

## **PCR13: Supplementary materials**

**Title:** Content Validation of the Patient Attainment Scale-Essential Tremor (PAS-ET): A Novel Patient-Reported Outcome Measure Assessing Patient-level Perceptions of the Importance, Current Function and Definitions of Meaningful Improvement in Tremor-related Impacts on Activities of Daily Living

### **PAS-ET V1.0 – Overview of content**

- Patient reported outcome (PRO) measure designed for administration in electronic format
- Designed for use in adult populations with essential tremor (ET)
- Developed by Sage Therapeutics in partnership with Acaster Lloyd. Included concepts were based on the content of The Essential tremor Rating Assessment Scale – Activities of Daily Living (TETRAS ADL) subscale<sup>1-3</sup>
- Assesses 10 tremor-related impacts on activities of daily living (ADLs; eating, drinking, hygiene, dressing, pouring, carrying items, writing, using keyboard/smartphone, using keys, working)
- Item stem 1: Respondents rate the importance of improving each ADL on a 5-point Likert scale (1 = 'Not at all important' to 5 = 'Extremely important')
- Item stem 2: Respondents are presented with all ADLs they indicated to be important (i.e., 2 = A little important to 5 = Extremely important) and select which is most important ADL to improve with treatment
- Item stem 3: Respondents rate their current ability to perform each ADL indicated to be important as well as overall ADLs on a numeric response scale (NRS; 0-10 integers; 0 = No problems, 10 = Cannot do) accompanied by illustrative verbal anchors (1-3 = Mild problems, 4-6 = Moderate problems, 7-9 = Severe problems)
- Item stem 4: At baseline administration, respondents are then asked to indicate the smallest improvement in their current score that would be meaningful to them on an NRS (0-10 integers)
- At post-baseline assessments, respondents complete only the items assessing their current ability on each ADL specified as important at baseline, and ADLs overall
- No recall period is specified, but the item 3 stem assesses 'current' ability to perform an ADL

## **Methods**

### **Institutional Review Board (IRB) approval statement:**

- This study was reviewed and approved by the WIRB-Copernicus Group (WCG) IRB on 19th October 2022 (tracking number: 20225601), with subsequent amendments as detailed below:

- Amendment 1 (3rd November 2022): Study contact information revised
- Amendment 2 (2nd March 2023): PAS-ET V1.1 approved
- Amendment 3 (3rd April 2023): PAS-ET V1.2 approved
- Amendment 4 (31<sup>st</sup> May 2023)/Amendment 5 (12<sup>th</sup> July 2023): Unrelated to current poster

**Table 1. Participant inclusion/exclusion criteria**

Inclusion	Exclusion
<ul style="list-style-type: none"> <li>• Aged 18-80 years</li> <li>• Live in the US</li> <li>• Fluent in spoken and written English</li> <li>• Clinician confirmed diagnosis of essential tremor defined by the following criteria: <ul style="list-style-type: none"> <li>○ Isolated tremor syndrome consisting of bilateral upper limb action tremor, with or without tremor in other locations</li> <li>○ At least 3 years duration</li> </ul> </li> <li>• Had a severity of tremor score of 2 (mild) 3 (moderate) or 4 (severe) on the Clinician Global Impression Scale – Severity of illness (CGI-S)</li> <li>• Had a severity of activities of daily living score of 2 (mild problems), 3 (moderate problems), 4 (severe problems), or 5 (unable to do) on the Patient Global Impression of Severity - Activities of Daily Living (PGI-S ADL) at screening</li> <li>• Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (e.g., voice, head), task- and position-specific tremors, sudden tremor onset or evidence of stepwise deterioration of tremor</li> </ul>	<ul style="list-style-type: none"> <li>• Onset of tremor was associated with direct or indirect injury or trauma to the nervous system</li> <li>• Previous procedure for the treatment of essential tremor, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, e.g., MR-guided focused ultrasound</li> <li>• Individual had botulinum toxin for treatment of upper limb tremor within 6-months of screening</li> <li>• Historical or clinical evidence of tremor with psychogenic origin</li> <li>• Participant had currently active and medically significant or uncontrolled hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic and / or metabolic disease</li> <li>• Participant was currently undergoing treatment for oncologic disease at screening or is planned to commence treatment within the next 30-days, excluding skin cancers</li> <li>• Participant had a history of substance or alcohol dependence in the last 6-months</li> </ul>

Inclusion	Exclusion
<ul style="list-style-type: none"> <li>Willing and able to provide consent to take part in a 60-minute audio-recorded interview</li> </ul>	<ul style="list-style-type: none"> <li>Was enrolled in a clinical trial at the time of recruitment</li> <li>Previously enrolled in a clinical trial sponsored by Sage Therapeutics</li> </ul>

## Recruitment targets

Table 2. Recruitment targets for age

	≤65 years	66-80 years	GRAND TOTAL
Number of participants	7	13	20

Table 3. Recruitment targets for PGI-S ADL score

	2 - Mild	3 - Moderate	4 - Severe / 5 - Unable to do	GRAND TOTAL
Number of participants	5	10	5	20

Recruitment targets assumed a total sample of N=20 and were adjusted proportionally to the final sample size.

## Participant ID codes

IDs were allocated in chronological order as participants were consented (starting from P001). IDs contained participants PGI-S ADL score (MLD = 2 / Mild; MOD = 3 / Moderate; SEV = 4 / Severe).

## Interview Process

- Interviews lasted approximately 60-minutes; participants completed a background questionnaire at the start of the interview. For the first n=16 interviews, a concept elicitation interview preceded the cognitive debriefing of the PAS-ET (and one other PRO measure), but was removed once conceptual saturation was obtained. The current poster summarises the cognitive debriefing of the PAS-ET only
- Cognitive debriefing interviews followed a structured interview guide. Participants completed the PAS-ET using a 'think-aloud' technique
- Interviews assessed participant comprehension of the instructions, item wording, response options

and recall periods utilised

- The patient-relevance of included concepts was evaluated
- Feedback on conceptual comprehensiveness and responder burden (i.e., length) of the PAS-ET was also obtained

## Results

**Table 4. Sample demographic characteristics for PAS-ET cognitive debriefing interviews**

Demographic characteristic	R1 (N=12)	R2 (N=4)	R3 (N=6)	Total (N=22)
<b>Mean (range)</b>				
<b>Age (years)</b>	66.08 (53-80)	66.25 (52-73)	60.2 (38-73)	64.2 (38-80)
<b>Median</b>				
	67.5	70	67.5	68
<b>N (%)</b>				
<b>Age categories (years)</b>				
≤65 years	4 (33)	1 (25)	2 (33)	7 (32)
66-80 years	8 (67)	3 (75)	4 (67)	15 (68)
<b>Gender</b>				
Male	8 (67)	2 (50)	3 (50)	13 (59)
Female	4 (33)	2 (50)	3 (50)	9 (41)
<b>Transgender</b>		-	-	
No	10 (83)	4 (100)	6 (100)	20 (91)
Yes	1 (8.5)	-	-	1 (4.5)
Prefer not to state	1 (8.5)	-	-	1 (4.5)
<b>Race</b>				
White	8 (67)	3 (75)	5 (83)	16 (73)
Black or African American	2 (17)			2 (9)
Mixed or multiple ethnic groups	1 (8)	1 (25)	-	2 (9)

Demographic characteristic	R1 (N=12)	R2 (N=4)	R3 (N=6)	Total (N=22)
<b>Ethnicity</b>				
Hispanic/Latino	1 (8)	-	1 (17)	2 (9)
<b>Highest level of education</b>				
College or university degree	6 (50)	1 (25)	4 (67)	11 (50)
Graduate degree	4 (33)	-	1 (16)	5 (23)
High school diploma	1 (8.5)	2 (50)	-	3 (14)
Associates degree	-	1(25)	-	1 (4.5)
Vocational school or other trade certificate	1 (8.5)	-	1 (16)	2 (9)
<b>Employment status<sup>1</sup></b>				
Retired	6 (50)	2 (50)	3 (50)	11 (50)
Self-employed	3 (25)	-	-	3 (14)
Employed full-time	2 (17)	1 (25)	3 (3)	6 (27)
Employed part-time	3 (25)	-	-	3 (14)
Full-time homemaker/caregiver	-	1 (25)	-	1 (4)

Note: R1/2/3 = Round 1/2/3; <sup>1</sup>The sum of counts exceeds the total as participants were able to select multiple responses. The sum percentages may be less or greater than 100 as all percentages are rounded to the nearest whole number (0.d.p)

**Table 5. Sample clinical characteristics for PAS cognitive debriefing interviews**

Clinical characteristic	R1 (N=12)	R2 (N=4)	R2 (N=6)	Total (N=22)
<b>Mean (SD, Range)</b>				
<b>Time since diagnosis (years)</b>	7.3 (4.9, 3.08-19.25)	11.4 (4.4, 6.92-16.75)	7.5 (3.8, 3.17-11.67)	8.7 (4.3, 3.08 to 19.25)
<b>N (%)</b>				
<b>CGI-S ADL<sup>1</sup></b>				
No problem*	-	-	1 (17)	1 (4.5)

Clinical characteristic	R1 (N=12)	R2 (N=4)	R2 (N=6)	Total (N=22)
Mild problems	6 (50)	1 (25)	1 (17)	8 (36)
Moderate problems	4 (33)	1 (25)	2 (33)	7 (32)
Severe problems	2 (17)	2 (50)	2 (33)	6 (27)
<b>CGI-S<sup>1</sup></b>				
Mild problems	4 (33)	1 (25)	-	5 (22)
Moderate problems	5 (42)	1 (25)	4 (67)	10 (45)
Severe problems	3 (25)	2 (50)	2 (33)	7 (32)
<b>PGI-S ADL<sup>2</sup></b>				
Mild problems	4 (33)	1 (25)	1 (17)	6 (27)
Moderate problems	6 (50)	1 (25)	3 (50)	10 (45)
Severe problems	2 (17)	2 (50)	2 (33)	6 (27)
<b>PGI-S<sup>3</sup></b>				
Mild problems	7 (58)	2 (50)	1 (17)	10 (45)
Moderate problems	4 (33)	-	3 (50)	7 (32)
Severe problems	1 (8)	2 (50)	2 (33)	5 (22)

Note: <sup>1</sup>Clinician-reported in participant screener; <sup>2</sup>Patient-reported in participant screener; <sup>3</sup>Patient-reported in participant background questionnaire; CGI-S / PGI-S = Clinician / Patient Global Impression – Severity (Tremor); CGI-S ADL / PGI-S ADL = Clinician / Patient Global Impression – Severity (Activities of Daily Living); SD = Standard deviation; R1/2/3 = Round 1/2/3. \*Inclusion criteria were based on CGI-S and PGI-S ADL only.

**Table 6. Summary of feedback on PAS-ET: Response options, recall period, missing concepts and responder burden**

PAS-ET V1.0 (Round 1; N=12)		PAS-ET V1.1 (Round 2; N=4)	PAS-ET V1.2/2.0 (Round 3; N=6)
<b>Response scales</b>			
<b>Importance Likert Scale</b>			
Understood by all participants.		Understood by all participants.	Understood by all participants.
<b>Ranking question (most important ADL)</b>			
Understood by most participants (n=10). Two did not clearly understand as enquired if they could select multiple responses. <sup>1</sup>		Understood by most participants (n=3). P015-SEV did not clearly understand as initially selected two responses.	Understood by five participants. One was not asked.
<b>Numeric response scale (0-10 integers)</b>			
Understood by five participants. Most demonstrated unclear understanding (n=7) as attempted to respond using an illustrative anchor (n=4), <sup>1</sup> indicated they did not understand/demonstrated confusion regarding anchors (n=3), perceived overlap between anchors (P006-MLD) or did not provide sufficient evidence of understanding (P012-MOD).		Understood by two participants. Two participants demonstrated unclear understanding as attempted to respond using an illustrative anchor. <sup>1</sup>	Understood by five participants. One was not asked.
<b>Recall period<sup>2</sup></b>			
Item stem 3 in the PAS V1.0 references 'current' ability. Over half of participants reported using a recall period of "right now" or "currently" (n= 6), while three reported they were thinking back over 1-5 years. P013-MOD reported using a recall period of		Item stems 1, 2 and 3 in the PAS V1.1 reference 'current' ability. Item stem 1 (ADL importance): two participants used shorter recall periods (1-week to 1-month). P016-MLD reported using different recall periods across concepts	Item stems 1, 2 and 3 in the PAS V1.2/V2.0 reference 'current' ability. Participants reported using a recall period of 'currently'/'now' (n=2/6), the past week (n=2/6), one/six months (P020-MOD) and one year (P021-MLD).

PAS-ET V1.0 (Round 1; N=12)	PAS-ET V1.1 (Round 2; N=4)	PAS-ET V1.2/2.0 (Round 3; N=6)
“since diagnosis”. P006-MLD did not understand the interview question. One was not asked.	including: the last 7-days; 1-year; and 2-years. P009-MOD reported that they were not using a specific recall period. For item stems 2 (Most important ADL) and 3 (Current ability): two participants reported using a shorter recall period (1-week to 1-month), while two reported using longer recall periods (2-5 years).	
<b>Missing items / concepts</b>		
Four participants perceived that the PAS-ET was conceptually comprehensive. When prompted, seven indicated that concepts were missing. Suggested ADLs included: using tools, grocery shopping, driving, <sup>3</sup> turning a page, and loading a dishwasher (n=1 each). Some participants suggested unsuitable concepts: <sup>4</sup> proximal impacts/symptoms of tremor (n=2) and wider HRQoL impacts (n=2). One was not asked.	P009-MOD reported that the PAS-ET was conceptually comprehensive. Some participants suggested unsuitable concepts: <sup>4</sup> wider HRQoL impacts (n=2) and preferred treatment outcomes (P016-MLD).	Half of participants perceived that the PAS-ET was conceptually comprehensive (n=3). P024-SEV suggested including an item on driving. <sup>3</sup> Two participants suggested unsuitable concepts: <sup>4</sup> wider HRQoL impacts (P018-MOD) and use of alcohol to manage tremors (P021-MLD).
<b>Responder burden (length)</b>		
Most participants felt the PAS-ET was an appropriate length. P006-MLD reported the PAS could be shorter and that the items were repetitive. P011-MOD did not provide feedback when prompted, and three were not asked.	Two participants reported that the length was acceptable. Two did not provide feedback when prompted.	No participants completed all PAS items due to time constraints in the interview. Two participants reported that the length was acceptable. P023-SEV noted that the measure may have been quicker to complete if item stem 1 (ADL importance) was



PAS-ET V1.0 (Round 1; N=12)	PAS-ET V1.1 (Round 2; N=4)	PAS-ET V1.2/2.0 (Round 3; N=6)
		presented once with a list of ADL concepts. Three were not asked.
<p>HRQoL = Health-related quality of life; N=Number of responses; PAS-ET = The Patient Attainment Scale-Essential Tremor</p> <p><sup>1</sup>Interviews were conducted using 'live' PDFs of the PAS-ET rather than ePRO devices. The issue of trying to select an illustrative anchor rather than a numeric response or multiple responses is unlikely to be encountered when administered in ePRO format.</p> <p><sup>2</sup>Concept elicitation interviews preceded the cognitive debriefing of the PAS-ET for the first n=16 interviews (Round 1 and 2), in which participants were asked to reflect on their overall experience of living with ET. This may have caused some participants to use a longer recall periods than specified ('current') when subsequently completing the PAS-ET. As such, participant misunderstanding in Round 1/2 may be an artifact of the interview scenario.</p> <p><sup>3</sup>Driving was considered unsuitable for assessment in the PAS-ET as may not be broadly applicable to patients (i.e., as some individuals may not have a driving license, car, or may choose not to drive).</p> <p><sup>4</sup>Concepts were considered suitable given the objective of the PAS-ET is to assess impact on tremor-related ADLs (i.e., suggested concepts were not ADLs).</p>		

**Table 7. Item tracking matrix - Revisions to PAS-ET following Round 1 (PAS-ET V1.0 to V1.1)**

PAS-ET V1.0	Revision made	Rationale for revision	PAS-ET V1.1
Item stems			
<b>Item stem 1:</b> How important is it that a treatment for essential tremor improves your ability to perform the following activity of daily living?	<ul style="list-style-type: none"> <li>Addition of '<u>current</u>' ability</li> </ul>	<ul style="list-style-type: none"> <li>n=4/12 reported using an extended recall period when responding to the PAS (number of years / since diagnosis)</li> <li>Updated so a consistent recall period ('current') is used throughout the PAS</li> </ul>	<b>Item stem 1:</b> How important is it that a treatment for essential tremor improves your <u>current</u> ability to perform the following activity of daily living?

PAS-ET V1.0	Revision made	Rationale for revision	PAS-ET V1.1
<b>Item stem 2:</b> Which activity do you consider <u>most important</u> to improve with treatment? (Select one activity)	<ul style="list-style-type: none"> <li>• Addition of 'Based on your current ability'</li> <li>• Bolding of 'Select one activity'</li> </ul>	<ul style="list-style-type: none"> <li>• n=2/12 found it unclear the item is assessing what is important to them personally</li> <li>• Updated so a consistent recall period ('current') is used throughout the PAS</li> <li>• n=2/12 enquired if they could select multiple responses</li> </ul>	<b>Item stem 2:</b> <u>Based on your current ability</u> , which activity do you consider <u>most important</u> to improve with treatment? <b>Select one activity.</b>
<b>Example item: Item stem 3</b>	Example item removed	<ul style="list-style-type: none"> <li>• n=8/12 did not understand this was an example and attempted to provide a response</li> </ul>	-
<b>Item stem 3:</b> On a scale from 0 to 10, where '0' means you have no problems at all with the activity and '10' means you cannot perform the activity at all (even when using alternate strategies or devices, e.g., using other or both hands, using a straw): How would you rate your <u>current</u> ability to perform the activity below?	<ul style="list-style-type: none"> <li>• Description of alternative strategies / devices modified</li> <li>• Bolding of 'On a scale from 0 to 10'</li> </ul>	<ul style="list-style-type: none"> <li>• n=3/12 did not understand the wording regarding use of 'alternate strategies or devices'</li> <li>• n=4/12 attempted to respond using a descriptive label rather than numeric score when responding for one or more concept</li> </ul>	<b>Item stem 3:</b> <u>On a scale from 0 to 10</u> , where '0' means you have no problems at all with the activity and '10' means you cannot perform the activity at all (even when using alternate strategies <del>or devices, e.g., using other or both hands, using a straw</del> ): How would you rate your <u>current</u> ability to perform the activity below?

PAS-ET V1.0	Revision made	Rationale for revision	PAS-ET V1.1
<b>Item stem 4:</b> The <u>smallest change</u> that would be a <u>meaningful improvement to me</u> <u>would lower my current score</u> to (select a number below):	<ul style="list-style-type: none"> <li>Wording amended to improve clarity</li> </ul>	<ul style="list-style-type: none"> <li>n=3/12 did not recognize that they had to select the 'smallest' change that would be meaningful</li> <li>n=2/12 <i>misinterpreted</i> this item stem to be assessing what physical change they could make to reduce their tremor symptoms</li> </ul>	<b>Item stem 4:</b> Following treatment, the <u>smallest improvement</u> that <u>would be meaningful to me</u> would <u>lower my current score</u> to (select a number below):
Item concepts (ADLs)			
Hygiene (shaving, brushing teeth, applying make-up)	<ul style="list-style-type: none"> <li>Addition of 'for example'</li> </ul>	<ul style="list-style-type: none"> <li>Updated for consistency with other concepts</li> </ul>	Hygiene ( <u>for example</u> , shaving, brushing teeth, applying make-up)
Writing	<ul style="list-style-type: none"> <li>Concept renamed 'Handwriting'</li> </ul>	<ul style="list-style-type: none"> <li>n= 3/11 of those asked interpreted this to include typing.</li> </ul>	<u>Hand</u> writing
Using keyboard/smartphone	<ul style="list-style-type: none"> <li>Addition of 'a'</li> <li>The ' / 'has been changed to 'or'</li> </ul>	<ul style="list-style-type: none"> <li>To improve readability</li> <li>n=3/12 indicated that using a 'keyboard' and 'smartphone' were conceptually distinct activities as they were impacted by tremor differently. Revision allows responders to answer based on activity <u>or</u> the other</li> </ul>	Using <u>a</u> keyboard <u>or</u> smartphone
Working (paid / household and maintenance work)	<ul style="list-style-type: none"> <li>Example revised</li> </ul>	<ul style="list-style-type: none"> <li>n=2/12 were confused by the description of 'paid work'</li> </ul>	Working (paid <u>employment or</u> household and maintenance work)

PAS-ET V1.0	Revision made	Rationale for revision	PAS-ET V1.1
Blue text indicates wording or formatting revisions			

**Table 8. Item tracking matrix - Revisions to PAS-ET following Round 2 (PAS-ET V1.1 to V1.2/V2.0)**

PAS-ET V1.1	Revision made	Rationale for revision	PAS-ET V1.2/V2.0
<b>Item concepts (ADLs)</b>			
Working (paid employment or household and maintenance work)	<ul style="list-style-type: none"> <li>Example revised</li> </ul>	<ul style="list-style-type: none"> <li>n=2/12 in Round 1 were confused by the description of 'paid work' and n=1/4 in Round 2 misunderstood the item to be assessing paid household work (employment).</li> </ul>	Working (paid employment or <b>unpaid</b> household and maintenance work)
Blue text indicates wording or formatting revisions			

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### Supplementary materials

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