SCIMITAR- South Asia

Tobacco Cessation Intervention for Individuals with Severe Mental Illness: A Pragmatic, Multicountry Randomised Controlled Trial

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Table of Contents

Table of Contents **3**
List of Abbreviations **5**
1. Introduction **9**
1.1 Aim of the Study 10
1.2 Research Questions 10
2. Methods **10**
2.1 Study Design 10

2.2 Study Settings 10
2.3 Study Participants and Eligibility Criteria 12
2.3.1 Inclusion Criteria 12
2.3.2 Exclusion Criteria 12
2.4 Intervention and comparator 13
2.4.1 Very Brief Advice (Comparator Arm) 13
2.4.2 SCIMITAR-SA Intervention (Intervention Arm) 14
2.5 Identification and Screening 16
2.6 Recruitment 16
2.7 Randomisation and Allocation Concealment 17
2.8 Blinding 18
3. Outcomes and Data Collection 18
3.1 Trial Outcomes 18
3.1.1 Primary Outcome 18
3.1.2 Secondary Outcomes 19
3.2 Data Collection & Follow-up 19
3.2.1 Baseline Data Collection 20
3.2.2 Follow-up Data Collection 20
3.2.3 Participant Retention and Follow-up Strategies 22
4. Sample Size and Statistical Methods 23
4.1 Sample Size 23
4.2 Statistical Methods 24
5. Process Evaluation 25
5.1 Delivery of SCIMITAR-SA 25
5.2 Implementation and scale-up of SCIMITAR-SA 26
5.3 Mechanisms of action 26
5.4 Data analysis and triangulation 27
6. Economic Evaluation 27
7. Data Management 28
7.1 Data Handling and Storage 29
7.2 Data Sharing and Access 29
7.3 Data Monitoring and Quality Assurance 30
7.4 Data Security 30
7.5 Archiving 30
8. Adverse Events 30
8.1 Identification of Potential Adverse Events 31
8.2 Definition of Adverse Events 32

8.3 Adverse Event Monitoring 32
8.4 Identification and Reporting of Adverse Events 32
8.5 Trial Facility Assessment 33
8.6 Safety Oversight 34
9. Incidental Findings 34
10. Ethics 35
10.1 Ethics and Regulatory Approvals 35
10.2 Informed Consent and Participant Rights 35
10.3 Participant and Research Staff Safety 36
10.4 Data Confidentiality 37
11. Trial Oversight 37
References 38

List of Abbreviations

AE	Adverse Events
AR	Adverse Reaction
ASTRA	Addressing Smokeless Tobacco Use and Building Research Capacity in South Asia
BCTs	Behaviour Change Techniques
BMRC	Bangladesh Medical Research Council
CEI	Community Engagement and Involvement
CFIR-ERIC	Consolidated Framework for Implementation Research - Expert Recommendations for Implementing Change
CRFs	Case Report Forms
DALYs	Disability Adjusted Life Years
ECT	Electroconvulsive Therapy
ENDS	Electronic Nicotine Delivery Systems
ENNDS	Electronic Non-Nicotine Delivery Systems
FGDs	Focus Group Discussions
GCP	Good Clinical Practice
GHRG	Global Health Research Groups
HMSC	Health Ministry's Screening Committee
HNBs	Heat Not Burn
HRQoL	Health Related Quality of Life
HTPs	Heated Tobacco Products

IAB	Independent Advisory Board
ICMR	Indian Council of Medical Research
IMPACT	Improving Outcomes in Mental and Physical Multimorbidity and Developing Research Capacity
IOP	Institute of Psychiatry
IREF	Institutional Research & Ethics Forum
LMICs	Low- and Middle-Income Countries
MLTCs	Multiple-Long Term Conditions
MOA	Mechanisms of Action
MOHFW	Ministry of Health and Family Welfare
MPSS	Mood and Physical Symptoms Scale
MRC	Medical Research Council
MTQ	Motivation to Quit
NCDs	Non-Communicable Diseases
NCSCT	National Centre for Smoking Cessation and Training
NIHR	National Institute for Health and Care Research
NIMH	National Institute of Mental Health
NIMHANS	National Institute of Mental Health and Neurosciences
NREC	National Research Ethics Committee
NRT	Nicotine Replacement Therapy

ONPs	Oral Nicotine Pouches
PHQ	Patient Health Questionnaire
PMG	Programme Management Group
PTSD	Post Traumatic Stress Disorder
PRC	Patient Record Card
RA	Research Assistant
RMU	Rawalpindi Medical University
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCIMITAR- SA	Smoking Cessation Intervention for Severe Mental Ill Health - South Asia
SES	Socio-Economic Status
SLT	Smokeless Tobacco
SMI	Severe Mental Illness
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDA	Tobacco Dependence Advisor
TMSS	Thengamara Mohila Sabuj Sangha
UAR	Unexpected Adverse Reaction
UID	Unique ID
UN's SDGs	United Nations' Sustainable Development Goals
VBA	Very Brief Advice

WHO-UMC	WHO Uppsala Monitoring Centre
YLD	Years Lived with Disability

1. Introduction

Tobacco use remains one of the leading preventable causes of morbidity and mortality worldwide, responsible for more than 8 million deaths annually.(1) While global tobacco control efforts have contributed to declining prevalence in many populations,(2,3) tobacco use remains disproportionately high among individuals with severe mental illness (SMI), including Schizophrenia, Schizoaffective disorder, Psychosis, Bipolar disorder and Severe Depression with psychosis.(4,5) Individuals with SMI are estimated to smoke at rates two to three times higher than the general population and consume a disproportionate share of tobacco globally.(6–8) Tobacco use is a major contributor to the reduced life expectancy observed in this population, primarily due to preventable physical health conditions such as cardiovascular disease, respiratory illness, and cancer.(9–11) Despite this, tobacco dependence has historically been under-recognised and undertreated within mental health services, partly due to misconceptions about the role of smoking in symptom management and concerns regarding cessation exacerbating psychiatric symptoms.(12–14) There is now robust evidence that people with SMI are motivated to quit and can successfully do so with appropriate support, without worsening mental health outcomes.(15–17) Behavioural interventions have been shown to improve cessation outcomes in this population. However, most of this evidence is derived from high-income countries,(18–20) and there remains a critical gap in contextually appropriate, scalable interventions for low- and middle-income countries (LMICs).

The burden of tobacco use is particularly high in South Asia, which is home to a substantial proportion of the global population of tobacco users.(21,22) A recent multi-country survey of 3874 individuals with SMI across Bangladesh, India, and Pakistan found that tobacco use was highly prevalent among this population, with 46.8% of men and 15.0% of women reporting current tobacco use. Only 38.4% of tobacco users reported receiving advice to quit from a healthcare provider, despite regular contact with mental health services.(23) This highlights both the high burden of tobacco use among individuals with SMI in these countries and the substantial missed opportunities for intervention within existing mental health services. Furthermore, health systems across Bangladesh, India, and Pakistan face additional challenges, including limited resources, high patient volumes, and variability in access to tobacco cessation services.(24,25) Together, these factors necessitate the development of interventions that are not only effective but also feasible, culturally appropriate, and deliverable within routine mental health care settings.

The Smoking Cessation Intervention for Severe Mental Ill Health (SCIMITAR), originally developed and evaluated in the United Kingdom, demonstrated that a tailored behavioural approach delivered by trained practitioners could significantly improve smoking cessation outcomes among individuals with SMI.(26,27) Building on this evidence, SCIMITAR-South

Asia (SCIMITAR-SA) has been developed as a culturally adapted, behavioural tobacco cessation intervention designed specifically for individuals with SMI in Bangladesh, India, and Pakistan. The intervention incorporates established behaviour change techniques, is tailored to individual needs, and is designed to be integrated into routine mental health services. Importantly, it addresses both smoked and smokeless tobacco use, as well as dual-use patterns, which are highly prevalent in the region.

1.1 Aim of the Study

We aim to test if SCIMITAR-SA, delivered in mental health settings can achieve tobacco cessation among individuals with SMI in Bangladesh, India and Pakistan.

1.2 Research Questions

The following research questions will be addressed:

Among people with SMI:

1. Is SCIMITAR-SA +VBA more effective than VBA alone in achieving biochemically-verified continuous abstinence from tobacco at 7 months post-randomisation?
2. Is SCIMITAR-SA + VBA more effective than VBA alone in achieving self-reported continuous abstinence from tobacco at 13 months post-randomisation?
3. Does SCIMITAR-SA +VBA lead to more improvement in physical health, mental health and quality of life than VBA alone at 4, 7 and 13 months post-randomisation?
4. What are the barriers and drivers to the delivery, implementation and potential future scale-up of SCIMITAR-SA?
5. Is SCIMITAR-SA +VBA more cost-effective than VBA alone , and what is its impact on health inequalities?
6. What are the mechanisms of action in achieving tobacco cessation?

2. Methods

2.1 Study Design

We will conduct a two arm, parallel group, individually randomised, multi-country, multicentre, controlled-trial, with an embedded mixed-methods process evaluation and economic evaluation.

2.2 Study Settings

The study will be conducted at the following locations in Bangladesh, India, Pakistan:

1. Institute of Psychiatry (IOP), Rawalpindi, Pakistan
2. Civil Hospital Karachi (CHK), Karachi, Pakistan
3. Karwan-e-Hayat (KEH), Karachi, Pakistan
4. Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan
5. National Institute of Mental Health (NIMH), Dhaka, Bangladesh
6. Thengamara Mohila Sabuj Sangha (TMSS) Medical College, Bogura, Bangladesh
7. Shaheed Ziaur Rahman Medical College Hospital (SZRMCH), Bogura , Bangladesh
8. National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India

In Pakistan, the trial will be conducted at four locations: Institute of Psychiatry (IOP) Rawalpindi, Civil Hospital Karachi, Karwan-e-Hayat Karachi and Jinnah Postgraduate Medical Centre (JPMC), Karachi. The IOP Rawalpindi is one of the largest specialised mental health facilities in the country, providing comprehensive psychiatric and psychological services. In addition to identifying participants at IOP *(please see section 2.5 on identification and screening for more details)*, the site will utilise additional facilities for participant identification. Participants identified at these additional facilities will be referred to IOP for screening and recruitment. These additional facilities will not be considered trial sites; rather, they will be used solely for participant identification and referral. Civil Hospital Karachi (CHK) delivers a wide range of inpatient, outpatient, and acute psychiatric services to a diverse urban and rural population. The Karwan-e-Hayat (KEH) Karachi operates one of the largest dedicated psychiatric inpatient facilities in the city, including a 100-bed unit offering treatment and rehabilitation services. Jinnah Postgraduate Medical Centre (JPMC), is one of the largest public-sector mental health setups in the country, providing dedicated inpatient care, emergency psychiatric services, and behavioral medicine for diverse populations.

In Bangladesh, the trial will be conducted at three locations: National Institute of Mental Health (NIMH) Dhaka, Thengamara Mohila Sabuj Sangha (TMSS) Medical College Bogura and Shaheed Ziaur Rahman Medical College Hospital, Bogura, Bangladesh. The NIMH Dhaka is a 200-bed tertiary-level psychiatric hospital under the Ministry of Health and Family Welfare (MoHFW) and serves as the country's leading centre for mental health care, training, and research. The TMSS Medical College Hospital is a large 850-bed tertiary care hospital providing comprehensive medical, surgical, and specialised services, particularly to underserved rural populations, while also supporting clinical education. Shaheed Ziaur Rahman Medical College Hospital is a 500-bed government tertiary-level teaching hospital providing specialist clinical services including psychiatric care.

In India, the study will be conducted at the National Institute of Mental Health and Neurosciences (NIMHANS) Bangalore, a 1,098-bed tertiary care institute recognised for its leadership in mental health and neurosciences, combining patient care with advanced research and academic training.

2.3 Study Participants and Eligibility Criteria

The trial aims to recruit adult users of tobacco (smoked and/or smokeless) with a confirmed diagnosis of one or more SMI, who are willing to quit all forms of tobacco use within the next 30 days.

2.3.1 Inclusion Criteria

- Adults (≥18 years) receiving or referred for outpatient mental health services at the recruitment facility.
- Individuals with at least one SMI (schizophrenia, schizoaffective disorder, bipolar affective disorder, psychosis, or severe depression with or without psychotic features), diagnosed by their treating psychiatrist.
- Individuals using tobacco either smoked products (e.g., cigarettes, bidis, waterpipe) and/or smokeless (e.g., betel-quid, naswar, gutkha, khaini, zarda, paan, pan-masala, gul, shada pata), for a minimum of six months (daily or non-daily), and who, in the last 30 days, will have used tobacco on at least 25 days.
- Individuals who were considered as clinically stable* by their treating psychiatrist at the time of enrolment and who will be able to provide informed consent.
- Individuals who are the sole participant in this trial from their household..
- Individuals willing to quit all forms of tobacco within the next 30 days and able to attend at least three** face to face counselling modules delivered by trained healthcare staff.

**Clinical stability will be determined by the treating psychiatrist and will be defined as no more than a 25% change in medication dosage and no receipt of electroconvulsive therapy (ECT) or other neurostimulation interventions during the preceding three months.*

*** The first appointment of each of the first three modules (two pre-quit and quit day) should be delivered face-to-face. Any additional appointments and post quit modules could be delivered remotely where necessary,with flexibility to provide an additional appointment if required.*

2.3.2 Exclusion Criteria

As this will be a pragmatic trial, exclusion criteria will be kept to a minimum:

- Individuals who used electronic nicotine delivery systems (ENDS), electronic non-nicotine delivery systems (ENDS), heated tobacco or heat-not-burn products (HTP/HNB), or oral nicotine pouches (ONPs) in the last 30 days in addition to combustible or smokeless tobacco products.**
- Individuals who have comorbid substance use disorders (drug or alcohol), as well as those diagnosed with personality disorders, eating disorders, autism spectrum

disorders, disorders of intellectual development, or post-traumatic stress disorder (PTSD), identified through medical records and/or confirmed by the treating psychiatrist.

- Individuals who have received any pharmacological treatment for tobacco cessation (e.g., bupropion or varenicline), nicotine replacement therapy (NRT), or any behavioural tobacco cessation intervention other than brief advice within the previous 30 days, or who are currently taking bupropion for any indication (eg., depression).

***Individuals using e-cigarettes, heated tobacco products, or other alternative nicotine products are excluded because these products may influence tobacco use behaviours and cessation outcomes. Their concurrent use could confound the evaluation of the intervention's effectiveness for conventional tobacco cessation, which is the primary focus of this trial.*

2.4 Interventions

2.4.1 Very Brief Advice (Comparator Arm)

All trial participants will receive Very Brief Advice (VBA). VBA is an evidence-based intervention designed to increase quit attempts among people who smoke(28). VBA was developed by the National Centre for Smoking Cessation Training (NCSCT) in the United Kingdom (UK) (www.ncsct.co.uk/VBA) and involves three steps:

1. "Ask" patients about their tobacco use,
2. "Advise" them about quitting, and
3. "Act" by supporting them with making a quit attempt using available cessation support.

VBA has been adapted from the ASTRA(29) smokeless tobacco pilot trial where VBA was provided as a standard provision for participants receiving neither of the active intervention (NRT or BISCA). It will include: "Ask", a brief conversation on tobacco use status (smoked and/or smokeless), "Advice", to stop using tobacco, and "Act", providing a self-help leaflet(30).

VBA will be delivered by health professionals at recruiting sites in an interaction lasting up to

1 minute to all the patients attending the OPD. VBA will fulfil the duty of care responsibility but it is less intense and hence less likely to dilute the SCIMITAR-SA intervention effect. Guidance on VBA will be provided as part of the trial orientation/setup/initiation to all health professionals involved in the treatment and management of SMI patients at the study sites. VBA has been shown to increase the frequency and success of quit attempts when compared to no intervention(28).

Usual care may vary across recruitment locations and countries, reflecting differences in health systems and resource availability. Participants may access additional tobacco cessation support, including pharmacological treatments such as nicotine replacement therapy (NRT) or medications for tobacco cessation, where these are routinely available within the healthcare system or through private purchase. The trial will not restrict access to such services, and any use of additional cessation support or pharmacotherapy during the study period will be systematically recorded in both trial arms.

2.4.2 SCIMITAR-SA Intervention (Intervention Arm)

Participants allocated to the intervention arm will receive SCIMITAR-SA intervention in addition to the VBA. SCIMITAR-SA is a structured behavioural tobacco cessation programme specifically adapted for individuals with SMI in South Asian settings. The intervention is grounded in established behaviour change theory and incorporates evidence-based techniques such as goal setting, action planning, problem solving, relapse prevention, and provision of social support. It adopts a patient-centred approach, allowing the content and delivery to be tailored to individual needs, preferences, and clinical circumstances. The intervention has been culturally adapted from the SCIMITAR-UK programme(26,27) to address the use of both smoked and smokeless tobacco, dual use patterns, cultural norms and beliefs, and the varying levels of literacy and health system capacity across Bangladesh, India, and Pakistan.

The SCIMITAR-SA intervention was tested for feasibility of delivery and content as part of the feasibility trial. Data from Advisor Record Books (detailed account of intervention delivery schedule per participant and adherence to content that was delivered across each session), FGDs with Tobacco Dependence Advisors (TDAs), and Trainer-of-Trainers (ToTs), and interviews with intervention arm trial participants and mental health staff, showed that:

1. The intervention was transferable to each country's context and effectively adopted by the TDAs.
2. No further refinements to the intervention’s design or content were required.

3. Challenges identified by the TDAs during implementation, including: differing views of dual users on the cessation of both smoked and smokeless products, difficulties in setting quit dates, splitting modules over a number of appointments, and scheduling appointments, led to the refinement of and further enhancements in the training programme. These enhancements involved a greater emphasis in training on communication skills, developing additional supporting materials for use during appointments (for example, for holding sensitive communications and managing defensiveness), designing a TDA competency framework and a Quality of Interaction checklist/Practice Observation Form (adapted from the NCSCT advanced practitioner framework).

The SCIMITAR-SA intervention will be delivered by trained TDAs, who are healthcare workers with experience in mental health care and who have undergone standardised training in providing tobacco cessation support using SCIMITAR-SA intervention. Participants will be offered 7 tobacco cessation behavioural support modules corresponding to each flipbook (2 pre-quit, 1 quit and 4 post-quit) over 7 to 10 individual appointments, each lasting approximately 20 to 60 minutes, delivered over 7 to 10 weeks.

As each session offers the flexibility to be delivered in more than one appointment, any additional appointments for the first three modules (two pre-quit and the quit day) except the first appointment may be delivered remotely, where necessary. (This would be the first appointment of each session up to quit day, so for e.g. if Preparing to Quit was being delivered over 2 appointments, the first appointment would be face to face, with the option of remote if the patient could not attend the second appointment in person to complete the session). The first post-quit session is encouraged to be delivered face-to-face, however, where participants face challenges in attending face-to-face appointments, post-quit modules may be delivered remotely. Where remote appointments are scheduled, video calls are preferred over telephone calls.

The intervention is structured around key stages of the quit process, including committing to quit, preparation for quitting, setting a quit date, supporting the quit attempt, and maintaining abstinence through relapse prevention strategies. Participants will be encouraged to set a quit date within 30 days of enrolment, with flexibility to accommodate individual readiness and clinical circumstances. TDAs are advised to deliver the first appointment within 3 days of enrollment, at the latest.

The content of the intervention focuses on enhancing motivation to quit, understanding individual patterns of tobacco use, identifying triggers, and developing personalised coping strategies to manage cravings and withdrawal symptoms. Participants will be supported to anticipate and manage high-risk situations, reinforce behaviour change, and address barriers to quitting. While the intervention is centred on the individual participant, involvement of

caregivers for practical or logistical support will be encouraged where appropriate, without requiring their direct participation in counselling modules.

The delivery of the intervention will be supported by a set of culturally adapted materials, including flipbooks designed for use during counselling modules and aligned with different stages of the quit journey, and an advisor record book to document individual goals, triggers, and coping strategies. All materials will be translated into relevant local languages and tailored to reflect the cultural and contextual realities of the participating countries. We will implement a master trainer model to build local capacity and to transfer expertise in behaviour change training to the local contexts. ToTs trained by tobacco cessation behaviour change experts will train all TDAs, alongside ongoing supportive supervision to maintain quality and consistency of delivery in their corresponding countries. Training will be provided to TDAs prior to trial commencement and will include theoretical instruction, practical exercises, and role-play.

The SCIMITAR-SA intervention is behavioural in nature. However, participants will be guided to use NRT where available/affordable. TDAs will provide guidance on the appropriate use of such therapies, including dosing, duration, and potential side effects. The trial will not supply pharmacotherapy directly, reflecting its pragmatic design, and any use of cessation medications or external support will be recorded for both intervention and comparator participants.

2.5 Identification and Screening

Participants will be identified from outpatient mental health facilities at recruitment facility in Bangladesh, India, and Pakistan**. Screening will be embedded within routine clinical pathways to reflect real-world practice. Treating mental healthcare professionals, including psychiatrists, psychologists, and trained clinical staff, will opportunistically identify patients with at least one of the conditions grouped under SMI who report current use of tobacco.

***At IoP, Pakistan Potentially eligible participants will principally be identified through referrals from treating clinicians at IoP. Additionally, research assistants (RAs) will also search clinic lists for potentially eligible participants with permission from the research institution. RAs will also be situated at the emergency departments where some patients first present with SMI symptoms. In addition, potential trial participants will be identified in settings where people with SMI are known commonly to present at an early stage of diagnosis, e.g. psychology and psychiatry clinics in the public or private sector. These referral sites will only serve to identify potential participants and to signpost them to the trial site i.e. IoP - no study assessments will be undertaken in these settings. Initial screening checklists may be used to aid the process of identifying those potentially eligible, but these will only be based on*

*routinely collected clinical information. Particip*ants referred and recruited in the study will be reimbursed for their time and travel.

Individuals identified as potential participants will be referred to a trained Research Assistant (RA) for further assessment. The RA will first confirm the patient's willingness to undergo screening and will then assess eligibility using the predefined inclusion and exclusion criteria.

All individuals approached for screening will be assigned a unique screening identification number. Basic anonymised information will be recorded for all screened individuals, including gender, diagnosis, tobacco use status, and eligibility outcome. For those who are eligible but decline participation, reasons for non-participation will be documented where available. Screening data will be recorded in a secure electronic database to enable monitoring of recruitment processes.

2.6 Recruitment

Eligible individuals will be invited to participate in the trial by the site RA. Participants will be provided with a Participant Information Sheet (PIS) in the appropriate local language (Kannada and Hindi in India, Urdu and Sindhi in Pakistan, Bangla in Bangladesh), which will include detailed information about the purpose of the study, trial procedures, intervention and comparator arms, potential risks and benefits, data confidentiality, and the voluntary nature of participation.

For individuals with limited literacy, the information sheet will be read aloud in the presence of a caregiver or impartial witness, and any questions will be addressed to ensure comprehension. Written informed consent will be obtained from all participants prior to the collection of any study-specific baseline data. Participants who are unable to provide a written signature may provide consent via thumb impression in accordance with local ethical and regulatory requirements, with an independent witness present.

Participants will have up to 7 days (one week) from the date of screening to provide informed consent. If consent is not obtained on the day of screening, the RA will follow up by telephone during this period to provide additional information, address any questions, and support the participant's decision-making. Participants who provide informed consent but only after 7 days of initial screening will be required to undergo repeat screening to confirm eligibility prior to enrolment. For those who consent, baseline assessments will be conducted prior to randomisation. Participants will be reminded of their right to withdraw from the study at any time without any impact on their routine care.

Recruitment strategies will be integrated into standard clinical workflows to enhance feasibility. To enhance recruitment, healthcare staff will be trained to systematically identify

eligible individuals and refer them to the research team. Study materials will be culturally adapted and available in local languages to support engagement. Recruitment progress will be monitored regularly.

2.7 Randomisation and Allocation Concealment

Eligible and consenting participants who have completed baseline assessments will be recruited into the study and randomly allocated to either the intervention arm (SCIMITAR-SA plus VBA) or the comparator arm (VBA alone). Randomisation will be conducted on a 1:1 basis using a block stratified sequence, generated by an independent statistician at York Trials Unit (using STATA v19 or later). Stratification will be based on study location and type of tobacco use (smoked tobacco products only, smokeless tobacco products only, or dual use).

The randomisation sequence will be implemented using a secure, centralised Google Form–based system developed by the software developers at York Trials Unit. Following completion of baseline assessments, the RA will submit a randomisation request via a google form where the participant's unique study ID and stratification factors will be specified. Upon submission, the study arm will be allocated to the participant's ID and the RA will be informed of this via an automated email. The underlying allocation sequence will be managed by the software developers at York Trials Unit and not made accessible to any participant facing research staff in order to maintain concealment.

Following randomisation, the RA will inform the participant of their allocated group. For participants assigned to the intervention arm, relevant details will be communicated to the TDA who will initiate contact with the participant to schedule intervention appointments. Participants allocated to the comparator arm will continue to receive usual care, including VBA, with no additional intervention from the trial team beyond scheduled follow-up assessments.

2.8 Blinding

Given the nature of the intervention, it is not feasible to blind participants, caregivers and research staff from knowing the arm allocation. However, objective verification of the primary outcome (tobacco cessation) will be ensured through biochemical validation.

3. Outcomes and Data Collection

3.1 Trial Outcomes

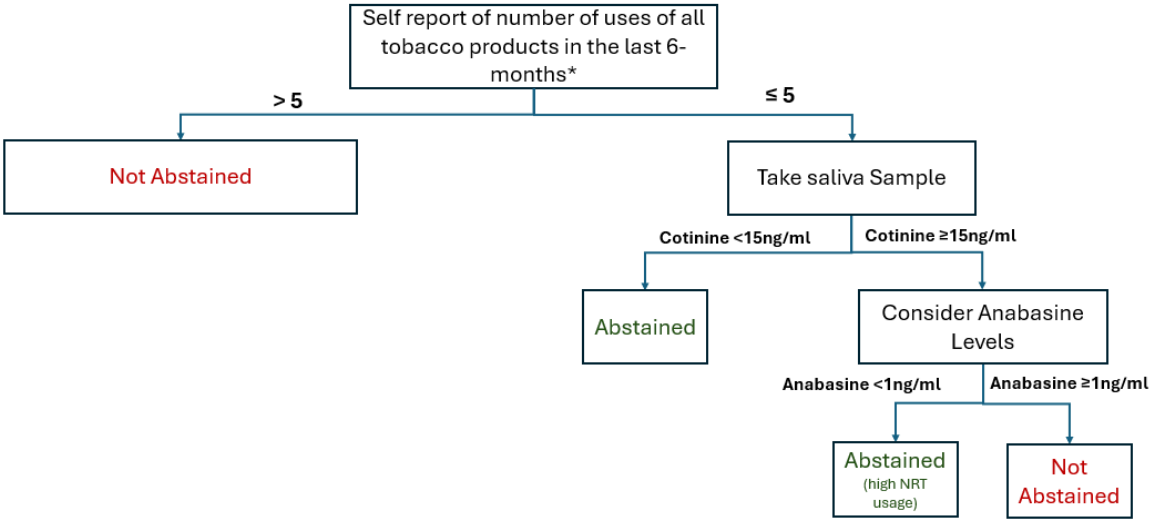
3.1.1 Primary Outcome

The primary outcome (Figure-1) of the trial is biochemically verified continuous abstinence from all tobacco products in the last 6 months. The outcome will be collected at 7-months post-randomisation to allow for a 30- day grace period.

Participants will self-report on sustained abstinence from all tobacco products at 4, 7 and 13 months post-randomisation; this will be biochemically verified for participants reporting continuous abstinence at the primary endpoint only (7-months post randomisation). As per the Russel standard (31), abstinence will be defined as no more than 5 uses of all tobacco products.

Saliva samples will be obtained for biochemical verification of those reporting abstinence only where a threshold of <15 ng/mL cotinine in conjunction with <1 ng/ml of anabasine will be used to verify self reported abstinence from all forms of tobacco and nicotine products(32). Those with cotinine levels >15ng/ml and anabasine levels<1ng/ml will also be verified as abstinent from tobacco but likely using NRTs or other nicotine products. Participants exceeding both thresholds will be classified as tobacco users regardless of self-report.

Those with unavailable outcome data will be assumed as not abstained as per the Russel standard of abstinence except in the case of death.(31)



*Reported at 7-months post randomisation

Figure 1: Primary outcome derivation

3.1.2 Secondary Outcomes

Secondary outcomes include self-reported tobacco continuous abstinence at 4, 7, and 13 months; changes in physical and mental health, psychiatric symptom severity, quality of life, and anthropometric and physical health measures.

3.2 Data Collection & Follow-up

Data will be collected at baseline (pre-randomisation) and at 4, 7, and 13 months post-randomisation. Baseline data will be collected after obtaining informed consent and prior to randomisation. Follow-up assessments will be conducted primarily through in-person visits, particularly where saliva samples and physical measurements are required, although remote data collection may be used, where face-to-face data collection is not possible. All data will be collected by trained RAs using standardised Case Report Forms (CRFs) and entered into a secure REDCap database on electronic tablets. RAs will receive comprehensive training in data collection procedures, including administration of standardised instruments and biological sample handling. Standard operating procedures will be implemented to ensure consistency in data collection, measurement, and sample processing. Regular monitoring, data quality checks, and coordination will be undertaken to ensure completeness and accuracy of the trial data.

3.2.1 Baseline Data Collection

At baseline, socio-demographic and household characteristics, such as age, gender, education, employment, and living conditions, will be collected. The Quick Structured Clinical Interview for DSM-5 (QuickSCID-5)(33) and Brief Psychiatric Rating Scale (BPRS)(34) will be used at baseline. QuickSCID will be for describing population while the BPRS will be used for assessing severity of symptoms. A comprehensive history of tobacco use will be obtained, including type of tobacco used (smoked, smokeless, or dual use), duration, frequency, and previous quit attempts. Nicotine dependence will be assessed using the Fagerstorm test for nicotine dependence (Standard version(35) and modified version for smokeless tobacco(36) will be used for assessing nicotine dependence). Motivation to quit will be measured using the Motivation to Quit (MTQ) questionnaire.(37) General mental and physical health status will be assessed using the SF-12 Health Survey.(38) Information on comorbid physical and mental health conditions and current treatments will be recorded. Data on health-related quality of life (EQ-5D-5L)(39) and health service utilisation (healthcare use, tobacco cessation treatment, productivity loss, and tobacco expenditure)

will also be collected at baseline. Physical measurements will include height, weight, measured according to standardised protocols, and used to calculate body mass index (BMI) will also be recorded.

3.2.2 Follow-up Data Collection

At all follow ups (4, 7, and 13 months post-randomisation) tobacco use status will be assessed through self-report, including use in the past 7 days and tobacco use in the last 3 months, 6 months and 12 months. Information on relapse of tobacco use, quit attempts, and use of alternative nicotine products will be recorded. Psychiatric symptom severity will be reassessed using the BPRS while mental and physical health will be reassessed using the SF-12 at all follow ups. Data on health-related quality of life (EQ-5D-5L) and health service utilisation will also be collected at all follow ups. At 7 months follow up, salivary samples will be collected for biochemical verification of tobacco abstinence using salivary cotinine and anabasine analysis from participants who self-report using tobacco products, on no more than 5 occasions during the last 6 months. The saliva sample will be collected on the day at which 7th month follow up data will be collected. However, if the data is being collected remotely for any participant who is eligible for saliva sample collection,the saliva sample will be collected within the predefined sample collection window of up to 3 weeks after the participant's 7-month follow-up due date (i.e., the expected follow-up date, calculated as 7 months after randomisation) . Any delay in saliva sample collection beyond the due date, will be documented by the RAs. The abstinence period will be measured at the 4, 7 and 13-month follow-ups respectively, allowing for a one month grace period following randomisation. Weight and height* (if not recorded at baseline) will be recorded at all followups.

Samples will be collected following standardised procedures. A saliva sample (optimum volume 0.5 mL; minimum 0.12 mL) will be obtained using a Salivette collection device. Salivettes will be procured centrally to ensure consistency across countries. To ensure sample integrity, participants will be instructed not to eat, drink, or take medication for at least 30 minutes prior to sample collection. Participants will place the swab under the tongue without handling it directly and retain it until adequately saturated (typically up to five minutes), after which it will be returned to the collection tube.

Each sample will be labelled using a unique participant identifier along with the date and time of collection, with no personal identifying information included, ensuring confidentiality. Following collection, saliva samples will be temporarily stored at 4°C or −20°C prior to shipment. Collected samples will be securely packaged and transported to an accredited laboratory for analysis (ACM Global Laboratories, UK for Bangladesh and Pakistan and the Laboratory of the Department of Clinical Psychopharmacology and Neurotoxicology for India). Where immediate shipment is not feasible, samples will be frozen and later

shipped under appropriate conditions. All shipments will comply with international transport regulations. Samples will be packaged using appropriate materials and labelled as “Biological substance, Category B (UN3373)”, along with required safety and customs documentation. Samples will be described as non-hazardous human saliva intended for research purposes only. Saliva samples will be analysed for cotinine and anabasine concentrations using Liquid Chromatography–Tandem Mass Spectrometry (LC-MS/MS) at accredited laboratories.

Table 1: Baseline and follow up assessments

	Measurement/data collection	Baseline	4 month follow-up	7 month follow-up	13 month follow-up
1	Socio-demographic and household information	X			
2	Quick SCID	X			
3	BPRS	X	X	X	X
4	History of tobacco use	X			
5	Tobacco use status		X	X	X
6	Fagerström Test for Nicotine Dependence	X			
7	Motivation To Quit (MTQ)	X			
8	Health-related quality of life (EQ-5D-5L)	X	X	X	X
9	Comorbidities and Current Treatment	X			
10	Mental and physical health (SF-12)	X	X	X	X
11	Health service use	X	X	X	X
12	Physical measurements – height and weight	X	X	X	X

13	Salivary cotinine and anabasine (for biochemical verification)			X	
14	Participant session records held by TDAs	-	X		
15	Monitoring forms held by ToTs		X		
16	FGDs with TDAs and ToTs		X		
17	Interviews with trial participants		X		
18	Interviews with mental health facility staff		X		
19	Survey questions on acceptability and engagement with SCIMITAR-SA or VBA		X		

3.2.3 Participant Retention and Follow-up Strategies

Follow-up assessments at 4, 7 and 13 months post-randomisation will be conducted within a ±1-week window around the scheduled follow-up date. Assessments completed within this period will be considered on time. Any follow-up conducted outside this window will be documented as delayed. RAs will initiate contact with participants one week prior to the scheduled follow-up date and continue follow-up efforts for up to three weeks after the due date. During this period, RAs will make at least three contact attempts per week, varying the timing and days of contact to improve the likelihood of reaching participants and scheduling assessments. Participants who cannot be contacted despite these efforts will be recorded as "missed/absent". If any follow-up visit is missed, every effort will still be made to encourage attendance at subsequent follow-up visits.

The RA will be contacting the participant for follow up one week before and for 3 weeks after the due date of follow up. The RA will make three phone calls per week at different times and on different days of the week to schedule the follow up with the participant before being declared as missing. If data is missing for the four month follow-up and/or seventh month follow up, an attempt will still be made to obtain seventh and/or thirteenth

month follow-up data, respectively. Participants and/or their caregivers (where caregiver's number is available instead of patient's) will be informed in advance about upcoming visits, and flexible scheduling will be offered to accommodate participant's availability and reduce inconvenience. Where appropriate, follow-up visits will be aligned with routine clinical appointments. To support engagement, participants will be provided with locally translated information materials, including information leaflets and periodic updates using a quarterly (3-monthly) newsletter. Participants will also be encouraged to inform the study team of any changes in contact details or relocation plans to facilitate continued follow-up. Efforts will be made to ensure that all retention procedures, including frequency and mode of contact, are applied consistently across both study arms. This approach will ensure equitable follow-up and enable timely identification of changes in participant status or adverse events.

Participants will not receive financial incentives for participation in the trial. However, they will be reimbursed for reasonable expenses incurred as a result of participation. At each in-person visit, participants will receive reimbursement to cover travel costs and time associated with attending intervention modules and follow-up assessments. Reimbursement will be provided either as a fixed allowance or based on documented travel expenses, in line with local practices. Where study procedures are conducted remotely, participants may receive a reduced reimbursement reflecting time costs, excluding travel expenses. All reimbursement arrangements will be reviewed and approved by the relevant local and national ethics committees to ensure compliance with country-specific regulations and ethical standards.

4. Sample Size and Statistical Methods

4.1 Sample Size

The UK based SCIMITAR trial(26) observed 6-month quit rates as 6% in the control group and 14% in the intervention group (absolute difference of 8%). Given SCIMITAR-SA also includes users of smokeless tobacco, a more conservative absolute difference of 5% (relative risk (RR) 1.83 assuming a 6% quit rate in the control arm) will be used.

Assuming a quit rate of 6% in the control group, a total sample size of 1450 (725 per treatment group) is required to detect a minimum RR of 1.83 with 90% power, 5% two-sided alpha, and 10% attrition.

4.2 Statistical Methods

Screening and recruitment data will be summarised and progression throughout the trial will be represented using a CONSORT(40) flow diagram. Baseline demographics and all trial outcomes will be presented descriptively by trial arm with missing data indicated. Continuous data will be summarised using means and standard deviations (or medians and interquartile ranges where there is skew) and categorical data with frequencies and percentages.

Biochemically verified continuous abstinence at 7-months post-randomisation will be analysed using a logistic regression model. The adjusted odds ratio and relative risk will be reported to inform on the treatment effect in addition to a p-value and 95% confidence intervals. Treatment allocation, recruitment location, and type of tobacco used at baseline (smoked, smokeless or dual) will be included as covariates in addition to any clinically relevant baseline variables. In the event of non-convergence or quasi-complete separation, a penalisation method will be used instead.

Participants with missing primary outcome data will be assumed as not continuously abstinent from tobacco products as per the Russel standard of abstinence(31), except in the case of death. To assess the impact of this assumption on the treatment effect, a pattern mixture model and/or multiple imputation will be carried out as sensitivity analyses. A complier average causal effect (CACE) analysis will be conducted to assess the impact of any lack of compliance with the intervention. Additionally, auxiliary analyses will be conducted considering a lower threshold of 10 ng/ml for cotinine as well as the inclusion of self-reported data at 4-months in the derivation of the primary outcome. Subgroup analyses by country and type of tobacco products used at baseline will also be conducted.

Secondary outcomes on continuous abstinence will use the same structure as the primary model. For all other secondary outcomes, repeated measures will be accounted for using linear or logistic mixed effects models for continuous and binary outcomes respectively. Fixed effects will include those specified in the primary analysis in addition to time and a time by allocation interaction term. Participant will be included as a random effect to account for repeated measures.

Adverse events will be summarised by trial arm with details on diagnoses, seriousness, expectedness and relatedness to the intervention. Formal withdrawals from the trial and the intervention only will be summarised with reasons where available.

5. Process Evaluation

A mixed-methods process evaluation will be embedded within the SCIMITAR-SA main trial to examine (1) the barriers and drivers to delivery, implementation, and potential scale-up of

SCIMITAR-SA, and (2) the mechanisms of action(41) in achieving tobacco cessation among individuals with SMI. It will be informed by the Medical Research Council (MRC) guidance for process evaluation of complex interventions(42) and build on methods developed and refined during the feasibility phase.

5.1 Delivery of SCIMITAR-SA

Following completion of intervention delivery, fidelity will be examined using advisor records of intervention delivery schedule and content delivered per participant completed by the TDAs (supplementary file). In addition, ToT monitoring and supportive supervision of TDAs will include implementation of a competency checklist (adapted from NCSCT advanced competencies framework). This checklist, called the Practice Observation Form, will be implemented during observation sessions that ToTs will conduct as part of routine monitoring of 2-3 appointments per TDA per month (supplementary file). The TDAs will participate in an online focus group discussion (FGD, 60–90 minutes) to explore barriers and drivers to delivering SCIMITAR-SA, including fidelity to the intervention protocol, practical challenges in mental health outpatient settings, and administrative issues such as session scheduling. The ToTs will also take part in an online FGD to share their experiences of training, supervising and monitoring the TDAs to deliver SCIMITAR-SA. Both FGDs will be conducted using a semi-structured topic guide (supplementary files).

At 4-month follow-up a brief quantitative survey (supplementary file) will be administered to all participants as part of routine data collection. Participants in the intervention arm will be asked about their engagement with and acceptability of the SCIMITAR-SA intervention. Participants in the comparator arm will be asked similar questions in relation to the VBA and accompanying information materials.

At this time point, a sub-sample of intervention arm participants (6 per site, 48 total) will be interviewed in local languages at their mental health facility. Participants will be purposively sampled to ensure a mix of those who smoked tobacco products and/or smokeless tobacco at baseline, and those who completed or disengaged with the programme. Caregivers may join interviews if participants wish. A semi-structured topic guide (supplementary file) will be used to explore barriers and drivers to engaging with, and completing the SCIMITAR-SA. Interviews will last up to 30 minutes.

5.2 Implementation and scale-up of SCIMITAR-SA

Following completion of intervention delivery, a sample of mental health staff and managers (3 per site, 24 total) involved in referring people to SCIMITAR-SA, VBA delivery, or project oversight will be interviewed to gather feedback on implementation and ideas for future scale-up of the intervention within routine services. A semi-structured topic guide

(supplementary file) will be used to explore barriers and drivers to implementation during the trial, and the feasibility of integrating/scaling-up the intervention into routine care. The interviews will draw on previous work done in the feasibility trial that identified site specific implementation barriers and future implementation strategies.

5.3 Mechanisms of action

The above-mentioned interviews with the intervention arm participants (see 5.2) and some shorter interviews with comparator arm participants (3 per site, 24 total) will explore their quit experience including challenges and solutions. The focus will be on identifying the presence or absence of individual and contextual mechanisms of action(41) from the causal model (See Figure 2, and supplementary file for the comparator arm topic guide)

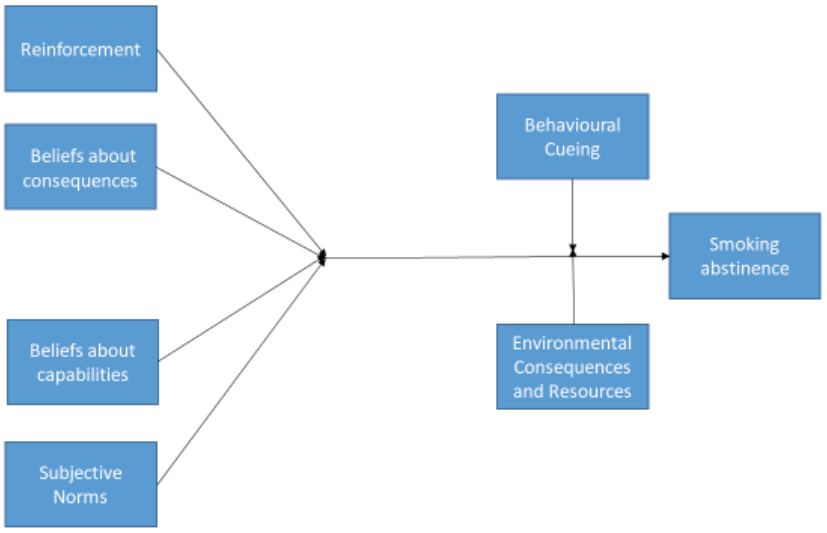


Figure 2: Causal model for the SCIMITAR-SA intervention

5.4 Data analysis and triangulation

The audio-recordings of interviews and FGDs will be transcribed verbatim, translated into English, and analysed using the Framework Approach(43) to address the two process evaluation research questions. Microsoft Excel will be used to support data management and analysis.

Quantitative process evaluation data, including TDA record forms, ToT implemented competency checklists and participant questionnaire responses, will be analysed descriptively and, where appropriate, linked to trial outcomes.

Integration of qualitative and quantitative findings will be undertaken using a triangulation protocol(44), enabling comparison and synthesis of findings across data sources. This approach will enhance the robustness of conclusions and provide a comprehensive understanding of how SCIMITAR-SA was delivered and implemented, how participants engaged with it, and how individual and contextual factors influenced outcomes. In particular, they will help to distinguish between intervention failure and implementation failure, and will provide important insights into scalability of the SCIMITAR-SA intervention.

6. Economic Evaluation

An economic evaluation will be conducted alongside the trial to assess the cost-effectiveness of the SCIMITAR-SA intervention. Costs will include the intervention, healthcare resource use, and productivity loss. The costs of SCIMITAR-SA intervention, including training, delivery and supervision, will be estimated via logs. Healthcare resource utilisation and productivity losses will be collected at baseline and follow-ups using self-report and structured service-use questionnaires developed and tested in the pilot trial. Unit costs will be obtained from national costing sources and the literature, and costs will be calculated in local currencies for the relevant price year. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs), derived from EQ-5D-5L data using the most appropriate national tariff at the time of analysis, and supplemented by quit rates to estimate cost per additional quitter.

The primary analysis will be a within-trial cost-utility analysis (CUA) from a health system perspective over a 13-month time horizon, estimating incremental cost per QALY gained. A secondary cost-effectiveness analysis (CEA) will estimate incremental cost per additional quitter. Incremental cost-effectiveness ratios (ICERs) will be the estimate using regression methods adjusted for baseline differences and relevant covariates. Uncertainty will be explored using bootstrapping techniques, with results presented on cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). Calculated cost per QALY estimates will be compared against willingness-to-pay thresholds of one to three times gross domestic product (GDP) per capita, as recommended by the World Health Organization, given the absence of country-specific thresholds. Sensitivity analyses, including complete case analysis and multiple imputation where appropriate, will be conducted to assess the robustness of findings.

To capture the long-term impacts of SCIMITAR-SA beyond the trial period, a model-based CUA using a lifetime horizon will be conducted for the India context. An existing economic

model for tobacco users with mental disorders will be adapted and updated using trial data, the National Family Health Survey (NFHS), and national costing databases to reflect India's healthcare system. Results will be presented as incremental costs and QALYs, with uncertainty explored through probabilistic sensitivity analysis (PSA).

To investigate the impact of SCIMITAR-SA on health equity, a distributional cost-effectiveness analysis (DCEA) for the India context will be conducted. Based on the trial outcomes, existing literature, and the developed long-term economic model, the net health benefit (NHB) across equity-relevant subgroups will be estimated by combining distributed health gains and health opportunity costs; while health inequality will be estimated using appropriate summary indices. Results will be presented on an equity-efficiency impact plane (EEIP) to illustrate the relationship between the change in total population NHB (efficiency) and the change in population health inequality (equity). Finally, to support decision-making, social welfare functions will be applied to facilitate a formal equity-efficiency trade-off analysis across a range of inequality aversion parameters, and sensitivity analyses will be conducted to handle the uncertainty.

7. Data Management

Data will be managed in accordance with International Conference on Harmonisation Good Clinical Practice (ICH-GCP), the General Data Protection Regulation (GDPR), the UK Data Protection Act 2018, and all applicable national data protection regulations in participating countries (Bangladesh, India, and Pakistan).

Data management activities will be coordinated between the ARK Foundation (Bangladesh and Pakistan) and NIMHANS (India). Designated data managers at ARK and NIMHANS will be responsible for maintaining data quality, performing routine checks, and ensuring consistency under the guidance of the York Trial Unit. Access to identifiable participant data will be restricted to authorised study personnel, including principal investigators, country investigators, trial coordinators, research fellows, and research assistants, strictly for purposes such as participant follow-up and safety monitoring. All datasets used for analysis will be anonymised using unique participant identifiers (UIDs), ensuring that no directly identifiable information is included.

7.1 Data Handling and Storage

All trial data, including screening, baseline and follow-up assessments, will be captured electronically using REDCap, accessed via encrypted tablet devices. The REDCap systems hosted by ARK Foundation (for Bangladesh and Pakistan) and NIMHANS (for India) will serve as the primary databases for the trial. These systems are compliant with Good Clinical Practice and provide role-based access control, audit trails, and data validation features.

Data entry will be performed directly by trained RAs, with built-in range checks, validation rules, and mandatory fields to minimise data entry errors.

Personally identifiable information, including consent forms and participant contact details, will be stored separately from research data and linked only through unique trial IDs. A secure, password-protected linkage file connecting participant identifiers with UIDs will be maintained and accessible only to authorised personnel. All electronic data will be stored on secure, password-protected servers with appropriate encryption and regular backups. Hard copy documents containing identifiable information will be stored in locked cabinets in secure offices at each study site, with access restricted to authorised research staff. All data transfers between ARK Foundation, NIMHANS, and the trial statisticians based at the University of York will be conducted using encrypted file transfer systems approved by the University of York to ensure data security during transmission.

Qualitative data collected through interviews and FGDs will be anonymised prior to transcription and analysis. Audio recordings will be stored in secure, password-protected locations and deleted from recording devices once transcription is complete. Transcripts will be anonymised and labelled using trial IDs to ensure confidentiality. Participants will be informed about how their data will be collected, stored, and used, and consent will be obtained in accordance with ethical and legal requirements. If a participant withdraws consent for data use, all personally identifiable data will be deleted, while anonymised data already collected may be retained for analysis, in line with GDPR and ethical approvals.

7.2 Data Sharing and Access

Research teams will have access only to data from their respective sites. Data sharing agreements will be established between collaborating institutions to govern the transfer and use of data across countries. Anonymised datasets will be shared with the statisticians of York Trial Unit for statistical analysis and reporting. No identifiable data will be transferred outside the country of origin unless explicitly approved under data sharing agreements and regulatory requirements. All data access will be logged and auditable within REDCap.

7.3 Data Monitoring and Quality Assurance

A comprehensive data management and quality assurance plan will be developed prior to trial initiation. Data managers at ARK Foundation and NIMHANS, in collaboration with statisticians of York Trial Unit will conduct routine data quality checks to ensure completeness, accuracy, and consistency. These checks will include validation rules, range checks, logic checks, and cross-variable consistency assessments. Queries arising from data checks will be communicated to research teams for resolution in a timely manner. An audit trail of all data entries and modifications will be maintained within the electronic data

capture system. The York Trials Unit will conduct additional independent data quality checks following each data transfer. Data will be monitored throughout the trial to ensure high levels of completeness and accuracy. Efforts will be made to minimise missing data; however, participant burden and wellbeing will be prioritised, particularly in cases where further data collection may cause distress. At the end of the trial, datasets will undergo final cleaning and validation prior to database lock. Once locked, datasets will be read-only and accessible only to authorised trial investigators and statisticians.

7.4 Data Security

All study data will be handled in accordance with strict confidentiality requirements. Identifiable information will be protected through the use of unique identifiers, restricted access, and secure storage systems. Electronic systems will be password-protected and encrypted, and physical documents will be stored securely. Only authorised personnel will have access to identifiable data, and all study staff will be trained in data protection and confidentiality procedures. Data breaches or security incidents will be reported and managed in accordance with institutional and regulatory policies. Appropriate measures will be taken to mitigate risks and prevent recurrence.

7.5 Archiving

In accordance with the Data Protection Act, GDPR, and the Research Governance Framework for Health and Social Care Research, all study data and essential documents will be securely archived at the end of the trial. The University of York will be responsible for long-term archiving of anonymised datasets. The trial documentation will be retained for a minimum of 25 years following study completion.(45) At the end of the retention period, data will be securely destroyed in accordance with institutional policies.

8. Adverse Events

The principles of International Conference on Harmonisation Good Clinical Practice (ICH-GCP) require that both investigators and sponsors follow defined procedures for the identification, assessment, documentation, and reporting of adverse events and adverse reactions in clinical trials. Although the SCIMITAR-SA main trial evaluates a behavioural intervention and is therefore considered low risk, the study population comprises individuals with Severe Mental Illness (SMI), who have an inherently increased risk of adverse health outcomes, including psychiatric relapse, comorbid physical illness, and social vulnerabilities. Accordingly, robust systems for adverse event (AE) monitoring and reporting will be implemented to ensure participant safety. This section describes the identification of potential adverse events, their definitions, monitoring procedures, classification, and reporting requirements.

8.1 Identification of Potential Adverse Events

The SCIMITAR-SA intervention involves behavioural support for tobacco cessation and associated research procedures. While the risk of direct harm from the intervention itself is low, adverse events may arise due to a range of factors including tobacco withdrawal, underlying mental health conditions, psychosocial stressors, or engagement with research activities. Participation in the study may lead to psychological distress, particularly when discussing tobacco use, mental health, or other sensitive issues. In addition, withdrawal from tobacco may result in symptoms such as irritability, anxiety, low mood, sleep disturbance, and difficulty concentrating. Quitting tobacco smoking may necessitate a reduction of the dose of some antipsychotics - clozapine and olanzapine. Otherwise, the person may experience dose-dependent side effects. There is also a minimal risk of fluctuation or relapse of SMI symptoms, including worsening depression, anxiety, psychotic symptoms, suicidal ideation, or risk of harm to self or others.

Research procedures such as questionnaire administration, saliva sample collection, and anthropometric measurements are considered low risk but may cause minor discomfort or inconvenience. All procedures will be conducted by trained RAs and TDAs, who will ensure participant privacy, confidentiality, and wellbeing. Participants will be informed that they may decline to answer any questions they find distressing and may pause or discontinue participation at any time. If distress is observed or reported, the researcher or TDA will pause the session, provide appropriate support, and refer the participant to clinical staff where necessary.

Although NRT is not provided as part of the trial, participants may access NRT through routine clinical care. Known side effects include mouth or throat irritation, nausea, headache, dizziness, palpitations, and skin irritation depending on the form of NRT used. Participants will be advised to report any such side effects to the study team and to seek medical attention if required.

Adverse events will be identified through participant self-report, caregiver report, routine intervention appointments, scheduled follow-up assessments at four,seven months and thirteen months, reports from healthcare providers, and review of medical records where available. Participants and caregivers will be informed of how to report adverse events at any time using contact details provided in study materials. Active enquiry regarding adverse events will be undertaken at all participant contacts.

Given the vulnerability of the study population, particular attention will be paid to the identification and management of suicidal ideation and self-harm risk. If a participant expresses thoughts of self-harm or suicide during any interaction with the study team, an immediate assessment will be initiated. A designated health professional at each

recruitment location, experienced in mental health risk assessment, will be contacted to undertake or oversee a formal risk assessment using a structured pathway adapted from established protocols. Appropriate referral to mental health services will be arranged where necessary. All such events will be documented and reported as adverse events.

8.2 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a participant during their involvement in the trial, regardless of whether it is considered related to the intervention. This includes new medical or psychiatric conditions, exacerbation of pre-existing conditions, increased frequency or severity of symptoms, any event requiring medical attention, infectious diseases such as tuberculosis, dengue, or COVID-19, SMI-related complications including relapse or suicidality, and any adverse effects associated with NRT use.

8.3 Adverse Event Monitoring

Adverse events will be monitored throughout the duration of the trial. This will include assessment at each intervention session, regardless of whether it is delivered face-to-face or remotely, as well as at all follow-up visits. Researchers and TDAs will actively enquire about adverse events using a structured checklist to ensure systematic and consistent reporting. This checklist will include prompts for common withdrawal symptoms, mental health changes, and potential NRT-related side effects. All adverse events, whether directly observed or reported by participants, will be recorded in case report forms and entered into the secure electronic database.

8.4 Identification and Reporting of Adverse Events

Information on adverse events will be collected continuously throughout participants' involvement in the trial. Participants and caregivers will be encouraged to report adverse events at any time, including between scheduled contacts. Study staff will also receive reports from clinical teams where relevant. Periodic communication with participants, such as newsletters will be provided, which will include information on recognising and reporting adverse events.

All reported adverse events will be documented using standardised forms. Each event will be assessed by appropriately qualified clinical staff for seriousness, severity, causality, and expectedness. Causality assessment will follow standard categories (unrelated, unlikely, possible, probable, definite), taking into account alternative explanations such as underlying illness or concomitant treatments. Seriousness will be determined based on established criteria, including whether the event results in death, is life-threatening, requires hospitalisation, results in significant disability, or is otherwise medically important.

Non-serious adverse events will be recorded and included in routine monitoring and reporting. Serious adverse events (SAEs) will be reported within 24 hours of the study team becoming aware of the event to the country coordinating centre and the central trial team. All SAEs will be followed up until resolution, stabilisation, or return to baseline.

Adverse events that are both serious and considered related to the intervention will be classified as serious adverse reactions (SARs). If such events are also unexpected, they will be classified as suspected unexpected serious adverse reactions (SUSARs). SUSARs will be reported to the sponsor and relevant ethics committees and regulatory authorities within required timelines, specifically within seven days for fatal or life-threatening events and within fifteen days for other SUSARs. Follow-up information will be provided as it becomes available.

Reports will include essential information such as participant trial ID, description of the event, and reason for classification as serious. Completed forms will be submitted to the country coordinating centre, where medically qualified staff will review the report. Follow-up reports will be submitted as additional information becomes available. The research teams will also comply with local institutional requirements for reporting adverse events to Research Ethics Committees or Institutional Review Boards. Participants experiencing adverse events will be followed up until the event has resolved or stabilised.

8.5 Trial Facility Assessment

At each recruitment location, the clinical team responsible for participant care will assess all adverse events. The seriousness of each event will be determined according to standard definitions. The severity of events will be graded as mild, moderate, or severe based on their impact on the participant's daily functioning. It is noted that severity and seriousness are distinct concepts, with seriousness relating to outcomes and severity relating to intensity.

Causality will be assessed by the clinical team, taking into account the timing of the event, the nature of the intervention, and alternative explanations. Where there is disagreement between assessors, all opinions will be documented. Expectedness will be determined by reference to known effects of tobacco cessation, SMI, and NRT where applicable.

8.6 Safety Oversight

Country Principal Investigators or designated leads will oversee adverse event reporting within their respective countries. They will review all serious adverse event reports, ensure appropriate classification and coding, and report events to relevant regulatory authorities and ethics committees in accordance with national guidelines. All SUSARs will be reported within regulatory timelines. The country leads will also ensure that adverse event data are

communicated to the central trial team and sponsor. The Programme Management Group will regularly review adverse event data to identify trends or safety concerns. An independent Advisory Board will periodically review unblinded safety data and make recommendations regarding trial continuation, modification, or termination. Urgent safety measures will be implemented if necessary to protect participants, and relevant authorities will be notified in accordance with regulatory requirements.

9. Incidental Findings

The procedures undertaken in the SCIMITAR-SA main trial may give rise to incidental findings identified during screening and throughout the course of participation. Appropriate procedures will be in place to manage such findings in a safe, ethical, and clinically appropriate manner.

At the screening stage, validated tools such as the Alcohol Use Disorders Identification Test (AUDIT)(46) and the ASSIST-Lite(47) will be administered to assess alcohol and psychoactive substance use, respectively. These assessments are primarily intended to support eligibility screening and to characterise the study population. However, they may identify individuals who are at risk of harmful alcohol use or problematic substance use. Where such findings arise, participants will be provided with brief, structured feedback on their scores, including an explanation that these tools do not constitute a formal diagnosis. Participants will also be given information on the potential risks associated with unhealthy substance use and, where appropriate, provided with locally relevant informational materials routinely used by addiction services. If indicated, participants will be signposted or referred to appropriate clinical or community-based addiction services for further assessment and management, in line with local care pathways.

During the course of the trial, additional incidental findings may arise in relation to participants' mental or physical health. These may include, but are not limited to, relapse or worsening of severe mental illness symptoms, hospitalisation, emergence of suicidality, physical health complications, or initiation of new treatments (e.g. pharmacological or procedural interventions such as electroconvulsive therapy). Such events are anticipated within this population and will be managed according to standard clinical care pathways at each site. All relevant events will be documented and reported in accordance with the trial's adverse event reporting procedures. Where necessary, participants will be referred promptly for appropriate clinical care, and their safety and wellbeing will remain the primary priority throughout the trial.

10. Ethics

The SCIMITAR-SA main trial will be conducted in accordance with the fundamental ethical principles outlined in the Declaration of Helsinki and in compliance with International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines. The trial will also follow guidance on good research practice issued by the Medical Research Council (MRC) and Wellcome Trust, as well as all applicable national and institutional regulations governing research in Bangladesh, India, Pakistan, and the United Kingdom. The Programme Management Group (PMG) and Independent Advisory Board (IAB) will review trial progress, safety data, and ethical issues. Any ethical concerns arising during the trial will be addressed promptly, and appropriate actions will be taken in consultation with relevant oversight bodies.

10.1 Ethics and Regulatory Approvals

Ethical approval for the trial will be obtained from all relevant national and institutional ethics committees prior to study initiation. In the United Kingdom, approval will be sought from the Health Sciences Research Governance Committee at the University of York. In Bangladesh, approval will be obtained from the National Research Ethics Committee (NREC) functioning under the Bangladesh Medical Research Council (BMRC). In India, approvals will be secured from the Screening Committee on Research Proposals (SCRP) of the Ministry of Health and Family Welfare, Government of India , as well as from institutional ethics committees including the Ethics Committee (Behavioural Science Division) at the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru. In Pakistan, ethical approval will be obtained from the National Bioethics Committee for Research (NBC-R) at the Health Research Institute, National Institutes of Health (NIH), along with institutional approvals from the Institutional Research & Ethics Forum (IREF) at Rawalpindi Medical University (RMU), Rawalpindi, and the Ethics Review Board of Dow University of Health Sciences (DUHS), Karachi. All approvals will be obtained in accordance with national regulatory requirements, and any protocol amendments will be submitted to relevant ethics committees for review and approval prior to implementation.

10.2 Informed Consent and Participant Rights

Participation in the trial will be entirely voluntary. Written informed consent will be obtained from all participants prior to enrolment, following the provision of detailed verbal and written information about the study in a language and format that is understandable to them. Participants will be informed about the purpose of the study, procedures involved, potential risks and benefits, data handling, and their rights as research participants. They will have the opportunity to ask questions before providing consent.

Given that the study population includes individuals with SMI, careful consideration will be given to participants' capacity to provide informed consent. Capacity will be assessed by trained research staff in accordance with local legal and ethical frameworks. Only individuals who are able to provide informed consent will be enrolled in the trial. Recognising that capacity may fluctuate over time in this population, consent will be treated as an ongoing process, and participants' willingness to continue will be reaffirmed at key points during the study. Where appropriate, caregivers may support participants in understanding study information, while ensuring that consent remains voluntary and participant-led.

Participants will be informed of their right to withdraw from the trial at any time without providing a reason and without any impact on their ongoing clinical care. Contact details for the study team and an independent ethics representative will be provided in the participant information materials to enable participants to raise concerns or complaints if needed. Written information outlining how to withdraw, including relevant contact details, will be provided to all participants. Withdrawal can be communicated to any member of the research team. If a participant withdraws from the study, no further data will be collected from that point onwards. Data collected prior to withdrawal will be retained and included in the analysis. Where a participant requests removal of their data, all personally identifiable information will be deleted, however, anonymised data may be retained and used for analysis in accordance with General Data Protection Regulation (GDPR) provisions for research.

To support intervention fidelity and quality assurance, Master Trainers (Trainer of Trainers) will observe a sample of intervention delivery sessions conducted by Tobacco Dependence Advisors (TDAs). Approximately two to three intervention sessions per TDA per month may be observed using a structured Practice Observation Form to assess adherence to the intervention manual, consistency of delivery, and identify any additional training or implementation support needs. Only participants randomised to the intervention arm whose counselling session is selected for observation will be invited to take part in this process. Prior to any observation, both the trial participant and the TDA will be provided with a supplementary Participant Information Sheet (PIS) and asked to provide written informed consent using a supplementary consent form specific to the observation process. For post-study implementation in routine practice, consent would not be required for ongoing monitoring and supervision by ToTs .

10.3 Participant and Research Staff Safety

The safety and wellbeing of participants will be prioritised at all times. Although the intervention is behavioural and low risk, procedures will be in place to identify and respond to participant distress, including deterioration in mental health or emergence of suicidal

ideation. Participants requiring additional support will be referred promptly to appropriate clinical services in line with established care pathways.

Efforts will be made to minimise participant burden by designing study procedures that are flexible, convenient, and as non-intrusive as possible. Follow-up assessments, where appropriate, will be scheduled in consultation with participants. Participants will not be subject to undue inducement to participate. Reimbursement for reasonable expenses will be provided in accordance with local regulations and ethical guidance. Engagement of community panel members and public contributors will be supported and reimbursed in line with established guidance on public involvement in research.

As the trial involves a vulnerable population, safeguarding procedures will be implemented to protect participants from harm. The study will operate in accordance with the University of York's Safeguarding Policy and international standards for safeguarding in research conducted in low- and middle-income countries. Study protocols will include procedures for identifying and responding to safeguarding concerns, and all research staff will receive appropriate training.

The safety and security of both participants and research staff will be carefully considered throughout the trial. Risk assessments will be conducted for all study activities, including fieldwork and international travel where applicable. For UK-based staff travelling to partner countries, risk assessments will be conducted in accordance with University of York policies. For in-country staff, risks will be assessed by site leads and appropriate mitigation measures implemented. All staff will be trained in ethical conduct, safety procedures, and risk management.

10.4 Data Confidentiality

The trial will involve the collection and management of sensitive personal and health data. All data will be handled in accordance with the General Data Protection Regulation (GDPR), the UK Data Protection Act 2018, and relevant national data protection regulations in participating countries. Participant confidentiality will be strictly maintained through the use of unique identifiers, and all identifiable information will be stored separately from research data.

Access to identifiable data will be restricted to authorised study personnel only. Data sharing across countries will be governed by formal data sharing agreements to ensure secure and compliant transfer of information. Participants will be informed about how their data will be used, stored, and protected as part of the consent process.

11. Trial Oversight

The Programme Management Group will be responsible for the day-to-day management and overall delivery of the trial. The Programme Management Group will include the Chief Investigator, co-investigators, country leads, trial managers, statisticians, health economists, and other key members of the research team. The group will oversee trial implementation, monitor recruitment and retention, ensure data quality, and address operational challenges. The PMG will also provide guidance to the research involved in study delivery, and will contribute to data interpretation, reporting, and dissemination of findings. The group will meet every two months, either virtually or in person, to review trial progress against predefined milestones, monitor risks, and ensure that the study is conducted in accordance with the protocol and regulatory requirements.

The IAB will provide external oversight of the SCIMITAR-SA programme. The IAB will be chaired by an independent expert and will comprise members with relevant expertise in global health, including tobacco control, mental health, clinical trials, and health systems in LMICs. The role of the IAB will be to monitor trial progress, provide independent advice on scientific and operational aspects, and recommend modifications where necessary to ensure successful delivery of the study objectives. The IAB will meet biannually (twice per year), however, additional meetings may be convened if required. A minimum of two independent members will be required for quorum. The IAB will review key aspects of the trial, including recruitment, retention, data quality, safety issues, and emerging evidence, and will provide recommendations to the Programme Management Group and Chief Investigator.

12. Community Engagement and Involvement

Community Advisory panels (CAP) will be convened in each country every 6 months throughout the duration of the trial. Each panel will help to ensure the programme remains focused on the prioritised needs of the community and that planned activities are ethically sound, culturally appropriate, feasible and have community support. Panel members will review plans and study materials for recruitment and data collection; they will also advise on and contribute to the dissemination of key findings to participants, healthcare providers, and the public. CAP involvement will improve research quality, help engender a sense of ownership of outputs by the community, help to accelerate uptake and maximise the reach and impact of our programme.

13. Dissemination Plans

The trial protocol will be registered on the ISRCTN registry. The findings from the trial will be submitted for publication in international, peer-reviewed journals. Findings will be shared with key stakeholders. Other outputs will include presentation of findings at relevant

national, regional, and international scientific conferences. We will also be using social media platforms such as LinkedIn for dissemination.

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