The Validity of the Alcohol, Smoking and Substance Involvement Screening Test in Patients with Psychotic Disorders

By

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Declaration

I, Rosalind Jane Adlard, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any 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 Given the high prevalence of substance use disorders among patients with persistent mental illnesses, with resultant negative health consequences, a brief and easily administered screening test is needed in this population to identify those at risk in order to intervene appropriately. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was developed by the World Health Organisation as a screening instrument. It has been validated in a variety of settings, including in primary care and treatment settings and in first episode psychosis.

Aim To determine the validity and reliability of the ASSIST in detecting substance use disorders in patients with multi-episode psychotic disorders.

Setting Western Cape, South Africa.

Methods The Structured Clinical Interview for DSM-IV Axis I Disorders was used as the gold standard for detecting DSM-IV substance abuse and dependence. Cronbach's alpha was used to determine the internal consistency of the ASSIST, and receiver operating characteristic analysis was used to evaluate its screening properties. Optimal cut off scores were calculated to maximize sensitivity and specificity.

Results A total substance involvement lifetime score of 13 was found to have both sensitivity and specificity of just over 74%. A specific substance involvement score of 4 for alcohol and 3 for cannabis, methamphetamine and 'other drugs' was found to have optimal balance between sensitivity and specificity.

Conclusion The ASSIST is a psychometrically valid screening test for substance use disorders in general, as well as for alcohol, cannabis and methamphetamine use disorders, in patients with multi-episode psychotic disorders.

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Last but not least I would like to thank my family and friends for their sacrifice, support and understanding throughout the MMed process, which has been invaluable.

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Abbreviations

ANOVA: Kruskal-Wallis analysis of variance

ASI: Addiction Severity Index

ASSIST: Alcohol, Smoking and Substance Involvement Screening Test

AUDIT: Alcohol Use Disorders Identification Test

AUC: Area under the curve

BMD: Bipolar disorder

CI: Confidence Interval

DAST: Drug Abuse Screening Test

DIS: Diagnostic Interview Schedule

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision

EEG: Electroencephalogram

HREC: Human Research Ethics Committee

LR+: Positive likelihood ratio

MAP: Maudsley Addiction Profile

MINI: Mini International Neuropsychiatric Interview

MPD: Methamphetamine induced psychotic disorder

NPV: Negative predictive value

OR: Odds ratio

PPV: Positive predictive value

RISC: Rating of Injection Site Condition

ROC: Receiver operating characteristics

RTQ: revised Fagerstrom Tolerance Questionnaire

SASQ: single alcohol screening question

SCID-I: Structured Clinical Interview for DSM-IV Axis I Disorders

SD: Standard deviation

SDS: Severity of Dependence Scale

SSI: Specific Substance Involvement score

SUD: Substance use disorders

SZP: Schizophrenia

TLFB: 90 day time line follow back

TSI: Total Substance Involvement score

UK: United Kingdom

USA: United States of America

WHO: World Health Organisation

Chapter 1: Introduction and Literature review

Introduction

The use of psychoactive substances is increasing worldwide. The majority of this constitutes the use of legal substances (alcohol and tobacco) while illicit drug use has an annual prevalence of about 3 – 4% of the world's population.[1] The harmful or hazardous use of alcohol or other drugs contributes to the global burden of disease,[2] increases the risk of non-communicable disease[3,4] as well as communicable disease,[5] and increases the risk of injury.[6] The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) classifies substance use disorders into substance abuse and substance dependence disorders.[7] South Africa has a lifetime prevalence of substance use disorders of 13.4%. The lifetime prevalence of any DSM-IV mental disorder is 30.3%, and substance use disorders make up the second most prevalent class of lifetime disorders at 13.3%. Of the individual lifetime disorders, alcohol use disorder is the most common at 11.4%. Of all the provinces, the Western Cape has the highest lifetime prevalence for both substance use disorders and any mental disorder.[8]

Substance use disorders (SUD) are highly prevalent among patients with psychiatric illness compared to the general population.[9] Moreover, substance abuse is known to precipitate and/ or contribute to psychotic symptoms. In schizophrenia, substance use is associated with more positive psychotic symptoms[10] and heavy cannabis use in particular is known to be associated with relapse.[11] However, substance use disorders are often underdiagnosed amongst patients with psychiatric illnesses, which in turn can contribute to poor outcomes due to the substance use disorder not being treated adequately.[12] Compared with patients with only a psychiatric or substance use disorder, patients with both disorders have more severe illness and a worse longitudinal course of illness, with increased risk of relapse; more psychological distress; poorer compliance with medication; higher rates of utilization of health services; impaired psychosocial function; and increased rates of institutionalization, violence, suicide, problems with the legal system, and other health problems. [12,13,14] In addition, where substance use disorder and psychotic disorders are co-morbid, failure to treat either one of them adequately results in worse outcomes for the other disorder, with regards to both illness severity and longitudinal course.[14]

The World Health Organisation (WHO) has identified drug, alcohol and tobacco use as being among the top twenty risk factors for poor health,[15] and recommends screening and early intervention for drug and alcohol use as a public health measure.[1] Screening is generally preferred to a diagnostic test such as the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I), which although considered valid and reliable in the identification of substance use disorders, is impractical in the clinical context as it requires training to administer and is time consuming.[16] Screening is important not only because of the negative impact of alcohol and other drug use, but also due to difficulties in easily identifying those using alcohol and drugs at problematic levels.[16] It is valuable as it can help to detect risk and can help to inform the most appropriate intervention, thus helping to prevent later morbidity.[17] Screening tests traditionally take one of two approaches: biological tests or self-screening reports. Biological tests, while often quick and accurate, can be invasive, require good hygiene standards and specialised equipment.[18] Self-report tests can be either direct or indirect. Most have been validated in the United States only and their usefulness in other cultures and settings is unclear.[19] Due to the strain on health services, especially at primary care level, a screening test which is brief and can be administered in minutes is warranted.[20] Many screening tests used in research settings are too long and cumbersome to be practical e.g. the Addiction Severity Index (ASI). Briefer screening tests are available, which are validated in patients with psychosis, e.g. the Alcohol Use Disorders Identification Test (AUDIT), the Severity of Dependence Scale (SDS), and the Drug Abuse Screening Test (DAST). However, these are designed to screen for a specific or generic substance of use, rather than screening for a variety of substance use.[21] Other brief screening tests e.g. the CAGE, tend to identify those with severe problems rather than those with more moderate but still problematic levels of drug use. Tests that can distinguish between high, moderate and low levels of use and associated risk are thus more useful.

Box 1: Overview of ASSIST questions

Q1	In your life, which of the following substances have you ever used (non-medical use only)? (alcohol, tobacco, cannabis, cocaine, amphetamines, inhalants, sedatives, hallucinogens, opioids and 'other' drugs)
Q2	In the past three months, how often have you used the substances you mentioned (first drug, second drug, etc)?
Q3	During the past three months, how often have you had a strong desire or urge to use (first drug, second drug, etc)?
Q4	During the past three months, how often has your use of (first drug, second drug, etc) led to health, social, legal or financial problems?
Q5	During the past three months, how often have you failed to do what was normally expected of you because of your use of (first drug, second drug, etc)?
Q6	Has a friend or relative or anyone else ever expressed concern about your use of (first drug, second drug, etc)?
Q7	Have you ever tried to cut down on using (first drug, second drug, etc) but failed?
Q8	Have you ever used any drug by injection (non-medical use only)?

The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) is a self-report screening tool which has been developed by the WHO to screen for psychoactive substance use and related problems in primary care patients.[1] It consists of eight items which measure recent (past three months) and lifetime use of ten substances. These include alcohol, tobacco, cannabis, cocaine, amphetamines, inhalants, sedatives, hallucinogens, opioids and 'other' drugs. See Box 1 above for a summary of the specific questions. At the end of the screening, a Total Substance Involvement score (TSI), relating to all substance use, and a Specific Substance Involvement score (SSI), relating to each substance used, is calculated. Depending on the score, either no intervention, a brief intervention, or more intensive treatment are indicated.

Literature review

The objective of the literature review was to determine what previous validation studies of the ASSIST had been done, and in which contexts and patient populations.

A literature search of Pubmed and Google Scholar was performed, using the search terms: 'ASSIST/ Alcohol, Smoking and Substance Involvement Screening Test' and 'Validation/ Validity'.

Inclusion criteria were any validation study of the ASSIST. Validation studies of modified versions of the ASSIST, or of other screening tests, were excluded, as was non-English language literature. In total, five validation studies were identified. The main features and outcomes of these studies are summarized in Table 1.

The multi-site international study by Humeniuk et al validated the ASSIST in a variety of settings and countries including Australia, India, Brazil, Thailand, United Kingdom (UK), United States of America (USA), and Zimbabwe.[22] One thousand and forty-seven patients from public health care settings, as well as from specialised drug treatment units, were included. This study demonstrated concurrent validity of the ASSIST by demonstrating significant correlations between the ASSIST scores and scores on the ASI Lite, AUDIT, and the Revised Fagerstrom Tolerance Questionnaire (RTQ) as well as the Mini International Neuropsychiatric Interview (MINI) Plus. Significant correlation between ASSIST scores and measures of risk factors for the development of problematic substance use demonstrated construct validity; and discriminant validity was also established by the ability of the ASSIST to distinguish between substance use, abuse and dependence.[22]

Table 1: Summary of literature on the validity of the ASSIST

Author and year	Population	Gold standard	Outcome
Humeniuk et al, 2007	Drug treatment in primary care settings, in Australia/ Brazil/ India/ Thailand/ UK/ USA/ Zimbabwe	ASI-Lite; SDS; MINI[1]-Plus; RISC[2]; DAST; AUDIT; RTQ[3]; MAP[4]; hair samples	Demonstrated concurrent validity (significant correlation between ASSIST and ASI-Lite, SDS, AUDIT and RTQ); construct validity (significant correlations for ASSIST and risk factor measures) and discriminative validity (ASSIST was able to differentiate between use, abuse and dependence). Cutoff ASSIST scores: *TSI:* Use/ abuse: 14.5 Abuse/ dependence: 28.5 *SSI – alcohol:* Use/ abuse: 5.5 Abuse/ dependence: 10.5 *SSI – cannabis:* Use/abuse: 1.5 Abuse/ dependence: 10.5 *SSI – cocaine:* Use/abuse: 0.5 Abuse/ dependence: 8.5 *SSI – amphetamines:* Use/abuse: 0.5 Abuse/ dependence: 11.5 *SSI – sedatives:* Use/abuse: 0.5 Abuse/ dependence: 10.5 *SSI – opioids:* Use/abuse: 0.5 Abuse/ dependence: 14.5
Johnson et al, 2015	Patients presenting to urgent care centers in urban Georgia, USA	SASQ[5]; DIS[6]; TLFB[7]	Unhealthy alcohol use: Cutoff of 5+ By gender: Males 6+/ Women 5+ AUD: All: 9+ Males: 10+, females 9+
Hides et al, 2009	214 inpatients and outpatients with first episode psychosis-Melbourne, Australia	SCID-I	The TSI score and the SSI scores for cannabis, alcohol and methamphetamine had high levels of internal consistency and acceptable concurrent and discriminative validity. TSI cutoff: 16 SSI for cannabis: 2 SSI for alcohol: 4 SSI for amphetamine: 1
Van Der Westhuizen et al, 2016	Emergency center patients (n=200) in Cape Town	MINI[1] version 6.0	Good internal consistency for TSI and alcohol, cannabis, methamphetamine and methaqualone. Cutoffs: *TSI:* Use/ abuse: 22 Abuse/ dependence: 42 *SSI – alcohol:* Use/ abuse: 6.5 Abuse/ dependence: 14.5 *SSI - Illicit drugs:* Use/abuse: 1 Abuse/ dependence: 18 Good sensitivity and specificity for discrimination especially for distinguishing between use and abuse

Author and year	Population	Gold standard	Outcome
Newcombe et al, 2005	Drug treatment and primary care settings in Australia	ASI-Lite; SDS; MINI[1]-Plus; RISC[2]; DAST; AUDIT; RTQ[3]; MAP[4]; hair samples	Demonstrated concurrent validity; construct validity; discriminative validity and predictive validity. Significantly higher ASSIST scores in participants with antisocial personality disorder or attention deficit/ hyperactivity disorder. Cutoff ASSIST scores: *TSI:* Use/ abuse: 15.0 Abuse/ dependence: 39.5 *SSI – alcohol:* Use/ abuse: 4.5 Abuse/ dependence: 10.5 *SSI – cannabis:* Use/abuse: 2.5 Abuse/ dependence: 9.5 *SSI – amphetamines:* Use/abuse: 0.5 Abuse/ dependence: 11.5 *SSI – sedatives:* Use/abuse: 0.5 Abuse/ dependence: 9.0 *SSI – opioids:* Use/abuse: 0.5 Abuse/ dependence: 14.5

[1]MINI: Mini International Neuropsychiatric Interview
[2]RISC: Rating of Injection Site Condition
[3]RTQ: Revised Fagerstrom Tolerance Questionnaire
[4]MAP: Maudsley Addiction Profile
[5]SASQ: Single Alcohol Screening Question
[6]DIS: Diagnostic Interview Schedule
[7]TLFB: 90 day time line follow back

The ASSIST has been validated in the urgent care context in the USA[23] and in South Africa.[16] The USA study was done in urban areas in Georgia, and participants were patients presenting to an urgent care center. This study focused on the alcohol SSI score. It used the 90-day time line follow back (TLFB) and Diagnostic Interview Schedule (DIS) as gold standard measures. Four hundred and forty-two participants took part in the study. The optimal ASSIST score for detecting problematic alcohol use was 6 for men, and 5 for women (sensitivity 68% for men, 62% for women, and specificity 66% for men, 70% for women), while the cutoff score for alcohol use disorder was 10 for men and 9 for women (sensitivity and specificity 85%). For all subjects, the optimal cutoff for identifying an alcohol use disorder was 9 (67% sensitivity, 83% specificity). However, for at risk drinking, the low sensitivity suggests that the AUDIT is a better tool for detecting at risk drinking in this setting.[23]

The South African urgent care study by van der Westhuizen et al. was done in two urban, low socio-economic areas in Cape Town, and recruited patients presenting to the emergency

department for assault or unintentional injury. The gold standard used to diagnose a substance use disorder was the MINI version 6.0. This study demonstrated good internal consistency for the TSI score. This study demonstrated good discriminative validity of the ASSIST in discriminating between users and those with an alcohol or other drug use disorder, for alcohol, cannabis and methamphetamine.[16]

One validity study of the ASSIST in psychotic disorders has previously been done by Hides et al. in patients with first episode psychosis in Australia. This study looked at two hundred and fourteen patients with a diagnosis of first episode psychosis (including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, major depressive disorder with psychotic features, bipolar I disorder with psychotic features, and psychosis not otherwise specified). The SCID-I was used as the gold standard for diagnosis of a substance use disorder. In this study, 47.7% of participants had a substance use disorder (with the main drug of abuse being cannabis, alcohol and amphetamines). With the exception of hallucinogens and sedatives, the ASSIST SSI scores had acceptable levels of reliability for all substances. The TSI was found to have a Cronbach's alpha coefficient of 0.9, and significantly correlated with the AUDIT and the SDS total score. Higher TSI scores correlated with both a higher likelihood of a substance diagnosis, as well as a greater number of diagnoses. The TSI had good levels of both internal consistency and concurrent validity in patients with first episode psychosis, with a cutoff score of 16 identifying 81% of true positives and 64% of true negatives. A TSI cutoff score of 16 or more significantly predicted a current substance diagnosis. SSI cutoff scores were calculated by ROC analysis as 2 for cannabis, 4 for alcohol and one for amphetamines, indicating that the ASSIST has discriminative ability.[21]

Rationale for the current study

The aim of this study is to validate the ASSIST in the South African context in patients with chronic psychotic disorders (schizophrenia, bipolar I disorder and methamphetamine induced psychotic disorder). A control group without a diagnosis of psychotic disorder, but including substance users, was included. Controls were included as patients with chronic disorders may be different from non-mentally ill controls in various ways, including cognitive changes or poor insight,[24] and different severity levels of substance use.[25] This would allow for the testing of the ASSIST across a range of substance use disorder severity. This is the first study

to validate the ASSIST in multi-episode psychosis and so will differ from the study done by Hides et al in 2009, which was limited to patients with first episode psychosis.

Aim of the study

The aim of this study is to validate the ASSIST in the South African context, in both controls and in patients with multi episode psychotic disorders (schizophrenia, bipolar I disorder and methamphetamine induced psychotic disorder).

Objectives and hypotheses

The objectives of the study were:

- To extract the relevant data from the existing dataset, including participant demographic information and psychiatric diagnosis; ASSIST scores; and presence or absence of a substance use disorder.
- To determine the internal consistency, discriminant validity and construct validity of the ASSIST.
- To determine optimal cut off scores to maximise sensitivity and specificity.

Our hypothesis was that the ASSIST would be a valid screening test for drug use in patients with chronic psychotic disorders, with good levels of discriminant validity.

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Abstract

Background Given the high prevalence of substance use disorders among patients with persistent mental illnesses, with resultant negative health consequences, a brief and easily administered screening test is needed in this population to identify those at risk in order to intervene appropriately. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was developed by the World Health Organisation as a screening instrument. It has been validated in a variety of settings, including in primary care and treatment settings and in first episode psychosis.

Aim To determine the validity and reliability of the ASSIST in detecting substance use disorders in patients with multi-episode psychotic disorders.

Setting Western Cape, South Africa.

Methods The Structured Clinical Interview for DSM-IV Axis I Disorders was used as the gold standard for detecting DSM-IV substance abuse and dependence. Cronbach's alpha was used to determine the internal consistency of the ASSIST, and receiver operating characteristic analysis was used to evaluate its screening properties. Optimal cut off scores were calculated to maximize sensitivity and specificity.

Results A total substance involvement lifetime score of 13 was found to have both sensitivity and specificity of just over 74%. A specific substance involvement score of 4 for alcohol and 3 for cannabis, methamphetamine and 'other drugs' was found to have optimal balance between sensitivity and specificity.

Conclusion The ASSIST is a psychometrically sound screening test for substance use disorders in general, as well as for alcohol, cannabis and methamphetamine use disorders, in patients with multi-episode psychotic disorders.

Introduction

South Africa has a lifetime prevalence of 13.4% of substance use in the general population, while the prevalence of mental illness as defined by a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis is 30.3%.[1] Substance use disorders (SUD), which the DSM-IV-TR classifies into substance abuse disorders and substance dependence disorders,[2] occur at a higher rate (odds ratio 2.7) in those with a diagnosed mental illness compared to those without.[3] Substance use disorders are often under-detected in those with mental illness,[4] which is problematic as the co-occurrence of these disorders worsens the prognosis of each disorder.[5] The comorbidity of substance use disorders with mental illness is associated with more severe illness and a worse illness

course.[5] This in turn is associated with increased risk of relapse; more psychological distress; poorer compliance with medication; higher rates of utilisation of health services; impaired psychosocial function; and increased rates of institutionalisation, violence, suicide, legal/ forensic problems, as well as other health problems.[4,6] Screening for substance use is thus recommended in order to detect these disorders and enable appropriate and timeous interventions to take place.[7] Screening tests are thus important in the context of mental illnesses specifically. However, many tests are too cumbersome to be appropriate for an overburdened health services, and few have been validated in developing countries.[8]

The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) is a substance use screening tool developed by the World Health Organisation (WHO).[9] To date, the ASSIST has been validated in the primary care context,[10] in emergency settings,[11] and in patients with first episode psychosis.[12] However, it has not yet been validated in the context of multi-episode, established psychotic disorders.

Given the high rate of substance use disorders in patients with persistent psychotic disorders, there is a need for a brief screening test such as the ASSIST to be validated in this population, thus enabling health care workers to identify SUD and to intervene appropriately where needed. The study aim is thus to determine the validity of the ASSIST in patients with psychotic disorders, as well as in non-psychotic controls.

Research methods and design

Study design

This study is a secondary data analysis of an existing database. The original database has been derived from a completed case-control study, investigating differences in electroencephalogram (EEG) delta/ alpha frequency activity in adults between the ages of 19 and 40 years with a diagnosis of psychotic disorder. The study also included controls without a psychotic illness.[13]

Study setting and sample

In the original study, participants were recruited using word of mouth methods, referral from clinicians and media advertisements. Clinically stable outpatients from the Western Cape province of South Africa were selected as cases. Controls were from similar socio-economic backgrounds as the participants. Cases were required to have a diagnosis of schizophrenia (SZP), bipolar I disorder (BMD) with psychosis, or methamphetamine induced psychotic disorder (MPD), diagnosed as per the Structured Clinical Interview for DSM-IV-TR Axis I

Disorders (SCID-I). They were required to be between 19 and 40 years of age and to be fluent in English. Exclusion criteria included any general medical conditions that required chronic treatment; history of learning disability; history of major brain injury or surgery; history of cardiovascular insult; individual or family history of epilepsy; and any medical implants or metal within their bodies. Females who were pregnant or lactating were excluded; and patients with a diagnosis of BMD or SZP were excluded if their disorder was deemed to be substance induced. However, co-morbid substance use *per se* was not excluded. The patients with MPD were required not to have evidence for another primary psychotic disorder. For the current analysis, patients with bipolar type II disorder who may have had psychotic symptoms as part of a major depressive episode, but not part of hypomania, were included. Controls were excluded if they had a personal history of psychosis or bipolar disorder. For the purposes of this study, all participants in the dataset who completed the ASSIST were included.

Measures and data collection

On the day of assessment all participants completed both the SCID-I and ASSIST. The SCID-I is a semi-structured interview, designed to detect Axis I disorders as defined in the DSM-IV. It is commonly used in research settings and its reliability has been demonstrated.[14] The principle psychotic disorder diagnosis as well as the DSM-IV substance use disorder diagnosis (either substance abuse or substance dependence) was determined by the SCID-I, utilizing modules A, B, C, D, and E. It uses a combination of closed and open-ended questions and is administered by trained interviewers. It takes an average of three hours to administer.

The ASSIST version 3.0 is a self-report screening tool which was developed by the WHO to screen for psychoactive substance use and related problems in primary care patients.[9] It consists of eight items which measure recent (i.e. past three months) and lifetime use of ten substances. The ASSIST can be administered in five to ten minutes, and is done in an empathic, non-judgmental manner, using open ended questions. The ASSIST begins with a broad question regarding lifetime substance use; it then goes on to cover frequency of use, cravings, frequency of substance related problems (health, social, legal, or financial) and effects on role responsibilities, in the last three months. Regarding lifetime use, it then asks about whether others are concerned, past attempts to cut down on substance use, and any intravenous drug use.[9] Each question on the instrument is differentially weighted with a

Likert-type scale. A total substance involvement score (TSI) is obtained by summation of scores on Q1 through to Q8 that measures both recent and lifetime substance use across all substances used. It can also assess past 3-month substance use only (TSI-3-month; the sum of Q2 – Q5). In addition, Specific Substance Involvement (SSI) scores can be calculated separately for each substance by summation of score across items Q2 to Q7.

Data analysis

The relevant variables, notably the ASSIST scores and the DSM-IV substance use diagnoses, were extracted from the data and tabulated. The SCID-I was used as the gold standard to determine the presence or absence of a DSM-IV substance use disorder - either substance abuse or substance dependence. Cronbach's alpha was used to determine the internal consistency, or reliability, of the ASSIST. The discriminant validity of the ASSIST was determined by comparing the TSI and SSI scores on the ASSIST obtained from patients with a SUD and to those without a SUD. Receiver Operating Characteristic (ROC) curves were used to evaluate the screening properties of the ASSIST. Optimal cut off scores were calculated to maximize sensitivity and specificity. The sensitivity, specificity, and positive and negative predictive values were calculated. We determined the normality of the data using histograms and the Shapiro Wilk's test for normality. Skewed data were normalized using logarithmic transformations where appropriate. Normal data were analysed using Student's t-test and Pearson's correlation coefficient. For non-normal data, Wilcoxon-rank sum test or Spearman's rank correlation coefficient were used. Categorical data were analysed using Chi-square test with Fisher's exact test where appropriate. For comparisons across three groups on the ASSIST TSI and SSI scores (no SUD, abuse and dependence), Kruskal-Wallis analysis of variance (ANOVA), with a Bonferroni correction for post-hoc pairwise comparisons, was used. Following the determination of optimal cut-points on the TSI scores, a logistic regression model was constructed to determine the unadjusted odds of having a SUD after testing positive (scoring at or above the cut-score) and the adjusted odds after accounting for covariates (sex, education level, and diagnostic group). Two-tailed tests were used throughout, with p-values <0.05 considered as statistically significant. Stata version 16 for Windows was used to analyse data.

Ethical considerations

Human Research Ethics Committee (HREC) approval was obtained for the original study (HREC 192/2010), as well as Western Cape Provincial and Hospital approval. Ethics

approval for the current secondary data analysis was granted by the Human Ethics Research Council (HREC 833/2019). As this is a secondary analysis of an existing dataset, the ethical considerations and risks were minimal.

Results

Sample characteristics

Of the 124 participants, 58 (46.8%) had a SUD diagnosis on the SCID-I, and 66 (53.2%) did not. Alcohol and methamphetamine were the most commonly abused substances, followed by cannabis and 'other drugs' (which includes methaqualone, cocaine, hallucinogens, opioids and inhalants). A substance use disorder diagnosis was significantly associated with gender (higher in males), having less than 12 years of education, and a diagnosis of either SZP, BMD or MPD (Table 1, below).

For patients with a major mood or psychotic disorder diagnosis, the duration of illness since reaching threshold for diagnosis was of a fairly long duration for most patients (BMD median = 72 months; SZP median = 72 months; MPD median = 12 months).

Table 1: Sociodemographic and clinical characteristics of study participants

		Total N=124	SUD absent N = 66	SUD present N = 58	Statistical test	P value
Age: mean (sd)		28.2 (5.4)	28.1 (5.2)	28.4 (5.8)	t = -0.3 (df=122)	0.781
Gender: n (%)						
	Male	70 (56.5%)	29 (43.9%)	41 (70.7%)	chi2(1) = 9.0	0.003
	Female	54 (43.6%)	37 (56.1%)	17 (29.3%)		
Education: n (%)						
	< 12 years	46 (37.1%)	16 (24.2%)	30 (51.7%)	chi2(1) = 10.0	0.002
	≥ 12 years	78 (62.9%)	50 (75.8%)	28 (48.3%)		
Diagnosis: n (%)						
	Controls	33 (26.6%)	29 (43.9%)	4 (6.9%)	chi2(3) = 40.6	<0.001
	SZP	35 (28.2%)	18 (27.3%)	17 (29.3%)		
	BMD[2]	31 (25.0%)	18 (27.3%)	13 (22.4%)		
	MPD	25 (20.2%)	1 (1.5%)	24 (41.4%)		
	Total	124	66 (53.2%)	58 (46.8%)		
Substance: n (%)						
	Alcohol		90 (72.6%)	34 (27.4%)		
	Cannabis		91 (73.4%)	33 (26.6%)		
	Meth[1]		90 (72.6%)	34 (27.4%)		
	Other[3]		113 (91.1%)	11 (8.8%)		

[1]Meth: methamphetamine
[2]BMD includes bipolar I (N=29) and bipolar II (N=2)
[3]Other' includes methaqualone (N=6), cocaine (N=4), hallucinogens (N=1), opioids (N=1), inhalants (N=0)

Internal consistency of the ASSIST

Cronbach's alpha for the TSI lifetime score (Q1 - Q8) was 0.9, while the 3-month TSI was 0.8. We were unable to calculate Cronbach's alpha for methaqualone, hallucinogens, opioids and sedatives due to low prevalence. For the lifetime SSI scores, alcohol had a Cronbach's alpha of 0.7, cannabis of 0.8, and methamphetamine of 0.9. Cronbach's alpha for the SSI scores for the last 3 months were 0.6 for alcohol, 0.7 for cannabis, and 0.9 for methamphetamine, respectively.

Discriminant validity of the ASSIST

Those with a SUD diagnosis on the SCID-I had significantly higher TSI scores compared to those without a SUD diagnosis (Table 2). The average lifetime TSI score in those diagnosed with a SUD was 31.3 with a standard deviation (SD) of 23.5, while for those without a SUD diagnosis it was 10.2 (SD 9.4), which was a statistically significant difference (Table 2). The 3-month mean TSI score in those diagnosed with a SUD was 22.7 (SD = 18.8), and for those without a SUD diagnosis it was 5.2 (SD = 7.4), which was also statistically significant. The SSI scores for alcohol, cannabis, methamphetamine and other drugs were also significantly higher for those participants who had a substance use disorder diagnosis.

Table 2: Comparison of TSI and SSI mean scores

	ASSIST score – Mean (SD)			
	SUD present	**SUD absent**	**Stat**	**P value**
TSI lifetime[1]	31.3 (23.5)	10.2 (9.4)	Z = -6.4	<0.001
TSI 3 months[2]	22.7 (18.8)	5.2 (7.4)	Z = -4.2	<0.001
SSI: Alcohol	6.9 (5.3)	3.7 (6.0)	Z = -4.2	<0.001
SSI: Cannabis	6.7 (7.5)	1.4 (4.4)	Z = -4.9	<0.001
SSI: Meth	10.0 (10.4)	0.1 (0.4)	Z = -9.1	<0.001
SSI: Other[3]	8.8 (11.0)	0.5 (1.7)	Z = -5.3	<0.001

[1]Total TSI score (sum of Q1 - Q8)
[2]TSI score for past 3 months only
[3]'Other' includes methaqualone, cocaine, hallucinogens, opioids, inhalants

The mean scores on the ASSIST TSI and SSI were then compared across the three categories of no-SUD, substance abuse, and substance dependence (Table 3). Bonferroni corrected post-hoc analysis for the TSI showed good discrimination between no-SUD and substance abuse ($p < 0.001$) and dependence ($P < 0.001$), respectively. However, discrimination between substance abuse and dependence was not significant ($P = 0.564$). This was also true for alcohol (no-SUD vs. abuse, $p = 0.003$; no-SUD vs. dependence, $p < 0.001$; abuse vs.

dependence, p = 0.538). The ASSIST did not distinguish well between no-SUD and abuse for cannabis (p = 0.18), or between abuse and dependence (p = 0.533). However, it discriminated well between no-SUD and dependence (p <0.001). Regarding methamphetamine, the ASSIST discriminated well between no-SUD and abuse (p = 0.003), no-SUD and dependence (p <0.001), and between abuse and dependence (p = 0.039). For other drugs, the ASSIST discriminated between no-SUD and dependence (p <0.001), however not between no-SUD and abuse (p = 0.189), or between abuse and dependence (p = 0.562).

Table 3: Comparison of TSI and SSI mean scores across categories of no substance use disorder, substance abuse and substance dependence

	Mean score (SD)				
	No SUD	**Abuse**	**Dependence**	**Stat (ANOVA)**	**P value**
TSI total	10.2 (9.4)	28.8 (22.4)	34.3 (25.0)	Chi2 = 41.7 df = 2	p<0.001
SSI alcohol	3.7 (6.0)	5.9 (4.3)	8.7 (6.4)	Chi2 = 17.3 df = 2	p<0.001
SSI cannabis	1.4 (4.4)	4.0 (5.9)	7.3 (7.8)	Chi2 = 16.7 df = 2	p<0.001
SSI meth	0.1 (0.4)	5.9 (8.9)	11.3 (10.6)	Chi2 = 48.3 df = 2	p<0.001
SSI other[1]	0.5 (1.7)	5.0 (7.1)	9.7 (11.8)	Chi2 = 13.0 df = 2	p = 0.002

[1]'Other' includes methaqualone, cocaine, hallucinogens, opioids, inhalants

ROC analysis

We then determined the optimal cut-points for the TSI and SSI's, with maximal balance between sensitivity and specificity (Table 4). It was found that a cut-off score of 13 on the TSI correctly classified 74.1% of cases and 74.2% of non-cases of substance use disorder. The 3-month TSI score cut-off of 11 was found to correctly identify 88.9% of cases and 86.1% of non-cases. For alcohol, cannabis, methamphetamine and 'other drugs', SSI lifetime cut-off scores of 4, 3, 3 and 3 respectively were found to have optimal balance between sensitivity and specificity. However, the cut-off scores for 3-month SSI scores for alcohol, cannabis, methamphetamine and 'other drugs' were found to be higher, at 7, 10, 13 and 10 respectively. The area under the curve (AUC) was 0.7 or above for both the TSI (figure 1 and 2) and SSI's.

Table 4: Cutoff points for TSI and SSI scores

	Cut point	Sensitivity	Specificity	LR+[1]	PPV[2]	NPV[3]	AUC
TSI (lifetime+3mo)	≥13	74.1%	74.2%	2.9	71.7	76.6	0.83
TSI (3mo)	≥11	88.9%	86.1%	6.4	88.8	86.1	0.92
SSI - alcohol (lifetime)	≥4	70.6%	72.2%	2.5	70.6	72.2	0.74
SSI - alcohol (past 3mo)	≥7	66.7%	85.1%	4.5	66.7	85.1	0.77
SSI - cannabis (lifetime)	≥3	60.6%	85.7%	4.2	60.6	85.7	0.74
SSI - cannabis (past 3mo)	≥10	100%	96.7%	30.5	100	96.7	0.98
SSI - meth (lifetime)	≥3	79.4%	97.8%	35.7	79.4	97.8	0.89
SSI - meth (past 3mo)	≥13	80.0%	98.3%	47.6	80.0	98.3	0.88
SSI - other (lifetime)	≥3	72.7%	86.7%	5.5	72.7	86.7	0.83
SSI – other[4] (past 3mo)	≥10	100% 4	98.4%	61.5	100	98.4	0.99

[1]LR+: positive likelihood ratio
[2]PPV: positive predictive value
[3]NPV: negative predictive value
[4]'Other' includes methaqualone, cocaine, hallucinogens, opioids, inhalants

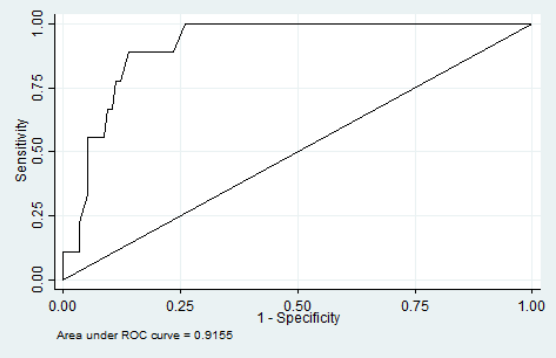

Fig 1. ROC curve for the 3-month TSI score

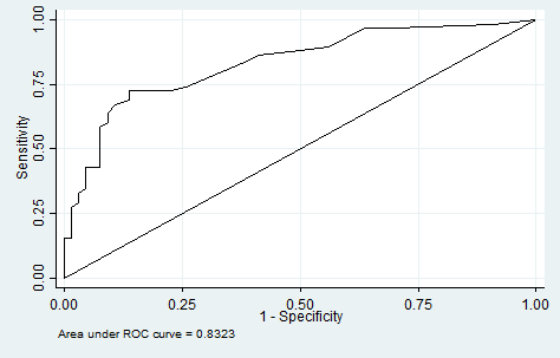

Fig 2. ROC curve for the TSI lifetime score

Logistic regression analysis

Univariate logistic regression analyses were then performed. A TSI of above 13 was found to be a significant predictor of the likelihood of any substance use disorder, with individuals scoring at or above 13, having an 8.3-fold increase in the odds of having a SUD. When adjusted for sex, education level and diagnosis (controls as reference vs. SZP, vs. BMD, vs. MPD), the odds ratio was slightly lower at 6.5. This cut-off correctly classified 80.7% of

cases. For the 3-month TSI score cut-off of 11, the odds ratio (OR) was 49.5, with an adjusted odds ratio of 66.8; 95.2% were correctly classified.

Table 5: Adjusted and unadjusted odds ratios for the 3 month and lifetime TSI cutoff scores

	OR	95% CI[1]	OR (adjusted)[2]	95% CI[1] (adjusted)[2]	P value
TSI lifetime cutoff ≥13	8.3	3.7 - 18.5	6.5	2.2 - 19.1	<0.001
TSI 3mo cutoff ≥11	49.5	5.8 - 422.8	66.8	5.6 - 794.0	<0.001

[1]CI: confidence interval
[2]adjusted for sex, education level, and diagnosis

Discussion

This is the first validation study to be done in individuals with multi-episode psychotic disorders. Over half of the cases in this study were found to meet criteria for SUD, compared to only 6.9% of controls, consistent with research showing the higher rate of SUD in this particular group.[3] This further emphasises the need for brief, easy-to-administer screening tests that are valid in this particular patient group. The TSI score (lifetime and 3 months) was found to have high levels of internal consistency (Cronbach's alpha 0.9), as did the SSI lifetime score (Cronbach's alpha 0.8). A score of over 0.75 is considered to indicate good reliability.[15]

The ASSIST TSI and SSI scores had high levels of discriminant validity, as they showed significant differences across SCID-I substance use diagnoses. A TSI cutoff score of 13 had a positive predictive value (PPV) of 71.7, and a negative predictive value (NPV) of 76.6. Individuals with this score or over were 6.5 times more likely to have a substance use disorder, when adjusted for sex, education and diagnosis. The 3-month TSI score had an even higher PPV at 88.8, with an NPV of 86.1. Bonferroni post-hoc analysis showed that the ASSIST TSI can discriminate well between individuals who have no substance use disorder, and those who have either substance abuse or dependence as per the DSM-IV-TR criteria. Altogether, the TSI discriminated well between no substance use disorder and abuse or dependence. For the SSI's, the discrimination between no substance use and either abuse or dependence was generally better than the discrimination between abuse and dependence. All the SSI scores were able to discriminate between no-SUD and dependence. However, it should be noted that the ASSIST was not able to discriminate well between substance abuse and dependence for all substances except for methamphetamine. These findings are in keeping with concerns about the substance abuse diagnosis in DSM-IV-TR, including the lack of a clear conceptual core; and a lack of empirical distinctions between substance abuse

and dependence.[16] The more recently published and current version of the DSM (DSM-5) no longer differentiates between substance abuse and dependence. Instead it classifies substance use disorders into mild (2 – 3 symptoms), moderate (4 – 5 symptoms), and severe (6 or more symptoms).[17] Thus our finding of a lack of distinction between abuse and dependence is in keeping with the latest changes to the DSM.

ROC analysis found a cutoff score for the lifetime TSI score to be 13. This is slightly lower than the score of 16 found by Hides et al,[12] 14.5 by Humeniuk et al,[10] 15 by Newcombe et al,[7] and the 22 determined by van Der Westhuizen et al.[11] The AUC value was between 0.8 and 0.9, which is considered to be an excellent level of diagnostic accuracy.[18] A score of above 13 would thus indicate a need for intervention or treatment for substance use disorder.

The area under the curve was greater for the 3-month TSI score compared to the lifetime TSI score, reflecting greater accuracy. We believe that this may in be in part due to recall bias, with recall of recent events being more accurate.

Regarding the SSI scores, we found that cutoff scores of 4 for alcohol, and 3 for cannabis, methamphetamine and 'other drugs', were indicative of a substance use disorder, thus indicating a need for further assessment and intervention in those scoring above these scores. This is generally in line with the WHO recommendations, which has a cutoff of 3 for a brief intervention for most drugs (except alcohol, which has a cutoff of 10). These scores are similar, if slightly higher, to those found by Hides (who also determined an alcohol SSI cutoff of 4, 2 for cannabis and 1 for amphetamine).[12] In line with other research, including by van Der Westhuizen et al, the SSI score for alcohol is lower than that found in the WHO study.[11]

As outlined above, substance use disorders in the context of psychotic illness pose significant challenges[12-14]. Given the constraints on health care services in South Africa[19] we surmise that providing regular screening in the outpatient setting may be challenging. A brief, validated screening test which facilitates early and appropriate interventions may thus potentially help to improve physical and mental health outcomes, general functioning and psychosocial problems in this vulnerable patient population. Dual diagnosis services, which integrate mental health services and substance use interventions, are recognised as an evidence based[20] intervention. However it has been shown that basic substance interventions are seldom offered in mental health care settings.[20] This suggests that access to services might be problematic, especially in the South African setting where resources for mental health are constrained.[19] The group of patients scoring highly on the ASSIST and found to have a substance use disorder would require comprehensive, holistic interventions including

motivational/ behavioural interventions, family interventions, assistance with housing, rehabilitation, and psychopharmacology.[21] While it would likely be challenging to provide this in the context on constrained outpatient settings, it has been shown that outpatient substance interventions are useful in practice, reducing subsequent psychiatric hospitalisations.[22]

Strengths and limitations

Limitations of this study include the exclusive use of clinical interviews (the SCID-I) to determine the presence or absence of a substance use disorder, without any confirmatory biological measures of substance use. Other limitations include the sample size that was limited to that of the parent study, possibility leading to diminished power in some analyses. While we were able to perform analyses for alcohol, cannabis and methamphetamine, the sample size for methaqualone, hallucinogens, opioids and sedatives was too low to be able to analyse data for these substances independently. Given that alcohol and cannabis are among the most abused substances in South Africa,[23] the ASSIST remains very relevant to local conditions despite this limitation. The 3-month ASSIST score was compared to a one-month ('current' SUD) measure on the SCID-I. Thus, the time frames were slightly different, possibly affecting the results relating to these measures. However, this would not apply to lifetime measures.

Although all participants were ambulatory, stable outpatients, it was a heterogenous group with differences in illness duration and illness severity that could have affected reporting of substance use. Future studies may need to consider the impact of variables such as psychosis severity and may benefit from fuller characterization of psychotic symptom course. Of note as this study is a secondary analysis, the sample was chosen with different study aims in mind. This may affect the generalisability of these findings to the real-world clinical populations. The controls were also chosen primarily for the parent study.

The strengths of the study include the fact that it is the first to examine the validity of the ASSIST in a population with multi-episode psychotic illness, with a diverse range of diagnoses, as well as the inclusion of a control group without psychotic illness. The patient sample included a diverse range of illness (schizophrenia, bipolar and methamphetamine induced psychosis).

Further research is needed to address some of the limitations of this study, including validating the ASSIST in an inpatient setting and using a larger sample size especially for

patients using methaqualone, hallucinogens, opioids and sedatives. A primary study rather than a secondary one may allow the findings to be more generalisable.

Conclusion

The ASSIST is a brief, easy to use intervention which has validity in individuals with multi-episode psychotic illnesses. It can be recommended as a tool to screen for substance use disorders in general, as well as specifically for alcohol, cannabis and methamphetamine use disorders, in this population in order to identify those requiring further intervention and/or treatment.

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We would like to acknowledge the work of Fleur Howells, Jennifer Hsieh, Andrea van Dijen, David Baldwin and Dan Stein, for their work in authoring the primary study on which this work is based.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Author contributions

RA conducted the literature review, drafted the protocol and did most of the write up. HT conceived the idea for the study, provided the raw data and performed the statistical analysis, as well as contributing to the write up and editing. TR provided editorial input as well as guidance and oversight of the research and write up process.

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Data availability

Data sharing is not applicable, as no new data were created or analysed in this study.

Disclaimer

The views expressed in this article are those of the authors and not an official position of the University of Cape Town**.**

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Appendices

South African Journal of Psychiatry – Author Submission Guidelines

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, clearly present the overall results and any meta-analysis.

Word limit	3000-4000 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Aim, Setting, Methods, Results and Conclusion.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Aim: State the overall aim of the study.
- Setting: State the setting for the study.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.

Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.

- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used orsteps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
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Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

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Example 5	A.B. and B.C. designed the model and the computational framework and analysed the data. A.B. and C.D. carried out the implementation. A.B. performed the calculations. A.B. and B.C. wrote the manuscript with input from all authors. D.E. and E.F. conceived the study and were in charge of overall direction and planning.
Example 6	A.B. designed and performed the experiments, derived the models and analysed the data. B.C. assisted with XYZ measurements and C.D. helped carry out the XYZ simulations. A.B. and D.E. wrote the manuscript in consultation with C.D., B.C. and E.F..
Example 7	A.B. devised the project, the main conceptual ideas and proof outline. B.C. worked out almost all of the technical details, and performed the numerical calculations for the suggested experiment. C.D. worked out the bound for quantum mechanics, with help from D.E.. E.F. verified the numerical results of the XYZ by an independent implementation. F.G. and G.H. proposed the XYZ experiment in discussions with A.B.. B.C., C.D., G.H. and A.B. wrote the manuscript.
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Example 5	A.B. and B.C. designed the model and the computational framework and analysed the data. A.B. and C.D. carried out the implementation. A.B. performed the calculations. A.B. and B.C. wrote the manuscript with input

	from all authors. D.E. and E.F. conceived the study and were in charge of overall direction and planning.
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Example 7	A.B. devised the project, the main conceptual ideas and proof outline. B.C. worked out almost all of the technical details, and performed the numerical calculations for the suggested experiment. C.D. worked out the bound for quantum mechanics, with help from D.E.. E.F. verified the numerical results of the xyz by an independent implementation. F.G. and G.H. proposed the xyz experiment in discussions with A.B.. B.C., C.D., G.H. and A.B. wrote the manuscript.
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Data available within the article or its supplementary materials	The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Data generated at a central, large-scale facility, available upon request	Raw data were generated at [facility name]. Derived data supporting the findings of this study are available from the corresponding author [initials] on request.
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A. WHO - ASSIST V3.0

INTERVIEWER ID		**COUNTRY**		**CLINIC**	
PATIENT ID		**DATE**			

INTRODUCTION ***(Please read to patient)***

Thank you for agreeing to take part in this brief interview about alcohol, tobacco products and other drugs. I am going to ask you some questions about your experience of using these substances across your lifetime and in the past three months. These substances can be smoked, swallowed, snorted, inhaled, injected or taken in the form of pills (show drug card).

Some of the substances listed may be prescribed by a doctor (like amphetamines, sedatives, pain medications). For this interview, we will not record medications that are used as prescribed by your doctor. However, if you have taken such medications for reasons other than prescription, or taken them more frequently or at higher doses than prescribed, please let me know. While we are also interested in knowing about your use of various illicit drugs, please be assured that information on such use will be treated as strictly confidential.

NOTE: BEFORE ASKING QUESTIONS, GIVE ASSIST RESPONSE CARD TO PATIENT

Question 1
(If completing follow-up please cross check the patient's answers with the answers given for Q1 at baseline. Any differences on this question should be queried)

In your life, which of the following substances have you ever used? ***(NON-MEDICAL USE ONLY)***	**No**	**Yes**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	3
d. Cocaine (coke, crack, etc.)	0	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3
j. Other - specify:	0	3

Probe if all answers are negative:
"Not even when you were in school?"

If "No" to all items, stop interview.

If "Yes" to any of these items, ask Question 2 for each substance ever used.

Question 2

In the past three months, how often have you used the substances you mentioned *(FIRST DRUG, SECOND DRUG, ETC)*?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	2	3	4	6
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	2	3	4	6
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	2	3	4	6
d. Cocaine (coke, crack, etc.)	0	2	3	4	6
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	2	3	4	6
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	2	3	4	6
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	2	3	4	6
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	2	3	4	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
j. Other - specify:	0	2	3	4	6

If "Never" to all items in Question 2, skip to Question 6.

If any substances in Question 2 were used in the previous three months, continue with Questions 3, 4 & 5 for each substance used.

Question 3

During the past three months, how often have you had a strong desire or urge to use *(FIRST DRUG, SECOND DRUG, ETC)*?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3	4	5	6
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	3	4	5	6
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	3	4	5	6
d. Cocaine (coke, crack, etc.)	0	3	4	5	6
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	3	4	5	6
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3	4	5	6
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	3	4	5	6
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3	4	5	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3	4	5	6
j. Other - specify:	0	3	4	5	6

Question 4

During the past three months, how often has your use of *(FIRST DRUG, SECOND DRUG, ETC)* led to health, social, legal or financial problems?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	4	5	6	7
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	4	5	6	7
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	4	5	6	7
d. Cocaine (coke, crack, etc.)	0	4	5	6	7
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	4	5	6	7
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	4	5	6	7
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	4	5	6	7
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	4	5	6	7
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	4	5	6	7
j. Other - specify:	0	4	5	6	7

Question 5

During the past three months, how often have you failed to do what was normally expected of you because of your use of *(FIRST DRUG, SECOND DRUG, ETC)*?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products					
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	5	6	7	8
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	5	6	7	8
d. Cocaine (coke, crack, etc.)	0	5	6	7	8
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	5	6	7	8
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	5	6	7	8
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	5	6	7	8
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	5	6	7	8
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	5	6	7	8
j. Other - specify:	0	5	6	7	8

Ask Questions 6 & 7 for all substances ever used (i.e. those endorsed in Question 1)

Question 6

Has a friend or relative or anyone else ever expressed concern about your use of *(FIRST DRUG, SECOND DRUG, ETC.)*?	**No, Never**	**Yes, in the past 3 months**	**Yes, but not in the past 3 months**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d. Cocaine (coke, crack, etc.)	0	6	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify:	0	6	3

Question 7

Have you ever tried and failed to control, cut down or stop using *(FIRST DRUG, SECOND DRUG, ETC.)*?	**No, Never**	**Yes, in the past 3 months**	**Yes, but not in the past 3 months**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d. Cocaine (coke, crack, etc.)	0	6	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify:	0	6	3

Question 8

	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
Have you <u>ever</u> used any drug by injection? ***(NON-MEDICAL USE ONLY)***	0	2	1

IMPORTANT NOTE:

Patients who have injected drugs in the last 3 months should be asked about their pattern of injecting during this period, to determine their risk levels and the best course of intervention.

PATTERN OF INJECTING		INTERVENTION GUIDELINES
Once weekly or less **Fewer than 3 days in a row**	or	→ **Brief intervention including "risks associated with injecting" card**
More than once per week **3 or more days in a row**	or	→ **Further assessment and more intensive treatment***

HOW TO CALCULATE A SPECIFIC SUBSTANCE INVOLVEMENT SCORE.

For each substance (labelled a. to j.) add up the scores received for questions 2 through 7 inclusive. Do not include the results from either Q1 or Q8 in this score. For example, a score for cannabis would be calculated as: **Q2c + Q3c + Q4c + Q5c + Q6c + Q7c**

Note that Q5 for tobacco is not coded, and is calculated as: **Q2a + Q3a + Q4a + Q6a + Q7a**

THE TYPE OF INTERVENTION IS DETERMINED BY THE PATIENT'S SPECIFIC SUBSTANCE INVOLVEMENT SCORE

	Record specific substance score	no intervention	receive brief intervention	more intensive treatment *
a. tobacco		0 - 3	4 - 26	27+
b. alcohol		0 - 10	11 - 26	27+
c. cannabis		0 - 3	4 - 26	27+
d. cocaine		0 - 3	4 - 26	27+
e. amphetamine		0 - 3	4 - 26	27+
f. inhalants		0 - 3	4 - 26	27+
g. sedatives		0 - 3	4 - 26	27+
h. hallucinogens		0 - 3	4 - 26	27+
i. opioids		0 - 3	4 - 26	27+
j. other drugs		0 - 3	4 - 26	27+

NOTE: *FURTHER ASSESSMENT AND MORE INTENSIVE TREATMENT may be provided by the health professional(s) within your primary care setting, or, by a specialist drug and alcohol treatment service when available.

B. WHO ASSIST V3.0 RESPONSE CARD FOR PATIENTS

Response Card - substances

a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)
b. Alcoholic beverages (beer, wine, spirits, etc.)
c. Cannabis (marijuana, pot, grass, hash, etc.)
d. Cocaine (coke, crack, etc.)
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)
i. Opioids (heroin, morphine, methadone, codeine, etc.)
j. Other - specify:

Response Card (ASSIST Questions 2 – 5)

Never: not used in the last 3 months

Once or twice: 1 to 2 times in the last 3 months.

Monthly: 1 to 3 times in one month.

Weekly: 1 to 4 times per week.

Daily or almost daily: 5 to 7 days per week.

Response Card (ASSIST Questions 6 to 8)

No, Never

Yes, but not in the past 3 months

Yes, in the past 3 months

C. ALCOHOL, SMOKING AND SUBSTANCE INVOLVEMENT SCREENING TEST (WHO ASSIST V3.0) FEEDBACK REPORT CARD FOR PATIENTS

Name_____ **Test Date** _____

Specific Substance Involvement Scores

Substance	Score	Risk Level
a. Tobacco products		0-3 Low 4-26 Moderate 27+ High
b. Alcoholic Beverages		0-10 Low 11-26 Moderate 27+ High
c. Cannabis		0-3 Low 4-26 Moderate 27+ High
d. Cocaine		0-3 Low 4-26 Moderate 27+ High
e. Amphetamine type stimulants		0-3 Low 4-26 Moderate 27+ High
f. Inhalants		0-3 Low 4-26 Moderate 27+ High
g. Sedatives or Sleeping Pills		0-3 Low 4-26 Moderate 27+ High
h. Hallucinogens		0-3 Low 4-26 Moderate 27+ High
i. Opioids		0-3 Low 4-26 Moderate 27+ High
j. Other - specify		0-3 Low 4-26 Moderate 27+ High

What do your scores mean?

Low: You are at low risk of health and other problems from your current pattern of use.

Moderate: You are at risk of health and other problems from your current pattern of substance use.

High: You are at high risk of experiencing severe problems (health, social, financial, legal, relationship) as a result of your current pattern of use and are likely to be dependent

Are you concerned about your substance use?

a. tobacco	Your risk of experiencing these harms is:..... **Low** ☐ **Moderate** ☐ **High** ☐ (tick one) **Regular tobacco smoking is associated with:**
	Premature aging, wrinkling of the skin
	Respiratory infections and asthma
	High blood pressure, diabetes
	Respiratory infections, allergies and asthma in children of smokers
	Miscarriage, premature labour and low birth weight babies for pregnant women
	Kidney disease
	Chronic obstructive airways disease
	Heart disease, stroke, vascular disease
	Cancers

b. alcohol	Your risk of experiencing these harms is:..... **Low** ☐ **Moderate** ☐ **High** ☐ (tick one) **Regular excessive alcohol use is associated with:**
	Hangovers, aggressive and violent behaviour, accidents and injury
	Reduced sexual performance, premature ageing
	Digestive problems, ulcers, inflammation of the pancreas, high blood pressure
	Anxiety and depression, relationship difficulties, financial and work problems
	Difficulty remembering things and solving problems
	Deformities and brain damage in babies of pregnant women
	Stroke, permanent brain injury, muscle and nerve damage
	Liver disease, pancreas disease
	Cancers, suicide

c. cannabis	Your risk of experiencing these harms is:..... **Low** ☐ **Moderate** ☐ **High** ☐ (tick one) **Regular use of cannabis is associated with:**
	Problems with attention and motivation
	Anxiety, paranoia, panic, depression
	Decreased memory and problem solving ability
	High blood pressure
	Asthma, bronchitis
	Psychosis in those with a personal or family history of schizophrenia
	Heart disease and chronic obstructive airways disease
	Cancers

d. cocaine	Your risk of experiencing these harms is:.... **Low** ☐ **Moderate** ☐ **High** ☐ (tick one) **Regular use of cocaine is associated with:**
	Difficulty sleeping, heart racing, headaches, weight loss
	Numbness, tingling, clammy skin, skin scratching or picking
	Accidents and injury, financial problems
	Irrational thoughts
	Mood swings - anxiety, depression, mania
	Aggression and paranoia
	Intense craving, stress from the lifestyle
	Psychosis after repeated use of high doses
	Sudden death from heart problems

e. amphetamine type stimulants	Your risk of experiencing these harms is:..... **Low** ☐ **Moderate** ☐ **High** ☐ (tick one) **Regular use of amphetamine type stimulants is associated with:**
	Difficulty sleeping, loss of appetite and weight loss, dehydration
	jaw clenching, headaches, muscle pain
	Mood swings –anxiety, depression, agitation, mania, panic, paranoia
	Tremors, irregular heartbeat, shortness of breath
	Aggressive and violent behaviour
	Psychosis after repeated use of high doses
	Permanent damage to brain cells
	Liver damage, brain haemorrhage, sudden death (ecstasy) in rare situations

f. inhalants	Your risk of experiencing these harms is:..... **Low** ☐ **Moderate** ☐ **High** ☐ (tick one) **Regular use of inhalants is associated with:**
	Dizziness and hallucinations, drowsiness, disorientation, blurred vision
	Flu like symptoms, sinusitis, nosebleeds
	Indigestion, stomach ulcers
	Accidents and injury
	Memory loss, confusion, depression, aggression
	Coordination difficulties, slowed reactions, hypoxia
	Delirium, seizures, coma, organ damage (heart, lungs, liver, kidneys)
	Death from heart failure

g. sedatives	Your risk of experiencing these harms is: Low ☐ Moderate ☐ High ☐ (tick one) **Regular use of sedatives is associated with:**
	Drowsiness, dizziness and confusion
	Difficulty concentrating and remembering things
	Nausea, headaches, unsteady gait
	Sleeping problems
	Anxiety and depression
	Tolerance and dependence after a short period of use.
	Severe withdrawal symptoms
	Overdose and death if used with alcohol, opioids or other depressant drugs.

h. hallucinogens	Your risk of experiencing these harms is:…….. Low ☐ Moderate ☐ High ☐ (tick one) **Regular use of hallucinogens is associated with:**
	Hallucinations (pleasant or unpleasant) – visual, auditory, tactile, olfactory
	Difficulty sleeping
	Nausea and vomiting
	Increased heart rate and blood pressure
	Mood swings
	Anxiety, panic, paranoia
	Flash-backs
	Increase the effects of mental illnesses such as schizophrenia

i. opioids	Your risk of experiencing these harms is: Low ☐ Moderate ☐ High ☐ (tick one) **Regular use of opioids is associated with:**
	Itching, nausea and vomiting
	Drowsiness
	Constipation, tooth decay
	Difficulty concentrating and remembering things
	Reduced sexual desire and sexual performance
	Relationship difficulties
	Financial and work problems, violations of law
	Tolerance and dependence, withdrawal symptoms
	Overdose and death from respiratory failure

D. RISKS OF INJECTING CARD – INFORMATION FOR PATIENTS

Using substances by injection increases the risk of harm from substance use.

This harm can come from:

- **The substance**
  - If you inject any drug you are more likely to become dependent.
  - If you inject amphetamines or cocaine you are more likely to experience psychosis.
  - If you inject heroin or other sedatives you are more likely to overdose.
- **The injecting behaviour**
  - If you inject you may damage your skin and veins and get infections.
  - You may cause scars, bruises, swelling, abscesses and ulcers.
  - Your veins might collapse.
  - If you inject into the neck you can cause a stroke.
- **Sharing of injecting equipment**
  - If you share injecting equipment (needles & syringes, spoons, filters, etc.) you are more likely to spread blood borne virus infections like Hepatitis B, Hepatitis C and HIV.

❖ **It is safer not to inject**

❖ **If you do inject:**

- ✓ always use clean equipment (e.g., needles & syringes, spoons, filters, etc.)
- ✓ always use a new needle and syringe
- ✓ don't share equipment with other people
- ✓ clean the preparation area
- ✓ clean your hands
- ✓ clean the injecting site
- ✓ use a different injecting site each time
- ✓ inject slowly
- ✓ put your used needle and syringe in a hard container and dispose of it safely

❖ **If you use stimulant drugs like amphetamines or cocaine the following tips will help you reduce your risk of psychosis.**

- ✓ avoid injecting and smoking
- ✓ avoid using on a daily basis

❖ **If you use depressant drugs like heroin the following tips will help you reduce your risk of overdose.**

- ✓ avoid using other drugs, especially sedatives or alcohol, on the same day
- ✓ use a small amount and always have a trial "taste" of a new batch
- ✓ have someone with you when you are using
- ✓ avoid injecting in places where no-one can get to you if you do overdose
- ✓ know the telephone numbers of the ambulance service

E. TRANSLATION AND ADAPTATION TO LOCAL LANGUAGES AND CULTURE: A RESOURCE FOR CLINICIANS AND RESEARCHERS

The ASSIST instrument, instructions, drug cards, response scales and resource manuals may need to be translated into local languages for use in particular countries or regions. Translation from English should be as direct as possible to maintain the integrity of the tools and documents. However, in some cultural settings and linguistic groups, aspects of the ASSIST and it's companion documents may not be able to be translated literally and there may be socio-cultural factors that will need to be taken into account in addition to semantic meaning. In particular, substance names may require adaptation to conform to local conditions, and it is also worth noting that the definition of a standard drink may vary from country to country.

Translation should be undertaken by a bi-lingual translator, preferably a health professional with experience in interviewing. For the ASSIST instrument itself, translations should be reviewed by a bi-lingual expert panel to ensure that the instrument is not ambiguous. Back translation into English should then be carried out by another independent translator whose main language is English to ensure that no meaning has been lost in the translation. This strict translation procedure is critical for the ASSIST instrument to ensure that comparable information is obtained wherever the ASSIST is used across the world.

Translation of this manual and companion documents may also be undertaken if required. These do not need to undergo the full procedure described above, but should include an expert bi-lingual panel.

Before attempting to translate the ASSIST and related documents into other languages, interested individuals should consult with the WHO about the procedures to be followed and the availability of other translations. Write to the Department of Mental Health and Substance Dependence, World Health Organisation, 1211 Geneva 27, Switzerland.

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
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06 July 2020

HREC REF: 833/2019

Dr H Temmingh
Department of Psychiatry & Mental Health
HA3 Building
Private Bag X 1 Valkenberg
Email: henk.temmingh@uct.ac.za
Student: eknros001@myuct.ac.

Dear Dr Temmingh

PROJECT TITLE: THE VALIDITY OF THE ALCOHOL, SMOKING AND SUBSTANCE INVOLVEMENT SCREENING TEST (ASSIST) ACROSS PATIENTS WITH PSYCHOTIC DISORDERS AND NON-PSYCHOTIC CONTROLS. (SUB-STUDY 192/2010) (MMED DEGREE - DR ROSALIND ADLARD)

Thank you for your response letter dated 31 March 2020, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study. Please confirm if 192/2020 is still recruiting.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 July 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Rosalind Adlard will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-enquiries@uct.ac.za)	☐ Yes	☐ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes	
1.3 Annual Approval for **full committee** review	- R 3450 (inclusive of vat)
For invoicing purposes, please provide:	
Sponsor's name	
Contact person	
Address	
Telephone number	
Email Address	

2. List of documentation for approval

No documents are submitted for approval.

3. Protocol status (tick ✓)

☐	Open to enrolment
☑	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☑	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	132
Number of participants enrolled, since last HREC Progress report (continuing review)	0
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	0

6. Cumulative summary of participants

Total number of participants who provided consent	132
Number of participants determined to be ineligible (i.e. after screening)	0
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	132
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	16
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	NA
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
Several empirical research papers are in preparation, delays are related to time available to PI.

8. Protocol violations and exceptions (tick ✓ all that apply)

☑	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

9. Amendments (tick ✓ all that apply)

☐	No prior amendments have been made since the original approval
☑	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
None.

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	☑ Not applicable
If yes, please describe:		
Not applicable.		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	☑ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	☑ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☑ Not applicable
		DSMB report attached	☐ Yes	☐ No	☑ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☑ No

If yes, please explain:

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☑	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
Not applicable

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☑ No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	10 July 2019