Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000128: Symptom Assessment for Bronchiectasis (SABRE)
Letter of Intent

Administrative Structure:

Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information not contained within the cover letter.

This clinical outcome assessment (COA) Qualification Letter of Intent (LOI) is being submitted under the qualification grant, U01FD006687-01, awarded to Insmed Inc. in support of the development of a patient-reported outcome (PRO) for use as a declared endpoint in clinical trials assessing the efficacy and safety of anti-infective therapies for non-cystic fibrosis bronchiectasis (NCFBE) with and without non-tuberculous mycobacterial (NTM) lung infection. The PRO instrument to be developed in this process has been named the ***Symptom Assessment for Bronchiectasis*** **(SABRE).**

The investigators/leadership team for the SABRE instrument development activities of the U01 grant award is as follows:

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Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of symptoms, limitations in performance of daily activities).

The concept(s) of interest (COI) to be assessed with the SABRE will focus on presence and severity of key NCFBE-related symptoms, which will be identified through a comprehensive qualitative development program. The qualitative development program will also determine the most

appropriate response metric (e.g. severity vs. frequency or duration) and recall period (daily diary vs. longer recall) for assessment of key patient-relevant NCFBE symptoms. The qualitative development will include patient concept elicitation interviews to identify the specific elements of this COI, and subsequent patient cognitive interviews to refine the instrument content and its conceptual framework.

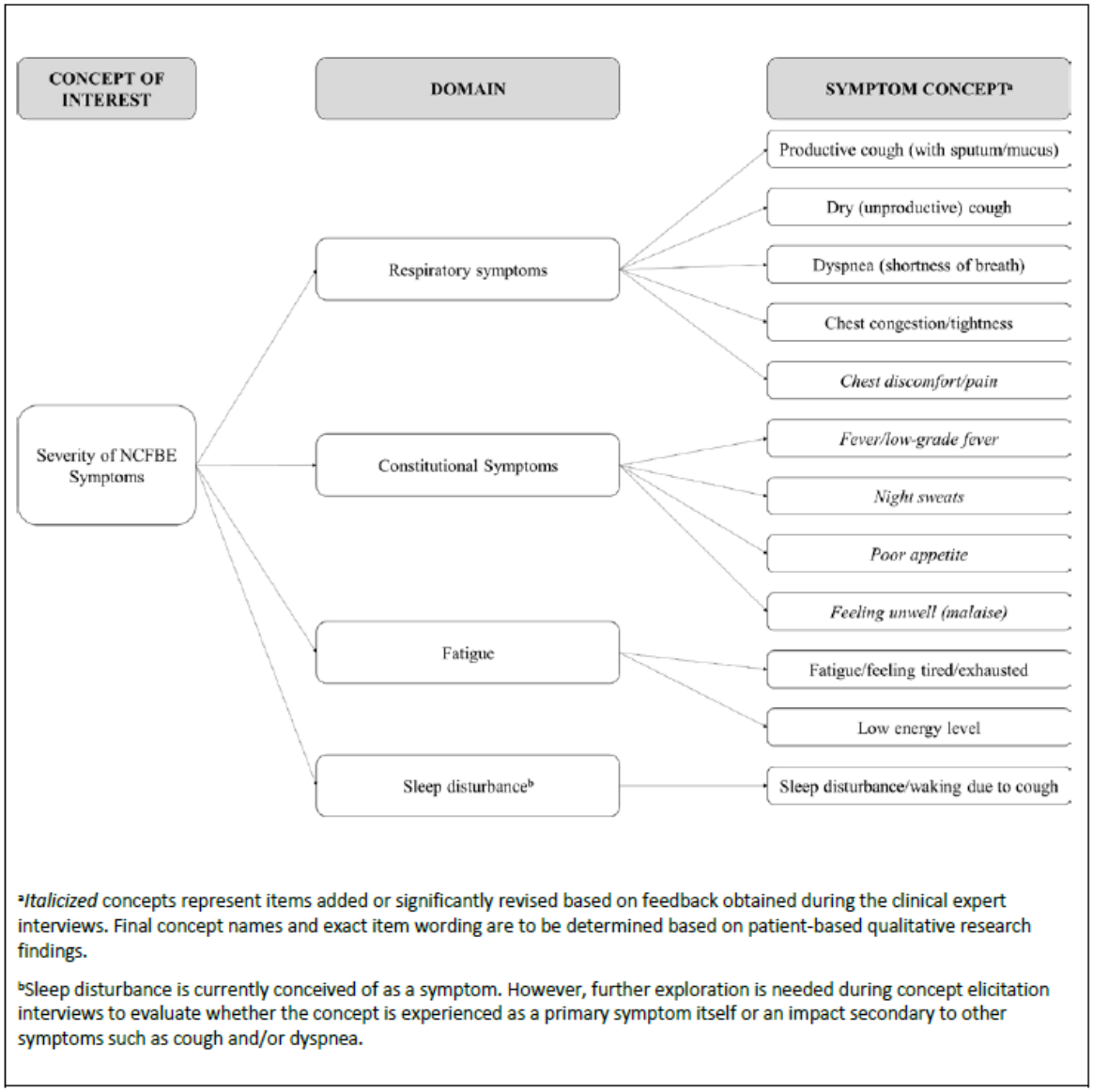
The homogeneity of COI between the NTM and non-NTM subpopulations will be evaluated during these qualitative instrument development activities. If small differences are detected in the key symptom concepts between these populations, then an NTM-specific submodule will be developed. If major differences are detected in symptom presentation between these populations during the concept elicitation process, then an NTM-specific PRO will be developed. Based on preliminary and ongoing research, including literature review and discussions with NCFBE clinical experts, we anticipate the conceptual framework to include respiratory symptoms, such as dyspnea and cough, as well as non-respiratory symptoms, such as fatigue. However, as stated, the analysis of qualitative patient interviews will elucidate the specific symptom concepts to be represented in the SABRE item content.

Provide a conceptual framework for the COA(s)

A preliminary/hypothesized conceptual framework for the SABRE instrument has been developed based on a targeted review of published quality of life-focused literature in NCFBE and relevant PRO instrument-related publications in this therapeutic area. The framework has been augmented via input from interviews with five NCFBE clinical experts. The preliminary conceptual framework is provided below (**Figure 1**).

This preliminary conceptual framework will be further revised and refined based on direct input from patients with NCFBE gathered through the qualitative development program (i.e., concept elicitation, item generation, and cognitive interviews) to detail the key symptom concepts relevant to patients, and the relationships between the draft items, domain, and concepts of the SABRE instrument.

Figure 1. Preliminary Conceptual Framework



[a]*Italicized* concepts represent items added or significantly revised based on feedback obtained during the clinical expert interviews. Final concept names and exact item wording are to be determined based on patient-based qualitative research findings.

[b]Sleep disturbance is currently conceived of as a symptom. However, further exploration is needed during concept elicitation interviews to evaluate whether the concept is experienced as a primary symptom itself or an impact secondary to other symptoms such as cough and/or dyspnea.

Context of Use for COA Qualification:

Targeted study population including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups).

The SABRE is intended to assess disease-related symptoms among adult patients with NCFBE, with or without NTM infection.

The study population participating in the development of the instrument is intended to have the following characteristics, which have been selected to align broadly with common sampling criteria typically employed in clinical trials of NCFBE treatments:

- Baseline symptom severity: All levels of severity and disease activity

- Patient demographics: Adults 21 years old or older, with sex, race, and ethnicity sampled approximately proportional to representation in the overall NCFBE population in the United States
- Comorbidities: NTM infection sampled in a manner approximately proportional to NTM infection prevalence within the NCFBE population
- Language/culture group: General United States population; English speaking

As detailed in this LOI, in the context of the COA Qualification Grant #U01FD006687-01, and in prior communication with the FDA, the planned qualitative and psychometric instrument development activities will be conducted in such a way as to clarify whether the symptom experience of NCFBE patients with comorbid NTM infection differs from those without NTM infection to the degree that the two groups represent distinct COUs for the purposes of PRO measurement. Based on the evidence gathered during instrument development, and in consultation with the FDA qualification review team, it is expected that the stated COU may be refined accordingly prior to submission of the full qualification package.

***Targeted study design and statistical analysis plan (includes the role of the planned COA in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate*).**

Once developed and qualified, it is anticipated that the endpoint (e.g., change in NCFBE symptom severity/frequency) derived from patients' SABRE responses may be used to quantify treatment benefit in clinical trials evaluating experimental treatments for NCFBE:

- as either a primary, co-primary or secondary endpoint to support label claims from randomized controlled clinical trials,
- as a secondary or exploratory endpoint in randomized controlled clinical trials, or
- to quantify effectiveness of treatment in open label trials and/or observational research.

Depending on the number of arms in the trial, it is anticipated that comparisons may be made using SABRE-derived endpoints between the experimental treatment and both placebo arms or active comparator arms based on the nature of the therapy.

We anticipate that the specific study design and endpoint selection/positioning within the measurement hierarchy will be determined by future study sponsors with input and guidance from appropriate regulatory agencies. As no specific study protocol exists yet for a NCFBE treatment trial utilizing the SABRE to support endpoint measurement, no formal statistical analysis plan is available at this time.

Applicable study settings for future clinical trials

- ***Geographic location with language/culture groups***
  The initial PRO development and testing will be conducted with English-speaking patients in North America (primarily the United States, with potential supplementation from Canada-based sites if deemed necessary based on study recruitment rates). A formal translatability assessment will be conducted as part of the planned qualitative development process. It is expected that additional translation and cultural adaptation processes will be completed prior to use in other languages and cultural groups (e.g., U.S. Spanish) within this geographic region or in trial settings outside of the U.S. and Canada.

- ***Other study setting specifics (e.g., inpatient versus outpatient)***
  The target population is adult patients (21 years and older) with NCFBE who are being treated in an ambulatory setting.

COA Type: Patient Reported Outcome (PRO)

Section 6: Summary of COA Development