alarms to remind the respondent to enter data at the correct time
- The *ADSD* will not be available outside of every evening between 7pm and 1am. If a respondent is unable to complete the *ADSD* during this window, he or she cannot complete the measure later.
- The *ANSD* will not be available on the device outside of every morning between 6am and 12pm. If a respondent is unable to complete the *ANSD* during this window, he or she cannot complete the measure later.
- The respondent should be shown how to access the *ADSD* and/or *ANSD* in a practice setting and then should answer all items in order to ensure comprehension of the *ADSD* and/or *ANSD* 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 measures until they are sufficiently familiar with the process.

Respondents should be instructed to answer all the items in one sitting and to save their answers at the end. Respondents should be encouraged to answer all items, but sponsors may choose to allow items to be actively skipped, so site staff should be aware of this possible option. If implemented, 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 *ADSD* at the same time each evening and the *ANSD* at the same time each morning, as it is not possible for respondents to go back and fill in missed entries. An audible alarm (on tablets or handheld devices) that sounds in the evening and/or morning can be used to remind the respondent to complete the *ADSD* and/or *ANSD* during the assessment window 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 and time.

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. Feedback from the cognitive interview and quantitative pilot study exit interviews provided evidence that the majority of participants asked found the quick reference guide easy to use and a useful introduction to the device.

3.4 Instructions for administration by study/clinic staff

The *ADSD* and *ANSD* are field-based assessments designed to be completed outside of a clinic setting. Therefore, administration by study staff will not be possible and interviewer administration is not recommended.

4.0 SCORING

4.1 Summary of provisional scoring instructions

4.1.1 *ADSD*

Participant responses to individual items of the *ADSD* are summarized as an average score across all six items of the *ADSD* ranging from 0 to 10 (no weighting applied so each item contributes equally). *ADSD* data from a single day will be referred to as the '*ADSD* Score.' A >50% rule will be employed for missing data at the item level with scores only calculated if data for four or more items are available.

During the quantitative pilot study, a summary score was derived and tested using *ADSD* scores from multiple days (i.e., Days 3 to 10). This score was referred to as the '6-Item *ADSD* Mean Day 3-10 Score' and demonstrated strong reliability and validity. For future studies, a summary score will be calculated as a weekly average using data from seven days. This score will be referred to as the '*ADSD* Weekly Score.' Depending on study aims and objectives, future research may also explore the measurement properties of summary scores over alternative time periods (e.g., 4 weeks).

The scoring of the *ADSD* is summarized in Table 2.

Table 1. Scoring of the *Asthma Daytime Symptom Diary* (*ADSD*)

***ADSD* item**	**Response**
[ITEM 1] Please rate your difficulty breathing at its worst since you got up this morning.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
[ITEM 2] Please rate your wheezing at its worst since you got up this morning.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
[ITEM 3] Please rate your shortness of breath at its worst since you got up this morning.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
[ITEM 4] Please rate your chest tightness at its worst since you got up this morning.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
[ITEM 5] Please rate your chest pain at its worst since you got up this morning.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
[ITEM 6] Please rate your cough at its worst since you got up this morning.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
***ADSD* Score** (Sum the individual completed *ADSD* responses and divide by the number of completed items)*	**Range 0 to 10**

*Assumes four or more items are available as per missing data rules (see section 4.3)

4.1.2 *ANSD*

Participant responses to individual items of the *ANSD* are summarized as an average score across all six items of the *ANSD* ranging from 0 to 10 (no weighting applied so each item contributes equally). *ANSD* data from a single day will be referred to as the '*ANSD* Score.' A >50% rule will be employed for missing data at the item level with scores only calculated if data for four or more items are available.

During the quantitative pilot study, a summary score was derived and tested using *ANSD* scores from multiple days (i.e., Days 3 to 10). This score was referred to as the '6-Item *ANSD* Mean Day 3-10 Score' and demonstrated strong reliability and validity. For future studies, a summary score will be calculated as a weekly average using data from seven days. This score will be referred to as the '*ANSD* Weekly Score.' Depending on study aims and objectives, future research may also explore the measurement properties of summary scores over alternative time periods (e.g., 4 weeks).

The scoring of the *ANSD* is summarized in Table 3.

Table 2. Scoring of the *Asthma Nighttime Symptom Diary* (*ANSD*)

***ANSD* item**	**Response**
[ITEM 1] Please rate your difficulty breathing at its worst since you went to bed last night.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
[ITEM 2] Please rate your wheezing at its worst since you went to bed last night.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
[ITEM 3] Please rate your shortness of breath at its worst since you went to bed last night.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
[ITEM 4] Please rate your chest tightness at its worst since you went to bed last night.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
[ITEM 5] Please rate your chest pain at its worst since you went to bed last night.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
[ITEM 6] Please rate your cough at its worst since you went to bed last night.	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
***ANSD* Score** (Sum the individual completed *ANSD* responses and divide by the number of completed items)*	**Range 0 to 10**

*Assumes four or more items are available as per missing data rules (see section 4.3)

4.2 Interpretation of scores

The *ADSD* and *ANSD* Scores range between 0 and 10. Higher scores indicate more severe asthma symptomatology. Currently, the measurement properties of the *ADSD* and *ANSD* 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 was in place, no analyses associated with the interpretation of change on the *ADSD* and *ANSD* 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 *ADSD* and *ANSD* Scores within a treatment trial. In terms of anchor-based methods, multiple anchors at multiple time-points that include at least a "current" state patient global impression of severity (PGIS) item and a patient global impression of change (PGIC) item (i.e., comparison of current state to the state of an earlier time-point) are recommended.

4.3 Handling missing data

If it is possible, incorporate ways to avoid missing data before the actual data collection takes place. In addition, it is advised to plan to use data analysis methods that are robust to missing data. An analysis is robust when confidence that mild to moderate violations of the technique's key assumptions will produce little or no bias, or distortion in the conclusions drawn about the population.

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

Form-level missing data refers to a respondent missing an entire PRO assessment for a given time-point (e.g., either the *ADSD* or the *ANSD* on a given day). In general, form-level data may be missing due to a respondent's early withdrawal from the study, the inability to evaluate an endpoint at a particular time-point, or non-compliance. Imputation is not recommended for *ADSD* or *ANSD* form-level missing data and instead scoring algorithms for the *ADSD* and *ANSD* have been constructed to account for missing data at the form level. Based on analyses exploring the impact of missed completions on scale reliability during the quantitative pilot study, a >50% rule will be employed for missing data at the form level for both measures. For example, the *ADSD* Weekly Score or *ANSD* Weekly Score will only be calculated if data for four or more days are available for that measure.

4.3.2 Item-level missing data

Sponsors may decide to allow respondents to skip individual items within the *ADSD* or *ANSD*. If respondents are allowed to skip items, missing data at the item level may be present.

Similar to section 4.3.1, a >50% rule will be employed for missing data at the item level with scores only calculated if data for four or more items in a given assessment are available, with the available item values summed and divided by the number of items available. If three or more items are missing, the assessment itself will be considered missing and will be treated as form-level missing data (handled as outlined in 4.3.1).

5.0 *ADSD/ANSD* PUBLICATIONS

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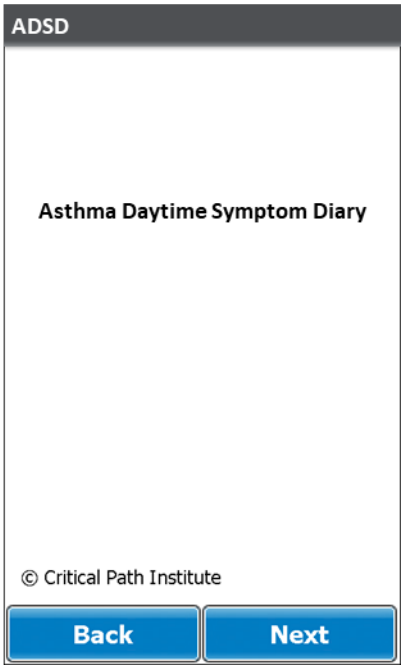
APPENDIX A: SCREEN SHOTS OF *ADSD* (FORMERLY *ADSD* EVENING DIARY) V1.0



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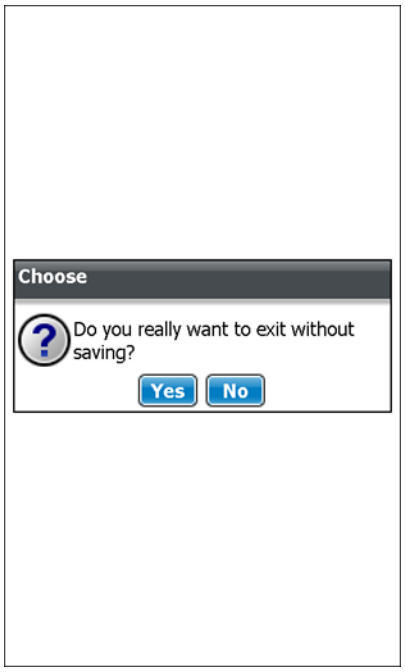

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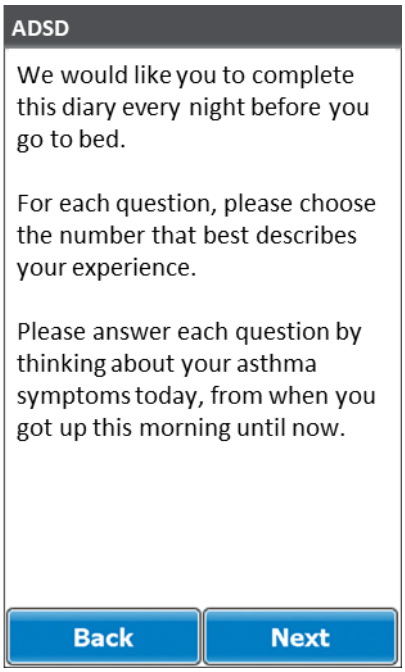

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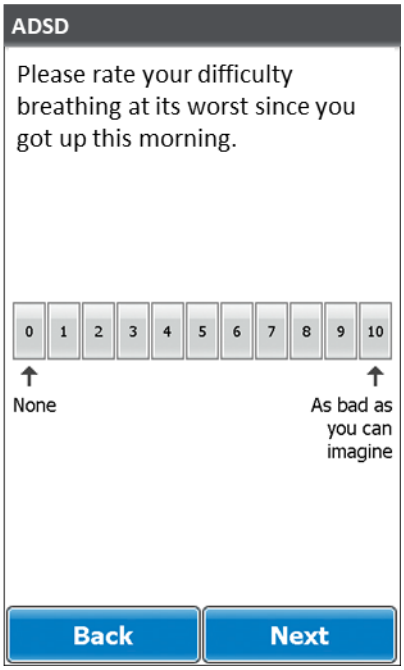

Screen 3

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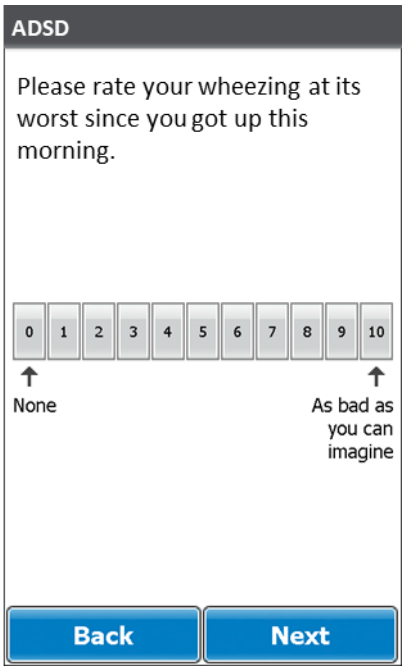

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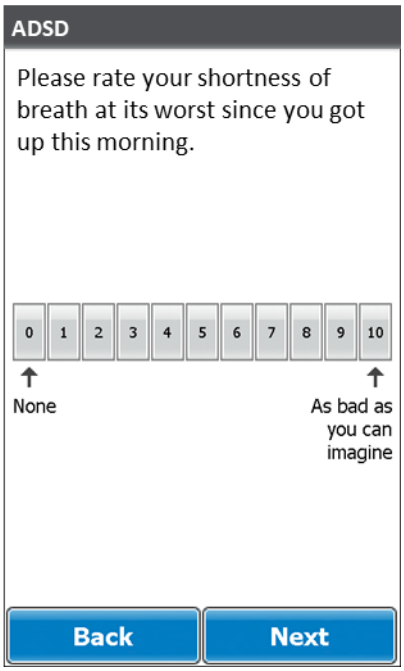

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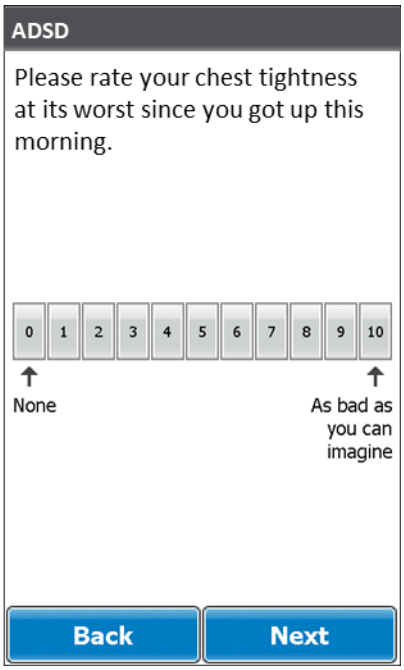

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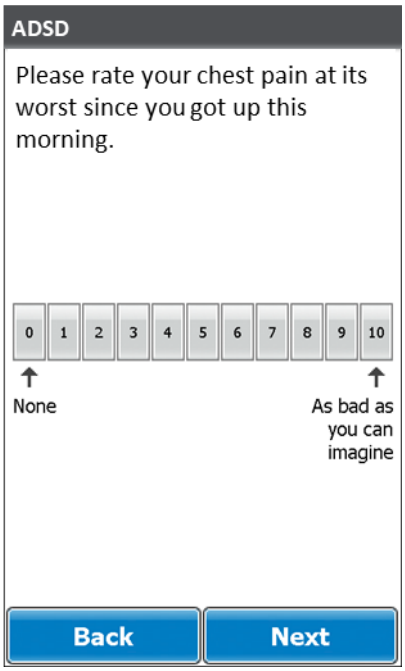

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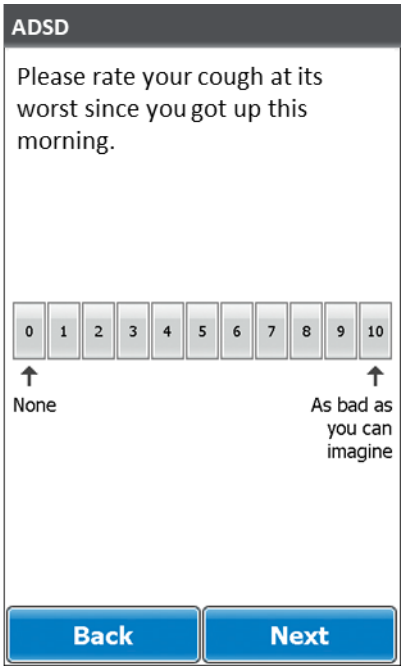
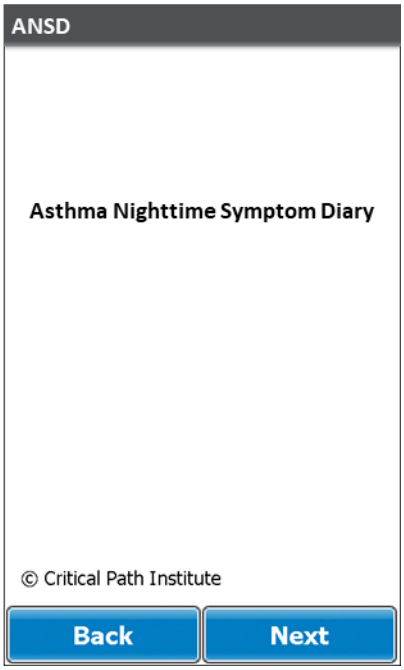


Screen 8

APPENDIX B: SCREEN SHOTS OF *ANSD* (FORMERLY *ADSD* MORNING DIARY) V1.0



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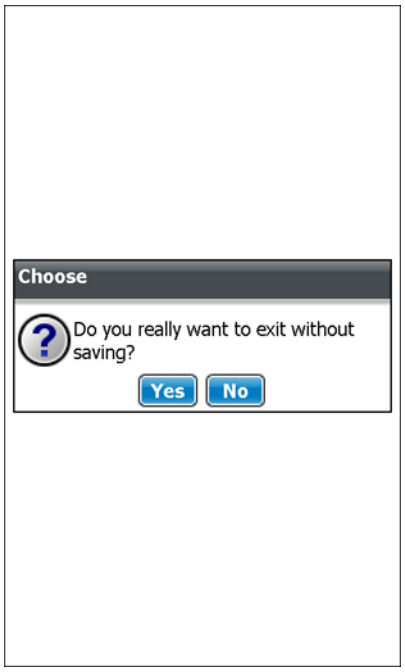

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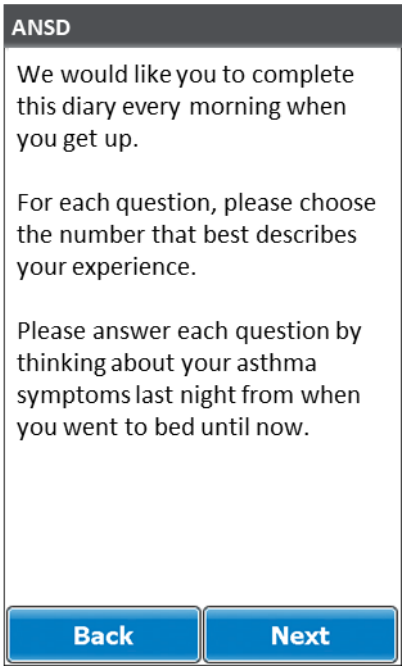

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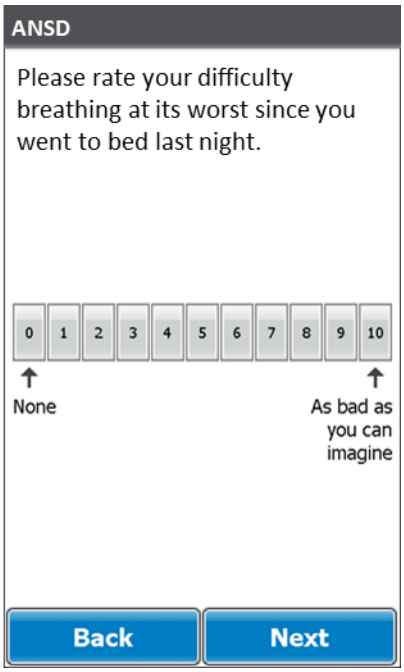
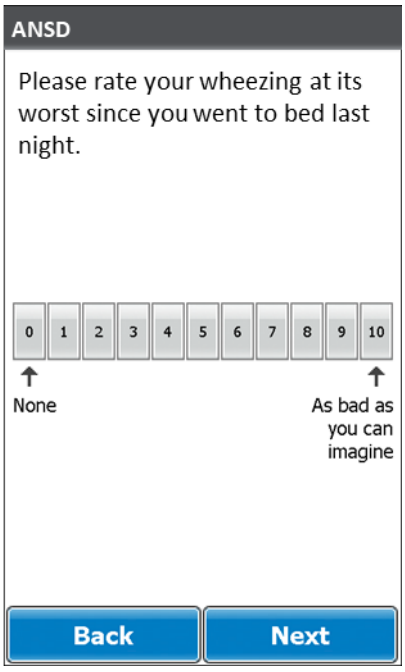
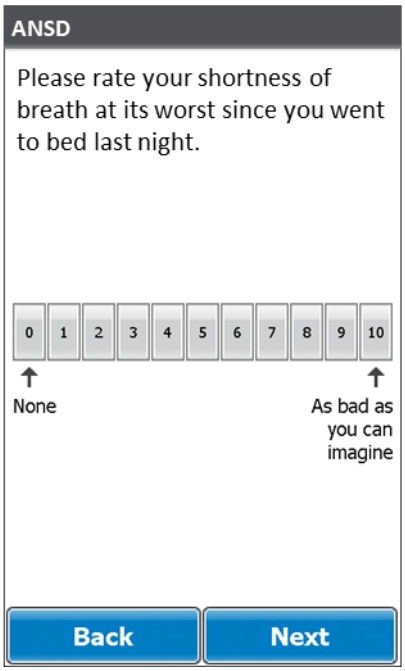


Screen 3

Message 2



Screen 4



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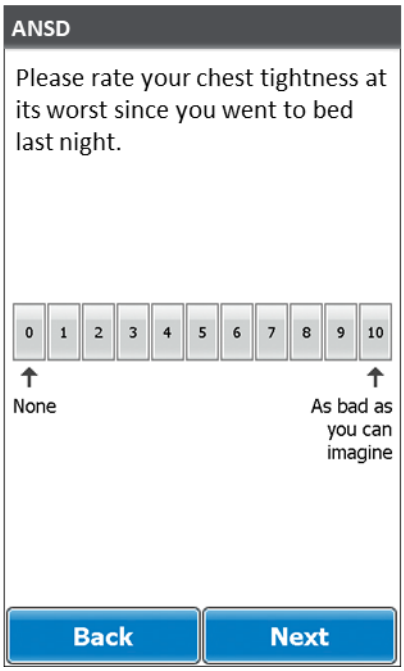

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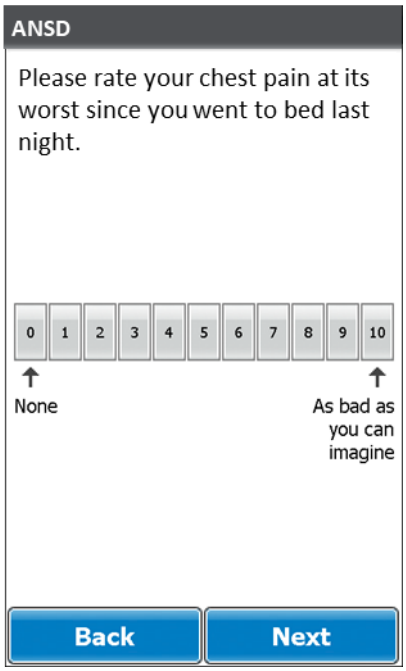

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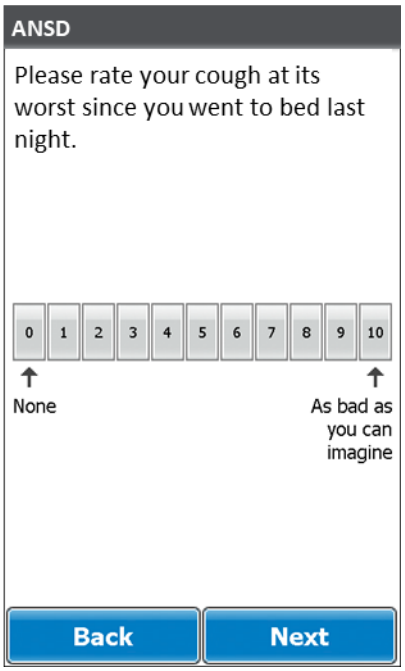

Screen 8

APPENDIX C: *ASTHMA DAYTIME SYMPTOM DIARY* (*ADSD*) V1.0 (PAPER FORMAT)

[INSTRUCTION 1] We would like you to complete this diary every night before you go to bed.

[INSTRUCTION 2] For each question, please choose the number that best describes your experience.

[INSTRUCTION 3] Please answer each question by thinking about your asthma symptoms today, from when you got up this morning until now.

[ITEM 1] Please rate your difficulty breathing at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 2] Please rate your wheezing at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 3] Please rate your shortness of breath at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 4] Please rate your chest tightness at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 5] Please rate your chest pain at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 6] Please rate your cough at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

APPENDIX D: *ASTHMA NIGHTTIME SYMPTOM DIARY* (*ANSD*) V1.0 (PAPER FORMAT)

[INSTRUCTION 1] We would like you to complete this diary every morning when you get up.

[INSTRUCTION 2] For each question, please choose the number that best describes your experience.

[INSTRUCTION 3] Please answer each question by thinking about your asthma symptoms last night from when you went to bed until now.

[ITEM 1] Please rate your difficulty breathing at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 2] Please rate your wheezing at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 3] Please rate your shortness of breath at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 4] Please rate your chest tightness at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 5] Please rate your chest pain at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 6] Please rate your cough at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

APPENDIX E: ITEM DEFINITION TABLES FOR THE *ASTHMA DAYTIME SYMPTOM DIARY* (*ADSD*) AND *ASTHMA NIGHTTIME SYMPTOM DIARY (ANSD)*

Note to the translator: These item definition tables are designed to provide you with detailed information about the intended concept of each item in *ADSD* and *ANSD*. 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 these item definition tables 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.**

Table E1. Item definition table for *Asthma Daytime Symptom Diary* (*ADSD*)

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Title: *Asthma Daytime Symptom Diary* (*ADSD*)	Symptom Diary - a daily record to keep track of asthma symptoms. Asthma is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation (GINA 2015) variable expiratory airflow = difficulty breathing air out of the lungs due to bronchoconstriction (airway narrowing), airway wall thickening, and increased mucus. Some variation in airflow can also occur in people without asthma, but it is greater in asthma. (2016 GINA pocket guide)	Alternative translations for: Diary: log, record Symptom: complaints Asthma Daytime Symptom Diary: diary of daytime symptoms – asthma Daytime: refers to the period from when the respondent woke up to the time when the respondent goes to bed. 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 parentheses.

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Instructions Sentence 1 (*ADSD*): We would like you to complete this diary every night before you go to bed.	This first instruction specifies the time frame when the diary is to be completed. The respondent should complete the diary before retiring to sleep every night.	Alternative translations for: Complete: fill in Every night before you go to bed: Every evening before you go to bed, before you go to bed, before you go to sleep, before going to bed Alternative translations for: Before you went to bed: (Hindi) “Go to bed” is understood by many readers as “go to sleep/fall asleep”. To avoid this confusion, it can be translated as “go to bed to sleep”. It sounds odd in English but is idiomatically appropriate in Hindi. (Russian) Before you go to sleep
Instructions Sentence 2 (*ADSD*): For each question, please choose the number that best describes your experience.	The second instruction asks respondents to select a number on the rating scale that best reflects their experience of their asthma symptoms during that day.	Alternative translations for: Question: Item Number: response option, figure Your experience: your asthma symptoms, your asthma experience, how your asthma felt. Describes: reflects, explains, represents
Instructions Sentence 3 (*ADSD* only): Please answer each question by thinking about your asthma symptoms today, from when you got up this morning until now.	For the evening assessment, the respondent is asked to consider the time frame from the last (morning) assessment to present time. The respondent is to complete each question thinking of his/her asthma symptoms experienced during the current day i.e. from when s/he filled in the diary when s/he got this morning up until now.	Alternative translations for: Your asthma symptoms: the symptoms that you had because of asthma

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Item 1: Please rate your difficulty breathing at its worst since you got up this morning.	Relevant symptom: Any type of breathing difficulty in general (e.g. wheezing, shortness of breath, heavy breathing), as opposed to item 3, which focuses on shortness of breath in particular.	a) How strong/severe was your difficulty breathing at its **worst** since you last completed the diary [this morning]. b) Rate the **worst** breathing difficulties you have had since you have completed the diary [this morning] Alternative translations for at its worst: At its most severe At its most intense At its strongest At its worst level At its highest level Greatest / Most severe breathing difficulty

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Response scale for item 1: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No breathing difficulty Worst possible difficulty (German) No breathing difficulties Worst possible breathing difficulties (Mandarin) No symptom The most severe symptom you can image (Italian) Could not have been greater/worse (Hindi) The worst you can imagine
Item 2: Please rate your wheezing at its worst since you got up this morning.	Wheezing: to breathe with difficulty and with a whistling sound Relevant symptom: a high-pitched whistle sound as you breathe through your mouth or nose.	Alternative translations for: Wheezing: whistling breathing sounds; whistling breath

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Response scale for item 2: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No wheezing Worst possible wheezing
Item 3: Please rate your shortness of breath at its worst since you got up this morning.	Shortness of breath refers to a feeling of difficult or labored breathing that is disproportionate to the patient's level of physical activity. Relevant symptom: dyspnea, breath is hard to catch.	No alternatives suggested.
Response scale for item 3: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No shortness of breath Worst possible shortness of breath

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Item 4: Please rate your chest tightness at its worst since you got up this morning.	Chest tightness: refers to a feeling of burning or fullness in the chest. Relevant symptom: constricting, squeezing feeling in the chest	Alternative translations for: Chest tightness: (Italian) Feeling of tightness Feeling of chest tightness
Response scale for item 4: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No tightness Worst possible tightness
Item 5: Please rate your chest pain at its worst since you got up this morning.	Chest pain: refers to any dull, aching pain in the thorax. Relevant symptom: any type of chest pain asthma patients may feel. This may be a dull ache or sharp, stabbing pain in the chest; it is sometimes associated with a burning sensation, too.	Alternative translations for: Your chest pain at its worst: the most intense/severe chest pain you had

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Response scale for item 5: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No chest pain Worst possible chest pain
Item 6: Please rate your cough at its worst since you got up this morning.	Relevant symptom: any form of coughing.	Alternative translations for: (Russian) Your cough at its worst: The most severe cough you had
Response scale for item 6: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No cough Worst possible cough

Table E2. Item definition table for *Asthma Nighttime Symptom Diary (ANSD)*

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Title: *Asthma Nighttime Symptom Diary* (*ANSD*)	Symptom Diary - a daily record to keep track of asthma symptoms. Asthma is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation (GINA 2015) variable expiratory airflow = difficulty breathing air out of the lungs due to bronchoconstriction (airway narrowing), airway wall thickening, and increased mucus. Some variation in airflow can also occur in people without asthma, but it is greater in asthma. (2016 GINA pocket guide)	Alternative translations for: Diary: log, record Symptom: complaints Asthma Nighttime Symptom Diary: diary of nighttime symptoms – asthma Nighttime: refers to the period of time from when the respondent goes to sleep to the time when the respondent wakes up, while the respondent should be sleeping. 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 parentheses.
Instructions Sentence 1 (*ANSD*): We would like you to complete this diary every morning when you get up.	This first instruction specifies the time frame when the diary is to be completed. The respondent should complete the diary upon getting up every morning, when waking from the usual sleep phase.	Alternative translations for: Complete: fill in Get up: wake up
Instructions Sentence 2 (*ANSD*): For each question, please choose the number that best describes your experience.	The second instruction asks respondents to select a number on the rating scale that best reflects their experience of their asthma symptoms during the previous night.	Alternative translations for: Question: Item Number: response option, figure Your experience: your asthma symptoms, your asthma experience, how your asthma felt. Describes: reflects, explains, represents

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Instructions Sentence 3 (*ANSD* only): Please answer each question by thinking about your asthma symptoms last night from when you went to bed until now.	For the morning assessment, the respondent is asked to consider the time frame from the last (evening) assessment to present time. The respondent is to complete each question thinking of his/her asthma symptoms experienced during the past night, i.e., from when s/he filled in the diary the previous evening before going to bed until the time of getting up in the morning	Alternative translations for: Your asthma symptoms: the symptoms that you had because of asthma From when you went to bed: From when you went to bed to sleep (Hindi) From when you went to sleep (Russian)
Item 1: Please rate your difficulty breathing at its worst since you went to bed last night.	Relevant symptom: Any type of breathing difficulty in general (e.g. wheezing, shortness of breath, heavy breathing), as opposed to item 3, which focuses on shortness of breath in particular.	a) How strong/severe was your difficulty breathing at its **worst** since you last completed the diary [last night]. b) Rate the **worst** breathing difficulties you have had since you have completed the diary [last night] Alternative translations for at its worst: At its most severe At its most intense At its strongest At its worst level At its highest level Greatest / Most severe breathing difficulty

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Response scale for item 1: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No breathing difficulty Worst possible difficulty (German) No breathing difficulties Worst possible breathing difficulties (Mandarin) No symptom The most severe symptom you can image (Italian) Could not have been greater/worse (Hindi) The worst you can imagine
Item 2: Please rate your wheezing at its worst since you went to bed last night.	Wheezing: to breathe with difficulty and with a whistling sound Relevant symptom: a high-pitched whistle sound as you breathe through your mouth or nose.	Alternative translations for: Wheezing: whistling breathing sounds; whistling breath

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Response scale for item 2: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No wheezing Worst possible wheezing
Item 3: Please rate your shortness of breath at its worst since you went to bed last night.	Shortness of breath refers to a feeling of difficult or labored breathing that is disproportionate to the patient's level of physical activity. Relevant symptom: dyspnea, breath is hard to catch.	No alternatives suggested.
Response scale for item 3: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No shortness of breath Worst possible shortness of breath

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Item 4: Please rate your chest tightness at its worst since you went to bed last night.	Chest tightness: refers to a feeling of burning or fullness in the chest. Relevant symptom: constricting, squeezing feeling in the chest	Alternative translations for: Chest tightness: (Italian) Feeling of tightness Feeling of chest tightness
Response scale for item 4: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No tightness Worst possible tightness
Item 5: Please rate your chest pain at its worst since you went to bed last night.	Chest pain: refers to any dull, aching pain in the thorax. Relevant symptom: any type of chest pain asthma patients may feel. This may be a dull ache or sharp, stabbing pain in the chest; it is sometimes associated with a burning sensation, too.	Alternative translations for: Your chest pain at its worst: the most intense/severe chest pain you had

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Response scale for item 5: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No chest pain Worst possible chest pain
Item 6: Please rate your cough at its worst since you went to bed last night.	Relevant symptom: any form of coughing.	Alternative translations for: (Russian) Your cough at its worst: The most severe cough you had
Response scale for item 6: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No cough Worst possible cough

ATTACHMENT 1: SUPPLEMENTARY ITEMS ASSESSING OTHER MEASUREMENT CONCEPTS V1.0

1.0 INTRODUCTION

The Asthma Working Group developed supplementary items to provide sponsors with standardized wording for measurement of optional relevant concepts associated with asthma that are often assessed in clinical trials. These supplementary (optional) items can be used in conjunction with the *ADSD* and *ANSD* and were designed to assess other measurement concepts including presence of mucus/phlegm, nighttime awakenings, activity limitations, and relief medication use. These items are not formally part of the *ADSD* or *ANSD* nor are they included as part of the scores derived from the *ADSD* or *ANSD*. These items are expected to be used as standalone items and intended to serve as standardized assessments of the respective measurement concepts for use by study sponsors in accordance with the objectives and design of the specific clinical study in question.

2.0 CONCEPTUAL FRAMEWORK

The conceptual framework for the supplementary items developed and tested alongside the *ADSD* and *ANSD* and representative of concepts commonly assessed by asthma symptom-based PRO measures is presented in Figure 1. These additional supplementary measurement concepts are intended to be scored separately from the *ADSD* and *ANSD*, as individual items.

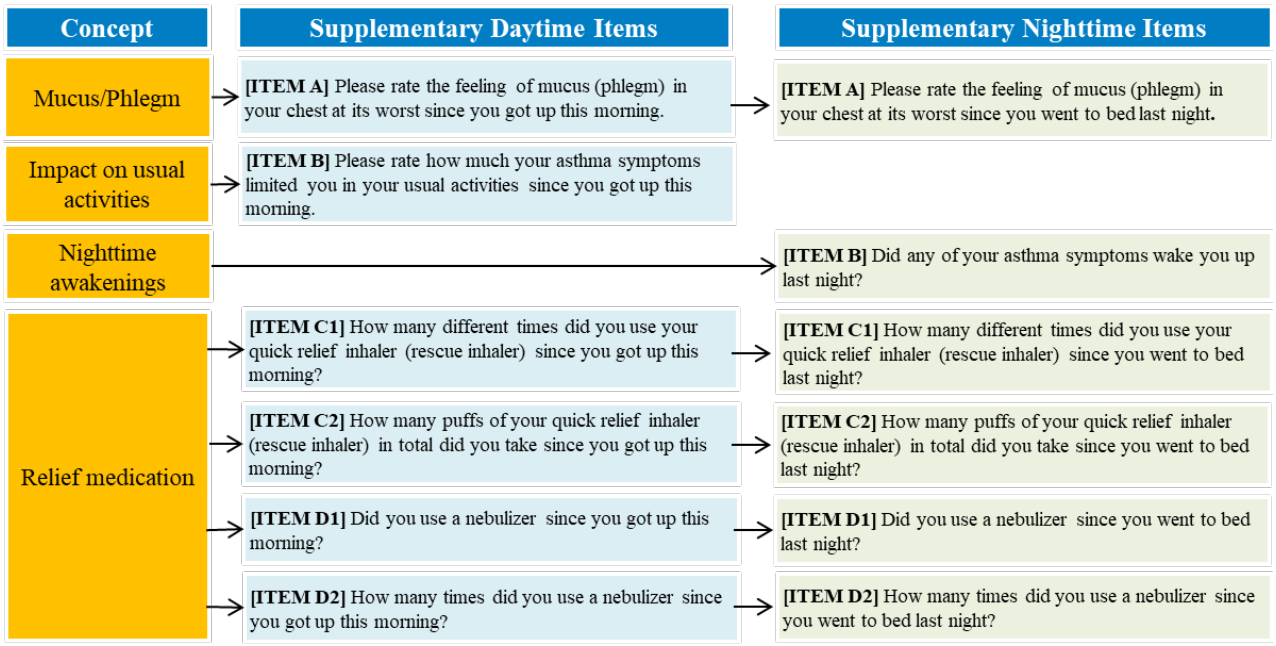

Figure 1. Supplementary measurement concepts (Optional)

3.0 ADMINISTRATION PROCEDURES

3.1 Modes of data collection

Like the *ADSD* and *ANSD*, the supplementary daytime and nighttime items were designed with electronic self-administration in mind. The quantitative pilot study utilized an electronic handheld device (i.e., smartphone) data collection approach.

3.1.1 Paper and pencil forms

US English paper and pencil formats of the supplementary daytime and nighttime items were developed and tested during cognitive interviews designed to evaluate the respondent understanding and interpretation of the *ADSD* and *ANSD* (round 1 only).

3.1.2 Handheld devices

The supplementary daytime and nighttime items were developed and migrated to an electronic handheld device format in accordance with industry best practices (Critical Path Institute ePRO Consortium 2014a; Critical Path Institute ePRO Consortium 2014b; Critical Path Institute ePRO Consortium 2014c). Usability of the supplementary items has been explored through qualitative (i.e., cognitive interviews and exit interviews) research.

3.1.3 Tablet devices

The supplementary daytime and nighttime items have not yet been implemented on tablet platforms.

3.1.4 Web-based applications

The supplementary daytime and nighttime items have not yet been implemented on web-based platforms.

3.1.5 Interactive voice response (IVR) systems

The supplementary daytime and nighttime items have not yet been implemented on IVR systems.

3.2 General principles for PRO measure completion

The general principles for completion of the supplementary daytime and nighttime items are as follows:

- Supplementary daytime items should be completed every evening between 7pm and 1am for the duration of the study period outlined in the protocol.
- Supplementary nighttime items should be completed every morning between 6am and 12pm for the duration of the study period outlined in the protocol.
- The supplementary daytime and nighttime items are designed as PRO items and should be completed only by the intended respondent (i.e., a person with asthma). Observers, including (but not limited to) clinicians and spouses/parents/caregivers should not complete the supplementary daytime and nighttime items on behalf of the intended respondent.

- When administered alongside the *ADSD* and/or the *ANSD*, supplementary daytime and nighttime items should be presented after presentation of the *ADSD* and *ANSD*, respectively.

3.3 Training

In general, no specific training is required to complete the supplementary daytime and nighttime items since the instructions are self-explanatory.

3.3.1 Investigator training

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

- Great care should be taken to avoid messages (verbal or otherwise) that might influence respondents 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 respondent may respond to an item.
- Investigator should not answer questions of interpretation or clarification for supplementary daytime and nighttime 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 item 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 to be avoided.

3.3.2 Respondent training

Study personnel should ensure that the following general information about the supplementary daytime and nighttime items is provided to respondents:

- Respondents should be informed that the supplementary daytime items are to be completed every evening between 7pm and 1am. Respondents should be informed that when completing these items, they will be asked to reflect on the time period “since you woke up this morning.”
- Respondents should be informed that the supplementary nighttime items are to be completed every morning between 6am and 12pm. Respondents should be informed that when completing these items, they will be asked to reflect on the time period “since you went to bed last night.”
- Respondents should be instructed to complete the items on their own without the help of others and should answer the questions based on their own experience of asthma.
- Respondents should be instructed to be honest and as accurate as possible in their responses.

3.4 Instructions for administration by study/clinic staff

The supplementary daytime and nighttime items are field-based assessments designed to be completed outside of a clinic setting. Therefore, administration by study staff will not be possible and interviewer administration is not recommended

4.0 SUPPLEMENTARY DAYTIME ITEMS (PAPER FORMAT)

[ITEM A] Please rate the feeling of mucus (phlegm) in your chest at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM B] Please rate how much your asthma symptoms limited you in your usual activities since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[INSTRUCTION C]

The next question asks about your use of your quick relief inhaler (rescue inhaler) since you got up this morning. Your quick relief inhaler is the inhaler that you use when you experience asthma symptoms.

We want to know about the number of different times you have used your quick relief inhaler and the total number of puffs you have taken.

Example: If you took your inhaler at two different times since you got up this morning (e.g., 2pm & 4pm) and took two puffs each time, please answer the number of different times as 2 and the total number of puffs as 4.

[ITEM C1] How many different times did you use your quick relief inhaler (rescue inhaler) since you got up this morning?

☐ Insert number of times

[ITEM C2] How many puffs of your quick relief inhaler (rescue inhaler) in total did you take since you got up this morning?

☐ Insert total number of puffs

[INSTRUCTION D]

The next question asks about your use of your nebulizer since you got up this morning. A nebulizer is a machine that creates a mist of medicine, which is then breathed in through a mask or mouthpiece.

We want to know about the number of times you have used your nebulizer today if at all.

[ITEM D1] Did you use a nebulizer since you got up this morning?

☐ Yes

☐ No

[ITEM D2] How many times did you use a nebulizer since you got up this morning?

☐ Insert number of times

5.0 SUPPLEMENTARY NIGHTTIME ITEMS (PAPER FORMAT)

[ITEM A] Please rate the feeling of mucus (phlegm) in your chest at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM B] Did any of your asthma symptoms wake you up since you went to bed last night?

☐ Yes

☐ No

[INSTRUCTION C]

The next question asks about your use of your quick relief inhaler (rescue inhaler) since you went to bed last night. Your quick relief inhaler is the inhaler that you use when you experience asthma symptoms.

We want to know about the number of different times you have used your quick relief inhaler and the total number of puffs you have taken.

Example: If you took your inhaler at two different times since you went to bed last night (e.g., 2am and 4am) and took two puffs each time, please answer the number of different times as 2 and the total number of puffs as 4.

[ITEM C1] How many different times did you use your quick relief inhaler (rescue inhaler) since you went to bed last night?

☐ Insert number of times

[ITEM C2] How many puffs of your quick relief inhaler (rescue inhaler) in total did you take since you went to bed last night?

☐ Insert total number of puffs

[INSTRUCTION D]

The next question asks about your use of your nebulizer since you went to bed last night. A nebulizer is a machine that creates a mist of medicine, which is then breathed in through a mask or mouthpiece.

We want to know about the number of times you have used your nebulizer last night, if at all.

[ITEM D1] Did you use a nebulizer since you went to bed last night?

☐ Yes

☐ No

[ITEM D2] How many times did you use a nebulizer since you went to bed last night?

☐ Insert number of times

6.0 ITEM DEFINITION TABLES

Note to the translator: These item definition tables are designed to provide you with detailed information about the intended concept of the supplementary daytime and nighttime items. 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 these item definition tables 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.**

Table 1. Item definition table for supplementary daytime items

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Item A: Please rate the feeling of mucus (phlegm) in your chest at its worst since you got up this morning.	Relevant symptom: chest mucus that cannot be coughed up, chest congestion due to mucus/phlegm. Mucus: refers to the viscous, slippery secretions of mucous membranes and glands, containing mucin, white blood cells, water, inorganic salts, and exfoliated cells. Phlegm: refers to thick, sticky, stringy mucus secreted by the mucous membrane of the respiratory tract.	Use of one single term for “mucus” and “phlegm” in languages where one single term is available. This is the case in French where “mucus” is usually used and Italian where only “phlegm” is appropriate: Alternative translations for In your chest: in your airways in the lungs in the bronchial tubes feeling of mucus/phlegm on your chest: excess of mucus in the chest lungs congested with mucus

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Response scale for item A: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No feeling of mucus (phlegm) on your chest Worst possible feeling of Mucus (phlegm) on your chest
Item B Please rate how much your asthma symptoms limited you in your usual activities since you got up this morning.	Asking about the level of limitation the subject experienced when doing their usual activities, and at the same time instructing the patient about the way to respond and the relevant time period to consider.	Alternative translations for: Limited: restricted, interfered with Usual activities: daily routine activities
Response scale for item B 0 Not at all 1 2 3 4 5 6 7 8 9 10 As much as you can imagine	"As much as you can imagine" refers to the most extreme degree, the respondent couldn't be more limited.	(Hindi) None - The worst one can imagine As much as you can imagine: very much

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Instruction C: The next question asks about your use of your quick relief inhaler (rescue inhaler) since you got up this morning. Your quick relief inhaler is the inhaler that you use when you experience asthma symptoms. We want to know about the number of different times you have used your quick relief inhaler and the total number of puffs you have taken. Example: If you took your inhaler at two different times since you got up this morning (e.g., 2pm & 4pm) and took two puffs each time, please answer the number of different times as 2 and the total number of puffs as 4.	Instruction announcing the next item, anticipating what this next item will be asking (use of a specific medication since this morning), and explaining a technical term (rescue inhaler) used. A rescue inhaler refers to a device used to treat a sudden asthma attack Experience: refers to feel, undergo or suffer It is explained that the rescue inhaler is the device that the patient uses when s/he has asthma symptoms.	Alternative translations for: Experience: have Rescue inhaler: Quick relief inhaler When needed inhaler Emergency spray Inhaler Pocket inhaler Reliever medication Quickly-acting expanding medication Short-acting saving inhalator. Doses/inhalations of your medication, which give you fast relief (or helps breath easily) Inhalation of drug that helps you to breathe
Item C1: How many different times did you use your quick relief inhaler (rescue inhaler) since you got up this morning?	Question related to instruction 4 asking how often a specific medication was administered since this morning.	Rescue inhaler: Quick relief inhaler When needed inhaler Emergency spray Inhaler Pocket inhaler Reliever medication Quickly-acting expanding medication Short-acting saving inhalator. Doses/inhalations of your medication, which give you fast relief (or helps breath easily) Inhalation of drug that helps you to breathe

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Response scale for item C1: Insert number of times	The patient is asked to write down the number of times s/he used his/her rescue inhaler.	Alternatives for number: "no" # Alternative for times: Separate times (Italian)
Item C2: How many puffs of your quick relief inhaler (rescue inhaler) in total did you take since you got up this morning?	Puff: refers to a released inhaler dose	Alternatives for puffs: breaths
Response scale for item C2: Insert number of puffs	The patient is asked to 'enter' or write down the number of puffs s/he took from his/her rescue inhaler.	Alternatives for number: "no" #
Instruction D: The next question asks about your use of your nebulizer since you got up this morning. A nebulizer is a machine that creates a mist of medicine, which is then breathed in through a mask or mouthpiece. We want to know about the number of times you have used your nebulizer last night if at all.	Instruction announcing the next item, anticipating what this next item will be asking (use of a specific device since this morning), and explaining a technical term (nebulizer) used. A nebulizer is a machine that changes liquid medicine into a fine mist. This can then be inhaled through a mask or mouthpiece. Nebulizers are used to give high doses of reliever medicine usually in an emergency.	Alternatives for nebulizer: Vaporizer Atomizer Breathing machine Pump
Item D1: Did you use a nebulizer since you got up this morning?	Question asking the participant whether they used their nebulizer since they got up this morning.	Alternatives for nebulizer: Vaporizer Atomizer Breathing machine Pump
Response scale for item D1: Yes No	Positive/negative answers	No alternatives suggested.

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Item D2: How many times did you use a nebulizer since you got up this morning?	Question asking the participant the number of times that they have used their nebulizer since they got up this morning.	Alternatives for number: "no" # Alternatives for nebulizer: Vaporizer Atomizer Breathing machine Pump
Response scale for item D2: Insert number of times	The patient is asked to 'enter' or write down the number times they used nebulizer.	Alternatives for number: "no" #

Table 2. Item definition table for supplementary nighttime items

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Item A: Please rate the feeling of mucus (phlegm) in your chest at its worst since you went to bed last night.	Relevant symptom: chest mucus that cannot be coughed up, chest congestion due to mucus/phlegm. Mucus: refers to the viscous, slippery secretions of mucous membranes and glands, containing mucin, white blood cells, water, inorganic salts, and exfoliated cells. Phlegm: refers to thick, sticky, stringy mucus secreted by the mucous membrane of the respiratory tract.	Use of one single term for "mucus" and "phlegm" in languages where one single term is available. This is the case in French where "mucus" is usually used and Italian where only "phlegm" is appropriate: Alternative translations for In your chest: in your airways in the lungs in the bronchial tubes feeling of mucus/phlegm on your chest: excess of mucus in the chest lungs congested with mucus

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Response scale for item A: 0 None 1 2 3 4 5 6 7 8 9 10 As bad as you can imagine	Anchor points indicating the upper and lower limits of the response scale As bad as you can imagine: refers to the most extreme degree	Alternative translations for the response choices: No feeling of mucus (phlegm) on your chest Worst possible feeling of Mucus (phlegm) on your chest
Item B: Did any of your asthma symptoms wake you up since you went to bed last night?	Question asking whether the respondent woke up during usual sleeping time on account of asthma symptoms Awakenings: refers to the act of awaking from sleep	Wake you up during the night Wake you from your sleep
Response scale for item B: Yes No	Positive/negative answers	No alternatives suggested.

Original English Item	Key Concepts and Explanations	Possible Wordings and Synonyms
Response scale for item B (evening diary): 0 Not at all 1 2 3 4 5 6 7 8 9 10 As much as you can imagine	"As much as you can imagine" refers to the most extreme degree, the respondent couldn't be more limited.	(Hindi) None - The worst one can imagine As much as you can imagine: very much
Instruction C: The next question asks about your use of your quick release inhaler (rescue inhaler) since you went to bed last night. Your quick relief inhaler is the inhaler that you use when you experience asthma symptoms. We want to know about the number of different times you have used your quick relief inhaler and the total number of puffs you have taken. Example: If you took your inhaler at two different times since you went to bed last night (e.g., 2am and 4am) and took two puffs each time, please answer the number of different times as 2 and the total number of puffs as 4.	Instruction announcing the next item, anticipating what this next item will be asking (use of a specific medication since going to bed last night), and explaining a technical term (rescue inhaler) used. A rescue inhaler refers to a device used to treat a sudden asthma attack Experience: refers to feel, undergo or suffer It is explained that the rescue inhaler is the device that the patient uses when s/he has asthma symptoms.	Alternative translations for: Experience: have Rescue inhaler: Quick relief inhaler When needed inhaler Emergency spray Inhaler Pocket inhaler Reliever medication Quickly-acting expanding medication Short-acting saving inhalator. Doses/inhalations of your medication, which give you fast relief (or helps breath easily) Inhalation of drug that helps you to breathe

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Item C1: How many different times did you use your quick relief inhaler (rescue inhaler) since you went to bed last night?	Question related to instruction 4 asking how often a specific medication was administered since going to bed last night.	Rescue inhaler: Quick relief inhaler When needed inhaler Emergency spray Inhaler Pocket inhaler Reliever medication Quickly-acting expanding medication Short-acting saving inhalator. Doses/inhalations of your medication, which give you fast relief (or helps breath easily) Inhalation of drug that helps you to breathe
Response scale for item C1: Insert number of times	The patient is asked to write down the number of times s/he used his/her rescue inhaler.	Alternatives for number: “no” # Alternative for times: Separate times (Italian)
Item C2: How many puffs of your quick relief inhaler (rescue inhaler) in total did you take since you went to bed last night?	Puff: refers to a released inhaler dose	Alternatives for puffs: breaths
Response scale for item C2: Insert number of puffs	The patient is asked to ‘enter’ or write down the number of puffs s/he took from his/her rescue inhaler.	Alternatives for number: “no” #

Original English Item	**Key Concepts and Explanations**	**Possible Wordings and Synonyms**
Instruction D: The next question asks about your use of your nebulizer since you went to bed last night. A nebulizer is a machine that creates a mist of medicine, which is then breathed in through a mask or mouthpiece. We want to know about the number of times you have used your nebulizer last night if at all.	Instruction announcing the next item, anticipating what this next item will be asking (use of a specific device within since going to bed last night), and explaining a technical term (nebulizer) used. A nebulizer is a machine that changes liquid medicine into a fine mist. This can then be inhaled through a mask or mouthpiece. Nebulizers are used to give high doses of reliever medicine usually in an emergency.	Alternatives for nebulizer: Vaporizer Atomizer Breathing machine Pump
Item D1: Did you use a nebulizer since you went to bed last night?	Question asking the participant whether they used their nebulizer since they went to bed last night.	Alternatives for nebulizer: Vaporizer Atomizer Breathing machine Pump
Response scale for item D1: Yes No	Positive/negative answers	No alternatives suggested.
Item D2: How many times did you use a nebulizer since you went to bed last night?	Question asking the participant the number of times that they have used their nebulizer since they went to bed last night.	Alternatives for number: “no” # Alternatives for nebulizer: Vaporizer Atomizer Breathing machine Pump
Response scale for item D2: Insert number of times	The patient is asked to ‘enter’ or write down the number times they used nebulizer.	Alternatives for number: “no” #