



Research Paper

Development and Feasibility of the Self-Report Quantified Tuberous Sclerosis Complex-Associated Neuropsychiatric Disorders Checklist (TAND-SQ)

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ABSTRACT

Background: Tuberous sclerosis complex-associated neuropsychiatric disorders (TAND) are often present but underidentified and undertreated in individuals with tuberous sclerosis complex (TSC). The clinician-completed TAND-Lifetime Checklist (TAND-L) was developed to address this identification and treatment gap. Stakeholder engagement identified the need for a TAND Checklist that can (1) be completed by caregivers or individuals with TSC and (2) quantify TAND difficulties. The aim of this study was to develop a self-report quantified TAND Checklist (TAND-SQ) and conduct feasibility and acceptability testing.

Methods: This aim was addressed in three phases: (1) development of the TAND-SQ Checklist, (2) feasibility and acceptability testing of the “near-final” TAND-SQ Checklist, and (3) preparation of the final TAND-SQ Checklist. Participants included 23 technical experts from the TAND consortium in all phases and 58 lived experts (caregivers and individuals with TSC) in phase 2. All participants completed a TAND-SQ Checklist and a checklist feedback form.

Results: Phase 1 additions to the TAND-SQ, when compared with the TAND-L, included four new items and a quantification rating. Phase 2 showed high ratings for the “near-final” TAND-SQ Checklist on comprehensiveness, clarity, ease of use, and overall acceptability. In phase 3, questions on strengths, strategies, and a TAND Cluster Profile were added.

Conclusion: The TAND-SQ Checklist is presented here for use by individuals with TSC and their caregivers. The next steps as part of the TANDem project include internal and external validation of the checklist and linking of TAND Cluster Profiles generated from the checklist to evidence-informed consensus recommendations within a smartphone application.

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Introduction

The year 2022 marked the tenth anniversary in the Tuberous Sclerosis Complex (TSC) community of the term “TAND”, an acronym referring to TSC-associated neuropsychiatric disorders. This term was coined in 2012 to draw attention to the multilevel range of neuropsychiatric difficulties that were often present but not identified or treated in individuals with TSC.^{1,2} TAND includes difficulties at the behavioral level (including social communication, attention, aggression, etc.), the psychiatric level (e.g., autism, attention-deficit/hyperactivity disorder, or anxiety disorders), the intellectual level (including a wide range of intellectual profiles), the academic level (e.g., reading, writing, or mathematics difficulties), the neuropsychologic level (including executive, dual-tasking, and memory deficits), and the psychosocial level (e.g., impact on self-esteem, relationships, and family stress). The coining of the term was intended to raise awareness of TAND, to introduce a “shared language” to talk about TAND in clinical practice, to increase understanding of TAND through research, and ultimately to reduce the TAND treatment gap.³ Since 2012, research on TAND has increased noticeably. In a recent comprehensive scoping review, Vanclooster and colleagues found that of 230 papers on TAND published between 1987 and 2020, more than half were published since 2012, the year that the term TAND was coined (118 of 230; 51%).⁴

To help families and clinicians screen for these difficulties, the TAND Checklist (Lifetime Version) (TAND-L) was developed.² The TAND-L Checklist was designed as a “memory aid” for clinicians to conduct an interview with individuals with TSC and their families, thus acting as a screening tool to guide clinical decision-making and appropriate referrals for intervention. Leclezio and colleagues⁵ documented preliminary evidence of good internal consistency in the domains and subdomains of the TAND-L Checklist. The authors also found that items endorsed on the TAND-L Checklist correlated significantly with other standardized measures, suggesting acceptable external validity. For example, the total number of behavioral items endorsed on the TAND-L Checklist

showed a strong positive correlation ($\rho = 0.81$; $P < 0.001$) with the total score on the Strengths and Difficulties Questionnaire.^{5,6} Similar correlations were observed between subdomain TAND-L Checklist items and subdomain scores on the Strengths and Difficulties Questionnaire for inattention ($\rho = 0.77$; $P < 0.001$) and social difficulties ($\rho = -0.65$; $P < 0.002$). TAND-L subdomain scores for neuropsychologic skills also correlated with the Behavior Rating Inventory of Executive Functions (BRIEF), a widely used standardized screening tool for executive deficits, specifically with the Global Executive Score ($\rho = 0.79$, $P < 0.001$), the BRIEF Behavior Rating Index score ($\rho = 0.74$, $P < 0.001$), and the Metacognition Index ($\rho = 0.59$, $P < 0.016$).⁵

Since its publication, the TAND-L Checklist has been translated into 18 languages (for authorized translations, please see www.tandconsortium.org/checklists/) and has been used to explore TAND in a range of research studies in various countries.^{7–11} The TAND-L Checklist was used as the basis for generating “natural TAND clusters” of symptoms^{12–14} and to identify naturally occurring patient profiles ranging from high to low symptom burden.¹⁵ These studies have significantly enhanced awareness and understanding of the prevalence and presentation of TAND in individuals with TSC.

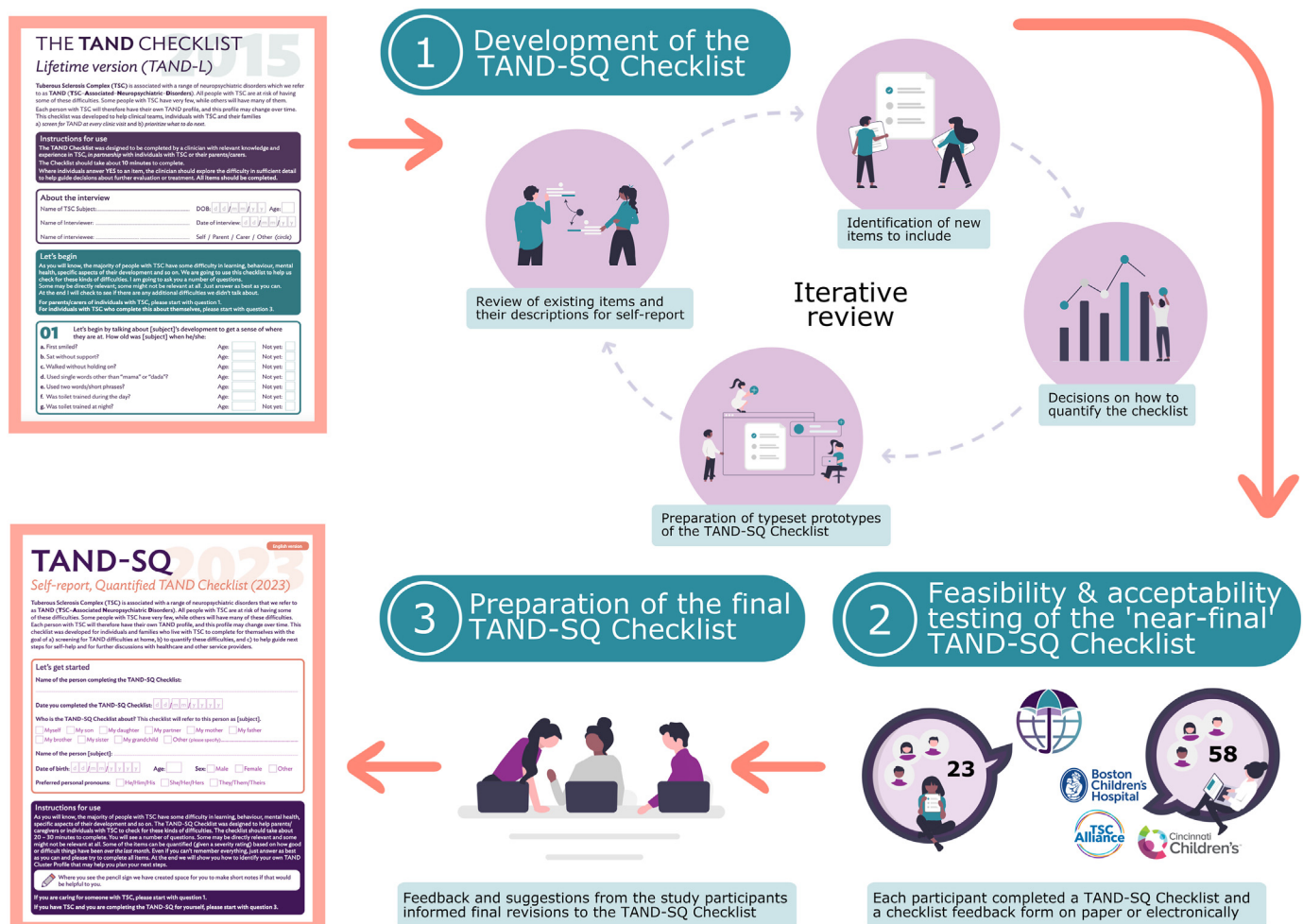
As part of the early natural TAND cluster study,¹² focus group interviews with families from Africa, the United States, Europe, and Australia were conducted with more than 50 individuals with TSC, parents/caregivers, family members, and professional experts in partnership with Tuberous Sclerosis International, European Tuberous Sclerosis Association, Tuberous Sclerosis Association (United Kingdom), and the TSC Alliance (United States). The main emphasis of the focus groups was to seek perspectives and recommendations from global TSC stakeholders about next step use of the TAND-L Checklist and TAND clusters. Thematic analysis of these interviews indicated that stakeholders felt that the TAND-L Checklist had provided the TSC community with a powerful tool to identify the range of TAND difficulties so commonly experienced by families. However, families expressed concern that the TAND-L Checklist was validated only as an interview between a clinician and a family. There was a clear desire to have a self-report version

The new checklist was named the “TAND-SQ Checklist,” with the “S” referring to “self-report” and the “Q” referring to the ability to quantify the severity of the difficulties experienced. The TAND-SQ Checklist has been designed for self-report by individuals with TSC and caregivers of individuals with TSC. Here we describe the development of the TAND-SQ Checklist, outline feasibility and acceptability data of the “near-final” version of the checklist, and present the final TAND-SQ Checklist for use in the TSC community.

Abbreviations:
TAND = Tuberous sclerosis complex-associated neuropsychiatric disorders
TAND-SQ = Self-report quantified TAND Checklist

Study Design

Development of the TAND-SQ Checklist was set up to be a highly iterative and participatory process that incorporated wide-ranging stakeholder involvement. The TAND-L Checklist was used as a baseline for development, and mixed methods were implemented in three phases, each phase corresponding to the objectives listed in [Table 1](#). [Figure 1](#) illustrates the development process of the checklist.



103

Phase 1: Development of the TAND-SQ Checklist

The first step involved a conceptual review of the TAND-L Checklist items by the TAND consortium (see [Study participants](#)) to determine their suitability for self-report and quantification, a process that began at the official launch meeting of the TANDem project in 2019. Activities at the project launch meeting included (1) a review of existing items and their descriptions for self-report, (2) identification of new items to include, and (3) decisions on how to quantify the checklist and the time frame for the quantification.

The next step entailed the preparation of typeset prototypes of the TAND-SQ Checklist and iterative review. Draft versions were prepared by the TANDem Action Group and were reviewed electronically by the TAND consortium. This led to the refinement of items and the addition of some new items. The checklist was typeset and copyedited to ensure consistent wording, grammar, and visual presentation. This included revisions of instructions to users to make the checklist appropriate for self-reporting, rather than as a clinical interview guide. The typeset versions were reviewed by the TANDem Action Group and the TAND consortium. Five draft versions of the TAND-SQ were reviewed in this iterative manner over a period of two years. Draft 6, referred to as the “near-final” TAND-SQ Checklist, was used for feasibility and acceptability testing.

Phase 2: Feasibility and acceptability testing of the “near-final” TAND-SQ Checklist

The sixth “near-final” version was used for feasibility and acceptability testing with stakeholders from the TAND consortium, the TSC Alliance, and Boston Children’s Hospital and Cincinnati Children’s Hospital (see [Study participants](#)). These participants were selected by convenience sampling to include “technical experts” (clinicians and researchers working in the TSC community) as well as “lived experts” (parents/caregivers of individuals with TSC and individuals with TSC). Each participant completed the “near-final” TAND-SQ Checklist and a checklist feedback form, either on paper or electronically (see [Data collection and analysis](#)).

Phase 3: Preparation of the final TAND-SQ Checklist

The TANDem Action Group prepared a summary of the feedback and suggestions from the study participants in phase 2 and presented these to the TAND consortium for further consideration. The TANDem Action Group then prepared the final revisions to the TAND-SQ Checklist.

Study participants

TAND Consortium

The TAND consortium consisted of an interdisciplinary, international group of 24 clinical, research, and technical experts in TSC (or related areas), and was set up as part of the TANDem project (www.tandconsortium.org). The TAND consortium included six “family representatives” with lived expertise in TSC, consisting of parents/caregivers of individuals with TSC. Most “family representatives” had dual roles (e.g., medical professional with technical expertise in TSC and having a child with TSC, or special educator who also had a child with TSC). The TANDem Action Group consisted of five members within the TAND consortium who were responsible for the day-to-day running of the TANDem project.¹⁷

TSC Alliance

Individuals with TSC and caregivers of individuals with TSC were invited to complete the TAND-SQ Checklist and checklist feedback form via the TSC Alliance electronic Self-Report Portal. This portal was added as a substudy to the existing TSC Alliance Natural History Database and allows families and/or individuals to

report on their own health outcomes. The TSC Alliance utilized various recruitment methods, including posting information about the project on their web site, online community support and Facebook pages, e-mail, and in print (e.g., TSC Alliance magazine and flyers at a TSC Alliance sponsored event).

Boston Children’s Hospital and Cincinnati Children’s Hospital

Individuals with TSC and caregivers of individuals with TSC were recruited from TSC clinics at Boston Children’s Hospital (BCH) and Cincinnati Children’s Hospital (CCH). Research coordinators at these sites invited participants to complete the pen-and-paper (hardcopy) TAND-SQ Checklist and checklist feedback form during routine clinical visits.

Data collection and analysis

Data collection

TAND consortium participants completed the TAND-SQ Checklist on paper and the checklist feedback form as an online survey. Family representatives were asked to complete the TAND-SQ and feedback form on their family member with TSC; consortium members who did not have a family member with TSC were asked to complete the TAND-SQ and feedback form for someone they knew (e.g., one of their patients with TSC) as if they were caregivers of an individual with TSC to create a “naturalistic” approach to the data collection. TSC Alliance participants completed the TAND-SQ and feedback form via the electronic portal, and BCH/CCH participants completed both on paper. The “near-final” TAND-SQ Checklist comprised 11 questions, capturing information on developmental milestones, current abilities, behaviors causing concern, psychiatric disorders, intellectual ability, difficulties in school, and difficulties with brain (neuropsychologic) skills. The checklist also included psychosocial aspects of the individual with TSC and the caregiver, an overall severity rating of all the difficulties mentioned, a list of priorities to focus on next, and a question for comments about other TAND concerns not covered in the checklist. The questions on behavioral concerns, difficulties in learning in school, and difficulties with brain skills included a quantification of severity over the last month (see [Results](#) for further details).

The checklist feedback form comprised six quantitative items wherein participants were asked to rate aspects of feasibility on a five-point Likert scale, including comprehensiveness and clarity of the checklist items, ease of use, likelihood of use by individuals with TSC or families/caregivers, likelihood of its use leading to better management of TAND, and an overall rating. Each rating was followed by corresponding open-ended items to capture richer information on quantitative ratings. Participants were also asked to report how long it took them to complete the TAND-SQ Checklist, and if they had completed the TAND-L Checklist previously, to compare the TAND-L and TAND-SQ checklists.

Data analysis

Quantitative responses to the checklist feedback form were analyzed descriptively. Given the relatively small sample size (23 TAND consortium participants, 45 TSC Alliance participants, and 13 BCH/CCH participants), responses for each item were reported. Open-ended responses were analyzed thematically.

Research ethics

This study was approved by the University of Cape Town, South Africa, the site of the principal investigator (HREC 849/2020), and the Ethical and Independent Review Services for the Natural History Database Study (protocol number 15039-08) in the United States that permits use of deidentified clinical data for TSC research

at the TSC Alliance. This study was also reviewed and approved by the BCH Institutional Review Board (IRB, IRB-P00041212). For BCH and CCH sites, BCH agreed to serve as the reviewing IRB for this study and CCH (IRB number 2022-0421) agreed to cede IRB review to the BCH IRB. All TAND consortium members, TSC Alliance participants, and BCH and CCH participants were asked to provide informed consent before participating in this study. As part of the TANDem project, all participating data collection sites signed a data transfer agreement.

Results

Phase 1: Development of the TAND-SQ Checklist

A summary of all changes to the TAND-L Checklist during the development of the TAND-SQ Checklist is listed in Table 2. During the iterative development and review process of phase 1, several changes were proposed by the TAND consortium. Throughout the checklist a pencil icon and open lines were added to allow respondents to make short notes. On the cover page, instructions were made more explicit and directed to caregivers or individuals with TSC for self-report, as opposed to the healthcare provider. In Question 01 specific age bands were added to the developmental milestone reporting to aid caregiver recall. In Question 03 new items on sensory sensitivities and “other behavioral difficulties” were added. An “Other” option was also added to Questions 04, 06, and 07. Further Question 07 additions included new items on motor skills, language skills, and processing speed. Question 12 of the TAND-L Checklist on the interviewer’s judgment of the impact of TAND on the individual/child/family was removed.

To address the specific request from families and TSC stakeholders to quantify TAND difficulties, a quantification component was introduced in Questions 03, 06, and 07 as a severity rating using a Likert scale from 0 (not at all a problem) to 10 (an extreme problem) for behaviors causing concern (Question 03), difficulties in learning in school (Question 06), and difficulties in specific brain skills (Question 07). Similar to other behavioral rating scales, the time frame for this severity rating was chosen to be “over the last month” to aid recall. Items in these questions of the TAND-SQ Checklist are thus evaluated in two ways, “has it ever been a

problem,” and “if yes, how much of a problem has it been over the last month”?

Further changes were made to Question 08, concerning the psychosocial impact on individuals’ lives. This question was expanded to Question 8.1 for individuals with TSC and Question 8.2 for caregivers of individuals with TSC. Additional items were added that refer to specific relationship categories, including relationships with siblings, parent-child relationships, parent-to-parent/partner relationships, family connections in the community, and difficulties to progress in one’s career.

Phase 2: Feasibility and acceptability testing of the “near-final” TAND-SQ Checklist

Sample demographics

The expert technical group consisted of 23 TAND consortium members with technical and/or lived expertise in TSC and/or its associated TAND. There were 45 TSC Alliance participants, 30 caregivers of children with TSC (16 sons, 14 daughters, mean age 11.9 years [S.D. = 9.82] ranging from 7 months to 33 years), two caregivers of adult siblings with TSC (ages 62 and 68 years), and 13 individuals with TSC who completed the checklist for themselves (three males, 10 females, mean age 36.69 years [S.D. = 13.05], ranging from 20 to 64 years). There were 13 participants from BCH and CCH, eight were caregivers of children with TSC (three sons and five daughters, mean age 10 years [S.D. = 4] ranging from 2 to 15 years), three were caregivers of adults with TSC (23, 25, and 27 years of age), and two were adult individuals with TSC (two females, 30 and 36 years old). Feasibility and acceptability ratings therefore reflected opinions of a wide range of 81 TSC stakeholders. Results are presented according to three subgroups: (1) technical experts (TAND consortium participants, $n = 23$), (2) caregivers (parents and adult siblings; $n = 43$), and (3) individuals with TSC ($n = 15$).

Quantitative findings

The technical expert group reported that the TAND-SQ Checklist took them on average 17.17 minutes (S.D. = 7.20) to complete, caregivers took a mean of 15.37 minutes (S.D. = 6.60), and individuals with TSC took 16.64 minutes (S.D. = 8.42) with one outlier reporting a completion time of 90 minutes. The quantitative

TABLE 2.
Summary of Changes to the TAND-L Checklist in the Development of the TAND-SQ Checklist

Phase of Development	TAND-SQ Question	Description of Changes
Phase 1	All questions	Pencil icon and open lines added for notes
	Cover page instructions	Instructions were refined for self-report Instructions for pencil icon were added
	Question 01: Developmental milestones	Specific age bands were added to assist parent recall
	Question 03: Behaviors causing concern	Items on sensory sensitivities and “other” item added Severity rating of 0-10 added for all items
	Question 04: Psychiatric disorders	“Other” item added
	Question 06: Difficulties in learning in school	“Other” item added
	Question 07: Difficulties in brain skills	Severity rating scale of 0-10 added for all items Items for motor skills, language skills, processing speed, and “other” added Severity rating of 0-10 added for all items
	Question 08: Psychosocial difficulties	Question divided into 8.1 for individuals with TSC and 8.2 for caregivers of individuals with TSC Additional items on relationships, etc., added in 8.1 and 8.2
	Question 12: Interviewer’s judgment	The TAND-L section on the clinician’s judgment of the TAND burden was removed
	Questions 9, 10, 11	Order of questions rearranged
Phase 3	Question 12: Strategies	New question on helpful strategies added
	Question 13: Strengths	New question on strengths, skills, and talents added
	Question 14: TAND Cluster Profile	New question for respondents to create a summary TAND Cluster Profile added

Abbreviations:

TAND = Tuberous sclerosis complex-associated neuropsychiatric disorders

TAND-L = TAND Checklist (Lifetime Version)

TAND-SQ = Self-report quantified TAND Checklist

responses from the checklist feedback form for all participant groups are presented in Fig 2. All groups had high ratings for comprehensiveness (coverage of neuropsychiatric features), clarity, ease of use, likely use by others, likelihood of referrals, and overall rating of the TAND-SQ Checklist, with modal scores of 5 (“very much”/“very good”) for most items on the 5-point Likert scale. Of those who had completed the TAND-L Checklist previously ($n = 36$), a third rated it as “equally good” (13 of 36 = 36%), whereas the majority (23 of 36 = 64%) rated it as “better” or “much better” than the TAND-L Checklist.

Qualitative Findings

The open-ended responses to each checklist feedback form question were analyzed thematically. Four main themes were identified: (1) positive feedback on the changes made to the TAND-L Checklist, (2) ending on a positive note, (3) desire for age-specific questions/checklists, and (4) next steps.

Positive feedback on the changes made to the TAND-L Checklist. There were a number of positive comments on the changes that had been made in the development of the TAND-SQ Checklist from participants familiar with the original TAND-L Checklist. For example,

“Some of the new response options on sections are really nice! I love that career, processing speed and sensory sensitivities have been added. Also really like that the first few developmental sections have more response options!”

Such comments confirmed the appropriateness of the changes made in phase 1 and contribute to explaining the high acceptability scores.

Ending on a positive note. This theme was only expressed by one participant but was felt to be such a striking and valuable sentiment that we classified it as a theme all on its own. This was the suggestion that an item on strengths and skills (as opposed to only challenges) should be added to conclude the TAND-SQ Checklist:

“I would really have liked the TAND-SQ to end on a positive note where we can comment on the skills and strengths of our family members. My brother has many amazing talents that were simply not captured. It therefore felt a bit as though we had only captured difficulties. In the case of my brother, many of his areas of strengths and interests are also the things we use to help him develop new skills, because they act as motivators and natural rewards. I would strongly recommend the additions of a strengths section at the end of the Checklist.”

Although the primary purpose of the TAND-SQ Checklist is to identify TAND challenges and address the identification and treatment gap, we felt that this point had a strong resonance within the TSC community. We agreed that ending this self-report checklist on a positive note would help mitigate the focus on challenges and give caregivers and individuals a sense of their own progress. This point was therefore taken into account in the phase 3 changes.

Desire for age-specific questions/checklists. This theme was identified from comments that related to the desire for specific questions (or even entire checklists) for specific ages. The three quotes below came from caregivers and individuals from different age groups:

“Some items don’t make sense for toddlers. I think there should be a different form for this age group”

“Is out of school so lots of the questions did not apply”

“Possibly include things about ADL [activities of daily living], independent skills, vocational skills, getting along with anyone (just not with age peers) - to extend the relevance of this checklist to adulthood.”

These comments are valid concerns and clearly reveal the impact of age on the experience of completing the checklist, particularly for caregivers of very young children, and for adults with TSC, where certain items and questions may not be applicable. This is a problem with any checklist that attempts to address concerns for populations with a wide age range like the TAND-SQ Checklist. Our solutions for addressing these concerns are discussed below (see Discussion).

Next steps. Numerous participants with lived experience with TSC (i.e., caregivers or individuals with TSC) were positive about the checklist itself but expressed concern about how it would help facilitate the next step in terms of accessing practical help. This sentiment was succinctly captured in the following comments:

“And once you understand that your child has so many of these challenges, the biggest question remains, now what do I do?”

“Some interventions – day to day how can this be managed? I know that is to come later but what really does the caregiver get from this survey?? The hope that a clinician will provide next steps? Perhaps next steps outline could encourage more people.”

The frustration of families was clearly evident in these comments. Although it is impossible to address every need with a paper checklist, it is precisely this perspective that led to the aims of the TANDem Project.¹⁷ We discuss below how next steps in this project are designed to address this need (see Discussion).

Phase 3: Preparation of the final TAND-SQ Checklist

Based on the feedback received in phase 2, three new questions were added to create the final TAND-SQ Checklist (see summary in Table 2). Specifically, a new Question 12 was added to give respondents the opportunity to document helpful strategies they are using, Question 13 on strengths was added, and Question 14 was added so that respondents could create a summary of their TAND Cluster Profile to guide their next steps. The order of Questions 09, 10, and 11 was also rearranged. The final TAND-SQ Checklist is presented in Fig 3 and is available as a supplement for download (see Supplementary Data) and on the TAND consortium web site (www.tandconsortium.org/checklists).

Discussion

In response to participatory feedback from the TSC community, the TAND consortium set out to develop a self-report TAND Checklist that could be completed by individuals with TSC and/or their caregivers and that could quantify TAND difficulties. A participatory and iterative method was chosen for the development of the checklist, and multiple stakeholder groups were included for feasibility and acceptability evaluation of the “near-final” version. The resulting final TAND-SQ Checklist is presented in this article (see Fig 3) and can now be used by caregivers and individuals with TSC. Notable additions to the TAND-SQ Checklist when compared with the TAND-L Checklist include the severity rating of behavioral difficulties, additional items related to neuropsychological and psychosocial difficulties, and sections highlighting strategies,

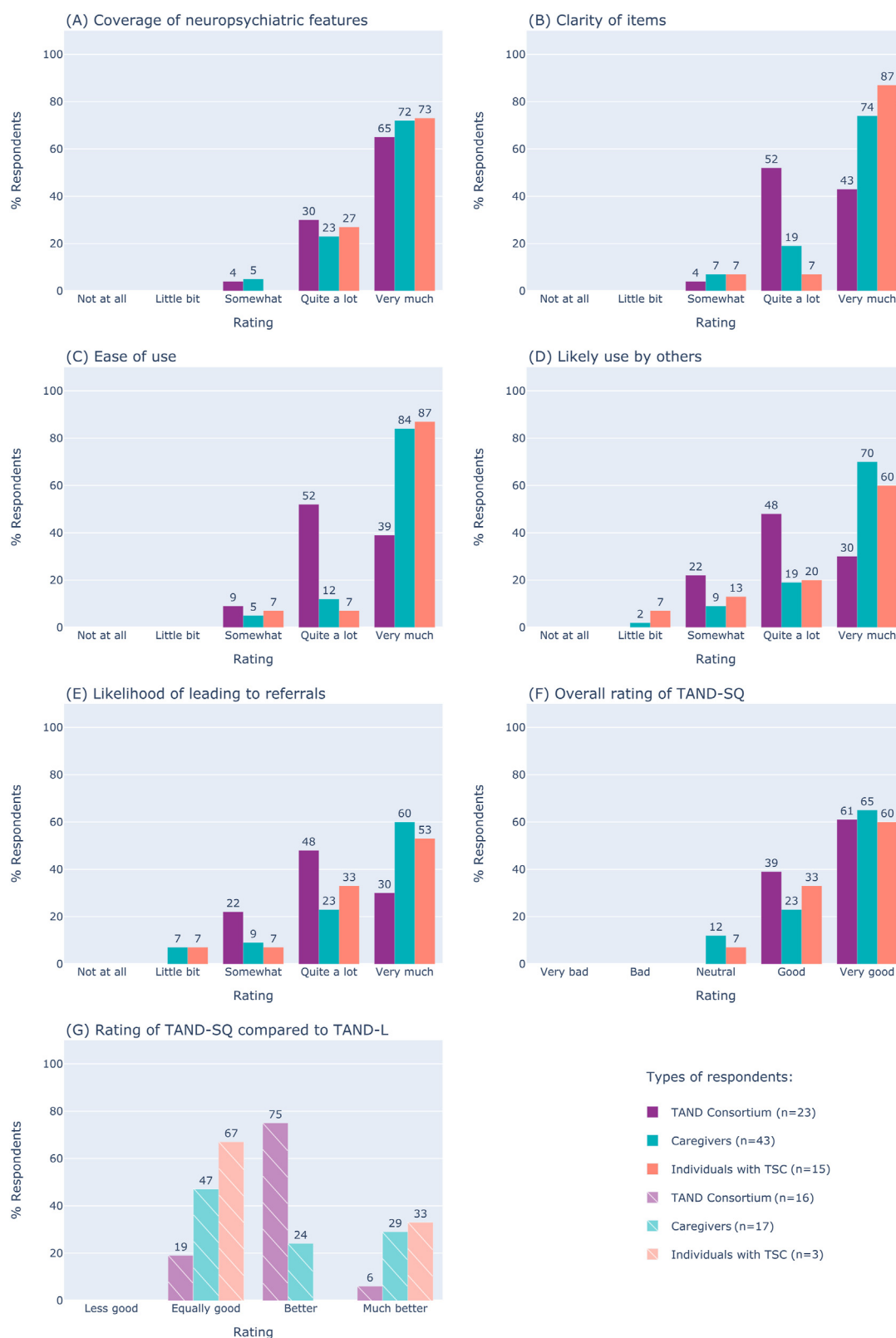


FIGURE 2. Quantitative responses on the TAND-SQ Checklist feasibility and acceptability testing. (A-G) The percentage respondents per group for each item of the checklist feedback form. The colour version of this figure is available in the online edition.

English version

TAND-SQ

Self-report, Quantified TAND Checklist (2023)

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders that we refer to as TAND (**TSC-Associated Neuropsychiatric Disorders**). All people with TSC are at risk of having some of these difficulties. Some people with TSC have very few, while others will have many of these difficulties. Each person with TSC will therefore have their own TAND profile, and this profile may change over time. This checklist was developed for individuals and families who live with TSC to complete for themselves with the goal of a) screening for TAND difficulties at home, b) to quantify these difficulties, and c) to help guide next steps for self-help and for further discussions with healthcare and other service providers.

Let's get started

Name of the person completing the TAND-SQ Checklist:

.....

Date you completed the TAND-SQ Checklist: dd/mm/yyyy

Who is the TAND-SQ Checklist about? This checklist will refer to this person as [subject].

☐ Myself ☐ My son ☐ My daughter ☐ My partner ☐ My mother ☐ My father

☐ My brother ☐ My sister ☐ My grandchild ☐ Other (please specify).....

Name of the person [subject]:

Date of birth: dd/mm/yyyy Age: Sex: ☐ Male ☐ Female ☐ Other

Preferred personal pronouns: ☐ He/Him/His ☐ She/Her/Hers ☐ They/Them/Theirs

Instructions for use

As you will know, the majority of people with TSC have some difficulty in learning, behaviour, mental health, specific aspects of their development and so on. The TAND-SQ Checklist was designed to help parents/ caregivers or individuals with TSC to check for these kinds of difficulties. The checklist should take about 20 – 30 minutes to complete. You will see a number of questions. Some may be directly relevant and some might not be relevant at all. Some of the items can be quantified (given a severity rating) based on how good or difficult things have been *over the last month*. Even if you can't remember everything, just answer as best as you can and please try to complete all items. At the end we will show you how to identify your own TAND Cluster Profile that may help you plan your next steps.



Where you see the pencil sign we have created space for you to make short notes if that would be helpful to you.

If you are caring for someone with TSC, please start with question 1.

If you have TSC and you are completing the TAND-SQ for yourself, please start with question 3.

FIGURE 3. The TAND-SQ Checklist. The colour version of this figure is available in the online edition.

01

Let's begin by talking about [subject]'s development to get a sense of where they are at. How old was [subject] when they:

a. First smiled?

- ☐ Not yet ☐ < 2 months ☐ 2 – 4 months ☐ 4 – 6 months ☐ > 6 months
☐ Not sure (*within normal range*) ☐ Not sure (*delayed*)

b. Sat without support?

- ☐ Not yet ☐ < 6 months ☐ 6 – 8 months ☐ 8 – 10 months ☐ 10 – 12 months
☐ > 12 months ☐ Not sure (*within normal range*) ☐ Not sure (*delayed*)

c. Walked without holding on?

- ☐ Not yet ☐ < 10 months ☐ 10 – 12 months ☐ 12 – 14 months ☐ 14 – 16 months
☐ 16 – 18 months ☐ > 18 months ☐ Not sure (*within normal range*) ☐ Not sure (*delayed*)

d. Used single words other than 'mama' or 'dada'?

- ☐ Not yet ☐ < 12 months ☐ 12 – 14 months ☐ 14 – 16 months ☐ 16 – 18 months
☐ 18 – 20 months ☐ > 20 months ☐ Not sure (*within normal range*) ☐ Not sure (*delayed*)

e. Used two word or simple phrases (e.g. play park, drink juice...)?

- ☐ Not yet ☐ < 18 months ☐ 18 – 22 months ☐ 22 – 26 months ☐ 26 – 30 months
☐ 30 – 36 months ☐ > 36 months ☐ Not sure (*within normal range*) ☐ Not sure (*delayed*)

f. Was toilet trained during the day?

- ☐ Not yet ☐ < 24 months ☐ 24 – 30 months ☐ 30 – 36 months ☐ 36 – 48 months
☐ > 48 months ☐ Not sure (*within normal range*) ☐ Not sure (*delayed*)

g. Was toilet trained at night?

- ☐ Not yet ☐ < 3 years ☐ 3 – 4 years ☐ 4 – 5 years ☐ 5 – 6 years
☐ 6 – 8 years ☐ > 8 years ☐ Not sure (*within normal range*) ☐ Not sure (*delayed*)

**02**

What is [subject]'s current level of:

- a. Language:** ☐ non-verbal/minimally verbal ☐ simple language ☐ fluent
b. Self-care: ☐ dependent on others ☐ some self-care skills ☐ independent
c. Mobility: ☐ wheelchair ☐ needs significant support ☐ some difficulty
☐ completely mobile



Figure 3. (continued).

03

Let's talk about behaviours causing concern to you or to other people.

a. Has anxiety ever been a problem?NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**b. Has depressed mood ever been a problem?**NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**c. Has extreme shyness ever been a problem?**NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**d. Have mood swings ever been a problem?**NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**e. Have aggressive outbursts ever been a problem?**NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**f. Have temper tantrums ever been a problem?**NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**g. Has self-injury, such as hitting self, biting self, scratching self, ever been a problem?**NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**h. Has absence or delayed onset of language ever been a problem?**NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely

Figure 3. (continued).

i. Has **repeating words or phrases over and over again** ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



j. Has **poor eye contact** ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



k. Has **getting on with other people of a similar age** ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



l. Have **repetitive behaviours, such as doing the same thing over and over again**, ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



m. Has **very rigid or inflexible behaviour, such as wanting to do things in a particular way or not liking change in routines**, ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



n. Have **sensory sensitivities (hyper- or hyposensitivity), such as either being very interested in or very sensitive to the sight, smell, touch or sound of things**, ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



o. Has **overactivity/hyperactivity, such as being constantly on the go**, ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



Figure 3. (continued).

p. Has paying attention or concentrating ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



q. Has restlessness or fidgetiness, such as wriggling or squirming, ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



r. Has impulsivity, such as butting in or not waiting your turn, ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



s. Has eating and/or drinking, such as too much, too little, unusual things, ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



t. Has sleep, such as falling asleep or waking, ever been a problem? NO ☐ YES ☐

If YES, how much of a problem has it been over the last month?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



u. Have any other behaviours ever been a problem? NO ☐ YES ☐

If YES, please list and specify how much of a problem it has been over the last month? Score (0-10)

1.
2.
3.

If you answered YES to any of the items in question 3:

– Have you/has [subject] had further evaluation or support for any of these behavioural difficulties? NO ☐ YES ☐

– Would you like to have further evaluation or support for yourself/[subject]? NO ☐ YES ☐



Figure 3. (continued).

04

Problem behaviours may add up to meet criteria for specific psychiatric disorders. Have you/has [subject] ever received a diagnosis using standardised assessments/tools of any of the following:

- | | |
|--|--|
| a. Autism Spectrum Disorder (ASD), <i>including autism, Asperger's</i> | NO ☐ YES ☐ |
| b. Attention Deficit Hyperactivity Disorder (ADHD) | NO ☐ YES ☐ |
| c. Anxiety Disorder, <i>including panic, phobia, separation anxiety disorder</i> | NO ☐ YES ☐ |
| d. Depressive Disorder | NO ☐ YES ☐ |
| e. Obsessive Compulsive Disorder (OCD) | NO ☐ YES ☐ |
| f. Psychotic Disorder, <i>including schizophrenia</i> | NO ☐ YES ☐ |
| g. Other psychiatric disorder(s)? | NO ☐ YES ☐ |

If YES, please specify here.

1.
2.
3.

If you answered YES to any of the items in question 4:

- | | |
|--|--|
| – Have you/has [subject] had further evaluation or support for any of these psychiatric disorders? | NO ☐ YES ☐ |
| – Would you like to have further evaluation or support for yourself/[subject]? | NO ☐ YES ☐ |



.....

.....

Figure 3. (continued).

05

About half of people with TSC will have significant difficulties in their overall intellectual development and may have ‘intellectual disability’.

a. Have you ever been concerned about this for yourself/[subject]? NO ☐ YES ☐

b. Have you/has [subject] ever had a formal evaluation of intelligence by a professional using IQ-type tests? NO ☐ YES ☐

If YES, what did results show?

- Normal Intellectual Ability (IQ > 80) ☐
 Borderline Intellectual Ability (IQ 70–80) ☐
 Mild Intellectual Disability (IQ 50–69) ☐
 Moderate Intellectual Disability (IQ 35–49) ☐
 Severe Intellectual Disability (IQ 21–34) ☐
 Profound Intellectual Disability (IQ < 20) ☐
 I don’t know ☐

c. What is your view of your/[subject]’s intellectual ability? Above Average Intellectual Ability ☐
 Normal Intellectual Ability ☐
 Mild – Moderate Intellectual Disability ☐
 Severe – Profound Intellectual Disability ☐

d. Would you like to have further evaluation or support for yourself/[subject]? NO ☐ YES ☐



.....

.....

Figure 3. (continued).

06

Many people with TSC who are of school age will have difficulties in school.

a. Has reading ever been a problem?Not yet in school ☐ NO ☐ YES ☐If YES, how much of a problem has it been *over the last month*?Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**b. Has writing ever been a problem?**Not yet in school ☐ NO ☐ YES ☐If YES, how much of a problem has it been *over the last month*?Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**c. Has spelling ever been a problem?**Not yet in school ☐ NO ☐ YES ☐If YES, how much of a problem has it been *over the last month*?Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**d. Has mathematics ever been a problem?**Not yet in school ☐ NO ☐ YES ☐If YES, how much of a problem has it been *over the last month*?Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely**e. Have there ever been any other difficulties related to learning in school?**Not yet in school ☐ NO ☐ YES ☐If YES, please list and specify how much of a problem it has been *over the last month*? Score (0-10)

1.
2.
3.

If you answered YES to any of the items in question 6:

– Have you/has [subject] had further evaluation or support for any of these scholastic difficulties?

NO ☐ YES ☐

– Have you/has [subject] been considered for any additional support in school such as extra help or an Individual Educational Plan (IEP)?

NO ☐ YES ☐

– Would you like to have further evaluation or support for yourself/[subject]?

NO ☐ YES ☐

Figure 3. (continued).

07 The majority of people with TSC will have difficulties in some specific brain skills.

a. Have motor skills, such as clumsiness, poor coordination or gait problems, ever been a problem?

NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



b. Have language skills, such as difficulty understanding or expressing language, ever been a problem?

NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



c. Has attention, such as concentrating well, not getting distracted, ever been a problem?

NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



d. Has dual-tasking/multi-tasking, such as doing two tasks at the same time, ever been a problem?

NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



e. Has memory, such as remembering things that have happened, ever been a problem?

NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



f. Have visuo-spatial tasks, such as solving puzzles or using building blocks, ever been a problem?

NO ☐ YES ☐

If YES, how much of a problem has it been *over the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



Figure 3. (continued).

g. Have executive skills, such as planning, organising or flexible thinking, ever been a problem?

NO ☐ YES ☐

If YES, how much of a problem has it been over *the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



h. Has being disoriented, such as not knowing the date or where you are, ever been a problem?

NO ☐ YES ☐

If YES, how much of a problem has it been over *the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



i. Has processing speed, such as being very slow to do a task, ever been a problem?

NO ☐ YES ☐

If YES, how much of a problem has it been over *the last month*?

Not at all 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Extremely



j. Have any other brain skills ever been a problem?

NO ☐ YES ☐

If YES, please list and specify how much of a problem it has been over *the last month*? Score (0-10)

1. _____
2. _____
3. _____

If you answered YES to any of the items in question 7:

– Have you/has [subject] had further evaluation or support for any of these neuropsychological difficulties?

NO ☐ YES ☐

– Would you like to have further evaluation or support for yourself/[subject]?

NO ☐ YES ☐



Figure 3. (continued).

08

Apart from the challenges listed above, TSC can have a big impact on people’s lives in other ways.
– If you have TSC, please complete question 8.1.
– If you are a caregiver, please complete question 8.1 for [subject] and question 8.2 for yourself as caregiver.

8.1

Have you/has [subject] ever had any difficulties with:

a. Low self-esteem

b. Very high levels of stress in the family

c. Very high levels of stress in relationship with siblings

d. Very high levels of parent-child relationship difficulties

e. Very high levels of parent-to-parent/partner relationship difficulties

f. Very high levels of stress leading to difficulty for the family to connect with others in their community

g. Very high levels of stress leading to difficulty for you to progress in your career

NO ☐ YES ☐

NO ☐ YES ☐

NO ☐ YES ☐

NO ☐ YES ☐

NO ☐ YES ☐

NO ☐ YES ☐

NO ☐ YES ☐

If you answered YES to any of the items in question 8.1:

– Have you and/or your family had further evaluation or support for any of these psychosocial difficulties?

– Would you like to have further evaluation or support for it for you and/or your family?

NO ☐ YES ☐

NO ☐ YES ☐



8.2

As the caregiver, have you ever had difficulties with:

a. Low self-esteem

b. Very high levels of stress in your family

c. Very high levels of stress in your relationship with your siblings

d. Very high levels of parent-child relationship difficulties

e. Very high levels of parent-to-parent/partner relationship difficulties

f. Very high levels of stress leading to difficulty for your family to connect with others in your community

g. Very high levels of stress leading to difficulty for you to progress in your career

NO ☐ YES ☐

NO ☐ YES ☐

NO ☐ YES ☐

NO ☐ YES ☐

NO ☐ YES ☐

NO ☐ YES ☐

NO ☐ YES ☐

If you answered YES to any of the items in question 8.2:

– Have you and/or your family had further evaluation or support for any of these psychosocial difficulties?

– Would you like to have further evaluation or support for it for you and/or your family?

NO ☐ YES ☐

NO ☐ YES ☐



Figure 3. (continued).

118

09

Please feel free to make notes of any other worries about TAND that were not covered in the TAND-SQ Checklist.



10

Taking together all the difficulties discussed in the TAND-SQ Checklist, how much have these bothered, troubled or distressed you and/or your family over the last month?

Not at all012345678910Extremely

11

Of all the concerns listed above, what are your top priorities to work on next?



12

We all develop or learn strategies to manage our day-to-day lives with TAND. Write down any strategies that are helping you/[subject] at the moment. This could be helpful when monitoring progress over time.



13

So far we have focused on difficulties and challenges. However, our journeys with TSC often also bring good things. Each person with TSC has their own strengths, skills and talents that can bring joy into our lives! Write down some of those good things, thinking particularly over the last month. This may include happy moments, small victories, or anything else you might be celebrating at the moment.



Figure 3. (continued).

14

TAND Cluster Profile

Now that you have rated the TAND challenges you/[subject] may be experiencing, here we will help you identify your own TAND Cluster Profile. We hope that this will help you to plan your next steps for assessment, intervention and support.

The seven natural TAND Clusters*

This table shows all the items that make up specific TAND Clusters. If you ticked 'YES' for any of these items in **question 3** (p3), **question 6** (p8) or **question 7** (p9) of the TAND-SQ Checklist, make a tick in the relevant row. Once you have gone through the whole list, you will see which of the seven natural TAND Clusters might be relevant to you and your family.

TAND-SQ Checklist Number and Checklist Item	Autism-like cluster	Dysregulated behaviour cluster	Eat/sleep cluster	Mood/anxiety cluster	Neuropsychological cluster	Overactive/Impulsive cluster	Scholastic cluster
3a Anxiety	-	-	-	☐	-	-	-
3b Depressed mood	-	-	-	☐	-	-	-
3c Extreme shyness	-	-	-	☐	-	-	-
3d Mood swings	-	-	-	☐	-	-	-
3e Aggressive outbursts	-	☐	-	-	-	-	-
3f Temper tantrums	-	☐	-	-	-	-	-
3g Self-injury	-	☐	-	-	-	-	-
3h Delayed language	☐	-	-	-	-	-	-
3i Repeating words / phrases	☐	-	-	-	-	-	-
3j Poor eye contact	☐	-	-	-	-	-	-
3k Getting on with peers	☐	-	-	-	-	-	-
3l Repetitive behaviour	☐	-	-	-	-	-	-
3m Rigid or inflexible behaviour	☐	-	-	-	-	-	-
3o Overactivity	-	-	-	-	-	☐	-
3p Paying attention / concentrating	-	-	-	-	☐	-	-
3q Restlessness / fidgetiness	-	-	-	-	-	☐	-
3r Impulsivity	-	-	-	-	-	☐	-
3s Eating difficulties	-	-	☐	-	-	-	-
3t Sleeping difficulties	-	-	☐	-	-	-	-
6a Reading difficulties	-	-	-	-	-	-	☐
6b Writing difficulties	-	-	-	-	-	-	☐
6c Spelling difficulties	-	-	-	-	-	-	☐
6d Mathematics difficulties	-	-	-	-	-	-	☐
7c Neuropsychological attention deficits	-	-	-	-	☐	-	-
7d Dual-tasking / multi-tasking difficulties	-	-	-	-	☐	-	-
7e Memory difficulties	-	-	-	-	☐	-	-
7f Visuo-spatial difficulties	-	-	-	-	☐	-	-
7g Executive difficulties	-	-	-	-	☐	-	-
7h Disorientation	-	-	-	-	☐	-	-

Figure 3. (continued).

The Wraparound Psychosocial Cluster

If you ticked ‘YES’ for any of the items in question 8 (p11) of the TAND-SQ Checklist, make a tick in the relevant row below. It will show whether the psychosocial cluster might be an area of concern to you.

	Psychosocial Cluster – Individual	Psychosocial Cluster – Caregiver
8.1a Low self-esteem	☐	
8.1b Stress in family	☐	
8.1c Stress in sibling relationships	☐	
8.1d Parent-child relationship difficulties	☐	
8.1e Parent-parent/partner relationship difficulties	☐	
8.1f Difficulty connecting in community	☐	
8.1g Difficulties in career	☐	
8.2a Low self-esteem		☐
8.2b Stress in family		☐
8.2c Stress in sibling relationships		☐
8.2d Parent-child relationship difficulties		☐
8.2e Parent-parent/partner relationship difficulties		☐
8.2f Difficulty connecting in community		☐
8.2g Difficulties in career		☐

*This table is based on the natural TAND clusters as identified in a paper published by de Vries and colleagues in *Orphanet Journal of Rare Diseases*, 2021, 16: 447. You may notice that the TAND-SQ has additional items not included in the earlier cluster work.



Thank You!

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Figure 3. (continued).

strengths, and a summary TAND Cluster Profile. The TAND Cluster summary was specifically added to allow families to identify their own cluster profile that could then be linked to “next step” recommendations in the recently developed international consensus recommendations for the identification and treatment of TAND and the TAND Toolkit, developed as part of the TANDem project.¹⁸

Feasibility and acceptability ratings of the “near-final” TAND-SQ Checklist showed high scores on the comprehensiveness, clarity,

ease of use, and overall acceptability of the checklist. We were encouraged by the similarity in acceptability ratings by those completing the checklist for themselves (adults with TSC), those completing it as a proxy (for example, caregivers of children with TSC), technical experts in TSC, and lived experts, which suggests the TAND-SQ Checklist has broad applicability for the TSC community. Overall, we feel that this checklist therefore fulfills an expressed need of the TSC community to identify and track TAND difficulties,

equipping caregivers and individuals with TSC to raise their concerns with their healthcare providers, and thus guiding their search for help.

Open-ended feedback revealed some concerns about the checklist, some of which we could not address in this final paper version. Caregivers of very young children and adults with TSC found that some applicability to their specific age group was lost in having one checklist for all. As the TAND identification and treatment gap is still so wide, we feel that one self-report checklist is preferable to increase usage across the TSC community, rather than many different checklists. Also, some provision has been made for very young children in Question 06 (difficulties in learning in school) where caregivers have the option to check “Not yet in school.” In other questions, where relevant, respondents have the option to skip questions or to simply answer “No.” Some of these concerns will also be addressed in the next steps of the TANDem project.¹⁷ The TAND-SQ Checklist is being built into a smartphone application (app), allowing for the automated selection of certain questions to display. In the app, the caregiver has the option to select school status “Not yet in school” for a toddler, for instance, then Question 06 on difficulties in learning in school will be skipped. Similarly, if an individual is completing the checklist about themselves, Questions 01 and 02 on developmental milestones and current abilities and Question 8.2 on psychosocial impact of the caregiver will not display. We are hopeful that this automated selection functionality within the app will improve the experience of completing the checklist for caregivers of very young children and adults with TSC. To ensure that there will always be consistency between the app-based TAND-SQ and the paper version, we will ensure consistency between the two, including any future revisions of TAND cluster or severity quantification.

We acknowledge that TAND is highly heterogeneous and that the sample size used here may at first glance appear relatively small. For the purpose of feasibility and acceptability evaluation, the priority was to seek feedback from a diverse sample of participants (across ages, abilities, and difficulties) and including self and caregiver report. Although the sample size is therefore relatively small, it represented a broad group of participants that showed remarkably consistent feasibility and acceptability data; this reassured us that the TAND-SQ will therefore have broad applicability in the TSC community.

We are also hopeful that another component of the TANDem project will address the very valid concerns raised about “next steps,” or what to do after completing the checklist. In aim 2 of the TANDem project¹⁷ evidence-informed consensus recommendations for the identification and treatment of TAND have been developed.¹⁸ These recommendations include a set of “core principles” for the identification and treatment of TAND, as well as cluster-specific recommendations. In addition to the published consensus clinical recommendations, the smartphone app developed as part of the TANDem project will include a “TAND toolkit.” Once respondents have completed the TAND-SQ Checklist in the app, the app will generate a personalized TAND Cluster Profile designed to guide caregivers and individuals with TSC to prioritize their next steps. Each cluster will then be linked to an evidence-informed set of recommendations of “what to seek” (further evaluations or interventions from specialists or other health care providers) and “what to do” (a curated set of evidence-informed tips, strategies, or resources that can be implemented or accessed independently) for that cluster. We hope that these two elements will help to address this vitally important feedback on the TAND-SQ Checklist.

In a strategy similar to our work on the TAND-L Checklist, we are presenting the TAND-SQ and its feasibility findings in this article, and validation data separately.^{2,6} Evaluation of the psychometric

properties of the TAND-SQ is clearly important to ensure that the tool measures in a feasible and acceptable way (data presented here) what it purports to measure, with internal consistency in the expanded clusters, and external validity in relation to widely used and standardized rating scales and diagnostic instruments, both from “real-world” clinical data and from research data. In addition, we will present novel ways to quantify TAND item, cluster, and total TAND severity and explore these severity quantifications in relation to external measures. These are all goals of the ongoing TANDem project.¹⁷

Conclusion

The new paper version of the TAND-SQ, a self-report quantified TAND Checklist, was described and is presented here for public use. The TAND-SQ Checklist appears to be feasible to complete and highly acceptable to a broad range of stakeholders within the TSC community, including caregivers and individuals with TSC. We feel it fulfills an expressed need by caregivers and individuals for a checklist they could fill out themselves and take to clinical visits to help advocate for and guide intervention for TAND. We outlined important next steps for the TAND-SQ Checklist and how the incorporation of the final TAND-SQ Checklist into a smartphone app as part of the TANDem project¹⁷ may directly empower families by linking them to evidence-informed recommendations for intervention.

Declaration of competing interest

S.B. has received seed funding as part of the TANDem project to investigate caregiver experiences in TSC. P.E.D. receives partial salary support from Aucta Pharmaceuticals for a study of topical sirolimus for facial angiofibromas in TSC and Marinus Pharmaceuticals for a study of ganaxolone for TSC-related epilepsy. D.K. reports personal fees from Novartis Pharmaceuticals, personal fees from Greenwich Bioscience, grants from Marinus Pharmaceuticals, personal fees from Nobelpharma America, and personal fees from REGENXBIO outside the submitted work. M.S. reports grant support from Novartis, Biogen, Astellas, Aeovian, Bridgebio and Aucta. M.S. has served on scientific advisory boards for Novartis, Roche, Regenxbio, SpringWorks Therapeutics, Jaguar Therapeutics, and Alkermes. C.S. is an employee of the TSC Alliance, a non-profit organisation which reports revenue from individual donors and corporations including Aeovian, Jazz Pharmaceuticals, BridgeBio, LivaNova, Lundbeck, Mallinckrodt, MassMutual, Neurelis, Nobelpharma America, Novartis, Ovid, UCB, and Upsher-Smith. A.M.v.E. has provided consultancy to GW Pharma and reports a grant from GW Pharmaceuticals for TAND-related research during the conduct of the study. A.C.J. was on the scientific advisory group of the TOSCA international disease registry sponsored by Novartis and has provided consultancy to GW Pharma. P.J.d.V. was a study steering committee member of three phase III trials sponsored by Novartis, was on the scientific advisory group of the TOSCA international disease registry sponsored by Novartis and has provided consultancy to GW Pharma. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.pediatrneurol.2023.07.001>.

References

1. Krueger DA, Northrup H, Krueger DA, et al. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatr Neurol.* 2013;49:255–265. <https://doi.org/10.1016/j.pediatrneurol.2013.08.002>.
2. de Vries PJ, Whittemore VH, Leclezio L, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND checklist. *Pediatr Neurol.* 2015;52:25–35. <https://doi.org/10.1016/j.pediatrneurol.2014.10.004>.
3. Leclezio L, de Vries PJ. Towards an improved understanding of TSC-associated neuropsychiatric disorders (TAND). *Adv Autism.* 2016;2:76–83. <https://doi.org/10.1108/AIA-12-2015-0025>.
4. Vanclooster S, Bissell S, van Eeghen AM, et al. The research landscape of tuberous sclerosis complex – associated neuropsychiatric disorders (TAND)— a comprehensive scoping review. *J Neurodev Disord.* 2022;14:13. <https://doi.org/10.1186/s11689-022-09423-3>.
5. Leclezio L, Jansen A, Whittemore VH, de Vries PJ. Pilot validation of the tuberous sclerosis-associated neuropsychiatric disorders (TAND) checklist. *Pediatr Neurol.* 2015;52:16–24. <https://doi.org/10.1016/j.pediatrneurol.2014.10.006>.
6. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry.* 2001;40:1337–1345. <https://doi.org/10.1097/00004583-200111000-00015>.
7. Cervi F, Saletti V, Turner K, et al. The TAND Checklist: a useful screening tool in children with tuberous sclerosis and neurofibromatosis type 1. *Orphanet J Rare Dis.* 2020;15:237. <https://doi.org/10.1186/s13023-020-01488-4>.
8. Park S, Eom S, Kang HC, Lee JS, Kim HD, Chung HJ. Screening of tuberous sclerosis-associated neuropsychiatric disorders in Korea using the TAND Checklist. *Ann Child Neurol.* 2021;29:8–14. <https://doi.org/10.26815/acn.2020.00220>.
9. Pokharel S, Jyotsana P, Maharjan RS, Singh R, Pandit K. Tuberous sclerosis complex-associated neuropsychiatric disorder (TAND) in a low-resource setting – from seizure to psychosis: a case report. *Ann Med Surg.* 2020;60:734–736. <https://doi.org/10.1016/j.amsu.2020.11.084>.
10. Toldo I, Brasson V, Miscioscia M, et al. Tuberous sclerosis-associated neuropsychiatric disorders: a paediatric cohort study. *Dev Med Child Neurol.* 2019;6:168–173. <https://doi.org/10.1111/dmcn.14055>.
11. Uematsu M, Numata-Uematsu Y, Aihara Y, et al. Behavioral problems and family distress in tuberous sclerosis complex. *Epilepsy Behav.* 2020;111:107321. <https://doi.org/10.1016/j.yebeh.2020.107321>.
12. Leclezio L, Gardner-Lubbe S, de Vries PJ. Is it feasible to identify natural clusters of TSC-associated neuropsychiatric disorders (TAND)? *Pediatr Neurol.* 2018;81:38–44. <https://doi.org/10.1016/j.pediatrneurol.2017.12.006>.
13. de Vries PJ, Belousova E, Benedik MP, et al. Natural clusters of tuberous sclerosis complex (TSC)-associated neuropsychiatric disorders (TAND): new findings from the TOSCA TAND research project. *J Neurodev Disord.* 2020;12:24. <https://doi.org/10.1186/s11689-020-09327-0>.
14. de Vries PJ, Leclezio L, Gardner-Lubbe S, et al. Multivariate data analysis identifies natural clusters of tuberous sclerosis complex associated neuropsychiatric disorders (TAND). *Orphanet J Rare Dis.* 2021;16:447. <https://doi.org/10.1186/s13023-021-02076-w>.
15. Alperin S, Krueger DA, Franz DN, et al. Symptom rates and profile clustering in tuberous sclerosis complex-associated neuropsychiatric disorders (TAND). *J Neurodev Disord.* 2021;13:60. <https://doi.org/10.1186/s11689-021-09408-8>.
16. Leclezio L. Identification of natural TSC-associated neuropsychiatric disorders (TAND) clusters (Doctoral Dissertation). University of Cape Town. 2017. Available at: <https://open.uct.ac.za/handle/11427/27084>. Accessed March 9, 2023.
17. Heunis T-M, Bissell S, Byars AW, et al. Empowering families through technology : a mobile-health project to reduce the TAND identification and treatment gap (TANDem). *Front Psychiatry.* 2022;13:834628. <https://doi.org/10.3389/fpsy.2022.834628>.
18. de Vries PJ, Heunis T-M, Vanclooster S, et al. International consensus recommendations for the identification and treatment of TSC-associated neuropsychiatric disorders (TAND). *J Neurodev Disord.* (in press).