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Qualitative Interviews to Develop the MACrO₂ Patient-Reported Outcome Measure in Treatment-Refractory MAC Lung Disease (TR-MAC-LD)

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INTRODUCTION

- Nontuberculous mycobacterial (NTM) lung disease caused by *Mycobacterium avium* complex (MAC-LD) is a chronic infectious disease resulting in significant morbidity and mortality and impacts on patients' health-related quality of life (HRQoL). Symptoms vary greatly across patients (e.g., cough, dyspnea, fatigue, hemoptysis, night sweats, weight loss), and symptom presentation is directly related to the individual based on underlying lung disease and other comorbid conditions.¹
- The FDA encourages the use of patient-reported outcome (PRO) measures in clinical trial endpoints as a way to incorporate the patient experience in drug development programs.²
- PROs have been developed for MAC-LD and similar conditions. These measures have been preliminarily validated,^{3,4} but they demonstrated lower sensitivity in patients with treatment-refractory MAC lung disease (TR-MAC-LD), likely due to irreversible underlying lung damage.⁴ Use of non-validated PROs in MAC-LD has yielded inconsistent and unreliable results.^{5,6}
- We followed FDA PRO Development Guidance to develop and test a new PRO measure for use in this population.

All unique symptom concepts were reported by the 17th CE interview, and by the 11th CD interview; as no new symptoms were reported in the final 25% of interviews, saturation of concept was considered to have been achieved.

RESULTS (continued)

The top symptoms reported across both CE and CD interviews are in Table 2, along with example patient quotes. Other symptoms reported across
the two interview studies included wheezing, chest pain, lack of appetite, and unexplained weight loss.

Table 2. Top Reported Symptoms Across Studies with Example Quotes

Symptom Concont	Total n (%) Reporting		Example Patient Quates	
Symptom Concept	CE (N=22)	CD (N=14)		
Any couch (with or			CE 001-008: "Well, at one point, I asked my doctor if she could please help with some kind of cough medicine because I	
without sputum)	18 (82%)	14 (100%)	coughed so hard and so much that, I mean, my throat got raw and sometimes you'd even throw up, you cough so much.	
			The coughing, I think, over the years, is the most annoying."	
Cough <u>with</u> sputum (dry	16 (73%)	12 (86%)	CD 002-101: "I need to get rid of the phlegm, and it's usually fairly productive it usually does mean phlegm at night	
cough)	10 (7370)	12 (00 /0)	when I'm in bed, you know, it just kind of fills the back of my throat, the phlegm, and down my throat."	
Fatigue / tiredness	13 (59%)	13 (93%)	CD 001-101: "Even when I do get up, and I do stuff, I get tired a whole lot easier and quicker than before I got this."	
Cough <u>without</u> sputum	13 (59%)	12 (86%)	CD 003-157: "like you get when you're having an allergy attack, you know, just that cough, cough, cough. There's no	
			phlegm, there's nothing you need to cough up. It's just irritating."	
Shortness of broath	10 (45%)	13 (93%)	CE 001-003: "I was trying to wash some dishes earlier this morning and I got real short of breath Yesterday we were	
Shormess of bream			going to walk out in the yard and I just couldn't do it."	
Chest congestion	9 (41%)	10 (71%)	CE 001-001: "Well, in my case, it's just a lot of rattling around in your chest, you can feel the congestion in your chest. I	
			just can't bring it up to try to get it out, so it just constantly stays there in my chestalways trying to clear."	
Coughing up blood	8 (36%)	8 (57%)	CE 002-005: 'usually when I've been coughing all day long and there would be little flecks of blood in the sputum, and	
			sore throat, but by the next day, it had passed, and we start all over again."	
Night Sweats / Unusual	8 (36%)	8 (57%)	CD 001-103: "you wake up and sometimes you have to get up and change your clothes, they're so wet, you're sopping	
Sweating			wet."	

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- 1.Identify common clinical symptom experiences among TR-MAC-LD to inform development of a new PRO for use in this population
- 2.Evaluate the content validity of the novel PRO, including clarity of the items, recall period, and response scale

METHODS

Study Design and Population

Objectives

- This study was conducted in 2 stages (concept elicitation [CE] and cognitive debriefing [CD]) in which each patient completed a single, semi-structured qualitative telephone interview and a selection of self-administered questionnaires
- Adult patients with a current diagnosis of TR-MAC-LD completed an interview in English that was audio-recorded with patient permission
- Patients were recruited from 2 clinical sites in the US—The University of Texas at Tyler (UT Tyler), and the Oregon Health and Science University (OHSU)—and through a patient advocacy group, NTMir
- CE interviews were conducted with patients to obtain information on their symptoms. A new measure—the MACrO₂ PRO—was developed and then tested in the CD interviews, and modifications were made based on patient feedback
- Trained interviewers from Evidera conducted all interviews using semi-structured IRB-approved interview guides (Figure 1)
- Interviews were transcribed for analysis using ATLAS.ti

Figure 1. General Flow of the CE and CD Interview Guides

CD = cognitive debriefing; CE = concept elicitation.

- Based on the top symptoms reported in the CE interviews, and input from clinical experts, the draft MACrO₂ PRO was developed with 7 symptom items (cough with phlegm, mucus, or sputum; dry cough [no phlegm, mucus, or sputum]; chest congestion; coughing up blood; shortness of breath or difficulty taking a deep breath; fatigue or tiredness; and night sweats or unusual sweating). One additional item was also created for participants to identify the symptom that is most important to them to improve; this item is intended to only be administered at baseline in clinical trials.
- CD interviews were conducted to test the novel PRO. Overall, participants demonstrated good understanding of the items, instructions, recall period, and response scale. Minor revisions were made based on patient feedback during the first round of CD interviews, including adding a definition of "chest congestion" ("needing to clear mucus or feeling pressure or tightness in the lungs") and adding more instructions. The changes were confirmed in the second round of CD interviews.
- During the CD interviews, patients were asked which of the 7 symptoms of the MACrO₂ PRO were "most relevant" to them; participants were allowed to choose multiple symptoms. Item 8 of the MACrO₂ PRO asked participants to choose which symptom included in the measure would be most important to them to improve. These answers are presented together in Figure 2, along with the total number of participants endorsing each symptom during the concept confirmation part of the CD interview. Shortness of breath and fatigue were prominent symptoms both in terms of the total number of patients reporting them (n=13/14 both) as well as being chosen as "most relevant" and "most bothersome."



Figure 2. Symptoms that are Most Relevant and Most Important to Improve (CD Interviews, N=14)



- A total of 22 CE interviews were conducted between April and August 2021. A total of 14 CD interviews were conducted between February and May 2022.
- Sample characteristics are reported in Table 1. No participants were Hispanic or Latino.

Table 1. Sample Characteristics

Patient characteristics	CE Study (N=22)	CD Study (N=14)
Age (years), mean (SD) [Range]	68.5 (7.28) [53-81]	69.1 (9.60) [49-87]
Sex, female, n (%)	16 (73%)	10 (71%)
Race, white, n (%)	20 (91%)	14 (100%)
Highest educational level, n (%)*		
Secondary/high school	4 (18%)	1 (7%)
Some college	5 (23%)	3 (21%)
College degree	6 (27%)	5 (36%)
Post graduate degree	6 (27%)	5 (36%)
Other	2 (9%)	2 (14%)
Time since initial MAC diagnosis/first positive culture (years), Mean (SD) [Range]	9.3 (9.51) [0.8-33.9]	5.4 (2.70) [1.3-9.4]
Patients undergoing ≥5 treatment regimens for MAC, n (%)	10 (46%)	5 (35.7%)
Comorbid bronchiectasis, n (%)	17 (90%)	9 (64.3%)
Comorbid COPD, n (%)	3 (16%)	2 (14%)

CONCLUSIONS

- The MACrO₂ PRO v1.0 is a new PRO instrument developed according to FDA guidance that may be appropriate for use in clinical trial endpoints in future studies of TR-MAC-LD
- The next step was to test the psychometric performance of the novel PRO, using clinical trial data (refer to Poster #71 for details)

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t Author contributions made while affiliated with AN2 Therapeutics, but author may no longer be affiliated with the organization

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DMB and LS are paid consultants to the pharmaceutical industry, including AN2 Therapeutics.

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CD = cognitive debriefing; CE = concept elicitation; COPD = chronic obstructive pulmonary disease; MAC = *Mycobacterium avium* complex. *Not mutually exclusive – patients were able to select multiple responses.