Pilot validation of the Tuberous Sclerosis Associated Neuropsychiatric Disorders (TAND) Checklist as a screening tool for neuropsychiatric manifestations

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DECLARATION

I, Loren Leclezio (LCLLOR001), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor part of it has been, is being, or is to be submitted for another degree in this or any other university.
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Abstract

Background: Tuberous Sclerosis Complex (TSC) is a multi-system disorder that includes a range of neuropsychiatric manifestations. The majority of individuals with TSC will have neuropsychiatric problems, with lifetime prevalence rates in the region of 90%. Survey results unfortunately suggest a vast gap between need and actual assessment/treatment. At the 2012 International TSC Consensus Conference the Neuropsychiatry panel coined the term TAND (TSC-Associated Neuropsychiatric Disorders) and recommended that all individuals with TSC should be screened for TAND at least annually. To aid in the systematic enquiry of the behavioural, psychiatric, intellectual, neuropsychological, academic and psycho-social difficulties experienced by individuals with TSC, a 'TAND Checklist' was developed to act as an 'aide-mémoire' to clinicians. Here we performed a pilot validation of the TAND Checklist.

Method: Mixed-methods were used across three stages in the pilot validation of the TAND Checklist. In stage 1 we gathered feedback on the Checklist from 16 international TSC experts and 42 parents/carers. The aim was to examine face and content validity. Stage 2 involved the administration of the refined TAND Checklist to 20 South African parents of individuals with TSC concurrently with four other validated assessment tools. The aim of this stage was to examine concurrent validity and to obtain qualitative feedback on face-to-face administration of the TAND Checklist. Stage 3 involved the collection of demographic and clinical data about the individuals with TSC evaluated in Stage 2.

Results: Expert clinicians as well as families rated the TAND Checklist to have good face and content validity as reflected in quantitative analysis which showed high overall mean and median scores of 4 and 5 (five being the maximum rating). Interestingly, face to face administration was associated with significant higher ratings for 'clarity' (P = 0.003) supporting advantages of face-to-face administration of the Checklist. Qualitative analysis highlighted some concerns about the likely use of the TAND Checklist, in particular suggesting that family members of individuals with TSC should drive its usage. Stage 2 results showed moderate to very good external validity across the behaviour domain, social-communication subdomain, hyperactivity subdomain, intellectual ability, neuropsychological domain and executive subdomain. Limited validation was performed around scholastic skills, and the psycho-social domain did not show very robust correlation with external instruments used. The TAND Checklist clinician impact score correlated very well with the impact score generated by the SDQ. Internal consistency of domains and subdomains was acceptable to very good. Stage 3 demographic data suggested that only 25% of the study population had received any tertiary education, and that 50% of the sample earned <R3,000 (~$300/£250) per month.

Conclusion: Pilot validation of the TAND Checklist supported face and content validity, and showed good external validity. Findings suggest that this simple, pen-and-paper tool may be a quick (about 10 minutes) and helpful aide-mémoire in the identification and subsequent treatment of TAND even when administered by a non-clinician with relatively little expertise in TSC. Results of other aspects of validity and qualitative feedback were used to shape the Checklist to be both clinically meaningful and a useful research tool for future studies.

Keywords: TSC, TAND.

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
AMPK	AMP-activated protein kinase
ASD	Autism spectrum disorder
BRIEF	Behaviour rating inventory of executive function
BRI	Behaviour rating index (of the BRIEF)
M	Mean
MAPK	Mitogen-activated protein kinases
Mdn	Median
MI	Metacognition index (of the BRIEF)
mTOR	Mammalian target of rapamycin
SCQ	Social communication questionnaire
SD	Standard deviation
SPSS	Statistical package for social sciences
TAND	Tuberous sclerosis associated neuropsychiatric disorders
TSC	Tuberous sclerosis complex

Key Terms

Angiomyolipomas

Attention deficit hyperactivity disorder (ADHD)

Autism spectrum disorder (ASD)

Behavioural phenoype

Disruptive behaviour disorders

International tuberous sclerosis complex consensus conference

Lymphangioleiomyomatosis (LAM)

Neuropsychiatric disorders

Neuropsychiatric phenotype

Subependymal giant cell astrocytomas (SEGA)

Subependymal nodules (SEN)

Tuberous sclerosis associated neuropsychiatric disorders (TAND)

Tuberous sclerosis complex (TSC)

Chapter 1 Tuberous Sclerosis Complex

This thesis will outline the pilot validation of the Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND) Checklist. Chapter 1 will provide background information on Tuberous Sclerosis Complex (TSC), its genetic origins, diagnostic criteria, physical manifestations and a literature review of the neuropsychiatric manifestations. Next it will look at TAND and the TAND Checklist. Chapter 2 will discuss the methodology used across 3 stages and results will be presented in Chapter 3. Chapter 4 will present a discussion of the results from the pilot validation of the Checklist and Chapter 5 will draw together conclusions from the study.

1.1 Background

Tuberous sclerosis complex (TSC) is a genetic disorder with multi-system involvement. TSC can affect virtually any organ system, with some more prevalent during infancy and childhood and others more likely to affect individuals as adults (Crino *et al*., 2006; Curatolo *et al.,* 2008). The most common manifestations are benign tumours in the heart, kidneys, lungs, skin and brain. TSC is also associated with a vast range of neuropsychiatric disorders, typically neurodevelopmental, behavioural and psychiatric difficulties.

The disorder is caused by mutations in either of two genes, the *TSC1* gene on chromosome 9q34 (van Slegtenhorst *et al.,* 1997; Povey *et al*., 1994) or the *TSC2* gene on chromosome 16p13.3. (The European Chromosome 16 Consortium 1993; Povey *et al*., 1994). The protein products of *TSC1* (hamartin) and *TSC2* (tuberin) regulate and integrate intracellular signalling pathways, including the PI3K, AMPK and MAPK pathways (de Vries and Howe, 2007). A mutation in either *TSC1* or *TSC2* may disrupt the *TSC1-2* complex, resulting in over-activation of mammalian target of rapamycin (mTOR) signalling, which

critically regulates cell growth and proliferation (Tee *et al*., 2002; Kenerson *et al*., 2002). The TSC1/2-TOR signalling pathway also regulates various other intracellular processes, including protein synthesis, in response to growth factors and nutrient availability. The TSC1/2-mTOR proteins act as integrators of a range of intracellular signalling pathways and not only TSC but also in various other genetic disorders are associated with abnormalities in this signalling pathway (de Vries, 2010; Serfontein *et al*., 2011).

Serfontein *et al.* (2010) examined the evolution of the TSC1/2-TOR signalling pathway and, using complete genome sequences, found that the present pathway was built up from an ancestral one linking growth and energy supply. The authors proposed that, after the divergence of the main eukaryote lineages, the pathway became more sophisticated in some lineages through the incorporation of additional input (such as TSC1-TSC2) and output elements to a central core (Serfontein *et al*., 2010). Further evolutionary explorations showed showed that not all model organisms with TSC1 and TSC2 have high similarities to the human sequence with regards to structure and functional elements. Results suggested that other mammalian proteins rat (*Rattus norvegicus*) and mouse (*Mus musculus*), share the largest number of residues with human proteins, making these generally appropriate as models for human TSC (Serfontein *et al.,* 2011).

The birth incidence of TSC is estimated to be 1 in 6,000 (Osborne *et al*., 1991; O'Callaghan *et al*., 1998; Thiele and Jozwiak, 2010) and appears to have an equal male/female distribution. The majority of cases (up to 75%) occur as spontaneous mutations and the remaining ~25% are familial and inherited in an autosomal dominant fashion (Crino *et al*., 2006). Among familial cases *TSC1* and *TSC2* are equally distributed; the majority of sporadic cases have a *TSC2* gene mutation (Jones *et al*., 1997). There is significant phenotypic variability in the number and severity of physical features of the disorder (Povey *et al.,* 1994). It is important to note that most individuals with TSC will have a normal life expectancy. Appropriate management and coordination of medical specialist

care is crucial across the lifespan of individuals with TSC to limit morbidity and mortality in this disease (Krueger *et al*., 2013).

Lagos and Gomez, based at the Mayo Clinic reported in 1967 the findings from a family of 71 individuals (over five generations) affected by TSC. These data led to the first set of diagnostic criteria proposed by Gomez. The so-called 'Gomez' criteria were revised in 1979 (Verdecchia *et al*., 2006). In 1998, the National Institutes of Health (NIH) sponsored the first Consensus Conference with the aim to develop consensus recommendations for diagnosis (Roach *et al*., 1998) and clinical management of individuals with TSC (Roach *et al*., 1999). The 1998 diagnostic criteria and 1999 monitoring guidelines were used over the past 15 years.

The last 15 years have however seen a number of significant advances in understanding the pathogenesis and potential treatments of TSC. In the 1990s, the *TSC1* and *TSC2* genes were discovered and a molecular diagnostic test for TSC was launched in the early 2000s (The European Chromosome 16 Consortium 1993; and Van Slegenhorst *et al.,* 1997). In 2001, the *Drosophila* homologues, *TSC1* and *TSC2,* were found to be involved in regulation of cell and organ size (Potter *et al.,* 2001; Tapon *et al*., 2001). This discovery led to two areas of additional important progress in 2002, firstly that tuberin (*TSC2* gene product) was found to be a target of the PI3k/akt signalling pathway (Manning *et al.,* 2002) and secondly, the identification that the *TSC1* and *TSC2* gene products worked together in a complex (Tee *et al*., 2002). This in turn led to discovering the critical role of the TSC genes in regulation of the mTOR pathway (Kenerson *et al*., 2002). Thereafter, an mTOR inhibitor, rapamycin, has been shown to reduce renal tumours in Eker rats (Kenerson *et al.,* 2005) and mouse models (Lee *et al*., 2005), and to reduce the size of SEGAs (Franz *et al*., 2006) and renal angiomyolipomas in individuals with TSC (Bissler *et al*., 2008; Davies *et al*., 2008). By the end of the first decade of the 21st century a number of large-scale clinical trials of mTOR inhibitors were underway for a number of organ systems in TSC.

Given the key advances in TSC, there was growing interest in convening a consensus conference to revisit the diagnostic criteria, and in particular, the monitoring and treatment guidelines for the disorder. The second International Tuberous Sclerosis Complex Consensus Conference was held in June 2012 in Washington DC, and brought together 79 individuals from 14 countries to review and reach consensus on diagnostic, surveillance, and management recommendations for individuals with TSC (Northrup *et al*., 2013). **Table 1.1** shows the updated diagnostic criteria for Tuberous Sclerosis Complex.

Table 1.1 Updated diagnostic criteria for tuberous sclerosis complex 2012

A. Genetic diagnostic criteria

The identification of either a *TSC1* or *TSC2* pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of Tuberous Sclerosis Complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen-Westerveld et al., 2012 and 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.

B. Clinical diagnostic criteria

Major features

1. Hypomelanotic macules (≥3, at least 5-mm diameter)

2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias*
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyomatosis
10. Lymphangioleiomyomatosis (LAM)**
11. Angiomyolipomas (≥2)**

Minor Features

1. "Confetti" skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (≥2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

Definite diagnosis: Two major features or one major feature with ≥2 minor features
Possible diagnosis: Either one major feature or ≥2 minor features

* Includes tubers and cerebral white matter radial migration lines
** A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for definite diagnosis

A variety of organs are involved in TSC and manifestations can occur at various times during an individual's lifespan. One of the organ systems most commonly affected is the brain, with manifestations seen in 90-95% of individuals with TSC. The main neuropathological features of TSC are cortical dysplasias (which

include cortical tubers and white matter radial migration lines), subependymal nodules (SENs), and subependymal giant cell atrocytomas (SEGAs) (Thiele and Jozwiak, 2010, Franz *et al.,* 2010). SENs typically occur in the area of the foramen of Monro in the lateral wall of the lateral ventricle and usually remain static throughout an individual's lifetime. Yet, in up to one-fifth of individuals with TSC progressive growth of a SEN is seen to lead to SEGA. SEGAs typically occur within the first 20 years of life (Franz *et al.*, 2010). They generally exceed 1cm in diameter (but can grow to >10cm), causing hydrocephalus, focal neurological deficits, and even death (Goh *et al*., 2004). These three lesions (CT, SEN, SEGA) demonstrate shared histopathological features including abnormal cellular morphology, different regional architecture, and excessive numbers of astrocytes (Crino *et al.*, 2010). For growing but otherwise asymptomatic SEGAs, either surgical resection or medical therapy with mTOR inhibitors can be effective treatment options (Krueger *et al*., 2010; Franz *et al*., 2013; Northrup *et al*., 2013).

Epilepsy is the most common neurological disorder in TSC, affecting 75-90% of individuals (Webb e*t al*., 1991; Thiele, 2004; Thiele and Weiner, 2010). Seizure onset occurs within the first year of life in a significant proportion of individuals. Partial and partial complex seizures are common in TSC, as well as secondarily generalised seizures. A third of infants with TSC will develop infantile spasms and a proportion will develop Lennox-Gastaut syndrome (LGS), both potentially catastrophic epilepsy syndromes (Muzykewics *et al.,* 2006; Thiele and Weiner, 2010). Anticonvulsant medications are currently used as first-line treatment options for seizures. However, up to three-fourths of individuals with TSC who have seizures will develop refractory epilepsy not effectively controlled by medical therapy (Kwan and Brodie, 2000; Chu-Shore *et al.,* 2009). Epilepsy surgery can be an effective therapeutic option, especially for children with TSC who have refractory epilepsy (Thiele *et al.*, 2010). Other treatment strategies for refractory epilepsy may include ketogenic diet and vagal nerve stimulation. More recently, early phase results have suggested that mTOR inhibitors may be an anti-epilepsy treatment in TSC. After a promising phase II trial (Krueger *et al.,*

2010) there is currently a multi-centre, international trial underway to evaluate the efficacy and safety of mTOR inhibitors as adjunctive treatment for partial seizures in TSC (ClinicalTrials.gov: NCT01713946 (EXIST-3)).

The second most frequently affected organ system in TSC is the skin, with manifestations also seen in 90-95% of individuals with TSC (Darling *et al*., 2010). TSC skin lesions have a characteristic appearance and include hypomelanotic macules (oval shaped off-white spots also known as “ash leaf spots”), facial angiofibromas (small reddish spots or bumps that consist of fibrous tissue and blood vessels), ungual fibromas, shagreen patches (firm irregular plaque with coalescing papules and nodules) and “confetti” skin lesion (small hypopigmented macules) (Northrup *et al*., 2013; Darling *et al*., 2010). Even though these skin lesions are benign, they may be painful and lead to bleeding. They can compromise normal functions of the nasal passage or nails, and distorts normal skin structures (Darling *et al*., 2010).

Ophthalmologic features include retinal hamartomas and are seen in ~50% of individuals with TSC (Thiele and Jozwiak, 2010). These lesions have similar histologic features to the brain tubers seen in TSC, are generally benign and typically do not affect vision (Northrup *et al*., 2013).

Cardiac rhabdomyomas are the earliest detectable hamartoma, often seen on foetal ultrasound or foetal MRI in TSC, and are the only lesions in TSC likely to regress with age (Jozwiak and Respondek-Liberska, 2010). These tumours are believed to occur in 50% of individuals with TSC and can be associated with cardiac arrhythmias including atrial and ventricular arrhythmia and Wolff-Parkinson-White syndrome (Thiele and Jozwiak 2010; O’Callaghan *et al*., 1998).

Lymphangioleiomyomatosis (LAM) is the primary pulmonary manifestation of TSC and occurs predominantly in females (McCormack and Henske, 2010). Cystic pulmonary parenchymal changes consistent with LAM are observed in 30-40% of female patients with TSC, although these women are frequently

asymptomatic (McCormack and Henske, 2010; Northrup *et al*., 2013). LAM is characterised by a proliferation of smooth muscle cells in nodules throughout the lung and associated with interstitial expansion of the lung (Northrup *et al*., 2013).

The kidney is affected in ~80-85% of individuals with TSC across their lifespan and include renal cysts and angiomyolipomas (AML) (Thiele and Jozwiak, 2010). AMLs are benign tumours composed of vascular, smooth muscle, and adipose tissue. Hemorrhage from renal AMLs (proportional to size) can cause serious issues and lead to need for dialysis, renal transplantation, and sometimes mortality in adults with TSC (Bissler and Henske 2010; Patel *et al.,* 2005; Bissler and Kingswood, 2004)

Currently there is no known cure for Tuberous Sclerosis Complex. However, an understanding of the functional relationship between the TSC1-2 complex and mTOR has lead to important clinical advances in the use of mTOR inhibitors. Everolimus (Votubia®, Afinitor ®) has been licenced by the European Medicines Agency (EMA) and Federal Drug Administration (FDA) for the treatment of SEGA not amenable to surgery and for angiomyolipomas >3cm. There are ongoing studies of mTOR inhibitors for the treatment of various physical manifestations of TSC including SEGA, AML, skin, LAM and epilepsy (NCT00789828; NCT00790400; Krueger *et al*., 2013).

1.2 The Neuropsychiatry of TSC

A range of behavioural, psychiatric, intellectual, academic, neuropsychological, and psycho-social concerns are seen in individuals with TSC. Neuropsychiatric manifestations range from developmental disorders such as Autism Spectrum Disorders (ASD), Attention Deficit/Hyperactivity Disorder (ADHD) and Intellectual Disability (ID), to mood and anxiety, and other psychiatric disorders (Gillberg *et al*., 1994; Smalley *et al*., 1994; Prather and de Vries, 2004; de Vries, 2010b). Even though there are a number of key neuropsychiatric disorders

associated with TSC at a group-based level, each individual with TSC will present with their own unique combination of strengths and weaknesses across different neuropsychiatric levels. **Table 1.2** summarises the different levels of investigation of relevance in the neuropsychiatric study of TSC.

Table 1.2: Different levels of neuropsychiatric investigation

Level of Investigation	Assessment
1. Behavioural	Direct observation, parent & carer surveys, rating scale measures
2. Psychiatric	DSM-IV/5 (APA, 1994) and/or ICD-10 (WHO, 1993)
3. Intellectual	Standardised measures of both general intelligence and adaptive behaviours
4. Academic / Scholastic	Standardised measures of reading, writing, spelling and mathematics
5. Neuropsychological	Rating scale measures (as proxies for brain-referenced skills), formal neuropsychological tools
6. Psycho-social	Direct observation, parent & carer surveys, self report
7. Biological	Impact of peripheral characteristics of TSC and other medical conditions on neuropsychiatric presentation

1.2.1 Behavioural Level

TSC is known to be associated with a range of behavioural difficulties with the first comprehensive and systematic surveys conducted by Ann Hunt in the 1980s (Raznahan *et al.,* 2006; de Vries *et al.,* 2007; Muzykewicz *et al*., 2007; Pulsifer *et al*., 2007; Chung *et al*., 2011). After her early large-scale surveys, Hunt, based in Oxford, later joined the Cambridge team of de Vries and Bolton (2007) to conduct a postal survey of children and adolescent with TSC. This study found that up to 69% of the cohort had social-communication difficulties, 40-50% demonstrated disruptive behaviours as well as mood related difficulties and up to 50% experienced sleep problems.

1.2.1.1 Social Communication

As per de Vries (2010b), the social communication behaviours seen in TSC show a strong correlation with intellectual ability. In the UK postal survey conducted by de Vries *et al.* (2007), 44% (111/250) of participants were reported to have poor eye contact, 55% (136/248) had repetitive and ritualistic behaviours, and 48% (119/246) had been classified as having an Autism Spectrum Disorder. Forty one percent of the group (80/195) were reported to have no communicative language, a further 69% (133/194) had speech/language delay, and only 23% of the sample (45/194) had normal language with no delay.

Section 1.2.2.1 will focus exclusively on Autism Spectrum Disorders in TSC.

1.2.1.2 Disruptive Behaviours

The more intellectually impaired individuals with TSC are, the more likely they are to have disruptive behaviours. However, individuals with normal intellectual ability (IQ>70) also demonstrate high rates of behavioural problems (de Vries *et al*., 2007; de Vries, 2010b). Most notable, difficulties are associated with restless and impulsive behaviour , high rates of aggression (13.3 – 58%; Kopp *et al.,* 2008; de Vries *et al.,* 2007; Hunt, 1997), temper tantrums (57%; de Vries *et al*., 2007) and self-injury (10 – 41%; Staley *et al.,* 2008; de Vries *et al.,* 2007; Hunt, 1997).

Section 1.2.2.1 will focus exclusively on ADHD in TSC.

1.2.1.3 Sleep

Research on sleep and TSC has been very limited. Neuroanatomical abnormalities, intellectual disability, psychiatric comorbidities, epilepsy and seizures, in addition to anticonvulsant medications could all potentially affect the development of circadian rhythms and of sleep-wake cycles (van Eeghen *et al*., 2011; Hancock *et al*., 2005). It is therefore not surprising that sleep disturbance is one of the most common behavioural problems in children with TSC. These can range from night wakings, waking early, and excessive daytime sleeping to seizure-related sleep problems (Curatolo *et al*., 1991; Stores, 1992). In one

postal survey of 300 individuals with TSC, carers reported the presence of sleep problems in 58% of the children and seizure-related sleep problems in 41% (Hunt, 1993). Bruni *et al*. (1995) performed overnight polysomnography in 10 children with TSC and ten healthy age-matched controls. Sleep architecture abnormalities were observed in 9 of the TSC cases with the TSC group showing shorter total sleep time, reduced sleep efficiency, a higher number of awakenings and stage transitions, an increased wake after sleep onset and decreased REM sleep. In the first study of sleep in adults with TSC, Eeghen *et al.* (2011) confirmed a high prevalence (31% of the cohort) of sleep disorders in adults with TSC (n=35) and an association with epilepsy features.

Taken together all possible behavioural difficulties associated with TSC, 60-70% of children with TSC as well as intellectual impairment are likely to present with one or more behavioural difficulty, and 20-30% of children with TSC with normal intellectual ability may have such behavioural difficulties (de Vries *et al*., 2007; Prather and de Vries, 2004).

1.2.2 Psychiatric Level

Estimates of psychiatric comorbidity in individuals with TSC have been highly variable. This is likely due to different populations studied, methodological differences in how formal psychiatric diagnoses were reached, and a range of other sampling or methodological issues. As pointed out by Chung *et al*. (2011), the importance of clinical expertise in diagnosing psychiatric disorders cannot be over-emphasized given the inherent difficulty in distinguishing psychiatric illness from one another and from other central nervous system (CNS) aspects of TSC. However, for clinical research findings to be sufficiently robust and reproducible, ‘clinical expertise’ is best accompanied by reliable and valid diagnostic instruments.

1.2.2.1 Developmental Disorders

Autism Spectrum Disorders (ASD)

Autism is a developmental disorder characterised by deficits in three main domains: reciprocal social interaction (such as poorly modulated eye contact, limited facial expressions, and lack of subtle skills in reciprocal social interaction), verbal and non-verbal communication (delay or lack of communicative language, stereotyped or unusual use of language, and limited or poorly integrated gestures), and restricted or repetitive pattern of behaviours and interests (such as preoccupation with unusual objects, repetitive play, stereotyped hand and finger mannerisms or sensory interests). To meet ICD-10 and DSM-IV criteria for an ASD, some of the developmental concerns have to be present by the age of 3 years (de Vries, 2010; World Health Organisation, 1994; American Psychiatric Association, 2000). The diagnostic criteria for ASD has been changed in DSM-5 (American Psychiatric Association, 2013). Further discussion of these changes are outside the scope of this thesis.

Estimates of prevalence rates of Autism Spectrum Disorders (ASD) in individuals with TSC have been reported at much higher rates than expected, ranging from 16-61% (see **Table 1.3**). The general population rate for autism spectrum disorders is around 1% (de Vries, 2010b). The variability in these rates can be explained by the definition of ASD being used (classic autism versus autism spectrum disorders) and the methodology employed (clinic based studies versus population based). The most comprehensive and detailed population-based study using the ADOS and ADI-R showed that 26% of children with TSC across all levels of intellectual ability met criteria for classic infantile autism and that about 50% met criteria for an ASD (Bolton *et al.,* 2002). Other studies using rating scale and survey methods have consistently reported rates of ASD in the order of 25-50% (Smalley *et al.,* 1992; Hunt, 1993; Hunt and Shepherd, 1993; de Vries *et al.* 2007). **Table 1.3** provides a summary of all studies conducted on TSC and Autism to date (de Vries *et al*., 2007;

Wong, 2006; Curatolo *et al.,* 2006; Calderon *et al*., 1994; Smalley *et al*., 1992; Riikonen and Simell, 1990).

Table 1.3: Frequency and demographic characteristics of autism in tuberous sclerosis complex

Authors	**Year**	**N with TSC**	**% of autism & ASD**	**M:F**	**Diagnostic Criteria / Assessment Tools used**
Hunt & Dennis	1987	90	50	24:22	Hunt & Dennis questionnaire
Riikonen & Simell	1990	24	17	Not specified	Not specified
Curatolo et al.	1991	23	26	12:11	Hunt & Dennis questionnaire
Smalley et al.	1992	13	54	5:2	ADI
Hunt & Shepherd	1993	21	25	3:2	Hunt & Dennis questionnaire
Gillberg et al.	1994	28	61	7:10	CARS, DSM-III-R, ICD-10
Calderon et al	1994	27	26	2:5	DSM-III-R, ICD-10
Webb et al.	1996	131	5	Not specified	Hunt & Dennis questionnaire
Bolton & Griffiths	1997	18	50	Not specified	ICD-10
Baker et al.	1998	20	20	3:1	ABC, ADI direct exam
Gutierrez et al.	1998	28	29	1:1	ADI, ADI-R, ADOS
Wong	2006	44	16	0.75:1	DSM-IV, ADI-R
De Vries	2007	246	48	Not specified	Postal survey

The overall consensus suggests that about 50% of individuals with TSC may meet criteria for an ASD which makes TSC one of the medical conditions most commonly associated with autism (de Vries, 2010b). There have been a range of hypotheses for the clear-cut overrepresentation of ASD in TSC. Many suggested tuber count, localisation of cortical tubers, abnormal genetic programme, and/or comorbidity with epilepsy and learning impairment (Curatolo *et al*., 1993; Gillberg *et al*., 1994; Bolton, 1998; Sampson, 2003). De Vries and Howe (2007) proposed an alternative molecular hypothesis and suggested that disruption of the TSC1-2 signalling cascade in TSC may be sufficient to disrupt the neurodevelopmental trajectory and lead to the neuropsychiatric manifestations of TSC, including ASD (de Vries and

Howe, 2007; de Vries, 2009; de Vries, 2010a). de Vries postulated that the increasing number of single gene disorders associated with ASD (*FMRP*, the fragile X associated gene; *TSC1* and *TSC2*, the tuberous sclerosis-associated genes; *MECP2*, Rett syndrome-associated gene) may point to an alternative etiological model of autism where disruption in a single gene might be sufficient to disrupt the neurodevelopmental trajectory towards ASD (de Vries, 2009).

Attention Deficit Hyperactivity Disorder

The 2nd developmental disorder very commonly associated with TSC is attention deficit hyperactivity disorder (ADHD). Curatolo *et al.* (2009) described ADHD in TSC as a multifactorial neurobiological disorder caused by the confluence of many genetic and environmental risk factors. Individuals with ADHD present with significant problems of attention (such as failure to attend to detail), hyperactivity (being fidgety, restless or overactive), and often act impulsively (such as butting into conversations or failing to wait their turn). To meet ICD-10 or DSM-IV criteria for ADHD, these difficulties should be present before the age of 7, should be out of keeping with the child's overall developmental level, lead to impairment in their functional skills, be present for at least 6 months, and should be observable in more than a single setting (World Health Organisation, 1993; and American Psychiatric Association, 2000). A diagnosis of ADHD requires comprehensive evaluation including developmental history, clinical observation of the child in more than one setting, and consideration of other developmental, educational, and social factors (de Vries, 2010; Taylor *et al.,* 2004).

General population rates of ADHD vary significantly and much of this variability could be explained by the different methodologies employed by researchers. A systematic review and meta-analyses of 102 studies comprising 171,756 subjects from around the globe showed that the ADHD worldwide-pooled prevalence was 5.29% (Polanczyk *et al.,* 2007). In contrast to the general population rate, the prevalence of ADHD in TSC

is as high as 50% in all individuals with TSC, and ~30% in those with normal IQ (Gillberg *et al.,* 1994; Prather and de Vries, 2004; de Vries *et al.,* 2006; Muzykewicz *et al.,* 2007).

The pathogenesis of ADHD in TSC is still largely unknown. The following have been proposed as potential contributors and risk factors that may predispose individuals with TSC to an increased risk for ADHD: cortical tuber location, number of tubers and 'load', epilepsy, comorbidity with intellectual disability, comorbidity with autism spectrum disorders, and molecular aberration (de Vries and Howe, 2007; D'Agati *et al.,* 2009).

1.2.2.2 Mood and Anxiety Disorders

In adults with TSC, high rates of depressed mood and anxiety have been shown (Pulsifer *et al*., 2007; Lewis *et al.,* 2004: Raznahan *et al.,* 2006; de Vries *et al.,* 2007; Muzykewicz *et al*., 2007; de Vries *et al.,* 2010; Chung *et al*., 2011;). Lewis *et al.* (2004) used a well-standardised diagnostic tool to evaluate anxiety and depression in individuals with TSC and showed that 56% of their study population met criteria for an anxiety disorder and 19% for a depressive disorder. Muzykewicz *et al*. (2007) showed increased rates of mood disorders, prevalent in 26% of the study population (recurrent, major, dysthymic, and NOS) and a further 28% had anxiety disorders (generalised, separation, NOS, panic disorder, obsessive-compulsive disorder). The rate of mood and anxiety disorders amongst adults with TSC, while often variable, remains consistently high.

1.2.2.3 Other Psychiatric Disorders

There is very limited information about other psychiatric disorders in TSC, but reports include schizophrenia and other psychotic disorders, eating disorders, dementias, bipolar affective disorder (a type of mood disorder), alcoholism, obsessive compulsive disorder and tic disorder (Sedky *et al.,* 2003; Goh and Thiele, 2005; Raznahan et al., 2006; Muzykewicz *et al*., 2007; de Vries, 2010b; Bhattacharya *et al*., 2012). The rates of psychotic disorders in TSC seem to be around 1-5%, either as a primary or

secondary diagnosis (Raznahan *et al*., 2006; Muzykewicz *et al*., 2007; de Vries, 2010b; Chung *et al.,* 2011). It therefore seems that, in contrast to developmental disorders, psychotic disorders are not overrepresented in TSC in comparison to the general population where rates are in the order of 1% (de Vries, 2010b). Psychotic phenomena in TSC (delusions and hallucinations) should therefore always raise the suspicion of seizure-related abnormalities such as temporal lobe epilepsy that has a clear association with psychosis (Lishman, 1997).

1.2.3 Intellectual Disability

The majority of individuals with TSC (~70%) will have intellectual ability that falls on a normal distribution similar to that of the general population except that the mean IQ score is shifted downward to 93 versus 100 in the general population (Joinsen *et al.,* 2003; de Vriesb, 2010). This means that about 50% of those with TSC will have normal intellectual abilities, and a further 20% will have mild, moderate or severe intellectual disability (de Vries, 2010b). The remaining 30% have profound intellectual disability with IQ equivalents below 20 (Prather and de Vries 2004; de Vries 2010b;). In the first systematic study of intellectual and neuropsychological skills in TSC, Jambaque *et al.* (1991) found that 30.5% (07/23) had IQ scores in the normal range (between 81 and 119, mean 100), eight between 43 and 65, and a further eight had IQs <40. The study was however based on a clinical case series, where more mildly affected individuals may have been under-represented. In a population-based sample of 108 individuals with TSC in the Wessex region of the UK, Joinsen *et al.* (2003) found that 55.5% had normal intellectual ability, 14% had mild, moderate or severe intellectual disability and 30.5% had profound intellectual disability. Earlier population-based studies, such as that estimated in the ascertainment of the Wessex population in Webb *et al*. (1996), showed higher prevalence rates of intellectual disability, but did not use any standardised measures to determine intellectual level. There are thus two intellectual subgroups or phenotypes in TSC, the normal distribution (ND) phenotype and the profound (P) phenotype (de Vries and Prather, 2007) representing a bimodal distribution of intelligence in

TSC. Humphrey *et al*. (2004) investigated the level and trajectory of cognitive functioning in children between the ages of 11 and 37 months. The Mullen scales of early learning (MSEL) (Mullen, 1995) were used to measure cognitive functioning at 6-month intervals. Researchers found that children with TSC slowly but steadily gained skills in many areas of functioning but also that they gradually fell further and further behind.

The majority of studies show that a history of seizures and/or infantile spasms correlates with the degree of intellectual impairment (Curatolo *et al*., 1991; Shepherd and Stephenson, 1992; Hunt *et al*., 1993; Humphrey *et al.,* 2004; Jansen *et al*., 2007;). The largest investigation of intellectual and adaptive development in patients with TSC was done by van Eeghen *et al*. in 2012. This longitudinal study identified significant associations with epilepsy characteristics and intellectual development, highlighting the need for early interventions in this population group. However, in these studies only a small percentage of the variance in IQ was explained by epilepsy, and other studies (de Vries, 2002; de Vries *et al.,* 2009; Tierney *et al*., 2011) were unable to show correlation between epilepsy and intellectual ability.

The number of tubers has long been suggestive of an increased risk of intellectual disability; those with more tubers being at higher risk (Jambaque *et al*., 1991; Shepherd *et al*., 1995; Goodman *et al*., 1997; Raznahan *et al*., 2007). However, studies conducted by Inoue *et al.* (1988), de Vries (2002) and more recently by Jansen *et al.* (2008) could not establish a link between number of tubers and cognitive functioning. Overall, some studies have found correlations and others were unable to. It is important to note that correlation does not equal causation. These findings led de Vries and Howe (2007) to propose the molecular model where neither tubers nor seizures were predicted to be necessary nor sufficient to explain the intellectual abilities observed in TSC. It is however possible that the best overall explanatory models may be combinatorial between molecular and other factors, which may include structural and other environmental modifiers.

Familial studies have shown significant variability and the phenotypic range within families with TSC is not well understood. IQ appears to show both interfamilial and intrafamilial variation (Gomez *et al.,* 1982; Joinsen *et al.,* 2003*;* Humphrey *et al.,* 2004; Lyczkowski *et al*., 2007*).*

1.2.4 Academic or Scholastic Level

In this subdomain of evaluation, the focus is on scholastic and academic performance, referred to as “learning disorders” in the DSM-IV revised (American Psychiatric Association, 2000). Children and adolescents with TSC are at higher risk of experiencing difficulties with reading, writing, spelling and mathematics. To date there has been no systematic studies of the rates and types of learning disorders individuals with TSC suffer from. Parental and teacher reports however indicate that children with TSC tend to struggle with academic skills. In de Vries (2002), a standardised rating scale measure showed that 36% of normally intelligent children with TSC were at high risk of learning disorders. Both the ICD-10 and DSM-IV postulate that maths disorders are common in children who have ADHD or other attention-related difficulties (American Psychiatric Association, 2000; World Health Organisation, 1993). Given the high rates of ADHD in TSC, this puts individuals with TSC at even further risk of experiencing math-related difficulties including linguistic aspects (understanding math terms), perceptual math skills (visuospatial aspects), attentional skills (copying numbers), or in learning maths facts. Anecdotal evidence in TSC suggests that mathematical difficulties are indeed a common challenge for many individuals with TSC, but further systematic studies are clearly warranted (de Vries, 2010b).

1.2.5 Neuropsychological Deficits

A range of neuropsychological deficits are seen in TSC and several studies have reported difficulties with executive functioning skills, attention skills, memory, and language skills (Harrison *et al*., 1999; de Vries, 2002; de Vries and Prather, 2004; Ridler *et al.,* 2007; de Vries *et al.,* 2009; de Vries, 2010b; Tierney

et al., 2011;). Suggestions to date suggest that the neuropsychological domain most commonly affects is that of executive control processes (de Vries, 2010b).

1.2.5.1 Executive skills

Executive skills, also referred to as executive control processes, are a family of functions that include the regulatory functions (such as response inhibition), attentional control functions (such as dual tasking) and goal-directed functions (such as planning) of the brain (de Vries, 2010b). These skills, processed in the cortico-striatal brain structures including the prefrontal cortex, enables an individual to develop and execute plans, solve problems, adapt to unexpected circumstances, do many tasks simultaneously, and obey social rules. Therefore, executive skills provide individuals with the strategies and tools needed to successfully navigate the world we live in. Studies that investigated the cognitive and neuropsychological aspects of children and adults with TSC have identified significantly poorer performance on executive skills tasks (Harrison *et al.,* 1999; Ridler *et al*., 2007; de Vries *et al*., 2009; Tierney *et al.,* 2011). Harrison *et al*. (1999) examined cognitive deficits in 7 adults with TSC using 8 standardised assessment tools. The researchers did not identify any single executive skills deficit across individuals, but found that 70% of participants performed below the 5th percentile on at least one task. Apart from inter-individual variability, there is also evidence of variability in executive function deficits amongst family members with TSC, which further highlights the need for individual assessment (Lyczkowski *et al.,* 2007*).*

1.2.5.2 Attentional Skills

In 2009, de Vries, Gardiner and Bolton conducted the first systematic evaluation of neuropsychological attentional skills in a population-derived sample of 20 children with TSC and 17 unaffected siblings. Three domains were assessed in this study; general intellectual ability, attention-related behaviour, and neuropsychological attention skills. The

Test of Everyday Attention for Children (TEA-Ch) was used (Manly *et al*., 1999) to assess various components of attention, specifically selective attention, sustained attention, attentional switching, and dual tasking. Thirty five percent of children with TSC showed impairment (defined as performance below the 2nd percentile for age and gender) in the selective attention tasks, 50% in the sustained attention tasks, and 75% were impaired in dual tasking. The study found that 90% of participants were impaired on one or more tasks with no obvious pattern of attention deficits. The neuropsychological attention skills of 19 adults with TSC and 21 matched controls were assessed by Tierney *et al*. in 2011, using identical tasks of the TEA-Ch used by de Vries *et al*. (2009), in addition to the Attention-Deficit Scales for Adults (ADSA), a behavioural rating scale for attention deficit behaviours in daily life. In contrast to the findings in children and adolescents above, no group differences were found in the sustained or selective attention tasks, but the TSC group demonstrated significant neuropsychological attention difficulty on the cross modal dual task, similarly to the children and adolescents in de Vries *et al.* (2009). The study showed a significant correlation between dual task and attentional performance in daily life. For instance, dual task decrements (the 'loss' of speed and accuracy under dual task conditions) were strongly correlated with the subjective perception of feeling easily overwhelmed and not being able to deal with competing task demands. These findings demonstrated that adults with TSC, similar to the performance of children with TSC (de Vries *et al*., 2009), have particular difficulty in dividing attentional resources between two tasks in daily life. Together, results suggested that children and adults with TSC are at a significantly increased risk of neuropsychological attention deficits that may have a direct impact on their living skills.

1.2.5.3 Memory skills

In the first study to explore neuropsychological skills in TSC, Jambaque *et al*. (1991) studied the intellectual and neuropsychological skills of 23

children with TSC aged 3-16 and found that 30% (7/23) had memory impairments. Much later in 2007, Ridler and colleagues examined 25 adults with TSC and 25 controls on a battery of neuropsychological tools (including the Cambridge Neuropsychological Test Automated Battery, CANTAB) with a primary focus on memory skills. Results showed that adults with TSC had significant deficits on tests of long-term memory, especially immediate recall rather than recognition and on tests of working memory (verbal and spatial). There have not been many studies examining memory skills in individuals with TSC, but it is clear from Ridler *et al*. (2007) that there are definitive group differences when comparing memory skills of individuals with TSC with those of a control group. Future research should focus on memory skills in family members with TSC, in children with TSC, and their developmental trajectory.

1.2.5.4 Language skills

Apart from indirect evaluation there have been no studies with a primary focus on language skills in TSC, to our knowledge. We do however know from indirect examination during research performed on other neuropsychological domains that individuals with TSC seem to have language difficulties (Jambaque *et al.,* 1991; Prather *et al.,* 2006; and survey evaluation done by de Vries *et al.,* 2007). In a significant proportion of individuals with TSC language delays may be associated with autism spectrum disorders. However, findings from e.g. de Vries *et al*. (2007) seem to suggest that even in individuals without ASD, language and language development may be compromised.

1.2.6 Psychosocial Level

At this level it is important to note that many psychological and social aspects may impact on the wellbeing of the individual with TSC and on their ability to function successfully within the family and society as a whole. Having a family member with a complex physical and developmental disability such as TSC can have a significant impact on family stress (Whittemore and Lewis, 2010; de

Vries, 2010b). Maladaptive family behaviour such as “over-caring”, parental withdrawal, and denial of the severity of problems can hinder the individual with TSC’s journey towards acceptance, empowerment, and adaptive behavioural strategies (de Vries, 2010b). In order to understand how an individual experiences his illness and copes with it requires knowledge of what the disease means to the individual. Psychosocial factors influence the trajectory and outcome of every illness, therefore it is imperative that their evaluation should form a part of medical diagnosis and management (Lipowsky, 1969).

1.2.7 Biological

As discussed earlier in the chapter, TSC involves multiple organ systems and any neuropsychiatric manifestations should be seen within the context of other physical problems. As suggested by de Vries 2010b, a change in one or more of the neurocognitive or neurobehavioural levels of investigation may be an indication of a physical disorder such as an infection or an electrolyte disturbance, may be a manifestation of epilepsy, a side-effect of medication, or herald a growing SEGA.

Taken together, the majority of individuals with TSC will have some neuropsychiatric problems in their lifetime, with lifetime prevalence rates in the region of 90%. There are no obvious ‘natural clusters’ of TAND profiles that have been identified to date, and this uniqueness prohibits clinicians from predicting a pattern of neuropsychiatric deficits. Research has enabled TSC experts to predict what to look for, but not what each individual will present with, clearly pointing to the need for a personalised approach to evaluation and treatment.

1.3 TAND (TSC-Associated Neuropsychiatric Disorders)

As outlined above, the 1998 consensus panel generated some basic monitoring guidelines for TSC. In an attempt to improve clinical guidelines for cognitive and

behavioural problems, an international consensus group were convened in Cambridge, UK, funded by the Tuberous Sclerosis Association (UK) and the TSAlliance (USA). A panel of 20 clinicians and family members produced consensus guidelines for assessment of individuals with TSC (de Vries *et al*., 2005).

In 2010, 5 years after the publication of the consensus guidelines (de Vries *et al*., 2005) a survey of members of the Tuberous Sclerosis Association in the UK indicated that only 18% of individuals with TSC had ever received an assessment or treatment for neuropsychiatric disorders (personal communication Prof P.J. de Vries). These results suggested a vast gap between need and actual assessment/treatment of around 70%, referred to as a 'treatment gap'. At the 2012 International TSC Consensus Conference in Washington DC, the neuropsychiatry panel chaired by Prof P.J de Vries, expressed concern about the enormous treatment gap and considered how to improve basic evaluation and onward referral for more comprehensive neuropsychiatric work-up of individuals as required. As a first step, the panel decided to coin the term TAND, TSC-Associated Neuropsychiatric Disorders. One of the key motivations for coining the term TAND was an attempt to draw attention to this important clinical area. An outcome from the consensus panel was therefore to recommend that all patients with TSC should be screened for TAND at each clinic visit, and at least annually (Krueger *et al*., 2013). To facilitate this process of screening, the Neuropsychiatry panel agreed to generate a TAND checklist that can be used as a screening tool by health care personnel in any clinical setting. The panel were clear that they did not want to develop a 'diagnostic' tool that would have the sensitivity and specificity to identify specific neuropsychiatric disorders, but rather to develop a screening 'Checklist' to guide healthcare teams in a systematic enquiry of the current behavioural, psychiatric, intellectual, academic, neuropsychological and psycho-social difficulties of the individual with TSC. If any of the above mentioned clinical and neuropsychiatric aspects are of concern to the parent/carer/individual with TSC, the goal of the TAND Checklist would be to

describe some of these areas of need and highlight the need for more comprehensive diagnostic workup and treatment.

As outlined above, the neuropsychiatric manifestations of TSC are present at multiple levels of investigation from behavioural to psychiatric, neuropsychological to educational. Assessment and treatment therefore requires multi-agency and multi-disciplinary involvement. Across each of these levels of investigation, standardised tools have been generated over the last few decades to aid screening, diagnosis and quantification of neuropsychiatric manifestations. These include rating scale measures for behaviour such as the Strengths and Difficulties Questionnaire (SDQ), the Behaviour Rating Inventory for Executive Functions (BRIEF), a simple screening tool for developmental and intellectual development (Wessex) and the Social-Communication Questionnaire (SCQ) for ASD features (Kushlick *et al*., 1973; Goodman, 1997; Gioia *et al*., 2000; Rutter *et al*., 2003). In addition, research tools have been developed to aid diagnosis of psychiatric disorders such as autism and depressive disorders. Tools include the ADI-R (Autism Diagnostic Interview-Revised) (Lord *et al.*, 1994), ADOS (Autism Diagnostic Observational Survey) (Lord *et al.*, 2000), SADS (Schedule for Affective Disorders and Schizophrenia) (Endicott and Spitzer, 1978), and numerous others (de Vries, 2010b). Many of these psychometric tools and sophisticated neuropsychological assessment tools such as Cambridge Neuropsychological Test Automated Battery (CANTAB) are excellent in their own right. However, they have significant limitations in terms of multi-level neuropsychiatric evaluation as required in TSC. The majority of the tools are not routinely available at clinics, and when they are used, tools are copyrighted with a charge per use, ranging from a few Dollars to many thousands of Dollars. Many health care providers are not adequately trained to use these tools or do not have easy access to clinical psychologists, psychometricians or neuropsychologists who could perform and interpret formal tests. Importantly, none of the tools capture the different levels of investigation required in TSC (behavioural, psychiatric, intellectual, neuropsychological, educational and psycho-social) or have been validated across all ages and

developmental levels. It would therefore have been extremely complicated to assemble a 'battery of screening tools' that would allow for screening across all the neuropsychiatric dimensions outlined, across age and ability level.

1.3.1. TAND Checklist

One of the goals of the International Neuropsychiatry Panel was therefore to develop a simple TSC Checklist that would be globally and freely available to all clinicians and families. Basic criteria for a clinically meaningful tool were therefore to be simple to use, free/inexpensive, pen-and-paper based (not requiring specialized equipment), and usable by a range of healthcare providers, not just highly specialist clinicians. Most importantly, the TAND Checklist should be deemed to have *face validity* (seen by professionals and families as capturing the essential and important aspects of concern), *content validity* (judged by experts to cover the range of neuropsychiatric concerns of relevance to TSC), and *transferability* (the ability of the tool to be used across different settings by different people).

The International TSC expert panel produced the first version of the TAND Checklist in December 2012. The TAND Checklist includes 7 milestone items (years, month, and weeks), 3 current functioning items (categorical), 38 dichotomous (yes/no) questions across behaviour (19 items), as well as diagnosis diagnosis (6), scholastic difficulties (4), neuropsychological skills (6) and psycho-social functioning (3) items. Finally impact scores (ordinal scale 1-10) completed by the parents and clinician/researcher were included. As mentioned above, the international panel was keen to develop a 'checklist' rather than a 'rating scale or questionnaire'. A checklist is a mnemonic device that allows for systematic evaluation of a number of features or criteria and is specifically aimed at acting as an 'aide-mémoire' for the clinician during their interaction with the family. Checklists are aimed at reducing errors of omission and are generally easier to administer and understand (Scriven, 2000). From a practicability point of view, a checklist should be straightforward to administer and the individual with TSC and/or their family members should find it easy to

understand. From a checklist validation/evaluation point of view, Stufflebeam (2000) recommended that a comprehensive checklist evaluation should target a minimum set of criteria. He recommended that these criteria included pertinence to the content area, comprehensiveness, clarity, applicability to full range of intended uses, concreteness, parsimony, ease of use, and fairness. No investigations to date have examined the psychometric properties and usefulness of the TAND Checklist.

1.4 Purpose of the study

In this study we performed the first pilot evaluation of the TAND Checklist with the aims to:

1. Refine the TAND Checklist - examine face and content validity of the TAND Checklist through expert review
   The purpose of this objective was to look at face and content validity of the TAND Checklist to ensure that the areas of neuropsychiatric concern in TSC are being covered. Feedback from the cohort was used to refine the TAND Checklist and make minor amendments. This analysis also explored the perceptions and perceived usefulness of the TAND Checklist.

2. Validate the TAND Checklist as a screening tool that identifies and quantifies neuropsychiatric manifestations in TSC - examine the external validity of the TAND Checklist through face-to-face administration.
   To investigate the external validity of the TAND Checklist by comparing it to the findings from other validated assessment and screening tools. During this stage of analysis, domain and subdomains were evaluated for correlations.

3. Demographic data review - determine the demographic characteristics of the face-to-face sample.
   Data used for this analysis was extracted from the participants who were involved in Stage 2 of the study. The the purpose was to determine whether the sample were representative of the population of the Western Cape and South Africa as a whole.

We hypothesised that the TAND Checklist would have good face and content validity amongst expert TSC clinicians as well as individuals with TSC and their families. Furthermore, we predicted that the TAND Checklist would correlate well with the four other widely used and validated assessment tools in terms of key domain areas being tested i.e. behaviour, psychiatric, intellectual ability, academic, neuropsychological, and psycho-social. Lastly, we hypothesised that the cohort used may not be representative of the South African general population, but rather characteristic of the population residing in the Western Cape province.

Chapter 2 Methodology

2.1 Study Design

The pilot study was conducted in three stages using mixed methodology (see **Figure 1.1**).

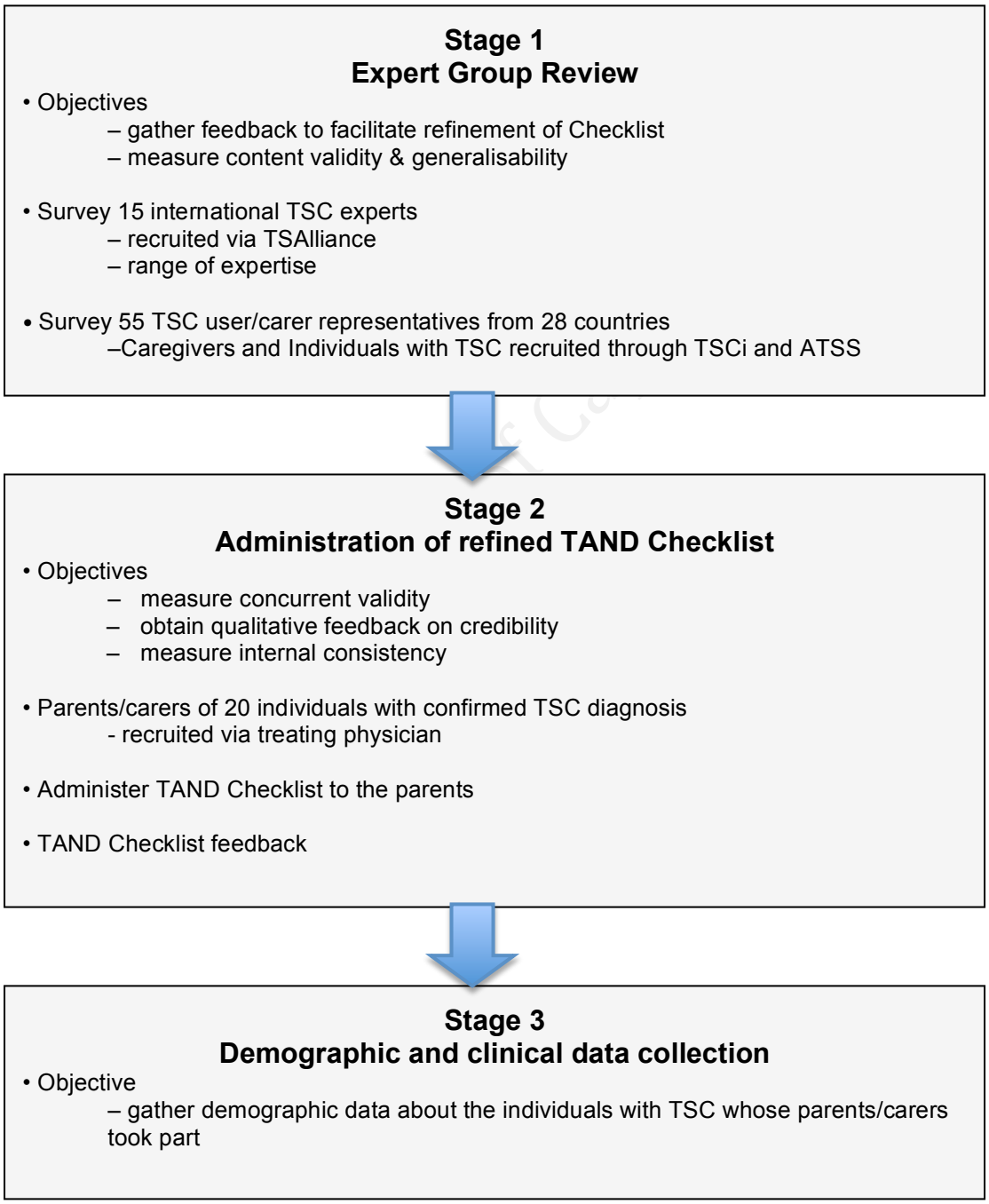

Figure 2.1 Summary flowchart of the pilot study

2.1.1 Stage 1

In **Stage 1** qualitative and quantitative feedback was collected on the draft TAND Checklist from two expert groups:

A) a multidisciplinary panel of international TSC experts (referred to as the 'professional expert' group) and

B) an international panel of user/carer representatives (referred to as the 'parent expert' group).

All professional experts were sent either an electronic copy or a paper version of the TAND Checklist v.1 (Appendix A) and an Expert Feedback Form (Appendix D). They were asked to provide scores and comments on the five questions on the Expert Feedback Form.

The Expert Feedback Form consisted of 5 quantitative and open-ended qualitative items to capture aspects of comprehensiveness, clarity, ease of use, applicability and subsequent validity:

1. **Comprehensiveness:** Does the Checklist cover the relevant range of neuropsychiatric features you think is important in TSC? Please indicate missing items.
2. **Clarity:** Are the items clear and understandable? Please indicate unclear items and how you would suggest improving them.
3. **Ease of Use:** Overall, how easy do you think the Checklist will be to use? What might improve ease of use?
4. **Applicability:** How likely do you think clinicians are to use the Checklist? What could be done to increase the likely use by clinical teams?
5. **Subsequent validity:** How likely is the Checklist to encourage clinicians to pursue further neuropsychiatric work-up or referral to relevant specialists? What can be done to increase the likelihood?

Lastly we examined internal consistency of the TAND Checklist to measure the correlations between different items on the same domains and subdomains.

2.1.2 Stage 2

In **stage 2** the TAND Checklist v.2, as modified based on feedback from stage 1 (Appendix B), was administered by the research team to parents/carers of individuals with TSC in the Western Cape, South Africa. On completion of the TAND Checklist with a researcher, the parents/carers were asked to complete the Expert Feedback Form. Thereafter, parents/carers were asked to complete 4 well-established and widely used rating scale measures (the SDQ, SCQ, BRIEF and the Wessex). Further details about these instruments are provided below. (Appendices E,F,G & H).

2.1.3 Stage 3

In **stage 3** demographic data about the individuals with TSC whose parents/carers participated in Stage 2 of the pilot study were collected from parents (Appendix I) in order to examine the characteristics of individuals with TSC who participated in the pilot project. Data collected included:

1. gender and age of individual with TSC
2. rural or urban living
3. household income
4. parental level of education
5. schooling placement, e.g. special education, private schooling, mainstream
6. current grade level (e.g. what year or grade in school)
7. clinical manifestations of TSC e.g. tumours and epilepsy
8. previous or existing neuropsychiatric diagnosis e.g. autism spectrum disorder
9. current medications

2.2 Research Site

The project was conducted in the Division of Child & Adolescent Psychiatry at the University of Cape Town, South Africa. Stage 1 data were collected remotely and sent to the research team for processing. Stage 2 data were collected by the research team in collaboration with the primary treating clinician at the Red Cross War Memorial Children's Hospital, Cape Town and/or in the Division of Child & Adolescent Psychiatry, based on participant preference. Stage 3 data were collected from families.

2.3 Participants

2.3.1 Stage 1

'Professional experts' (Stage 1A) were recruited in collaboration with the TSAlliance to represent wide-ranging areas of expertise relevant to TSC. The research team generated a list of internationally known academics in TSC including paediatricians, developmental paediatricians, paediatric neurologists, adult neurologists, geneticists, physicians, basic scientists, educationalists, psychologists, intellectual disability experts, specialist nurses and social workers. Professional experts were invited to participate electronically and were provided with the TAND Checklist and Expert Feedback Form, as outlined above. The team continued to invite experts until a minimum of n=15 responses were received.

'Parent experts' (Stage 1B) were recruited through two mechanisms. The first group consisted of parents/carers who were participants at an Annual Meeting of the ATSS (Australasian Tuberous Sclerosis Society). All parents/carers present at the ATSS meeting were invited to contribute to the evaluation of the TAND Checklist, but were free not to participate. To ensure a broad international representation, a second group of 'expert parents' were recruited. An electronic copy of the TAND Checklist and Expert Feedback Form was emailed to all

national representatives of Tuberous Sclerosis Complex International (TSCi) who were asked to provide scores and comments on the Expert Feedback Form. All feedback received by 30 September 2013 was included in the study.

2.3.2 Stage 2

Study participants for stage 2 were recruited through primary clinicians at the Red Cross War Memorial Children's Hospital TSC clinic, and from other UCT-affiliated hospitals (Groote Schuur, Lentegeur and Alexandra). Potential participants had to meet definite criteria for TSC (Roach *et al* 1998; Krueger *et al.,* 2013) and had to have a parent/carer who could complete the research questionnaires and interview in English. Participants were not required to speak English as a first language, but had to have a sufficient understanding of English to allow participation. Potential participating families were provided with information sheets and consent forms by the treating clinicians. Families interested in participating were then scheduled for face-to-face sessions. The team continued to recruit until n= 20 participants were identified. Given that the focus of this study was on neuropsychiatric manifestations in individuals with TSC across all ages, gender and developmental level, no inclusion criteria other than diagnostic status and parental ability to participate in English, were used.

2.4 Instruments used

2.4.1 The TAND Checklist, see Appendices A & B.

A pen-and-paper checklist, developed by the international TSC Neuropsychiatry Panel in 2012, to screen for neuropsychiatric manifestations of TSC across 10 different domains. This is the measure under investigation in this study.

2.4.2 The Strengths and Difficulties Questionnaire (SDQ), see Appendix E.

The SDQ is a widely-used behavioural screening questionnaire that can be completed by the parents and/or teachers of 4-16 year olds. There is also a self-completion version for 11-17 year olds (Goodman, 1997). The SDQ generates a

total difficulty score (out of a maximum of 40) and a pro-social score (out of maximum of 10). The total difficulty score consists of 4 domains (hyperactivity, emotional, conduct and peer relationships). Goodman (2001) examined a nationwide epidemiological sample of 10,438 British 5-15 year olds and reported satisfactory reliability across the 5-factor structure, with a mean Cronbach's alpha of 0.73 across the 5 domains suggesting good internal consistency of the SDQ as a screening tool. Its sensitivity in terms of hyperactivity and conduct problem was 68% and 74% respectively for the parent version. The percentage for the specificity was 89% for all parent, teacher and youth versions. In this study, the 5-factor parent version was used..

2.4.2 The Social-Communication Questionnaire, see Appendix F.

This is a brief pen-and-paper questionnaire developed by Rutter and colleagues (Berument *et al.*, 1999) as a secondary screening tool of the social-communication and repetitive/stereotyped behaviours of an individual who may have an autism spectrum disorder. A cut off score of ≥15 on the SCQ is suggestive of ASD and a cut off of 22 suggestive of Autism (Berument *et al*., 1999; and Eaves *et al.,* 2006). A score of 15 was reported to have a specificity of 0.80 and a sensitivity of 0.96 when differentiating individuals with autism spectrum disorders from other diagnoses (not including people with ID) and a specificity of 0.67 and sensitivity of 0.96 when differentiating individuals with ASD from those with ID. A score of 22 was reported to be associated with a specificity of 0.60 and a sensitivity of 0.75 for differentiating individuals with autism from other autism spectrum disorders (Rutter *et al.*, 2003). Subsequent studies to validate the SCQ also showed strong discrimination between ASD and non-ASD cases (sensitivity 0.88; specificity 0.72) and between autism and non-autism cases (sensitivity 0.90; specificity 0.86) (Chandler *et al*., in 2007).

2.4.4 The Behaviour Rating Inventory of Executive Functions (BRIEF), see Appendix G.

The BRIEF is a pen-and-paper questionnaire developed to quantify behavioural manifestations associated with executive functioning. It is used to assess

executive function behaviours in children and adolescents with an array of difficulties including developmental disorders and psychiatric conditions (Gioia *et al.*, 2000). Mean internal consistency ratings reported for clinical populations using the BRIEF Parent Form range from 0.82 to 0.98. Three-week test–retest reliability for clinical populations on the Parent Form range from 0.72 to 0.84 (Mahone *et al*., 2002). There are three versions of the BRIEF, each aimed at assessing a specific age range. The BRIEF–P is the preschool version for participants between 3 and 5 years of age, the BRIEF for age range 5-18 years, and the BRIEF-A which is the adult version for participants over the age of 18 years. All three versions were used in the study, as appropriate to the age of the individual participant.

2.4.5 The Wessex Scale, see Appendix H.

The Wessex Scale (Kushlick *et al.*, 1973) is used to measure adaptive behaviour and provides a proxy measure of degree of ID. It comprises two subscales including the Social and Physical Incapacity (SPI) scale and the Speech, Self-help and Literacy (SSL) subscale. Inter-rater reliability for the overall score on the SPI scale was reported at 65%, and 76% for the overall score on the SSL subscale (Palmer *et al.*, 1982).

2.5 Data Analysis

2.5.1 Scoring of the instruments used

2.5.1.1 TAND Checklist

Individual items were scored as simple Yes/No responses. Selected items were grouped together to form domains and subdomains for the purpose of analysis along with the four external assessment tools' total and subscale scores. These were a Behavioural domain (subdomains included 'hyperactivity' and 'social communication'), a Scholastic domain, a Neuropsychological domain (subdomain 'executive skills'), a Psycho-

Social domain, an Intellectual ability domain, and an Impact score. See **Table 2.1**.

TAND Checklist Level of Investigation	TAND Checklist Items	Maximum Score
1. Behavioural 1.1. Hyperactivity 1.2. Social Communication	**3**a,b,c,d,e,f,g,h,l,j,k,l,m,n,o,p,q,r,s **3**n,o,p,q **3**h,i,j,k,l,m	19 4 5
2. Psychiatric Disorder	**4**a,b,c,d,e,f	Yes/No
2. Intellectual	Yes/No	Yes/No
3. Academic or Scholastic	**6**a,b,c,d	4
4. Neuropsychological 4.1. Executive Functioning	**7**a,b,c,d,e,f **7**b,c,d,e	6 4
5. Psychosocial	**8**a,b,c	3
6. Impact Score	**9** & **10**	0-10 likert scale

Table 2.1: TAND Checklist Domains of Investigation and corresponding items

2.5.1.2 The SDQ

SDQs were scored using standard scoring methods for total scores, and for domain scores. Impact scores were calculated using standard SDQ procedures by adding together the items on overall distress and social impairment, generating the impact score that ranges from 0-10 for the parent completed version.

2.5.1.3 The SCQ

In this study the SCQ was used to discriminate between individuals at risk of having an ASD and those who fell below the 15 point cut off. Standard SCQ procedures were used to calculate scores and cut-off values.

2.5.1.4 The BRIEF

Standard BRIEF scoring procedures were used for the purpose of this study. Parents rated their child's behaviour on a three-point Likert scale (never, sometimes, and often). Eight scales were obtained (Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor, Inhibit, Shift, Emotional Control). Look-up tables across ages generated three main indices: a Meta-Cognition Index (MCI), Behaviour Regulation Index (BRI), and a Global Executive Composite (GEC).

2.5.1.5 The Wessex scale

No standardised scoring procedures for the Wessex have been published to date. For the purpose of this study, two researchers (the author and supervisor) generated consensus judgement scores of intellectual ability based on information provided in the Wessex questionnaire. Judgements were 'normal intellectual ability', 'mild-moderate ID' or 'severe-profound'. Ratings were assigned blind to parental ratings and to other data.

2.5.2 Statistical analysis

Data were analyzed using SPSS Version 21. Quantitative data analysis were performed using non-parametric tests given the relatively small sample size. Item by item analysis were examined by applying the Mann-Whitney test, and the Chi-Square test was used for dichotomous variables. For interpretation of Spearman rho values generated by correlations, standard convention was used (see **Table 2.2**). Lastly, internal consistency of the TAND Checklist was examined by applying Cronbach's alpha coefficient. For interpretation of Cronbach's alpha values generated by correlations, see **Table 2.3**. Qualitative data were analysed using summative content analysis (Hsieh and Shannon, 2005), which consisted of counting and comparing keywords and concepts followed by interpretation of the underlying context.

Table 2.2: Spearman rank-order correlation coefficient estimates for interpretation (Dancey and Reidy, 2004)

Spearman's rho	Correlation
0.70 and greater	Very strong relationship
0.40 to 0.69	Strong relationship
0.30 to 0.39	Moderate relationship
0.20 to 0.29	Weak relationship
0.01 to 0.19	No or negligible relationship

This descriptor applies to both positive and negative relationships

Table 2.3: Cronbach's correlation coefficient estimates for interpretation (Kline, 1999)

Cronbach's alpha	Internal consistency
$\alpha \geq 0.9$	Excellent (High-Stakes testing)
$0.7 \leq \alpha < 0.9$	Good (Low-Stakes testing)
$0.6 \leq \alpha < 0.7$	Acceptable
$0.5 \leq \alpha < 0.6$	Poor
$\alpha < 0.5$	Unacceptable

2.6 Ethics

The study was conducted in compliance with the Declaration of Helsinki. The protocol was peer-reviewed in the Department of Psychiatry at the University of Cape Town and submitted for Ethical approval at the Faculty of Health Sciences, Human Research Ethics Committee (Ethics Ref **200/2013**). All participants received information about the study, and provided written informed consent. No young people or individuals with intellectual disability directly participated in the study. All consent was therefore provided by adults. Participants were provided with a set amount for travel expenses (R200; ~$20), but no other payments were made to families.

Chapter 3 Results of the study

3.1. Stage 1 Results – Professional and Parent expert review of the TAND Checklist

Twenty expert feedback forms were returned by Expert Professionals. Sixty five percent (65% or 13/20) completed the quantitative items and 85% (17/20) provided both quantitative and qualitative feedback. All data were used for analysis. Forty two expert feedback forms were returned by expert parents/carers. 100% completed the quantitative items and 81% (34/42) completed both quantitative and qualitative questions. Results are presented below.

3.1.1 Quantitative Feedback

The expert feedback form asked respondents to rate five questions on a Likert scale from 0 to 5 with 5 as the highest score and allowed for comments on each question.

Given the relatively small sample size, means (M), median (Mdn) and standard deviations (SD) are presented (see **Table 3.1**).

Table 3.1: Stage 1 Quantitative expert feedback about the TAND Checklist

Item	Expert Professional Mean (SD) n=13	Expert Professional Mdn	Expert Parent M n=42	Expert Parent Mdn	*Mann-Whitney U	*P Value
Comprehensiveness	4.62 (0.87)	5	4.60 (0.80)	5	260	0.741
Clarity	4.31 (0.85)	4	4.48 (0.78)	5	229	0.466
Ease of Use	4.31 (0.95)	5	4.,56 (0.79)	5	214.5	0.332
Clinician Usage	3.77 (0.83)	4	3.43 (1.04)	3	178.5	0.232
Subsequent Referral	4.15 (0.69)	4	4.11 (0.84)	4	236.5	0.925

*Statistical comparison between Expert Professional and Expert Parent Scores.

Asymp. Sig ≤. 0.05 (2-tailed)

Key to score: 1 = not at all; 5 = very much

Group

Comprehensiveness

Clarity

Ease of Use

Clinician usage

Feedback from expert professional participants showed that the median score for items 1&2 were 5 out of a maximum 5 and items 3-5 were scored 4. Expert parents had a median score of 5 on items 1-3 relating to comprehensiveness, clarity and ease of use. Item 4 ('How likely do you think clinicians are to use the Checklist?') had a median score of 3. Item 5 ('How likely is the Checklist to encourage clinicians to pursue further neuropsychiatric work-up or referral to relevant specialists?') had a median score of 4.

As shown in **Table 3.1**, statistical comparison between expert professional and expert parent scores showed no significant differences.

3.1.2 Qualitative Feedback

For qualitative analysis all comments made by the expert professionals and expert parents (n = 51) were used. Summative analysis revealed 6 key themes, shown in **Table 3.2.** The frequency with which themes were raised by expert professionals or expert parents is shown in **Figure 3.1**.

Table 3.2*:* Stage 1 Qualitative expert feedback about the TAND Checklist

Qualitative Themes	Participant Feedback
1. Administration	"I think that this checklist should be utilized by people NOT knowledgeable in TSC as a way of getting them to recognize that the Neuropsychiatric Disorders are a manifestation of the TSC" (EX001). "I think it may take longer that 10 minutes if you try to describe more qualitative some of the "yes" responses. If it remain simple Yes-no, it should be fairly quick." (EX005) "I think if we could have access to it first and take it to them it would be more likely to be used and taken notice of." (ATSS 001)
2. Intellectual Ability	"Definitions of degrees of intellectual disability is not given (examples are needed)" (EX008) "Hard when child is intellectually disabled, can not speak to gauge feedback." (ATSS 010) "Difference between moderate and severe intellectual disability." (ATSS 019)

3. Examples	"Maybe include "processing speed" some patients with TSC may require more time to complete tasks in school or activities of daily life." (EX003) "Not sure most people will understand "visuospatial" without further explanation." (EX004) "Some of the items under 5 can be difficult to understand and needs explanation, examples." (TSCi002)
4. Missing Items	"Echolalia is not included but is seen frequently." (EX005) "opposition defiant disorder (ODD)" (EX010) "Difficulty in exploring new textures tactile." (TSCi 008)
5. Other Uses	"If it can be used as an educational tool as well as an evaluation and treatment tool." (EX001) "…to guide choice of medical therapy, use of medications, or progress with behavioral modification therapy, it will be quite useful." (EX005) "in medical training of medical students – of TAND" (ATSS026).
6. Driven by Parents	"Again, parents need to push for follow-up! Maybe more information for clinicians of how to follow-up concerns – with whom." (ATSS014) "As a parent you would need to insist on it often you are 'rushed through.'" (ATSS022) "Parent has to insist on this being used. Parent has to drive the care of the child." (ATSS026)

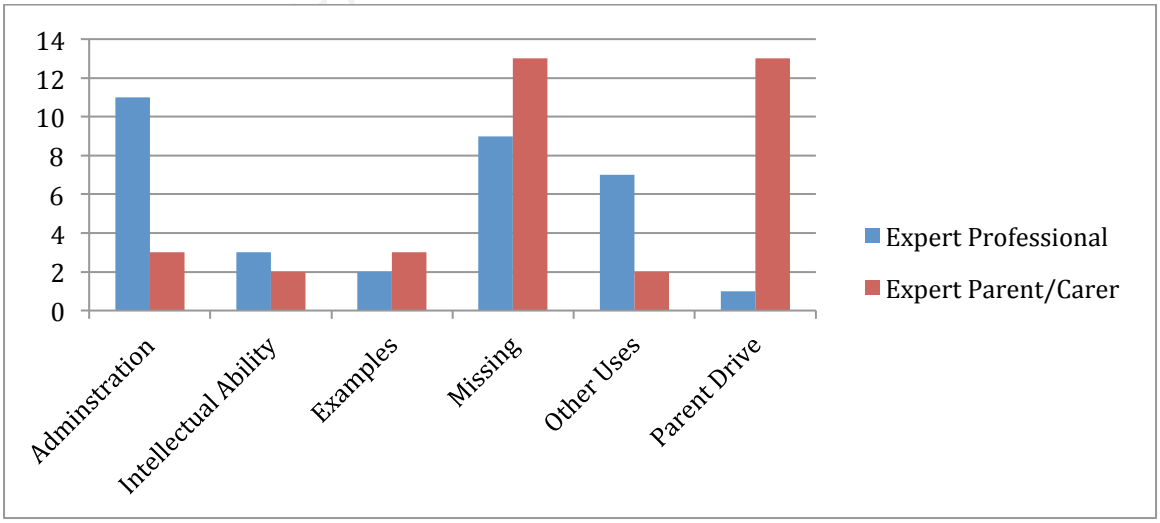

Figure 3.1: Frequency distribution of qualitative responses from Expert groups across 6 themes

The first of the six themes identified referred to items relating to administration, such as where the TAND Checklist should be administered and by whom. The second theme that emerged centered around intellectual ability/disability (ID). Respondents felt it was important to establish the level of intellectual ability of a participant at the start of the TAND Checklist as it may influence administration of the remaining questions. Both Expert professionals and parents suggested including examples that will make it easier for parents to understand specific technical/medical terms such as 'visuo-spatial skills'. There was a total of 22 comments on *missing items* where parents and clinicians suggested the inclusion of certain items. Seven comments from the Expert professional group, and 2 from the parent group proposed that the TAND Checklist also be used for other purposes. The last theme that emerged, overwhelmingly from the parent group (13 comments), highlighted the need for parents to drive clinical usage of the TAND Checklist.

Feedback from Stage 1 was used to revise the TAND Checklist (Appendix B) and the revised TAND Checklist was used in stage 2 of the study.

3.1.3 TAND Checklist internal consistency

3.1.3.1 Behavioural Domain

The total number of behavioural items on the TAND Checklist (items 3a to 3s) showed good internal consistency (α = 0.884). The hyperactivity subdomain items also generated a high Cronbach alpha (α = 0.751) whilst the social communication subdomain showed an acceptable level of internal consistency (α = 0.682).

3.1.3.2 Scholastic Domain

All four of the items in this domain showed excellent internal consistency (α = 0.954).

3.1.3.3 Neuropsychological Domain

Both the overall domain items and executive function subdomain items showed good internal consistency (overall α = 0.783; executive subdomain α = 0.792).

3.1.3.4 Psycho-Social Domain

The total number of psycho-social items on the TAND Checklist (items 8a to 8c) did not show good internal consistency (α = 0.365).

3.2. Stage 2 Results – Face-to-face administration of the TAND Checklist and external validation

A total of 20 parents, carers or individuals with TSC were recruited for stage 2. The mean age of our TSC population of 20 patients was 14.25 years (range: 3-42 years). The gender ratio was 12:8 Male and Female. Three of the index cases were children with TSC of pre-school age, 4 had not received any schooling as they were deemed 'ineducable', 10 were of school-going age and 3 were adults who had completed school. All participants were confirmed to meet definite criteria for TSC (Roach *et al*., 1998; Krueger *et al*., 2013) by the primary clinician and the principal investigator of the study. Mutational analysis was not available in South Africa at the time of the study, and was therefore not included.

3.2.1 Quantitative Feedback

Table 3.3 summarises the quantitative feedback from the 20 participants. The median scores assigned were **5** for items 1, 2 and 5 and **4** for items 3 and 4. Feedback scores on items 1 and 3 ranged between **3-5**, item 2 was scored either **4** or **5**, and items 4 and 5 had a slightly broader range between **2-5**.

Table 3.3*:* Stage 2 Quantitative feedback about the TAND Checklist following face-to-face administration with Stage 2 participants

Item	Median (n=20)	Mean (SD)
Comprehensiveness	5	4.8 (0.52)
Clarity	5	4.95 (0.22)
Ease of Use	4	4.45 (0.69)
Clinical Usage	4	3.65 (0.14)
Subsequent Referral	5	4.4 (0.88)

In order to determine whether live administration may have led to different perceptions of the TAND Checklist, results from parents in stage 2 was compared with parents/carers in stage 1. No statistical differences were seen across four of the five items between scores on Stage 2 live administration and Stage 1 expert parents. Interestingly item 2 (clarity) was rated as significantly higher in the Stage 2 live administration group (Mann-Whitney U = 249; p = 0.003). See **Table 3.4**.

Table 3.4: Comparison between group belonging in Stages 1 & 2 across the five items

Item	Expert Parent Stage 1 and Parent Stage 2 Mann-Whitney U	Expert Parent Stage 1 and Parent Stage 2 P-value
Comprehensiveness	364	0.259
Clarity	249	0.003*
Ease of Use	341.5	0.362
Clinical Usage	311.5	0.482
Subsequent Referral	292.5	0.162

3.2.2 Qualitative Feedback

Nine qualitative comments were received by parents during stage 2. Given the live administration format in stage 2, a number of families made comments about the TAND Checklist during the administration. These were documented by the researcher as contemporaneous notes. When asked if there are any areas of concern about TAND not covered during its administration (TAND Checklist final item), participants TP001, TP013 and TP015 mentioned the family's concerns regarding their child's future. TP003 raised concerns about social issues. Comments regarding missing items included "listening skills and emotional: cries a lot" (TP007) and "toilet training at school and fine motor control" (TP011). Participant TP009 recommended including items relating to family dynamics "relationship within marriage and with siblings". TP002 wanted to know more about TSC, "Where does TSC come from?" and participant TP015 asked about "the genetics of TSC and the impact of biological manifestations".

3.2.3 Correlation between TAND Checklist domains and External Assessment Tools

The TAND Checklist consists of a number of domains and subdomains as outlined in **Table 3.5.**

Table 3.5: TAND Checklist domains of investigation and corresponding items

TAND Checklist Level of Investigation	TAND Checklist Items	Maximum Score
1. Behavioural 1.1. Hyperactivity 1.2. Social Communication	**3.** a,b,c,d,e,f,g,h,I,j,k,l,m,n,o,p,q,r,s **3.** n,o,p,q **3.** h,i,j,k,l,m	19 4 5
2. Psychiatric Disorder	**4.** a,b,c,d,e,f	Yes/No
2. Intellectual	Yes/No	Yes/No
3. Academic or Scholastic	**6.** a,b,c,d	4
4. Neuropscyhological 4.1. Executive Functioning	**7.** a,b,c,d,e,f **7.** b,c,d,e	6 4
5. Psychosocial	**8.** a,b,c	3
6. Impact Score	**9** & **10**	0-10 likert scale

External validation therefore aimed to compare domains and subdomains with relevant well-validated external tools. Results are outlined for the Behavioural domain (in relation to the SDQ and SCQ), the Intellectual ability domain (in relation to the Wessex), the Neuropsychological domain (in relation to the BRIEF), the Scholastic domain (in relation to the Wessex), the Psycho-Social domain (in relation to the SDQ) and finally, the overall Impact score (in relation to clinician impact rating and impact scores on the SDQ).

Results are shown in **Figures 3.2-3.7** and **Tables 3.6** and **3.7**

3.2.3.1 Behavioural Domain

Figure 3.2 shows the correlation between the total number of behavioural items endorsed on the TAND Checklist (items 3a to 3s) and the total difficulties score on the Strength and Difficulties Questionnaire (SDQ). Results show a strong positive correlation (Rho = 0.81; $p < 0.001$).

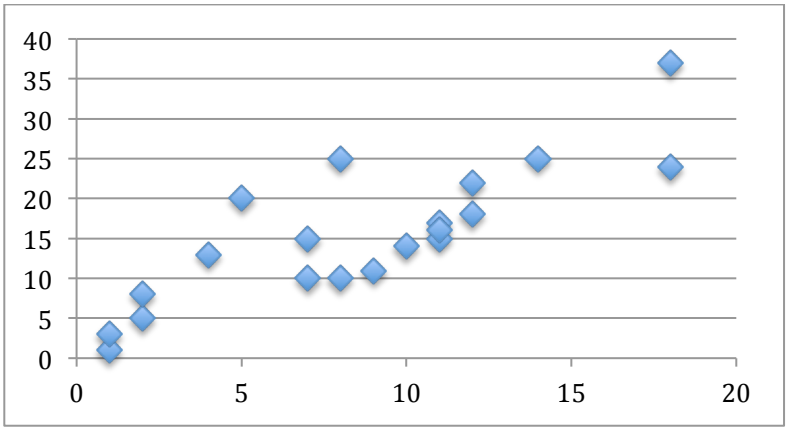

Figure 3.2: TAND Total Behaviour Score and SDQ Total Difficulties Score

3.2.3.1.1 Hyperactivity behaviours

In order to examine hyperactivity-related behaviours, the TAND Checklist hyperactivity subdomain items (items 3n – 3q) were plotted against the hyperactivity/inattention domain items of the SDQ (**Fig. 3.3).** Results showed a strong correlation (Rho = 0.77; $p < 0.001$).

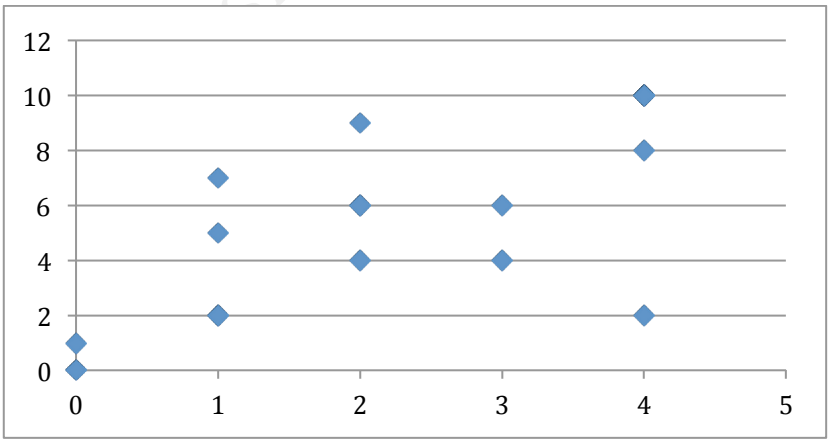

Figure 3.3: TAND Hyperactivity Items and SDQ Hyperactive/Inattentive Score

3.2.3.1.2 Social-Communication behaviours

Figure 3.4 shows the correlation between the TAND Checklist social communication subdomain items (items 3h – 3m) and the total scores on the Social Communication Questionnaire (SCQ). Results show a strong linear correlation between the TAND Checklist and the SCQ (Rho = 0.70; p = 0.002). The SDQ pro-social domain is a measure of positive or pro-social behaviours, predicted to correlate inversely with social-communication difficulties. Results confirmed a strong negative correlation (Rho = -0.65; p = 0.002) between the pro-social domain of the SDQ and the TAND Social-communication subdomain items.

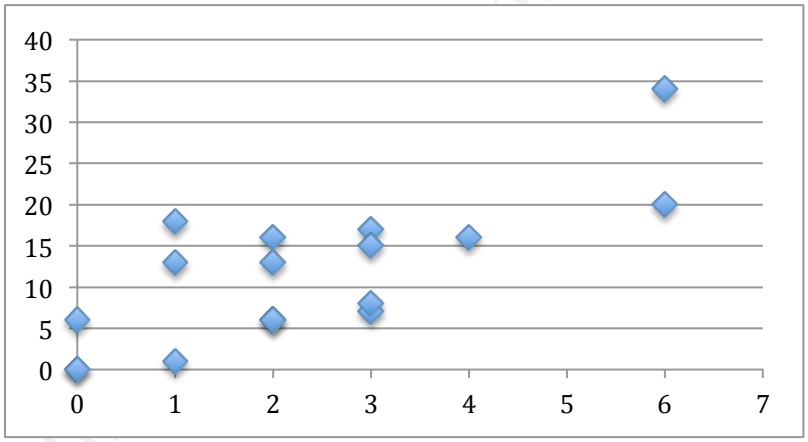

Figure 3.4: TAND Social Communication Score and SCQ Total Score

3.2.3.2 Intellectual Ability Domain

In item 5, parents were asked about intellectual disability in their child/family member. Parental judgement of the presence/absence of ID was compared to researcher judgement based on the Wessex questionnaire scores. Cross-tabulation of findings are shown in **Table 3.6** The two-by-two contingency table showed a significant association between the two classifications (Fisher's exact test $p < 0.001$).

Table 3.6: Cross-tabulation of relationship between parental intellectual ability concern and rating assigned by clinician based on feedback from the Wessex scale

Parental ID categorical rating	Wessex scale categorical rating: +	Wessex scale categorical rating: -
+	9	0
-	2	9

3.2.3.3 Neuropsychological Domain

Figure 3.5 shows the neuropsychological domain score (items 7a – 7f) plotted against the Global Executive (GEC) Score of the BRIEF. Results show a strong positive correlation between the two measures (Rho = 0.79; $p < 0.001$). The BRIEF behaviour rating index (BRI) score correlated strongly with the neuropsychological domain score of the TAND Checklist (Rho = 0.74; $p = 0.001$). The BRIEF metacognition index (MI) score correlated moderately with the TAND neuropsychological domain score (Rho = 0.59; $p = 0.016$).

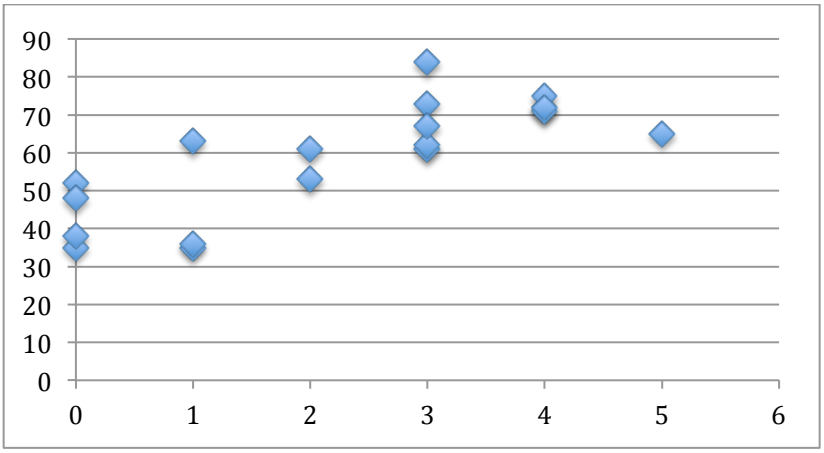

Figure 3.5: TAND Total Neuropsychological Score and BRIEF Global Executive Composite

3.2.3.3.1 Executive Functioning

Given the fact that the TAND Checklist Neuropsychological domain included a number of executive skills (specifically measured in the BRIEF), it was important to examine executive skills specifically. The correlation between the TAND Checklist executive skills subdomain items (items 7b – 7e) and the BRIEF GEC score showed a strong correlation (Rho = 0.79; $p < 0.001$). Similarly when correlating the BRIEF BRI score with the TAND Checklist executive skills subdomain, there was a strong correlation (Rho = 0.75; $p = 0.001$) (see **Fig. 3.6**). The BRIEF MI score also correlated (Rho = 0.65; $p = 0.006$) and showed a slightly higher spearman rho value than observed in the domain score.

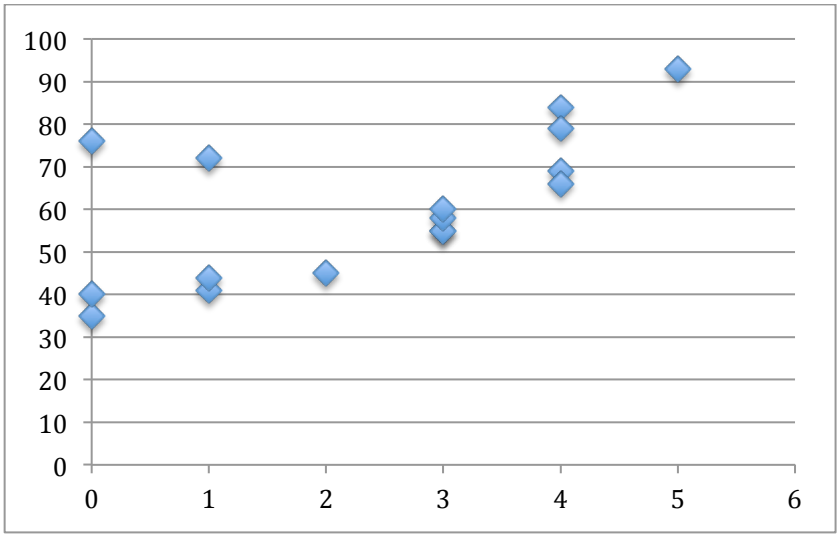

Figure 3.6: TAND Executive Function Score and BRIEF Behaviour Rating Index

3.2.3.4 Scholastic Domain

No external tools that specifically evaluated scholastic/academic skills were included in this study. However, we predicted that individuals with a lower Wessex score, suggesting intellectual disability, would have higher rates of scholastic difficulties reported in their TAND Checklists. Eighty percent (16/20) of participants were of school-going age or above and could be examined for scholastic difficulties. The TAND Checklist identified 7 individuals with scholastic difficulties of whom 6 were found to have ID as per Wessex judgement score.

3.2.3.5 Psycho-Social Domain

Individuals with psycho-social difficulties have an increased likelihood of behavioural challenges, including emotional and peer difficulties. We were therefore interested in the correlation between the TAND psycho-social domain and performance on the SDQ. Findings indicated moderate positive correlations between the TAND psycho-social scores and SDQ total difficulties (Rho = 0.593; p = 0.006) and between the TAND psycho-social scores and the SDQ emotion domain (Rho = 0.595; p = 0.006).

Interestingly TAND psycho-social scores did not correlate with SDQ peer problems (Rho = 0.221; p = 0.350).

3.2.3.6 Impact Scores

The Strengths and Difficulties Questionnaire contains a section that generates an impact score. In order to determine the association between the SDQ impact score and the TAND Checklist impact scores (TAND Checklist items 9 and 10) correlation analysis was applied to the SDQ impact score and the impact score assigned by the parent (item 9) and clinical researcher (item 10). See **Figs. 3.7** and **3.8.** A moderate correlation was found when comparing the SDQ impact score with that assigned by parents (Rho = 0.561; p = 0.010). There was however a very strong correlation (Rho = 0.796; p < 0.001) between SDQ impact score and clinical/researcher impact score.

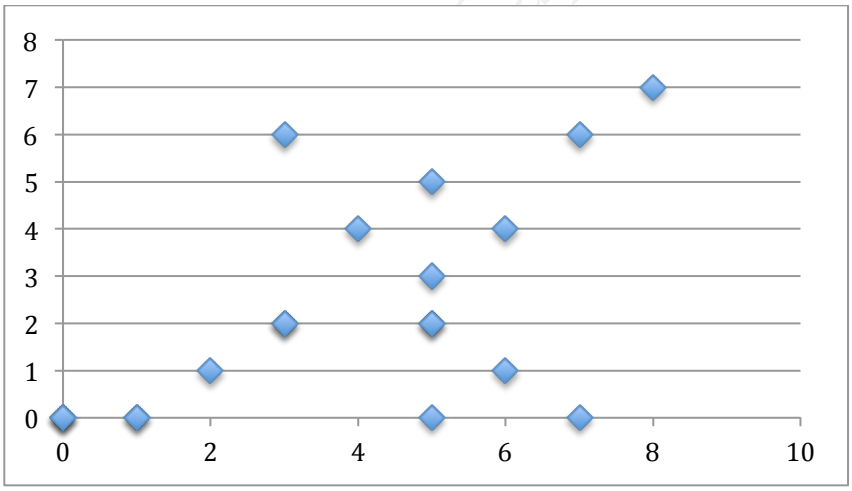

Figure 3.7 Stage 2: Correlation between impact score assigned by parent and impact score generated from SDQ.

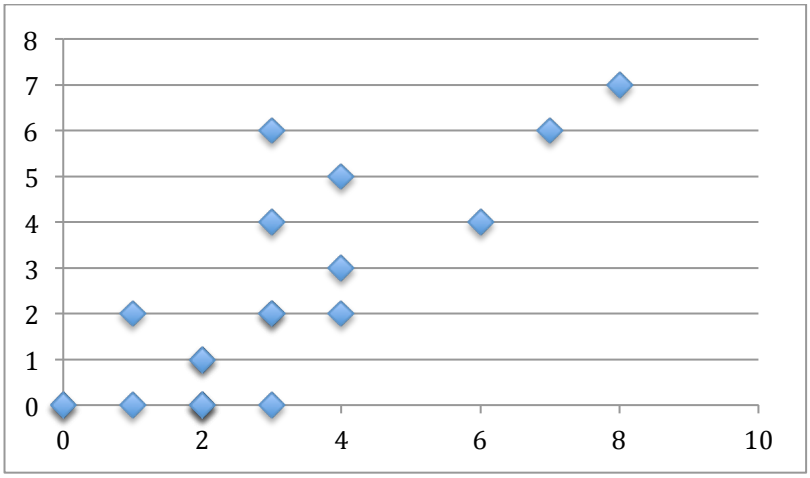

Figure 3.8 Stage 2: Correlation between impact score assigned by clinician and impact score generated from SDQ.

When looking at impact scores assigned by parents and the researcher respectively, 2 parents under-rated the impact, 9 agreed with the researcher's judgement and a further 9 parents assigned over-rated scores.

3.3. Stage 3 Results – Demographic profile of study participants

Demographic characteristics of the study participants are summarised in **Table 3.7**.

The aim in Stage 3 of this pilot study was to obtain a general sense of the study participants, to show how similar or different our participants were from the general population. In comparison with the general population, the Western Cape province of South Africa is not representative of national statistics in relation to employment, income and formal housing. For this reason we did not expect our sample to match that of the general population.

Table 3.7*:* Demographic information of the families who participated in Stage 2 live administration of the TAND Checklist (n=20***)***

	Male/ Female	Age	Rural/ Urban	Family Income	*Parental education	Current education	Type of Schooling
TP001	Male	12	Urban	5-10k	Grd 12	none	Special Ed
TP002	Male	13	Rural	<3k	Grd 11	none	None
TP003	Female	3	Urban	<3k	Grd 10	not yet	None
TP004	Male	15	Urban	<3k	Grd 7	9	Special Ed
TP005	Female	3	Urban	<3k	Grd 10	none	None
TP006	Female	27	Urban	<3k	Grd 10	adult	Special Ed
TP007	Female	5	Urban	<3k	Grd 11	none	Special Ed
TP008	Male	10	Urban	<3k	Grd 10	4	Mainstream
TP009	Male	13	Urban	5-10k	Grd 11	5	Special Ed
TP010	Male	16	Urban	<3k	Grd 7	10	Private
TP011	Male	6	Urban	<3k	Grd 12	1	Mainstream
TP012	Male	9	Urban	10-15k	Grd 12	2	Mainstream
TP013	Female	19	Urban	<3k	Certificate	none	None
TP014	Male	13	Urban	15-20k	Grd 12	7	Special Ed
TP015	Female	5	Urban	20k +	Degree	R	Private
TP016	Female	19	Urban	5-10k	Certificate	none	Special Ed
TP017	Male	36	Urban	20k+	Degree	Adult	Mainstream
TP018	Male	8	Urban	20k+	Degree	2	Special Ed
TP019	Male	42	Urban	20k+	Degree	Adult	Mainstream
TP020	Female	11	Urban	20k+	Degree	5	Mainstream

Parental Education: Grade numbers indicate highest level of primary education (up to grade 7) or secondary education (grade 8-12); 'Certificate' indicates a Grade 10-11 equivalent; 'degree' indicates Tertiary education

According to Statistics South Africa (2013), the general population is estimated at 52,982 million, roughly 6 million (11%) of whom live in the Western Cape. More than 1.3 million South Africans lived in informal dwellings in 2012 of which 135 000 (~10%) reside in the Western Cape. Nineteen of the twenty participating families were from urban areas around Cape Town, and only one family was from a rural community/informal settlement. In South Africa, 'rural living conditions' would include living on farmlands or in townships around major cities, most of which are not situated in the Western Cape.

With regard to family income, **Figure 3.9** shows the monthly income of families. The unemployment rate in South Africa is currently 24.7%. According to a

statistical release, *Monthly earnings of South Africans 2010*, by Statistics South Africa in November 2010 the median monthly earnings were R2,800 (~$280). Whilst earnings in the Western Cape were R2,700 (~$270) per month, it is important to note that its poorest 5% had the highest earnings amongst the poorest paid in all of the 9 provinces in South Africa. In our cohort, 50% of participating families earned less than R3,000 per month (~US$300), 15% earned between R5,000 and R10,000 per month (~$500-$1,000), 5% between R10,000 and R15,000, a further 5% between R15,000 and R20,000 and the remaining 25% earned more than R20,000 per month (~US$2,000).

In terms of level of education, the National Senior Certification (NSC), also referred to as 'matric', is the equivalent of Grade 12 education. The 2011 NSC examination results showed that 70.2% of full-time school candidates passed this examination whilst 82.9% of candidates in the Western Cape passed (Department of Basic Education, 2011). Interestingly, the 25% of families in our study who had showed monthly earnings exceeding R20 000 attained degree level education, whilst the remaining 75% ranged from Grade 7 (end of primary school) as the highest level of education up to and including Grade 12.

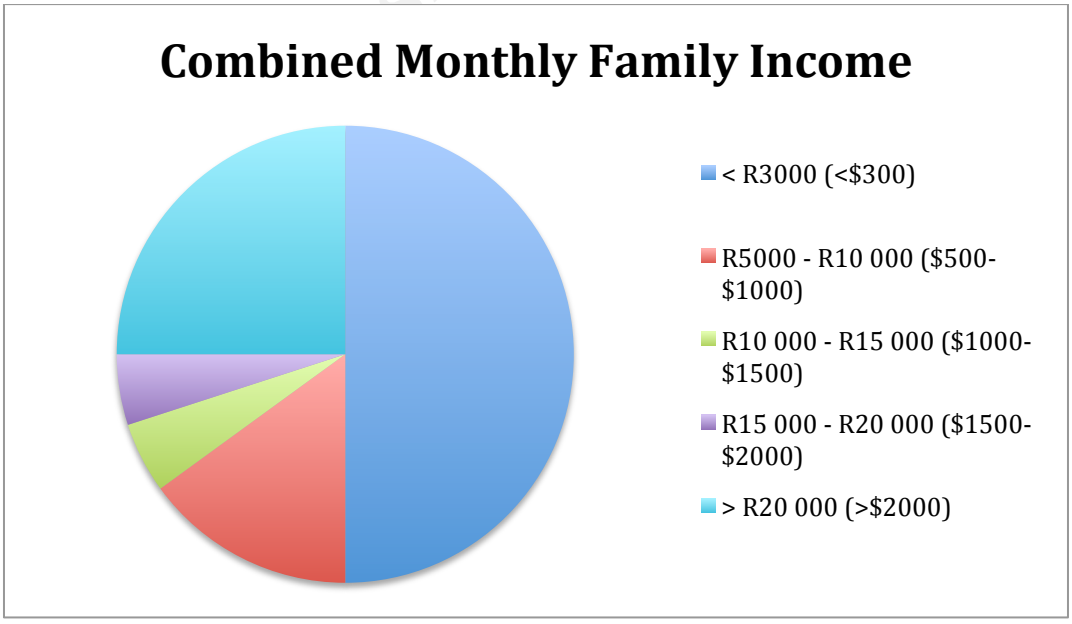

Figure 3.9: Combined Monthly Family Income

Participants reported that 12 (60%) of the TSC patients had a history of epilepsy, 4 (20%) had received a diagnosis of intellectual disability, 3 (15%) had a diagnosis of ADHD, and 1 (5%) patient had received a diagnosis of a mood disorder. None of the participants in the study had received a diagnosis of an autism spectrum disorder.

Chapter 4 Discussion

The purpose of the study was to perform a pilot validation of the TAND Checklist in order to create an acceptable TAND Checklist for larger-scale clinical use and research exploration. The pilot study focused on face and content validity, in order to establish whether the TAND Checklist was perceived to be comprehensive, clear, easy to use, applicable in real life settings and to determine whether it is likely to lead to further neuropsychiatric evaluation. In addition, the pilot examined external validation by comparing TAND Checklist scores to performance on a battery of widely-used and validated rating scales. Qualitative and quantitative data were used to refine the TAND Checklist.

4.1. Feedback on the TAND Checklist

The first aim of this study was to gather feedback to guide the refinement of the first version of the TAND Checklist. Results from the expert feedback form as completed by expert professionals, expert parents and parents in face-to-face administration showed high scores across the main areas of face and content validity. Taken together, results suggested that the TAND Checklist was regarded to be comprehensive, clear, easy to use, applicable and that it may lead to increased next-step assessments or treatments. Feedback was deliberately sought from numerous countries (28) with the aim of collecting global opinions and feedback. The hope is therefore that the tool would have a global utility. Feedback from participants was consistent suggesting that the TAND Checklist is generalisable/transferable and useful to clinicians and families.

One item showed a lower median score among expert professionals and expert parents. Results from item 4 (clinical usage) indicated hesitation as to whether clinical teams would use the TAND Checklist in practice. It is possible that there

may have been concern regarding the time requirements to complete the tool in the context of a busy clinic schedule, or that experts did not feel that they would have the necessary competence to complete the TAND Checklist with families. It was therefore interesting to note a strong theme from expert parents about the need for parents/families to take ownership and drive usage of the TAND Checklist.

No statistical differences were noted between responses of expert professionals and expert parents in stage 1. It was therefore interesting to observe a statistically significant difference between the Expert parents in Stage 1 and Stage 2 live administration participants with regards to item 2 addressing clarity. We interpret this to suggest that face-to-face administration of the TAND Checklist lead to increased clarity, providing good support for the face-to-face rather than a 'do it at home and bring to the clinic' approach when using the TAND Checklist.

4.2 Internal consistency

Examination of internal consistency suggested that the TAND Checklist has acceptable to excellent internal consistency within the domains and subdomains measured. However, the items from the Psycho-Social domain did not appear to have good internal consistency. These items do not refer to specific behaviours or outcomes, but rather to the subjective interpretation of the respondent. Furthermore, these 3 items refer to 2 separate constructs i.e TSC individual's self esteem; and parental and family stress. Thus, we did not anticipate them to render high internal consistency.

4.3 External validation

One of the main objectives of the study was to investigate external validity of the TAND Checklist, specifically concurrent validity, within particular domains and subdomains of the TAND Checklist.

4.3.1 Behavioural Domain

The behavioural domain items of the TAND Checklist correlated very strongly with the total difficulties score of the Strengths and Difficulties Questionnaire (SDQ). This indicated good convergent validity, that is, correspondence between the behavioural items in the TAND Checklist and similar behavioural constructs identified in the SDQ. Results showed that the behavioural domain of the TAND Checklist can be used as an effective indicator of behavioural difficulties associated with TSC. Results within the subdomain of hyperactivity also showed strong correlation between items associated with hyperactivity in the TAND Checklist and the total hyperactivity/inattention score produced by the SDQ assessment tool. The TAND Checklist social communication subdomain constructs correlated strongly with items from the Social Communication Questionnaire (SCQ), highlighting behaviours associated with autism spectrum disorders. Findings suggested that these items may be very useful markers of risk for ASD which is known to have a very high prevalence in TSC. The negative correlation seen between the SDQ Pro-social scale and the TAND social-communication items further strengthen the external validity of the items included in the TAND Checklist. Overall, results from the behavioural domain suggested that ADHD-related and ASD-related behaviours, two key developmental challenges in TSC, may usefully be identified through the TAND Checklist.

4.3.2. Intellectual Ability Domain

There was a moderate correlation between the level of intellectual ability as perceived by parents and researcher judgement based on the Wessex scale. Results suggest that parental perception of intellectual development is generally reasonably accurate. The TAND Checklist may be particularly helpful to identify individuals where there is a particular discrepancy between parental perception and clinical judgement. Given the multi-componential nature of intelligence, this might be a particular group of individuals who would benefit from formal assessment of their intellectual strengths and weaknesses.

It is important to emphasise that the TAND Checklist is not proposed to be a valid or reliable tool to measure or identify intellectual disability. However, it is known that about 50% of individuals with TSC may have intellectual disability, and that in turn shows very strong correlations with many neuropsychiatric and physical challenges. For these reasons, it may be very helpful to use the TAND Checklist to have a positive conversation with families about intellectual development and ability.

4.3.3 Neuropsychological Domain

The majority of individuals with TSC will have some neuropsychological deficits, even if they have normal intellectual ability (Harrison *et al*., 1999; Ridler *et al.,* 2007; de Vries *et al*., 2008; de Vries, 2010b; Tierney *et al*., 2011). Many of the behavioural screening tools for neuropsychological deficits are complicated to administer and score, and are expensive. It was therefore important to determine whether the neuropsychological questions in the TAND Checklist might provide a useful index of potential neuropsychological, and in particular executive, deficits. The TAND Checklist showed very strong correlation with the Behaviour Rating Inventory of Executive Functions (BRIEF), a widely-used and highly regarded rating scale. There were strong correlations when comparing the total TAND neuropsychological score with the global executive score (GEC) and behaviour rating index (BRI) of the BRIEF, suggesting that the TAND Checklist may be useful to highlight broad overall neuropsychological concerns and behaviour related difficulties such as inhibition, shifting between tasks or emotional control. The moderate correlation observed between the TAND total score and the metacognition index (MI) of the BRIEF suggested that the TAND Checklist did not fully capture the finer constructs identified by the MI including initiation, working memory, planning or organising and monitoring skills. It was very encouraging that the TAND Checklist executive function (EF) subdomain correlated strongly with all three subscales of the BRIEF. Taken together, results suggested that the TAND Checklist may be very helpful in identifying potential neuropsychological and in particular executive difficulties that would benefit from further evaluation and intervention.

4.2.3 Scholastic Domain

This pilot did not include any external validation instruments in the scholastic domain that could have examined the TAND Checklist items in a robust way, and this domain in particular would benefit from evaluation in future studies. It was however encouraging that, as predicted, there was a good correlation between those identified as having intellectual disability on the Wessex and the presence of scholastic problems in reading, writing, spelling and/or mathematics.

4.2.4 Psycho-Social Domain

Correlations indicated that the TAND Checklist was able to identify psycho-social difficulties in TSC, but only moderately when compared to the Strengths and Difficulties Questionnaire (SDQ) total score and sub-scale of emotional symptoms. No correlation was observed between the TAND Checklist psycho-social domain and the SDQ sub-scale for peer relationships. Results suggested that the TAND Checklist might be able to identify behavioural difficulties associated with emotional concerns, but not sufficiently regarding peer relationships. Taken together, findings suggest that the psycho-social items in the TAND Checklist could best be viewed as a starting place for conversations around self-esteem, family relationships and peer interactions, and that further exploration should take place in order to identify relevant clinical needs.

4.2.5 Impact Scores

The impact rating assigned by parents correlated very strongly with that assigned by the researcher indicating that the TAND Checklist was able to quantify the degree and impact of neuropsychiatric problems experienced by families and individuals living with TSC. The researcher impact scores correlated better with the Strengths and Difficulties Questionnaire (SDQ) impact score than the parent-rated impact score. These results support two potentially valuable contributions of the TAND Checklist. Firstly, it indicated that a clinician can generate a reasonably good sense of the impact of the neuropsychiatric

challenges of an individual with TSC after this short interview. Secondly, it supports the value of an external perspective of 'impact'. Where a family under-rated the impact (2 families), this could lead to a very helpful conversation regarding ways to find support; where a family over-reported impact (9 families), this may lead to a conversation around family stress, support systems and how to manage challenges.

4.4 Demographic Data

The final aim of the study was to gather demographic data of the families and individuals with TSC who participated in the study to show how similar or different our participants were from the general population. We did not anticipate our cohort to be fully representative of the general population as our sample was recruited from the Western Cape Province where unemployment rates are lower, access to amenities more readily available, and where level of education is highest (Stats SA, 2010; Department of Basic Education, 2011; Stats SA, 2013). Only a single family reported living in a rural setting, in keeping with the Western Cape's lower than national informal settlement rates. An interesting finding was that the quarter of families with monthly earnings exceeding R20,000 (~$2,000) also attained degree level education - an indication of the relationship between income and level of education.

The prevalence of epilepsy, intellectual disability and symptoms of mood disorders in this cohort (60%; 20%; 5%) were consistent with previous studies. With regards to autism spectrum disorders and attention deficit hyperactivity prevalence rates (0%; 15%) clinical diagnosis in this population was not in keeping with the literature (Smalley *et al*., 1994; Gillbert *et al*., 1994; Thiele, 2004; Prather and de Vries, 2004; de Vries, 2007; de Vries, 2010b). We predict that this is most likely due to under-diagnosis given that the four external assessment tools used, as well as the TAND Checklist, identified a substantial number of participants at high risk for ASD or ADHD. It would be an important

next step in future studies to examine whether high scores on the TAND Checklist a) lead to further evaluations and b) correlate with clinical diagnoses of, for instance, autism spectrum disorder or ADHD.

4.5 Limitations of the study

In spite of the positive initial findings of this pilot study, there are several limitations that should be acknowledged.

1. Concern regarding age ranges of the rating scales selected for concurrent validation of the TAND Checklist. The Strengths and Difficulties Questionnaire (SDQ) used in this study was aimed at individuals between the ages of 4 and 10 years and 11 – 17 years. This study had 2 participants below the age of 4 (both were 3.5 years of age) and a further 5 participants who were over the age of 17. The items and subscale may still be appropriate, however, there has been no validation studies to our knowledge on very young children or in the adult population. In contrast, three versions of the BRIEF were available and used in the study.

2.1 Selection of respondents required to complete the questionnaire. The tool used to establish concurrent validity with social communication problems on the TAND Checklist was the Social Communication Questionnaire (SCQ). The questionnaire was designed to be completed by the parent of an individual with possible ASD. However, during stage 2 live administration, the 5 adult participants did not have a parent/carer who could complete the SCQ about them. In these instances, participants completed the SCQ about themselves. These adults were unable to answer the questions that referred to behaviours before the age of 5 years of age. However, it is important to note that none of these 5 adult participants showed any signs of autistic-like behaviour on the 1st half of the questionnaire or in the social communication items of the TAND Checklist.

2.2 Assessment tools used. Albeit a reliable tool, the Wessex scale does not render an overall score or cut off point and the researcher needed to assign a judgement score to enable analysis. To mitigate this aspect of the tool, judgement scores were assigned by a pair of researchers with consensus.

These limitations with regards to the external assessment tools used also support the development of the TAND Checklist which has one single version for all ages, abilities and can be completed with a parent, carer or individual with TSC.

3. Aspects of reliability. It is important to acknowledge that this study did not examine certain aspects of reliability such as inter-rater or test-retest reliability. It might be very helpful to examine inter-rater reliability, in particular to see if relatively non-expert clinicians will get similar scores to very experienced TSC clinicians. Interestingly, in this study, the face-to-face administration was done by a non-clinician with relatively little experience in TSC. The reatively positive results on external validation suggest that a high level of clinical and TSC expertise may not be required. Whilst test-retest reliability is often examined for questionnaires, it is not clear how useful this would be for a TAND Checklist, given that new neuropsychiatric manifestations may present over the course of a few weeks, thus reducing the likelihood of high stability of measurement.

4. Subsequent validity. One of the aims of the TAND Checklist is to address the vast gap between need and actual assessment and treatment of neuropsychiatric disorders in TSC by acting as an aide-mémoire to clinicians. In order to establish subsequent validity, one would have to look at clinical usage of the TAND Checklist in practice and it is suggested that future research include this aspect of validity. It was however encouraging that qualitative data from parent and professional experts suggested a good likelihood of ‘next steps’ subsequent to administration of the TAND Checklist.

5. Sensitivity and specificity. It was outside the scope of this study to examine sensitivity and specificity of the tool. These measures of performance would be a natural next step in terms of validating the TAND Checklist as both a reliable and valid tool in identifying neuropsychiatric difficulties in TSC.

6. Language constraints. The stage 2 live administration participants were all from the Western Cape in South Africa and were required to understand English. South Africa has 11 official languages and it is therefore possible that the requirement for English may have introduced some bias in ascertainment. English is however generally understood across the country, being the language of business, politics and media (statistics south Africa, 2012), and the research team encouraged participation across all language groups by ensuring that there was access to English, Afrikaans and isiXhosa speaking staff for families and participants. In spite of these potential language challenges, results were extremely encouraging and suggested that the TAND Checklist may still be helpful and a valid tool across the vast majority of neuropsychiatric domains, even in families where the TAND Checklist is administered in a second language.

4.6 Future Directions

The next step involves the translation of the TAND Checklist into a range of international languages including Spanish, Portugese, Chinese, Flemish, French and German. In addition, South African translations will be made into the high-frequency languages (Afrikaans, isiXhosa and isiZulu). A standard procedure for translation and back-translation will be used, and all translated versions will be authorised by the primary authors of the tool to ensure accurate and consistent translations of the TAND Checklist. TAND Checklists will be made available via the Tuberous Sclerosis Alliance and Tuberous Sclerosis International associations.

This was the first study to focus on refining the TAND Checklist and to investigate aspects of its validity. Further larger scale research is required to investigate other features of the TAND Checklist's validity and reliability not examined in the pilot validation. Clinicians and researchers may benefit from training on usage of the TAND Checklist, both in a clinical and research settings. Once the TAND Checklist is in clinical use (2014), it is imperative that follow-up research focuses on potential 'next steps' where neuropsychiatric concerns are identified, ultimately addressing the vast gap between need and treatment. Families and clinicians may also benefit from a toolkit containing 'next steps', 'self-help' information and access to resources, especially in countries and areas where access to highly specialised clinicians and centres are limited.

Chapter 5 Conclusion

As outlined in Chapter 1, TSC is a genetic condition with an immense range of physical manifestations that can be very challenging to manage. Good progress has been made in recent decades to improve earlier diagnosis and early treatment (particularly of seizures). Molecularly targeted treatments have brought new medical treatments for some of the key physical features of TSC (de Vries, 2010a; Manning, 2010; Krueger *et al*., 2013).

TSC is also associated with a significant range of neuropsychiatric disorders and these have an enormous impact on the quality of life for individuals with TSC and their families. In contrast to the improved detection and treatment of physical manifestations of TSC, there is still a significant 'assessment and treatment gap' of neuropsychiatric difficulties in TSC (de Vries, 2013). The needs of an individual may change over time as some developmental difficulties improve or become more pronounced, or as new mental health, school or family difficulties emerge. Given the range of manifestations, the age and developmental variability, there have been to date no simple or single screening tool to help clinicians and families evaluate an individual with TSC for possible neuropsychiatric features. The coining of the term TAND (TSC-Associated Neuropsychiatric Disorders), the 2012 Neuropsychiatry Panel recommendation to perform annual screening for TAND, and the TAND Checklist were all initiated with the aim of improving awareness of TAND, and to encourage a systematic approach to TAND.

In this research project, we performed the first evaluation of the TAND Checklist as outlined in Chapter 2. Given the interest in the TSC community in getting access to the TAND Checklist, it was important to do a first-step evaluation to ensure that the TAND Checklist was appropriately comprehensive, clear and usable to clinicians and families. In addition, we were interested to determine whether clinicians and families felt that the TAND Checklist would be useful and

would encourage further assessment or treatment (so-called subsequent validity). The results of expert feedback forms and of parental feedback (Chapter 3) suggested that overall the TAND Checklist was deemed to be a good tool in identifying possible neuropsychiatric difficulties. Qualitative feedback provided information for minor improvements to the TAND Checklist (including an additional section on developmental history, examples provided for terms such as 'visuo-spatial skills' and 'executive functions', and the reduction/collapse of intellectual ability/disability categories to eliminate confusion and misinterpretation), and raised the importance of families leading the use of the TAND Checklist in partnership with their clinical teams.

Given that the TAND Checklist items had not been validated in any other setting, it was also important to check external validity by comparing the domains on the TAND Checklist with external tools that had already been validated and/or used widely (Chapter 2). We deliberately chose to perform pilot validation in South Africa where we expected baseline knowledge not to be very high, where levels of academic and socio-economic status, and competence in English would be quite variable. We argued that the tool needed to be such that it would be easily accessible to individuals from low/middle income countries. In addition, we also piloted the TAND Checklist with a researcher (the author) who does not have a clinical qualification or extensive expertise in TSC, to determine whether relative non-expert administrators could still collect meaningful and relevant neuropsychiatric information. Results of the concurrent/external validation were, on the whole, very encouraging (Chapter 3). The majority of domain and subdomain scores correlated strongly to very strongly with the external rating scales used in the study. Modest correlations were seen in the psycho-social domain, and we did not use any external validation tools for the scholastic or psychiatric levels, where actual clinical evaluation would have been required.

We acknowledged the range of limitations of the study (Chapter 4). However, it was very encouraging to observe that one simple tool that takes approximately 10 minutes to complete captured information relevant to TSC in a way that

correlated very well with 4 external tools (which took on average an hour to complete) and which would cost ~R2,500 (~$250) if used commercially. The TAND Checklist will be freely available to clinicians and researchers globally.

The third and final version is currently in the process of being translated into other languages for clinical use and will be made available in early 2014. Further subsequent validity research studies will need to be performed to ascertain whether annual screening of TAND will address the 'need and assessment/treatment gap' of neuropsychiatric disorders. The TAND Checklist will play a critical role in achieving this goal set out by the Neuropsychiatric panel at the 2012 International TSC Consensus Conference.

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Appendix A: TAND Checklist v.1

The TAND Research Checklist (2012)
Lifetime version (TAND-CL)

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which we refer to as TAND (TSC-Associated Neuropsychiatric Disorders).

All people with TSC are at risk to have some of these difficulties. Some people with TSC have very few of these issues, 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 to help clinical teams and families a) screen for TAND at every clinic visit and b) prioritize with families what to do next.

Instructions to use the checklist.
The TAND checklist was designed to be completed by a clinician with relevant knowledge and experience in TSC in partnership with an individual with TSC, their parents or carers. The checklist should take about 10 minutes to complete. Where individuals answer YES to an item, the clinician should explore the difficulty in sufficient detail to help guide decisions about further evaluation or treatment.

All items should be completed.

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. We are going to use this checklist to help us check for these kinds of difficulties. I am going to ask a number of questions. Some may be directly relevant to you; some might not be at all. Just answer as best as you can. At the end I will check to see if you have any additional difficulties we didn't talk about.

1. Firstly we will talk about behaviours causing concern to you or to other people. **Have you/your child/your family member ever had difficulties with any of the following?:**		
a. Anxiety	NO	YES
b. Depressed mood	NO	YES
c. Extreme shyness	NO	YES
d. Mood swings	NO	YES
e. Aggressive outbursts	NO	YES
f. Temper Tantrums	NO	YES
g. Self-injury such as hitting, biting, scratching self	NO	YES
h. Absent or delayed onset of language to communicate	NO	YES
i. Unusual use of language, such as strange words or sentences	NO	YES
i. Poor eye contact	NO	YES
j. Difficulties getting on with other people of similar age	NO	YES
k. Repetitive behaviours such as doing the same thing over and over again	NO	YES
l. Very rigid or inflexible about how to do things and not liking change in routines	NO	YES
m. Overactivity/hyperactivity	NO	YES
n. Difficulty paying attention or concentrating	NO	YES
o. Restlessness, fidgetiness	NO	YES
p. Impulsivity such as butting in, not waiting turn	NO	YES
q. Difficulties with eating (too much, too little, unusual things)	NO	YES
r. Sleep difficulties such as with falling asleep or waking in the night	NO	YES
If you answered YES to any of the above: Have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES

2. **Problem behaviours may add up to meet criteria for specific psychiatric disorders. Have you/your child/family member received a diagnosis of:**		
a. Autism Spectrum Disorder (ASD), including autism, asperger's etc.	NO	YES
b. Attention Deficit Hyperactivity Disorder (ADHD)	NO	YES
c. Anxiety Disorder	NO	YES
d. Depressive Disorder	NO	YES
e. Obsessive Compulsive Disorder (OCD)	NO	YES
f. Psychotic Disorder	NO	YES
If you answered YES to any of the above, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES
3. About half of people with TSC will have significant difficulties in their overall intellectual development and may have 'intellectual disability'. Have you ever been concerned about this for yourself/your child/family member?	NO	YES
If YES, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES
What is your view of your own/your child's/your family member's intellectual ability? (circle) **Normal Intellectual Ability** **Mild or Moderate Intellectual Disability** **Severe Intellectual Disability** **Profound Intellectual Disability**		
4. Many people with TSC who are of school age will have difficulties in school. Do you/your child/family member have any difficulty with one of the following:		
a. Difficulties with reading	NO	YES
b. Difficulties with writing	NO	YES
c. Difficulties with spelling	NO	YES
d. Difficulties with mathematics	NO	YES
If YES, have you had further evaluation or support for it? Have you/your child/family member been considered for	NO	YES

an Individual Educational Plan (IEP) or any additional support in school? Would you like to have further evaluation or support for it?	NO NO	YES YES
5. The majority of people with TSC will have some difficulties in some specific brain skills. Do you/your child/family member have any difficulties with any of the following brain skills:		
a. Memory, such as remembering things that have happened	NO	YES
b. Attention, such as concentrating well, not getting distracted	NO	YES
c. Dual-tasking/ Multi-tasking	NO	YES
c. Visuospatial tasks, such as spatial navigation	NO	YES
d. Executive skills, such as planning, organizing	NO	YES
e. Getting disoriented, such as not knowing the date or where you are	NO	YES
If YES, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES
6. Apart from the challenges listed above, TSC can have a big impact on people's lives in other ways. Have you/your child/family had any difficulties with:		
a. Low self-esteem	NO	YES
b. Very high levels of stress between parents leading to significant relationship difficulties	NO	YES
c. Very high levels of stress in families	NO	YES
If YES, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES

7. Taking together all the difficulties discussed above, how much have these bothered, troubled or distressed you/your child/family?

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

8. Interviewer's judgement of impact/burden on the person/child/family.

0 1 2 3 4 5 6 7 8 9 10

Not at all		**Extremely**
9. Of all the concerns listed above, what are your top priorities to work on next? a. b. c.		
10. Do you have any other worries about TAND that we have not talked about as we went through the checklist? If YES, please list:	NO	YES

Appendix B: TAND Checklist v.2

The TAND Research Checklist (2013)
Lifetime version (TAND-CL)

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which we refer to as TAND (TSC-Associated Neuropsychiatric Disorders). All people with TSC are at risk to have some of these difficulties. Some people with TSC have very few of these issues, 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 to help clinical teams and families a) screen for TAND at every clinic visit and b) prioritize with families what to do next.

Instructions to use the checklist.
The TAND checklist was designed to be completed by a clinician with relevant knowledge and experience in TSC in partnership with parents or carers of individuals with TSC. The checklist should take about 10 minutes to complete. Where individuals answer YES to an item, the clinician should explore the difficulty in sufficient detail to help guide decisions about further evaluation or treatment.

All items should be completed.

Study Code of Participant: **…….. Date of interview:……/……/……**

Name of Interviewer: **……**

Interviewee: Parent/Other**:** **……**

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. We are going to use this checklist to help us check for these kinds of difficulties. I am going to ask a number of questions. Some may be directly relevant; some might not be at all. Just answer as best as you can. At the end I will check to see if there are any additional difficulties we didn't talk about.

1. Let's begin by talking about your child's development to get a sense of where they are at.		
a. How old was ……. when he/she first smiled?	…weeks	Not yet
b. Sat without support?	…months	Not yet
c. Walk without holding on?	…months	Not yet
d. Used single words other than "mamma" or "dadda"?	…months	Not yet
e. Used two words/short phrases?	…months	Not yet

f. Toilet trained during the day?	…years	Not yet
g. Toilet trained at night?	…years	Not yet

2. What is ……. current level of: (circle)

a. **language:** nonverbal - simple language - fluent

b. **self-care:** dependent on others - some self-care skills independent

c. **mobility:** wheelchair - needs significant support - some difficulty - completely mobile

3. Next we will talk about behaviours causing concern to you or to other people.
Has [……] ever had difficulty with any of the following?:

a. Anxiety	NO	YES
b. Depressed mood	NO	YES
c. Extreme shyness	NO	YES
d. Mood swings	NO	YES
e. Aggressive outbursts	NO	YES
f. Temper Tantrums	NO	YES
g. Self-injury such as hitting, biting, scratching self	NO	YES
h. Absent or delayed onset of language to communicate	NO	YES
i. Repeating words or phrases over and over again	NO	YES
j. Poor eye contact	NO	YES
k. Difficulties getting on with other people of similar age	NO	YES
l. Repetitive behaviours such as doing the same thing over and over again	NO	YES
m. Very rigid or inflexible about how to do things and not liking change in routines	NO	YES
n. Overactivity/hyperactivity	NO	YES
o. Difficulty paying attention or concentrating	NO	YES
p. Restlessness, fidgetiness	NO	YES
q. Impulsivity such as butting in, not waiting turn	NO	YES
r. Difficulties with eating (too much, too little, unusual things)	NO	YES
s. Sleep difficulties such as with falling asleep or waking in the night	NO	YES

If you answered YES to any of the above: Have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	 NO NO	 YES YES
4. Problem behaviours may add up to meet criteria for specific psychiatric disorders. Has your child/family member received a diagnosis of:		
a. Autism Spectrum Disorder (ASD), including autism, asperger's etc.	NO	YES
b. Attention Deficit Hyperactivity Disorder (ADHD)	NO	YES
c. Anxiety Disorder	NO	YES
d. Depressive Disorder	NO	YES
e. Obsessive Compulsive Disorder (OCD)	NO	YES
f. Psychotic Disorder	NO	YES
If you answered YES to any of the above, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES
5. About half of people with TSC will have significant difficulties in their overall intellectual development and may have 'intellectual disability'. Have you ever been concerned about this for your child/family member?	NO	YES
If YES, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES
What is your view of your child's/your family member's intellectual ability? (circle) **Normal Intellectual Ability - Mild or Moderate Intellectual Disability** **Severe Intellectual Disability - Profound Intellectual Disability**		
6. Many people with TSC who are of school age will have difficulty in school. [For individuals of school age]: Does …….. have any difficulty with one of the following:		

[For individuals after school age]: Did ……. have any difficulty with one of the following:		
a. Reading	NO	YES
b. Writing	NO	YES
c. Spelling	NO	YES
d. Mathematics	NO	YES
If YES, have you had further evaluation or support for it? Has ……. been considered for any additional support in school such as extra help or an Individual Educational Plan (IEP)? Would you like to have further evaluation or support for it?	NO NO NO	YES YES YES
7. The majority of people with TSC will have some difficulties in some specific brain skills. Does your child/family member have difficulty with any of the following brain skills:		
a. Memory, such as remembering things that have happened	NO	YES
b. Attention, such as concentrating well, not getting distracted	NO	YES
c. Dual-tasking/ Multi-tasking	NO	YES
d. Visuo-spatial tasks, such as puzzles and building blocks	NO	YES
e. Executive skills, such as planning, organizing	NO	YES
f. Getting disoriented, such as not knowing the date or where you are	NO	YES
If YES, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES
8. Apart from the challenges listed above, TSC can have a big impact on people's lives in other ways. Has your child/family had any difficulties with:		
a. Low self-esteem	NO	YES
b. Very high levels of stress between parents leading to significant relationship difficulties	NO	YES
c. Very high levels of stress in families	NO	YES
If YES, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES
9. Taking together all the difficulties discussed above, how much have these bothered, troubled or distressed your child/family?		

0 1 2 3 4 5 6 7 8 9 10 **Not at all** **Extremely**		
10. Interviewer's judgement of impact/burden on the child/family.		
0 1 2 3 4 5 6 7 8 9 10 **Not at all** **Extremely**		
11. Of all the concerns listed above, what are your top priorities to work on next?		
a. b. c.		
12. Do you have any other worries about TAND that we have not talked about as we went through the checklist?	NO	YES
If YES, please list:		

Appendix C: TAND Checklist v3

The TAND Research Checklist (2013)
Lifetime version (TAND-CL)

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which we refer to as TAND (TSC-Associated Neuropsychiatric Disorders). All people with TSC are at risk to have some of these difficulties. Some people with TSC have very few of these issues, 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 to help clinical teams and families a) screen for TAND at every clinic visit and b) prioritize with families what to do next.

Instructions to use the Checklist.
The TAND Checklist was designed to be completed by a clinician with relevant knowledge and experience in TSC in partnership with parents or carers of individuals with TSC. The Checklist should take about 10 minutes to complete. Where individuals answer YES to an item, the clinician should explore the difficulty in sufficient detail to help guide decisions about further evaluation or treatment. All items should be completed.

TSC Patient: **…….** **DOB:** **……/……/…….** **Age:** **…….**

Name of Interviewer: **…….** **Date of interview:** **……/……/……**

Interviewee: Parent/Other**:** **…….**

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. We are going to use this checklist to help us check for these kinds of difficulties. I am going to ask a number of questions. Some may be directly relevant; some might not be at all. Just answer as best as you can. At the end I will check to see if there are any additional difficulties we didn't talk about.

1. Let's begin by talking about your child's development to get a sense of where they are at.		
a. How old was ……. when he/she first smiled?		Not yet

b. Sat without support?		Not yet
c. Walk without holding on?		Not yet
d. Used single words other than “mamma” or “dadda”?		Not yet
e. Used two words/short phrases?		Not yet
f. Toilet trained during the day?		Not yet
g. Toilet trained at night?		Not yet

2. What is ……. current level of:

a. **language:** nonverbal - simple language - fluent

b. **self-care:** dependent on others - some self-care skills - independent

c. **mobility:** wheelchair - significant support - some difficulty - completely mobile

3. Next we will talk about behaviours causing concern to you or to other people. Has [……] ever had difficulty with any of the following?:

a. Anxiety	NO	YES
b. Depressed mood	NO	YES
c. Extreme shyness	NO	YES
d. Mood swings	NO	YES
e. Aggressive outbursts	NO	YES
f. Temper Tantrums	NO	YES
g. Self-injury *i.e. hitting self, biting self, scratching self*	NO	YES
h. Absent or delayed onset of language to communicate	NO	YES
i. Repeating words or phrases over and over again	NO	YES
j. Poor eye contact	NO	YES
k. Difficulties getting on with other people of similar age	NO	YES
l. Repetitive behaviours i.e. doing the same thing over and over again	NO	YES
m. Very rigid or inflexible about how to do things or not liking change in routines	NO	YES
n. Overactivity/hyperactivity *i.e. abnormally active*	NO	YES
o. Difficulty paying attention or concentrating	NO	YES
p. Restlessness, fidgetiness *i.e wriggle or squirm*	NO	YES
q. Impulsivity *i.e. butting in, not waiting turn*	NO	YES
r. Difficulties with eating (too much, too little, unusual things)	NO	YES
s. Sleep difficulties *i.e. falling asleep or waking in the night*	NO	YES
If you answered YES to any of the above:		

Have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES

4. Problem behaviours may add up to meet criteria for specific psychiatric disorders. Has your child/family member received a diagnosis of:		
a. Autism Spectrum Disorder (ASD), *including autism, asperger's*	NO	YES
b. Attention Deficit Hyperactivity Disorder (ADHD)	NO	YES
c. Anxiety Disorder *i.e. panic, phobia, PTSD*	NO	YES
d. Depressive Disorder	NO	YES
e. Obsessive Compulsive Disorder		
f. Psychotic Disorder *i.e. schizophrenia*	NO	YES
If you answered YES to any of the above, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES

5. About half of people with TSC will have significant difficulties in their overall intellectual development and may have 'intellectual disability'. Have you ever been concerned about this for your child/family member?	NO	YES
If YES, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?	NO NO	YES YES

What is your view of your child's/your family member's intellectual ability? (circle)

Normal Intellectual Ability **Mild-Moderate Disability** **Severe - Profound Disability**

6. Many people with TSC who are of school age will have difficulty in school.
[For individuals of school age]: Does …….. have any difficulty with one of the following:
[For individuals after school age]: Did ……. have any difficulty with one of the following:

a. Reading	N/A	NO	YES
b. Writing	N/A	NO	YES

c. Spelling	N/A	NO	YES
d. Mathematics	N/A	NO	YES
If YES, have you had further evaluation or support for it? Has … been considered for any additional support in school such as extra help or an Individual Educational Plan (IEP)? Would you like to have further evaluation or support for it?		NO NO NO	YES YES YES
7. The majority of people with TSC will have some difficulties in some specific brain skills. Does your child/family member have difficulty with any of the following brain skills:			
a. Memory, *such as remembering things that have happened*		NO	YES
b. Attention, *such as concentrating well, not getting distracted*		NO	YES
c. Dual-tasking/ Multi-tasking, *such as doing 2 tasks at the same time*		NO	YES
d. Visuo-spatial tasks, *such as puzzles and building blocks*		NO	YES
e. Executive skills, *such as planning, organizing, inhibition, inflexible thinking*		NO	YES
f. Getting disoriented, *such as not knowing the date or where you are*		NO	YES
If YES, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?		NO NO	YES YES
8. Apart from the challenges listed above, TSC can have a big impact on people's lives in other ways. Has your child/family had any difficulties with:			
a. Low self-esteem		NO	YES
b. Very high levels of stress in families *i.e. siblings*		NO	YES
c. Very high levels of stress between parents leading to significant relationship difficulties		NO	YES
If YES, have you had further evaluation or support for it? Would you like to have further evaluation or support for it?		NO NO	YES YES
9. Taking together all the difficulties discussed above, how much have these bothered, troubled or distressed your child/family?			

0 1 2 3 4 5 6 7 8 9 10 **Not at all** **Extremely**		
10. Interviewer's judgement of impact/burden on the child/family.		
0 1 2 3 4 5 6 7 8 9 10 **Not at all** **Extremely**		
11. Of all the concerns listed above, what are your top priorities to work on next?		
a. b. c.		
12. Do you have any other worries about TAND that we have not talked about as we went through the checklist?	NO	YES
If YES, please list		

Appendix D: Expert Feedback Form

UNIVERSITY OF CAPE TOWN

DIVISION OF CHILD AND ADOLESCENT PSYCHIATRY

Pilot validation of the Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND) checklist as screening tool for neuropsychiatric manifestations

Expert Feedback Form

Please circle the number that is most representative of your views.

1. Does the checklist cover the relevant range of neuropsychiatric features you think is important in TSC?

1 **2** **3** **4** **5**

Not at all **Very much**

Please indicate missing items:

2. Are the items clear and understandable?

1 **2** **3** **4** **5**

Not at all **Very much**

Please indicate unclear items and how you would suggest improving them:

3. Overall, how easy do you think the checklist will be to use?

1 **2** **3** **4** **5**

Not at all **Very much**

What might improve ease of use?

4. How likely do you think clinicians are to use the checklist?

1 **2** **3** **4** **5**

Not at all **Very much**

What could be done to increase likely use by clinical teams?

5. How likely is the checklist to encourage clinicians to pursue further neuropsychiatric work-up or referral to relevant specialists?

1 **2** **3** **4** **5**

Not at all **Very much**

What can be done to increase the likelihood?

Appendix E: Strengths and Difficulties Questionnaire

Strengths and Difficulties Questionnaire P 4-16

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months.

Child's Name ..... Male/Female

Date of Birth.....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Do you have any other comments or concerns?

Please turn over - there are a few more questions on the other side

Overall, do you think that your child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes- minor difficulties	Yes- definite difficulties	Yes- severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress your child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
HOME LIFE	☐	☐	☐	☐
FRIENDSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐
LEISURE ACTIVITIES	☐	☐	☐	☐

- Do the difficulties put a burden on you or the family as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature ..... Date .....

Mother/Father/Other (please specify:)

Thank you very much for your help

Strengths and Difficulties Questionnaire S 11-17

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of how things have been for you over the last six months.

Your Name ..... Male/Female

Date of Birth.....

	Not True	Somewhat True	Certainly True
I try to be nice to other people. I care about their feelings	☐	☐	☐
I am restless, I cannot stay still for long	☐	☐	☐
I get a lot of headaches, stomach-aches or sickness	☐	☐	☐
I usually share with others (food, games, pens etc.)	☐	☐	☐
I get very angry and often lose my temper	☐	☐	☐
I am usually on my own. I generally play alone or keep to myself	☐	☐	☐
I usually do as I am told	☐	☐	☐
I worry a lot	☐	☐	☐
I am helpful if someone is hurt, upset or feeling ill	☐	☐	☐
I am constantly fidgeting or squirming	☐	☐	☐
I have one good friend or more	☐	☐	☐
I fight a lot. I can make other people do what I want	☐	☐	☐
I am often unhappy, down-hearted or tearful	☐	☐	☐
Other people my age generally like me	☐	☐	☐
I am easily distracted, I find it difficult to concentrate	☐	☐	☐
I am nervous in new situations. I easily lose confidence	☐	☐	☐
I am kind to younger children	☐	☐	☐
I am often accused of lying or cheating	☐	☐	☐
Other children or young people pick on me or bully me	☐	☐	☐
I often volunteer to help others (parents, teachers, children)	☐	☐	☐
I think before I do things	☐	☐	☐
I take things that are not mine from home, school or elsewhere	☐	☐	☐
I get on better with adults than with people my own age	☐	☐	☐
I have many fears, I am easily scared	☐	☐	☐
I finish the work I'm doing. My attention is good	☐	☐	☐

Do you have any other comments or concerns?

Please turn over - there are a few more questions on the other side

Overall, do you think that you have difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes-minor difficulties	Yes-definite difficulties	Yes-severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress you?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with your everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
HOME LIFE	☐	☐	☐	☐
FRIENDSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐
LEISURE ACTIVITIES	☐	☐	☐	☐

- Do the difficulties make it harder for those around you (family, friends, teachers, etc.)?

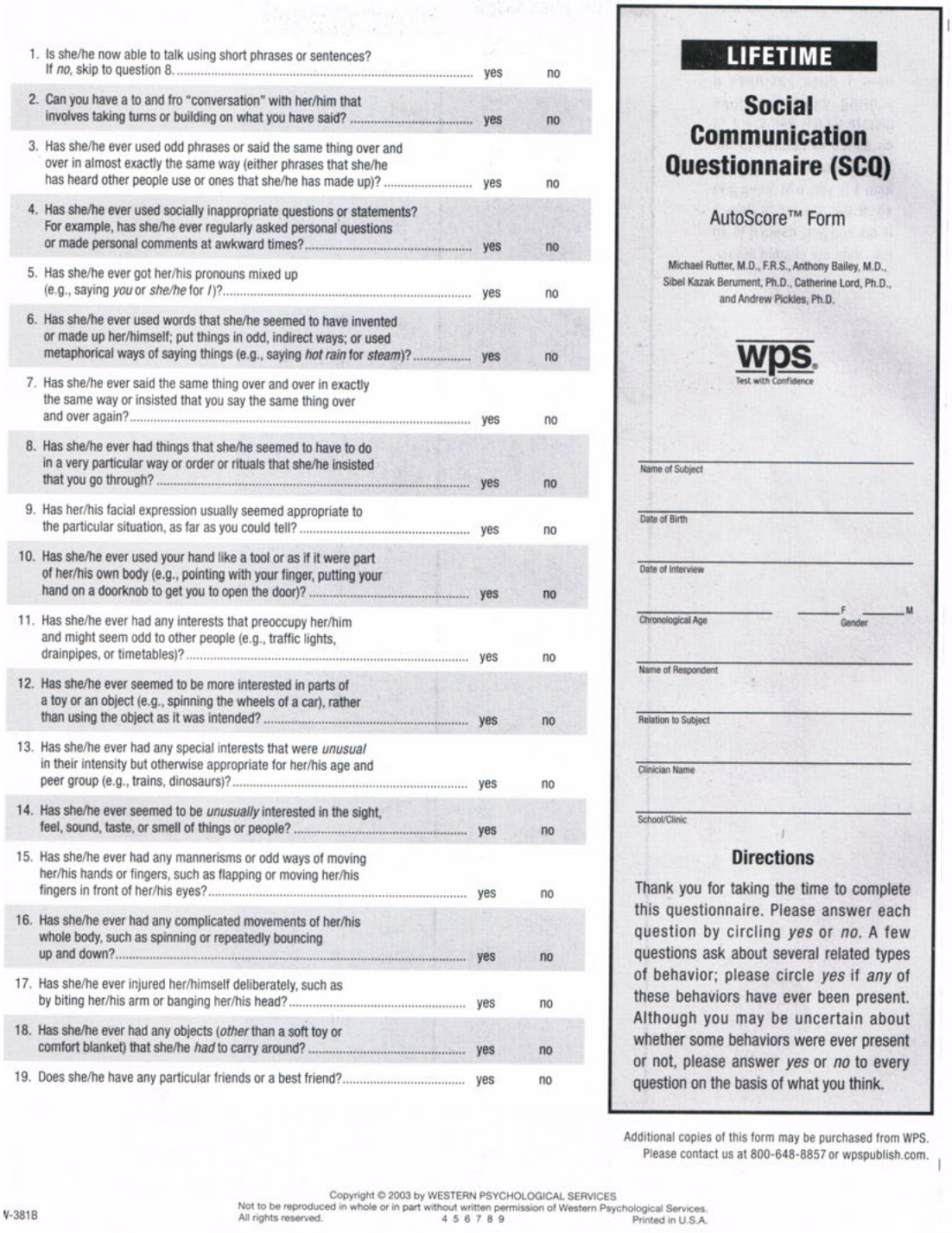
Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Your Signature .....

Today's Date .....

Thank you very much for your help

Appendix F: Social Communication Questionnaire



1. Is she/he now able to talk using short phrases or sentences? If *no*, skip to question 8. ..... yes no
2. Can you have a to and fro "conversation" with her/him that involves taking turns or building on what you have said? ..... yes no
3. Has she/he ever used odd phrases or said the same thing over and over in almost exactly the same way (either phrases that she/he has heard other people use or ones that she/he has made up)? ..... yes no
4. Has she/he ever used socially inappropriate questions or statements? For example, has she/he ever regularly asked personal questions or made personal comments at awkward times? ..... yes no
5. Has she/he ever got her/his pronouns mixed up (e.g., saying *you* or *she/he* for *I*)? ..... yes no
6. Has she/he ever used words that she/he seemed to have invented or made up her/himself; put things in odd, indirect ways; or used metaphorical ways of saying things (e.g., saying *hot rain* for *steam*)? ..... yes no
7. Has she/he ever said the same thing over and over in exactly the same way or insisted that you say the same thing over and over again? ..... yes no
8. Has she/he ever had things that she/he seemed to have to do in a very particular way or order or rituals that she/he insisted that you go through? ..... yes no
9. Has her/his facial expression usually seemed appropriate to the particular situation, as far as you could tell? ..... yes no
10. Has she/he ever used your hand like a tool or as if it were part of her/his own body (e.g., pointing with your finger, putting your hand on a doorknob to get you to open the door)? ..... yes no
11. Has she/he ever had any interests that preoccupy her/him and might seem odd to other people (e.g., traffic lights, drainpipes, or timetables)? ..... yes no
12. Has she/he ever seemed to be more interested in parts of a toy or an object (e.g., spinning the wheels of a car), rather than using the object as it was intended? ..... yes no
13. Has she/he ever had any special interests that were *unusual* in their intensity but otherwise appropriate for her/his age and peer group (e.g., trains, dinosaurs)? ..... yes no
14. Has she/he ever seemed to be *unusually* interested in the sight, feel, sound, taste, or smell of things or people? ..... yes no
15. Has she/he ever had any mannerisms or odd ways of moving her/his hands or fingers, such as flapping or moving her/his fingers in front of her/his eyes? ..... yes no
16. Has she/he ever had any complicated movements of her/his whole body, such as spinning or repeatedly bouncing up and down? ..... yes no
17. Has she/he ever injured her/himself deliberately, such as by biting her/his arm or banging her/his head? ..... yes no
18. Has she/he ever had any objects (*other* than a soft toy or comfort blanket) that she/he *had* to carry around? ..... yes no
19. Does she/he have any particular friends or a best friend? ..... yes no

LIFETIME

Social Communication Questionnaire (SCQ)

AutoScore™ Form

Michael Rutter, M.D., F.R.S., Anthony Bailey, M.D., Sibel Kazak Berument, Ph.D., Catherine Lord, Ph.D., and Andrew Pickles, Ph.D.

wps. Test with Confidence

Name of Subject

Date of Birth

Date of Interview

Chronological Age ____ F ____ M Gender

Name of Respondent

Relation to Subject

Clinician Name

School/Clinic

Directions

Thank you for taking the time to complete this questionnaire. Please answer each question by circling *yes* or *no*. A few questions ask about several related types of behavior; please circle *yes* if *any* of these behaviors have ever been present. Although you may be uncertain about whether some behaviors were ever present or not, please answer *yes* or *no* to every question on the basis of what you think.

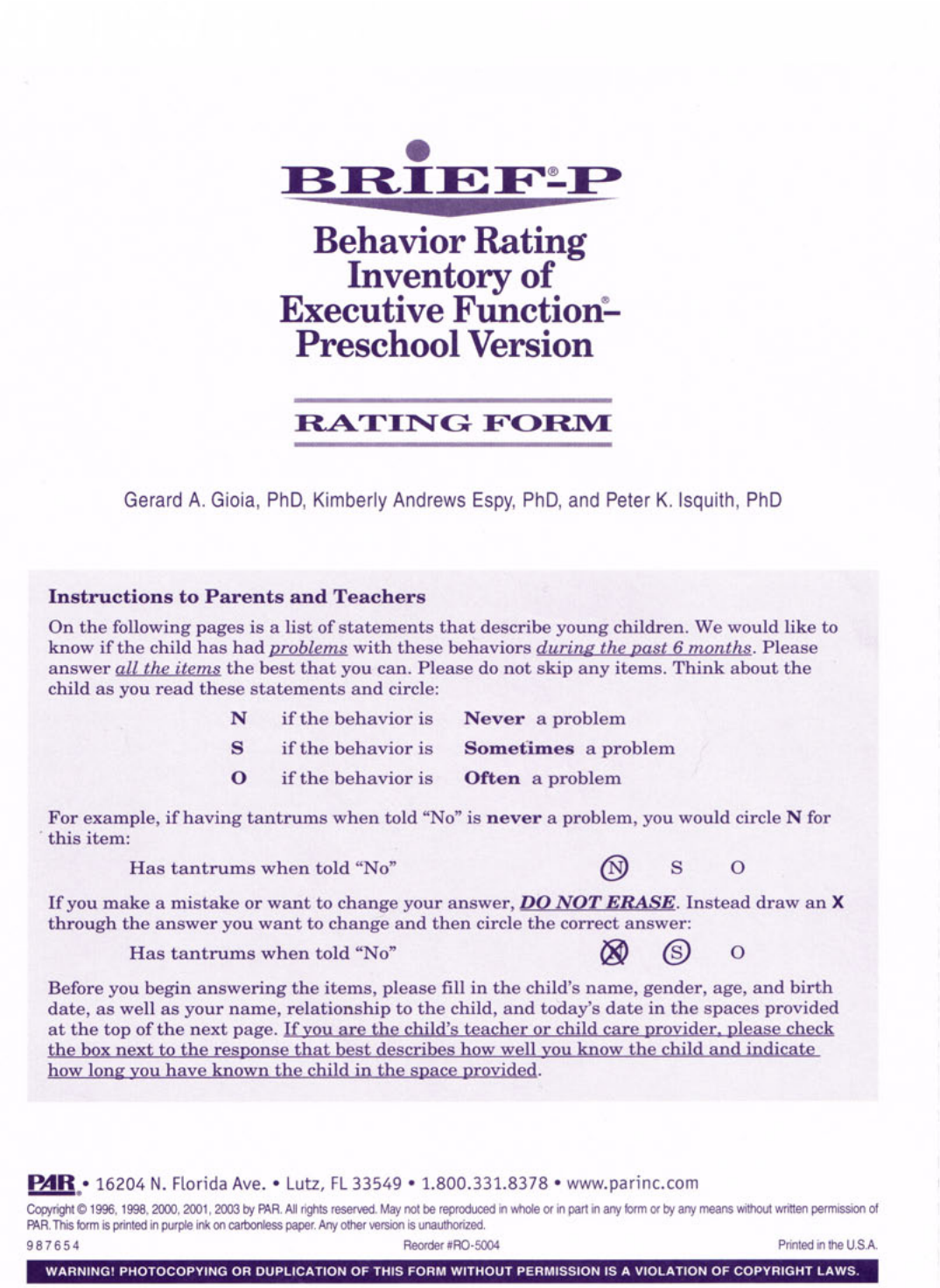
Additional copies of this form may be purchased from WPS. Please contact us at 800-648-8857 or wpspublish.com.

V-381B

For the following behaviors, please focus on the time period between the child's fourth and fifth birthdays. You may find it easier to remember how things were at that time by focusing on key events, such as starting school, moving house, Christmastime, or other specific events that are particularly memorable for you as a family. If your child is not yet 4 years old, please consider her or his behavior in the past 12 months.

20. When she/he was 4 to 5, did she/he ever talk with you just to be friendly (rather than to get something)?	yes	no
21. When she/he was 4 to 5, did she/he ever *spontaneously* copy you (or other people) or what you were doing (such as vacuuming, gardening, or mending things)?	yes	no
22. When she/he was 4 to 5, did she/he ever spontaneously point at things around her/him just to show you things (not because she/he wanted them)?	yes	no
23. When she/he was 4 to 5, did she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wanted?	yes	no
24. When she/he was 4 to 5, did she/he nod her/his head to mean *yes*?	yes	no
25. When she/he was 4 to 5, did she/he shake her/his head to mean *no*?	yes	no
26. When she/he was 4 to 5, did she/he usually look at you directly in the face when doing things with you or talking with you?	yes	no
27. When she/he was 4 to 5, did she/he smile back if someone smiled at her/him?	yes	no
28. When she/he was 4 to 5, did she/he ever show you things that interested her/him to engage your attention?	yes	no
29. When she/he was 4 to 5, did she/he ever offer to share things other than food with you?	yes	no
30. When she/he was 4 to 5, did she/he ever seem to want you to join in her/his enjoyment of something?	yes	no
31. When she/he was 4 to 5, did she/he ever try to comfort you if you were sad or hurt?	yes	no
32. When she/he was 4 to 5, when she/he wanted something or wanted help, did she/he look at you and use gestures with sounds or words to get your attention?	yes	no
33. When she/he was 4 to 5, did she/he show a normal range of facial expressions?	yes	no
34. When she/he was 4 to 5, did she/he ever spontaneously join in and try to copy the actions in social games, such as *The Mulberry Bush* or *London Bridge Is Falling Down*?	yes	no
35. When she/he was 4 to 5, did she/he play any pretend or make-believe games?	yes	no
36. When she/he was 4 to 5, did she/he seem interested in other children of approximately the same age whom she/he did not know?	yes	no
37. When she/he was 4 to 5, did she/he respond positively when another child approached her/him?	yes	no
38. When she/he was 4 to 5, if you came into a room and started talking to her/him without calling her/his name, did she/he usually look up and pay attention to you?	yes	no
39. When she/he was 4 to 5, did she/he ever play imaginative games with another child in such a way that you could tell that they each understood what the other was pretending?	yes	no
40. When she/he was 4 to 5, did she/he play cooperatively in games that required joining in with a group of other children, such as hide-and-seek or ball games?	yes	no

Appendix G: Behaviour Rating Index of Executive Function



BRIEF®-P

Behavior Rating Inventory of Executive Function®– Preschool Version

RATING FORM

Gerard A. Gioia, PhD, Kimberly Andrews Espy, PhD, and Peter K. Isquith, PhD

Instructions to Parents and Teachers

On the following pages is a list of statements that describe young children. We would like to know if the child has had *problems* with these behaviors *during the past 6 months*. Please answer *all the items* the best that you can. Please do not skip any items. Think about the child as you read these statements and circle:

N	if the behavior is	**Never** a problem
S	if the behavior is	**Sometimes** a problem
O	if the behavior is	**Often** a problem

For example, if having tantrums when told "No" is **never** a problem, you would circle **N** for this item:

Has tantrums when told "No" (N) S O

If you make a mistake or want to change your answer, ***DO NOT ERASE***. Instead draw an **X** through the answer you want to change and then circle the correct answer:

Has tantrums when told "No" (X) (S) O

Before you begin answering the items, please fill in the child's name, gender, age, and birth date, as well as your name, relationship to the child, and today's date in the spaces provided at the top of the next page. If you are the child's teacher or child care provider, please check the box next to the response that best describes how well you know the child and indicate how long you have known the child in the space provided.

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Child's Name _____ Gender _____ Age _____ Birth Date ____/____/____

Your Name _____ Today's Date ____/____/____

Relationship to Child: ☐ Mother ☐ Father ☐ Teacher* ☐ Other* _____

How well do you know the child? ☐ Not Well ☐ Moderately Well ☐ Very Well *Have known the child for____ ☐ months ☐ years.

During the past 6 months, how often has each of the following behaviors been a *problem?*	Never	Sometimes	Often
1. Overreacts to small problems	N	S	O
2. When given two things to do, remembers only the first or last	N	S	O
3. Is unaware of how his/her behavior affects or bothers others	N	S	O
4. When instructed to clean up, puts things away in a disorganized, random way	N	S	O
5. Becomes upset with new situations	N	S	O
6. Has explosive, angry outbursts	N	S	O
7. Has trouble carrying out the actions needed to complete tasks (such as trying one puzzle piece at a time, cleaning up to earn a reward)	N	S	O
8. Does not stop laughing at funny things or events when others stop	N	S	O
9. Needs to be told to begin a task even when willing to do it	N	S	O
10. Has trouble adjusting to new people (such as babysitter, teacher, friend, or day care worker)	N	S	O
11. Becomes upset too easily	N	S	O
12. Has trouble concentrating on games, puzzles, or play activities	N	S	O
13. Has to be more closely supervised than similar playmates	N	S	O
14. When sent to get something, forgets what he/she is supposed to get	N	S	O
15. Is upset by a change in plans or routine (for example, order of daily activities, adding last minute errands to schedule, change in driving route to store)	N	S	O
16. Has outbursts for little reason	N	S	O
17. Repeats the same mistakes over and over even after help is given	N	S	O
18. Acts wilder or sillier than others in groups (such as birthday parties, play group)	N	S	O
19. Cannot find clothes, shoes, toys, or books even when he/she has been given specific instructions	N	S	O
20. Takes a long time to feel comfortable in new places or situations (such as visiting distant relatives or new friends)	N	S	O
21. Mood changes frequently	N	S	O
22. Makes silly mistakes on things he/she can do	N	S	O
23. Is fidgety, restless, or squirmy	N	S	O
24. Has trouble following established routines for sleeping, eating, or play activities	N	S	O
25. Is bothered by loud noises, bright lights, or certain smells	N	S	O
26. Small events trigger big reactions	N	S	O
27. Has trouble with activities or tasks that have more than one step	N	S	O
28. Is impulsive	N	S	O
29. Has trouble thinking of a different way to solve a problem or complete an activity when stuck	N	S	O
30. Is disturbed by changes in the environment (such as new furniture, things in room moved around, or new clothes)	N	S	O

ıring the past 6 months, how often has each of the following behaviors been a *problem?*	Never	Sometimes	Often
1. Angry or tearful outbursts are intense but end suddenly	N	S	O
2. Needs help from adult to stay on task	N	S	O
3. Does not notice when his/her behavior causes negative reactions	N	S	O
4. Leaves messes that others have to clean up even after instruction	N	S	O
5. Has trouble changing activities	N	S	O
6. Reacts more strongly to situations than other children	N	S	O
7. Forgets what he/she is doing in the middle of an activity	N	S	O
8. Does not realize that certain actions bother others	N	S	O
9. Gets caught up in the small details of a task or situation and misses the main idea	N	S	O
0. Has trouble "joining in" at unfamiliar social events (such as birthday parties, picnics, holiday gatherings)	N	S	O
1. Is easily overwhelmed or overstimulated by typical daily activities	N	S	O
2. Has trouble finishing tasks (such as games, puzzles, pretend play activities)	N	S	O
3. Gets out of control more than playmates	N	S	O
4. Cannot find things in room or play area even when given specific instructions	N	S	O
5. Resists change of routine, foods, places, etc.	N	S	O
6. After having a problem, will stay disappointed for a long time	N	S	O
7. Cannot stay on the same topic when talking	N	S	O
8. Talks or plays too loudly	N	S	O
9. Does not complete tasks even after given directions	N	S	O
0. Acts overwhelmed or overstimulated in crowded, busy situations (such as lots of noise, activity, or people)	N	S	O
1. Has trouble getting started on activities or tasks even after instructed	N	S	O
2. Acts too wild or out of control	N	S	O
3. Does not try as hard as his/her ability on activities	N	S	O
4. Has trouble putting the brakes on his/her actions even after being asked	N	S	O
5. Unable to finish describing an event, person, or story	N	S	O
6. Completes tasks or activities too quickly	N	S	O
7. Is unaware when he/she does well and not well	N	S	O
8. Gets easily sidetracked during activities	N	S	O
9. Has trouble remembering something, even after a brief period of time	N	S	O
0. Becomes too silly	N	S	O
1. Has a short attention span	N	S	O
2. Plays carelessly or recklessly in situations where he/she could be hurt (such as playground, swimming pool)	N	S	O
3. Is unaware when he/she performs a task right or wrong	N	S	O

BRIEF®-A

Behavior Rating Inventory of Executive Function®– Adult Version

INFORMANT REPORT FORM

Robert M. Roth, PhD, Peter K. Isquith, PhD, and Gerard A. Gioia, PhD

Instructions

On the following pages is a list of statements that may describe your child/parent/spouse/sibling or another person with whom you are familiar. We would like to know if he/she has had problems with these behaviors over the past month. Please answer all the items the best that you can. Please DO NOT SKIP ANY ITEMS. Think about him/her as you read each statement and then circle your response.

N	if the behavior is	**Never** a problem
S	if the behavior is	**Sometimes** a problem
O	if the behavior is	**Often** a problem

For example, if he/she **never** has trouble making decisions, you would circle **N** for this item:

Has trouble making decisions (N) S O

If you make a mistake or want to change your answer, DO NOT ERASE. Draw an "X" through the answer you want to change, and then circle the correct answer:

Has trouble making decisions (X) (S) O

Before you begin answering the items, please fill in the name, gender, and age of the rated individual; your name; today's date; your relationship to the individual; and how well and how many years you have known him/her in the spaces provided at the top of the next page.

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Name of Rated Individual_____ Gender ☐ Male ☐ Female Age_____

Your Name_____ Today's Date___/___/___

Your relationship to him/her: ☐ Parent ☐ Spouse ☐ Sibling ☐ Friend ☐ Other_____

How well do you know him/her? ☐ Not well ☐ Moderately well ☐ Very well You have known him/her for ____ years.

During the past month, how often has each of the following behaviors been a *problem*?

N = Never S = Sometimes O = Often

1. Has angry outbursts	N	S	O
2. Makes careless errors when completing tasks	N	S	O
3. Is disorganized	N	S	O
4. Has trouble concentrating on tasks (such as chores, reading, or work)	N	S	O
5. Taps fingers or bounces legs	N	S	O
6. Needs to be reminded to begin a task even when willing	N	S	O
7. Has a messy closet	N	S	O
8. Has trouble changing from one activity or task to another	N	S	O
9. Gets overwhelmed by large tasks	N	S	O
10. Forgets his/her name	N	S	O
11. Has trouble with jobs or tasks that have more than one step	N	S	O
12. Overreacts emotionally	N	S	O
13. Doesn't notice when he/she causes others to feel bad or get mad until it is too late	N	S	O
14. Has trouble getting ready for the day	N	S	O
15. Has trouble prioritizing activities	N	S	O
16. Has trouble sitting still	N	S	O
17. Forgets what he/she is doing in the middle of things	N	S	O
18. Doesn't check work for mistakes	N	S	O
19. Has emotional outbursts for little reason	N	S	O
20. Lies around the house a lot	N	S	O
21. Starts tasks (such as cooking, projects) without the right materials	N	S	O
22. Has trouble accepting different ways to solve problems with work, friends, or tasks	N	S	O
23. Talks at the wrong time	N	S	O
24. Misjudges how difficult or easy tasks will be	N	S	O
25. Has problems getting started on his/her own	N	S	O
26. Has trouble staying on the same topic when talking	N	S	O
27. Gets tired	N	S	O
28. Reacts more emotionally to situations than his/her friends	N	S	O
29. Has problems waiting his/her turn	N	S	O
30. People say that he/she is disorganized	N	S	O
31. Loses things (such as keys, money, wallet, homework, etc.)	N	S	O
32. Has trouble thinking of a different way to solve a problem when stuck	N	S	O
33. Overreacts to small problems	N	S	O
34. Doesn't plan ahead for future activities	N	S	O
35. Has a short attention span	N	S	O
36. Makes inappropriate sexual comments	N	S	O
37. When people seem upset with him/her, doesn't understand why	N	S	O
38. Has trouble counting to three	N	S	O

During the past month, how often has each of the following behaviors been a *problem*?

N = Never S = Sometimes O = Often

Has unrealistic goals	N	S	O
Leaves the bathroom a mess	N	S	O
Makes careless mistakes	N	S	O
Gets emotionally upset easily	N	S	O
Makes decisions that get him/her into trouble (legally, financially, socially)	N	S	O
Is bothered by having to deal with changes	N	S	O
Has difficulty getting excited about things	N	S	O
Forgets instructions easily	N	S	O
Has good ideas but cannot get them on paper	N	S	O
Makes mistakes	N	S	O
Has trouble getting started on tasks	N	S	O
Says things without thinking	N	S	O
His/her anger is intense but ends quickly	N	S	O
Has trouble finishing tasks (such as chores, work)	N	S	O
Starts things at the last minute (such as assignments, chores, tasks)	N	S	O
Has difficulty finishing a task on his/her own	N	S	O
People say that he/she is easily distracted	N	S	O
Has trouble remembering things, even for a few minutes (such as directions, phone numbers)	N	S	O
People say that he/she is too emotional	N	S	O
Rushes through things	N	S	O
Gets annoyed	N	S	O
Leaves room or home a mess	N	S	O
Gets disturbed by unexpected changes in daily routine	N	S	O
Has trouble coming up with ideas for what to do with free time	N	S	O
Doesn't plan ahead for tasks	N	S	O
People say that he/she doesn't think before acting	N	S	O
Has trouble finding things in room, closet, or desk	N	S	O
Has problems organizing activities	N	S	O
After having a problem, does not get over it easily	N	S	O
Has trouble doing more than one thing at a time	N	S	O
Mood changes frequently	N	S	O
Doesn't think about consequences before doing something	N	S	O
Has trouble organizing work	N	S	O
Gets upset quickly or easily over little things	N	S	O
Is impulsive	N	S	O
Doesn't pick up after self	N	S	O
Has problems completing his/her work	N	S	O

Appendix H: Wessex Rating Scale

These items refer to the person you care for. For each question (A, B, C, D etc …), please enter the appropriate code in each box.

(Frequently = more than once a week)

A) Wetting (nights) **1** = frequently **2** = occasionally **3** = never ☐

B) Soiling (nights) **1** = frequently **2** = occasionally **3** = never ☐

C) Wetting (days) **1** = frequently **2** = occasionally **3** = never ☐

D) Soiling (days) **1** = frequently **2** = occasionally **3** = never ☐

E) Walk with help **1** = not at all **2** = not up stairs **3** = up stairs and elsewhere ☐

(note: if this person walks *by himself* upstairs and elsewhere, please also code '3' for 'walk with help')

F) Walk by himself **1** = not at all **2** = not up stairs **3** = up stairs and elsewhere ☐

G) Feed himself **1** = not at all **2** = with help **3** = without help ☐

H) Wash himself **1** = not at all **2** = with help **3** = without help ☐

I) Dress himself **1** = not at all **2** = with help **3** = without help ☐

J) Vision **1** = blind or almost **2** = poor **3** = normal ☐

K) Hearing **1** = deaf or almost **2** = poor **3** = normal ☐

L) Speech **1** = never a word **2** = odd words only **3** = sentences and normal **4** = can talk but doesn't ☐

If this person talks in sentences, is his/her speech:

1 = Difficult to understand even by acquaintances, impossible for strangers?

2 = Easily understood for acquaintances, difficult for strangers?

3 = Clear enough to be understood by anyone? ☐

M) Reads **1** = nothing **2** = a little **3** = newspapers and/or books ☐

N) Writes **1** = nothing **2** = a little **3** = own correspondence ☐

O) Counts **1** = nothing **2** = a little **3** = understands money values ☐

Appendix I: Demographic Information

UNIVERSITY OF CAPE TOWN

DIVISION OF CHILD AND ADOLESCENT PSYCHIATRY

DEMOGRAPHIC INFORMATION

DATE: …… **CODE:** ……

RESEARCHER:

……

PARTICIPANT/FAMILY:

……

1. Rural (1) or Urban living (2) 1 2

2. Household income

< R3000 R3000-R5000 R5000-R10 000

R10 000-R15 000 R15 000-R20 000 R20 000+

Notes:……

3. Parental level of education

< Grade 7/St.5 Grade 8/St.6 Grade 9/St.7 Grade 10/St.8

Grade 11/St.9 Grade 12/St.10 certificate/diploma degree

Notes:……

INDIVIDUAL WITH TSC

1. Gender: Male (1) or Female (2) 1 2

2. Age: ……..

3. Grade level: ……..

4. Schooling Placement:

Mainstream Private School Special Education Home School

5. Neurospychiatric diagnosis:

ASD ADHD EPILEPSY MOOD DISORDER ID

Notes:……

6. Clinical Complications:

CNS Features Dermatological Features Renal Lesions

Notes:……

7. Current Medication:

Notes:……