

Development and feasibility of the self-report quantified TSC-Associated Neuropsychiatric Disorders Checklist (TAND-SQ) (120 characters of 120 max)

Heunis, Tosca-Marie; Chambers, Nola; Vanclooster, Stephanie; Bissell, Stacey; Byars, Anna W.; Capal, Jamie K.; Cukier, Sebastián; Davis, Peter E.; de Vries, Magdalena C.; De Waele, Liesbeth; Flinn, Jennifer; Gardner-Lubbe, Sugnet; Gipson, Tanjala; Kingswood, J. Christopher; Krueger, Darcy A.; Kumm, Aubrey J.; Sahin, Mustafa; Schoeters, Eva; Smith, Catherine; Srivastava, Shoba

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Development and feasibility of the self-report quantified TSC-Associated Neuropsychiatric Disorders Checklist (TAND-SQ) (120 characters of 120 max)

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Tosca-Marie Heunis^a, Nola Chambers^b, Stephanie Vanclooster^a, Stacey Bissell^c, Anna W. Byars^d, Jamie K. Capal^e, Sebastián Cukier^{f,g}, Peter E. Davis^h, Magdalena C. de Vries^b, Liesbeth De Waele^{i,j}, Jennifer Flinn^k, Sugnet Gardner-Lubbe^l, Tanjala Gipson^{m,n}, J. Christopher Kingswood^{o,p}, Darcy A. Krueger^{q,r}, Aubrey J. Kumm^b, Mustafa Sahin^{h,s}, Eva Schoeters^{t,u}, Catherine Smith^v, Shoba Srivastava^{b,w}, Megumi Takei^x, Agnies M. van Eeghen^{y,z}, Robert Waltereit^{aa,ab}, Anna C. Jansen^{a,ac,ad} and Petrus J. de Vries^{b*}

^aMental Health and Wellbeing Research Group, Department of Public Health, Vrije Universiteit Brussel, Brussels, Belgium

^bCentre for Autism Research in Africa (CARA), Division of Child and Adolescent Psychiatry, University of Cape Town, Cape Town, South Africa

^cSchool of Psychology, University of Birmingham, Birmingham, United Kingdom

^dDivision of Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center/University of Cincinnati College of Medicine, Cincinnati, OH, United States

^eDepartment of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

^fArgentine Program for Children, Adolescents and Adults With Autism Spectrum Disorders (PANAACEA), Buenos Aires, Argentina

^gDepartment of Psychopathology and Mental Health, Pedro de Elizalde Hospital, Buenos Aires, Argentina

^hDepartment of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, MA, United States

ⁱDepartment of Paediatric Neurology, University Hospitals Leuven, Leuven, Belgium

^jDepartment of Development and Regeneration, KU Leuven, Leuven, Belgium

^kTSC Canada, Mississauga, ON, Canada

^lDepartment of Statistics and Actuarial Sciences, Stellenbosch University, Stellenbosch, South Africa

^mDepartment of Pediatrics, University of Tennessee Health Sciences Center, Memphis, TN, United States

ⁿLe Bonheur Children's Hospital and Boling Center for Developmental Disabilities, Memphis, TN, United States

^oDepartment of Clinical Genetics, St George's University Hospitals, London, United Kingdom

^pSussex Renal Unit, The Royal Sussex County Hospital, Brighton, United Kingdom

^qTSC Clinic Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

^rDivision of Neurology, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, United States

^sRosamund Stone Zander Translational Neuroscience Center, Boston Children's Hospital, Boston, MA, United States

^tBelgian TSC Association (Be-TSC), Mortsels, Belgium

^uTuberous Sclerosis International (TSCI), Mortsels, Belgium

^vTSC Alliance, Silver Spring, MD, United States

^wSociety of Parents of Children with Autistic Disorders (SOPAN), Maharashtra, India

^xJapanese Society of Tuberous Sclerosis Complex, Family Network, Tokyo, Japan

^yEmma Children's Hospital, Amsterdam University Medical Center, Amsterdam, Netherlands

^zTAND Expert Centre, 's Heeren Loo, Hoofddorp, Netherlands

^{aa}Child and Adolescent Psychiatry, University Medical Center Göttingen, Göttingen, Germany

^{ab}Child and Adolescent Psychiatry, LWL-Klinikum Marsberg, Marsberg, Germany

^{ac}Pediatric Neurology Unit, Department of Pediatrics, Antwerp University Hospital

^{ad}Department of Translational Neurosciences, University of Antwerp, Antwerp, Belgium

Corresponding author. Petrus J de Vries, Centre for Autism Research in Africa (CARA), Division of Child and Adolescent Psychiatry, University of Cape Town, 46 Sawkins Road, Rondebosch, Cape Town, South Africa, 7700. Email: petrus.devries@uct.ac.za

Abstract

Introduction: Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND) are often present but under-identified and under-treated 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, in comparison to 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 TSC individuals and their caregivers. 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.

Keywords: Tuberous Sclerosis Complex, TSC-Associated Neuropsychiatric Disorders (TAND), TAND Checklist, feasibility, acceptability, stakeholder engagement, self-report

INTRODUCTION

The year 2022 marked the 10th 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 multi-level range of neuropsychiatric difficulties that were often present, but not identified or treated in individuals with TSC ^{1,2}. TAND includes difficulties at the behavioural 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 neuropsychological 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 (118/230; 51%) ⁴.

To help families and clinicians screen for these difficulties, the TAND Checklist (Lifetime Version, TAND-L) was developed ². It 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. They also found that items endorsed on the TAND-L Checklist correlated significantly with other standardised measures, suggesting acceptable external validity. For example, the total number of behavioural 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 (SDQ) ⁵. Similar correlations were observed between subdomain TAND-L Checklist items and subdomain scores on the SDQ for inattention ($\rho = 0.77$; $p < 0.001$) and social difficulties ($\rho = -0.65$; $p < 0.002$). TAND-L subdomain scores for neuropsychological skills also correlated with the Behaviour Rating Inventory of Executive Functions (BRIEF), a widely used standardised screening tool for executive deficits, specifically with the Global Executive Score ($\rho = 0.79$, $p < 0.001$), the BRIEF Behavior Rating Index (BRI) score ($\rho = 0.74$, $p < 0.001$), and the Metacognition Index (MI; $\rho = 0.59$, $p < 0.016$) ⁶.

Since its publication, the TAND-L Checklist has been translated into 18 languages (for authorised translations, please see www.tandconsortium.org/checklists/) and has been used to explore TAND in

a range of research studies in various countries⁷⁻¹¹. It was used as the basis for generating 'natural TAND clusters' of symptoms¹²⁻¹⁴ and to identify naturally occurring patient profiles ranging from high to low symptom burden¹⁵. 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 study¹², focus group interviews with families from Africa, USA, 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 (UK) and the TSC Alliance (USA). 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 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 of the TAND-L Checklist that could be used by families outside the context of a clinical visit. Family stakeholders were very keen that technology should be used, for instance, by making the Checklist accessible via a smartphone 'app'. Secondly, stakeholders reported the desire for a version of the TAND Checklist that not only identified lifetime TAND difficulties, but also allowed for the quantification of severity of current difficulties^{16,17}. Thirdly, stakeholders expressed the need for 'next step' information of what can be done once these TAND difficulties had been identified.

These recommendations led to the aims and objectives of the TANDem project, a 4-year multi-step project funded by the King Baudouin Foundation¹⁷. Within the TANDem project, the first aim was to develop and validate a self-report quantified TAND Checklist (TAND-SQ), and to build it into a smartphone application. Here we focussed on one part of this aim – development of the TAND-SQ Checklist, including feasibility and acceptability testing. Three specific objectives were identified, as outlined in Table 1.

Table 1. Study Aim and Objectives

Aim	Objectives
To develop a self-report quantified TAND Checklist (TAND-SQ) and conduct feasibility and acceptability testing	1. Develop the TAND-SQ Checklist
	2. Conduct feasibility and acceptability testing of the 'near-final' TAND-SQ
	3. Prepare the final TAND-SQ Checklist

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.

METHODS

TAND-SQ Checklist Development

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.

[Insert Figure 1 about here]

Figure 1: Development of the TAND-SQ Checklist

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 which began at the official launch meeting of the TANDem project in 2019. Activities at the project launch meeting included a) a review of existing items and their descriptions for self-report, b) identification of new items to include, and c) decisions on how to quantify the checklist and the timeframe 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 copy-edited 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, 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 living 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

This expert group consisted of an interdisciplinary, international group of 24 clinical, research and technical experts in TSC (or related areas) who were all members of the TAND consortium, set up as part of the TANDem project (www.tandconsortium.org). The TAND consortium included 6 '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 5 members within the TAND consortium who were responsible for the day-to-day running of the TANDem project.

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 sub-study to the existing TSC Alliance Natural History Database and allows families and/or individuals to report on their own health outcomes. The TSC Alliance utilised various recruitment methods, including posting information about the project on their website, online community support and Facebook pages, email 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 co-ordinators 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, behaviours causing concern, psychiatric disorders, intellectual ability, difficulties in school, and difficulties with brain (neuropsychological) skills. It 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 behavioural 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 where participants were asked to rate aspects of feasibility on a 5-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 analysed 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 analysed 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 USA that permits use of de-identified 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 behavioural 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 on the interviewer's judgment of the impact of TAND on the individual/child/family was removed.

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: Behaviours 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 Severity rating scale of 0 – 10 added for all items
	Question 07: Difficulties in brain skills	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
Phase 3	Questions 9, 10, 11	Order of questions rearranged
	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

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 behaviours causing concern (question 03), difficulties in learning in school (question 06), and difficulties in specific brain skills (question 07). Similar to other behavioural rating scales, the timeframe 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 of 11.9 years (standard deviation, SD = 9.82) ranging from 7 months to 33 years], 2 caregivers of adult siblings with TSC (ages 62 and 68 years respectively), and 13 individuals with TSC who completed the checklist for themselves [3 males, 10 females, mean age of 36.69 years (SD = 13.05), ranging from 20 to 64 years]. There were 13 participants from BCH and CCH, 8 were caregivers of children with TSC [3 sons and 5 daughters, mean age of 10 years (SD = 4) ranging from 2 to 15 years], 3 were caregivers of adults with TSC (23, 25 and 27 years of age), and 2 were adult individuals with TSC (2 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, a) technical experts (TAND consortium participants, n = 23), b) caregivers (parents and adult siblings; n = 43), and c) individuals with TSC (n = 15).

Quantitative Findings

The technical expert group reported that the TAND-SQ Checklist took them on average 17.17 minutes (SD = 7.20) to complete, caregivers took a mean of 15.37 minutes (SD = 6.60), and individuals with TSC took 16.64 minutes (SD = 8.42) with one outlier reporting a completion time of 90 minutes. The quantitative responses from the checklist feedback form for all participant groups are presented in Figure 2. All groups had high mean 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 the 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' (13/36 = 36%), while the majority (23/36 = 64%) rated it as 'better' or 'much better' than the TAND-L Checklist.

[Insert Figure 2 about here]

Figure 2: Quantitative responses on the TAND-SQ Checklist feasibility and acceptability testing. Figures A – G represent the percentage respondents per group for each item of the checklist feedback form.

Qualitative Findings

The open-ended responses to each checklist feedback form question were analysed 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.”

While the purpose of the TAND-SQ Checklist is to identify TAND challenges to help 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. While it is impossible to address every need with a paper checklist, it is precisely this perspective that led to the aims of the TANDem Project¹⁷. 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 potentially guide their next steps. The order of questions 09, 10 and 11 was also rearranged. The final TAND-SQ Checklist is presented in Figure 3 and is available as a supplement for download (see *Supplementary Data*) and on the TAND consortium website (www.tandconsortium.org/checklists).

[Insert Figure 3 – the TAND Checklist about here]

Figure 3: The TAND-SQ Checklist

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 paper (see Figure 3) and can now be used by caregivers and individuals with TSC. Notable additions to the TAND-SQ Checklist as compared to the TAND-L Checklist include the severity rating of behavioural difficulties, additional items related to neuropsychological and psychosocial difficulties, and sections highlighting strategies, 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 ¹⁷.

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 fulfils 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 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. Whilst 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 developed¹⁸. 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 personalised TAND Cluster Profile designed to guide caregivers and individuals with TSC to prioritise 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 healthcare 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 manuscript, and validation data separately^{2,6}. Evaluation of the psychometric properties of the TAND-SQ is clearly important to ensure that the tool measures what it purports to measure in an acceptable way (data presented here), with internal consistency in the expanded clusters, and external validity in relation to widely-used and standardised 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 project¹⁷.

CONCLUSION

The new paper version of the TAND-SQ Checklist, a self-report quantified TAND Checklist, was described and 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 fulfils 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 further referrals 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 project ¹⁷ may directly empower families by linking them to evidence-informed recommendations for intervention.

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AUTHOR CONTRIBUTIONS

PJdV and ACJ were co-PIs and conceptualised the TANDem project, secured funding and recruited members of the TAND consortium. PdJV, ACJ, TH, NC, SV and LDW were all members of the Action Group and managed the overall project. All consortium members contributed to the design, drafting, and revising of the TAND-SQ Checklist. TH, NC and PJdV wrote the first draft of the manuscript. All consortium members reviewed and approved the final manuscript prior to submission.

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A special thanks to Deborah White from the Department of Shapes and Colours for her creative design of the TAND-SQ Checklist.

CONFLICT OF INTEREST

SB has received seed funding as part of the TANDem project to investigate caregiver experiences in TSC. PD 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. DK 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. MS reports grant support from Novartis, Biogen, Astellas, Aeovian, Bridgebio and Aucta. MS has served on scientific advisory boards for Novartis, Roche, Regenxbio, SpringWorks Therapeutics, Jaguar Therapeutics, and Alkermes. CS 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. AMvE has provided consultancy to GW Pharma and reports a grant from GW Pharmaceuticals for TAND-related research during the conduct of the study. ACJ was on the scientific advisory group of the TOSCA international disease registry sponsored by Novartis and has provided consultancy to GW Pharma. PJdV 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.

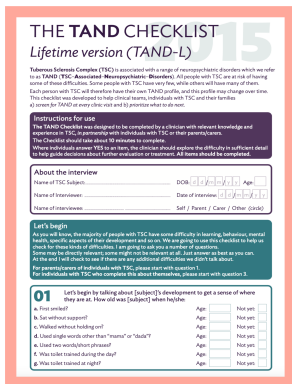
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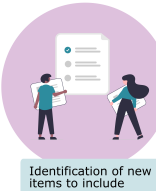
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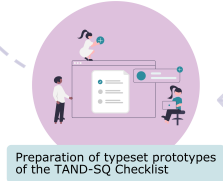
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1 Development of the TAND-SQ Checklist



Iterative review



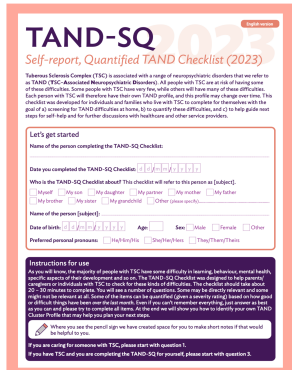
3 Preparation of the final TAND-SQ Checklist

2 Feasibility & acceptability testing of the 'near-final' TAND-SQ Checklist

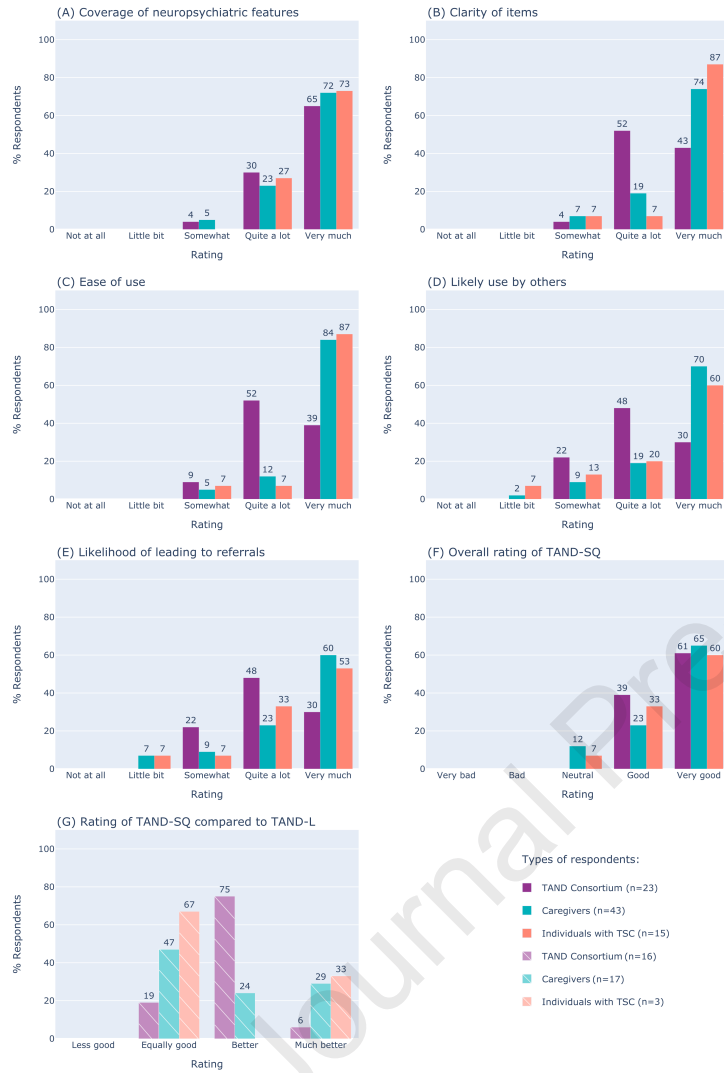


Feedback and suggestions from the study participants informed final revisions to the TAND-SQ Checklist

Each participant completed a TAND-SQ Checklist and a checklist feedback form on paper or electronically



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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: / /

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: / / 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.

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



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



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



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



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), *including autism, Asperger's* NO YES
- b. Attention Deficit Hyperactivity Disorder (ADHD) NO YES
- c. Anxiety Disorder, *including panic, phobia, separation anxiety disorder* NO YES
- d. Depressive Disorder NO YES
- e. Obsessive Compulsive Disorder (OCD) NO YES
- f. Psychotic Disorder, *including schizophrenia* 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



.....
.....

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



.....

.....

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



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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

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



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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



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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



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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



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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 | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| b. Very high levels of stress <i>in the family</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| c. Very high levels of stress <i>in relationship with siblings</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| d. Very high levels of <i>parent-child relationship difficulties</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| e. Very high levels of <i>parent-to-parent/partner relationship difficulties</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| f. Very high levels of stress leading to <i>difficulty for the family to connect with others in their community</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| g. Very high levels of stress leading to <i>difficulty for you to progress in your career</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |

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? | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| - Would you like to have further evaluation or support for it for you and/or your family? | NO <input type="checkbox"/> YES <input type="checkbox"/> |



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8.2

As the caregiver, have you ever had difficulties with:

- | | |
|---|--|
| a. Low self-esteem | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| b. Very high levels of stress <i>in your family</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| c. Very high levels of stress <i>in your relationship with your siblings</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| d. Very high levels of <i>parent-child relationship difficulties</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| e. Very high levels of <i>parent-to-parent/partner relationship difficulties</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| f. Very high levels of stress leading to <i>difficulty for your family to connect with others in your community</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| g. Very high levels of stress leading to <i>difficulty for you to progress in your career</i> | NO <input type="checkbox"/> YES <input type="checkbox"/> |

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? | NO <input type="checkbox"/> YES <input type="checkbox"/> |
| - Would you like to have further evaluation or support for it for you and/or your family? | NO <input type="checkbox"/> YES <input type="checkbox"/> |



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09

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



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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 all 0 1 2 3 4 5 6 7 8 9 10 Extremely

11

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



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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.



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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.



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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	-	-	-	<input type="checkbox"/>	-	-	-
3b Depressed mood	-	-	-	<input type="checkbox"/>	-	-	-
3c Extreme shyness	-	-	-	<input type="checkbox"/>	-	-	-
3d Mood swings	-	-	-	<input type="checkbox"/>	-	-	-
3e Aggressive outbursts	-	<input type="checkbox"/>	-	-	-	-	-
3f Temper tantrums	-	<input type="checkbox"/>	-	-	-	-	-
3g Self-injury	-	<input type="checkbox"/>	-	-	-	-	-
3h Delayed language	<input type="checkbox"/>	-	-	-	-	-	-
3i Repeating words / phrases	<input type="checkbox"/>	-	-	-	-	-	-
3j Poor eye contact	<input type="checkbox"/>	-	-	-	-	-	-
3k Getting on with peers	<input type="checkbox"/>	-	-	-	-	-	-
3l Repetitive behaviour	<input type="checkbox"/>	-	-	-	-	-	-
3m Rigid or inflexible behaviour	<input type="checkbox"/>	-	-	-	-	-	-
3o Overactivity	-	-	-	-	-	<input type="checkbox"/>	-
3p Paying attention / concentrating	-	-	-	-	<input type="checkbox"/>	-	-
3q Restlessness / fidgetiness	-	-	-	-	-	<input type="checkbox"/>	-
3r Impulsivity	-	-	-	-	-	<input type="checkbox"/>	-
3s Eating difficulties	-	-	<input type="checkbox"/>	-	-	-	-
3t Sleeping difficulties	-	-	<input type="checkbox"/>	-	-	-	-
6a Reading difficulties	-	-	-	-	-	-	<input type="checkbox"/>
6b Writing difficulties	-	-	-	-	-	-	<input type="checkbox"/>
6c Spelling difficulties	-	-	-	-	-	-	<input type="checkbox"/>
6d Mathematics difficulties	-	-	-	-	-	-	<input type="checkbox"/>
7c Neuropsychological attention deficits	-	-	-	-	<input type="checkbox"/>	-	-
7d Dual-tasking / multi-tasking difficulties	-	-	-	-	<input type="checkbox"/>	-	-
7e Memory difficulties	-	-	-	-	<input type="checkbox"/>	-	-
7f Visuo-spatial difficulties	-	-	-	-	<input type="checkbox"/>	-	-
7g Executive difficulties	-	-	-	-	<input type="checkbox"/>	-	-
7h Disorientation	-	-	-	-	<input type="checkbox"/>	-	-

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	<input type="checkbox"/>	
8.1b Stress in family	<input type="checkbox"/>	
8.1c Stress in sibling relationships	<input type="checkbox"/>	
8.1d Parent-child relationship difficulties	<input type="checkbox"/>	
8.1e Parent-parent/partner relationship difficulties	<input type="checkbox"/>	
8.1f Difficulty connecting in community	<input type="checkbox"/>	
8.1g Difficulties in career	<input type="checkbox"/>	
8.2a Low self-esteem		<input type="checkbox"/>
8.2b Stress in family		<input type="checkbox"/>
8.2c Stress in sibling relationships		<input type="checkbox"/>
8.2d Parent-child relationship difficulties		<input type="checkbox"/>
8.2e Parent-parent/partner relationship difficulties		<input type="checkbox"/>
8.2f Difficulty connecting in community		<input type="checkbox"/>
8.2g Difficulties in career		<input type="checkbox"/>

*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.



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Thank You!

CONFLICT OF INTEREST

SB has received seed funding as part of the TANDem project to investigate caregiver experiences in TSC. PD 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. DK 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. MS reports grant support from Novartis, Biogen, Astellas, Aeovian, Bridgebio and Aucta. MS has served on scientific advisory boards for Novartis, Roche, Regenxbio, SpringWorks Therapeutics, Jaguar Therapeutics, and Alkermes. CS 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. AMvE has provided consultancy to GW Pharma and reports a grant from GW Pharmaceuticals for TAND-related research during the conduct of the study. ACJ was on the scientific advisory group of the TOSCA international disease registry sponsored by Novartis and has provided consultancy to GW Pharma. PJdV 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.