FULL TITLE: Randomised controlled trial of fluoxetine for the treatment of problematic sexual arousal in adult males serving a custodial sentence.

SHORT TITLE: Fluoxetine-Assisted Sexual Arousal Reduction

ACRONYM: FASAR

This protocol has some regard for the Health Research Authority (HRA) guidance.

RESEARCH REFERENCE NUMBERS

IRAS Number	1007974
REC reference	26/WA/0041
Sponsor reference	1456415
Funder reference	NIHR 151549
ISRCTN ID	To be confirmed

PROTOCOL VERSION NUMBER AND DATE

Current protocol version: 1.0 dated 16th March 2026

SPONSOR REPRESENTATIVES

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PROTOCOL VERSION NUMBER AND DATE

Draft protocol versions are managed by electronic revision control.

Version control of all approved trial documents will be maintained using a **Version Control Log** which will be held separately.

Amendment No.	Protocol version	Protocol date	Author(s) of changes	Details of changes made
NA	1.0	12/01/2026	NA	NA
N/A	2.0	16/03/2026	Kym Carter	Response to REC and MHRA queries during initial application for approval
1				
2				

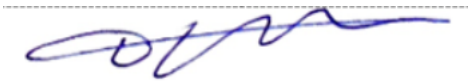
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigators (medical and non-medical) agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: 

Date: 16/03/2026

Name (please print): Prof Richard Emes

Position: Pro Vice-Chancellor Research and International

Chief Investigator (medical):

Signature: 

Date: 25/03/2026

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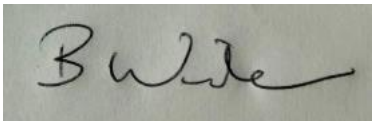
Chief Investigator (non-medical):

Signature: 

Date: 26/03/2026

Name: (please print): Prof Belinda Winder

Statistician:

Signature: 

Date: 26/3/2026

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NTU-based Trial Office	FASAR@NTU.ac.uk	Centre for Crime, Offending, Prevention and Engagement (COPE) NTU Psychology Nottingham Trent University (NTU) 50 Shakespeare Street Nottingham NG1 4BQ
For IMP-related unblinded queries	COPE.MMSA@ntu.ac.uk	
Trial document repository	Log in via the trial website and use the credentials provided by the Trial Office.	
For IT-related issues	If the Trial Office is not available, please email IT-STU@swansea.ac.uk	
Safety reporting (SAEs, SARs & SUSARs)	• Complete an **SAE form** (go to Investigator Site File: Section 7) • Email the form to: FASAR@swansea.ac.uk • Report SAEs within **24 hours** of the trial location team's awareness of the event.	
Urgent Safety Measures	• Complete a **USM reporting form** (go to Investigator Site File: Section 7) • Email the form to: FASAR@swansea.ac.uk • Implement an USM immediately to prevent immediate hazard to health or safety	
Qualitative study queries	• Email: FASAR@NTU.ac.uk	
Saliva testing Laboratory	• Post saliva sample tubes to: **CatSci Ltd,** CBTC2, Capital Business Park, Wentloog, Cardiff CF3 2PX	

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Funder(s)	Alan Marshall	Research Manager

	Email: mailto:monitoring@nihr.ac.uk	NIHR HTA
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	Adarsh Kaul (Forensic Psychiatrist at HMP Whatton) Tel: 07771 506182 Email: adarsh.kaul@nottshc.nhs.uk	Nottinghamshire Healthcare NHS Foundation Trust
Committees	Research Ethics Committee	Wales REC 3
	Trial Steering Committee (TSC) Data Monitoring Committee (DMC)	A membership list of the trial committees will be held in a separate document.

Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of covariance
APR	Annual Progress Report
AR	Adverse reaction
CA	Competent Authority
CAPAs	Corrective and Preventive Actions
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COPE	Centre for Crime, Offending, Prevention and Engagement
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EMEA	European Medicines Agency
EQ-5D	EuroQol 5D
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-releasing hormone
HADS	Hospital Anxiety and Depression Scale
HMPPS	HM Prison and Probation Service
HRA	Health Research Authority
HSP	Healthy Sex Programme
HTA	Health Technology Assessment
IB	Investigator Brochure
ICER	Incremental cost-effectiveness ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRAS	Integrated Research Application System
ISF	Investigator Site File (this forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to treat
KCL	King's College London
MA	Marketing Authorisation
MAOI	Monoamine oxidase inhibitor

MHRA	Medicines and Healthcare Products Regulatory Agency
MMPSA	Medication to Manage Problematic Sexual Arousal
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIMP	Non-Investigational Medicinal Product
NTU	Nottingham Trent University
PSIQ	Problematic Sexual Interest Questionnaire
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
PROMs	Patient-reported outcome measures
QA	Quality Assurance
QALYs	Quality-adjusted life years
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious adverse event
SAR	Serious adverse reaction
SDV	Source data verification
SF-SUS	Secure Facilities Service Use Schedule
SHEAP	Statistical and Health Economics Analysis Plan
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SNRI	Serotonin and noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STU	Swansea Trials Unit
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Thematic Analysis
TLM	Testosterone-lowering medication
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
USM	Urgent Safety Measure
WASI	Wechsler Abbreviated Scale of Intelligence
WEMBWS	Warwick–Edinburgh Mental Wellbeing Scale for wellbeing

TRIAL SUMMARY

Trial title	Randomised controlled trial of fluoxetine for the treatment of problematic sexual arousal (PSA) in adult males serving a custodial sentence	
Short title	Fluoxetine Assisted Sexual Arousal Reduction (FASAR)	
Clinical phase	Phase 3	
Trial design	Double-blind randomised controlled trial	
Trial patients	Potential patients will be drawn from the population of adult males currently in prison who exhibit or report problematic sexual thoughts and/or behaviours linked with sexual preoccupation or hypersexuality who are referred to the Medication to Manage Problematic Sexual Arousal (MMPSA) service at one of the approved UK prison treatment clinic sites.	
Sample size	RCT – Consent 196 patients to ensure 118 complete the RCT Interviews – 30 prison staff	
Treatment duration	6 months	
Follow up duration	6 months after dose 1	
Planned trial period	60 months	
	Objectives	**Outcome Measures**
Primary	To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg daily) for reducing PSA in adult males referred to the MMPSA service at 6 months compared to placebo.	Sexual Compulsivity Scale (SCS)
Secondary	To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg) for reducing PSA in adult males referred to the MMPSA service at 3 months compared to placebo.	SCS
	To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg) for improving wellbeing in adult males referred to the MMPSA service at 3 and 6 months compared to placebo.	Warwick–Edinburgh Mental Wellbeing Scale (WEMWS)
	To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg) for improving anxiety and depression in adult males referred to the MMPSA service at 3 and 6 months compared to placebo.	Hospital Anxiety and Depression Scale (HADS)
	To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg) for reducing paedophilic and /or hebophilic interests in adult males referred to the MMPSA service at 3 and 6 months compared to placebo.	Problematic Sexual Interest Questionnaire (PSIQ)
	To determine the cost-effectiveness of fluoxetine (dose 20mg / 40mg / 60mg daily) compared to placebo in adult males referred to the MMPSA service over 6 months.	Secure Facilities Service Use Schedule (SFSUS), EuroQol EQ-5D-5L
	To understand the triggers for and/or barriers to referring someone for medication and understand any systemic or individual barriers to people continuing with a referral.	Interviews with prison staff

	To understand the timing and motivations for change, prior help-seeking, and the service, treatment, and personal factors (including views on mandatory use, expectations, and expected continuation/discontinuation) that influence engagement with MMPSA.	Treatment Considerations questions in baseline PROMs booklet
	To understand participants' experiences, side-effects, wellbeing, and engagement over time while taking MMPSA, and how these factors influence continuation, perceptions of helpfulness, and evolving views on voluntary versus mandatory use.	Experience and Impact questions in (follow up) PROMs booklet
Investigational Medicinal Product(s)	**Intervention**: Fluoxetine capsules (Flamingo Pharma (UK) Ltd **Placebo**: Microcrystalline cellulose (Avicel ® PH-102) Both will be over-encapsulated to look identical in appearance and weight	
Formulation, dose, route of administration	The starting dose for fluoxetine/placebo will be 20mg daily. All patients will be reviewed at 4 weeks, with the dose increased to 40mg if no or partial clinical response, and then to 60mg after a further 4 weeks if needed. Maximum dose will be 60mg/day. Dispensing of medication will follow normal practice (collected daily or weekly from healthcare department, dependent upon individual needs). Placebo will be titrated to mimic the fluoxetine dosing regimen and maintain blinding.	

LAY SUMMARY

Problematic sexual arousal (PSA) is characterised by persistent and intense sexual thoughts, physiological arousal, urges, and behaviours that are distressing and difficult to control. Prisons have people with symptoms of PSA being exhibited during their stay, not all of which are people with a sexual conviction.

Recent research has provided evidence for selective serotonin reuptake inhibitors (SSRIs) as an alternative treatment to testosterone-lowering medications. A number of research studies have been conducted into the use of various SSRIs (mainly sertraline and fluoxetine). These studies have reported promising results for the role of SSRIs in the treatment of PSA, including a less severe side effect profile and cost-effectiveness.

This trial aims to investigate whether fluoxetine can reduce PSA in patients who have been referred to the prison's Medication to Manage Problematic Sexual Arousal (MMPSA) service by comparing its effectiveness and cost effectiveness over a 6-month period when compared with patients taking a placebo drug. We will undertake a double blind randomised controlled trial, recruiting at least 196 patients and randomising them to fluoxetine or a matching placebo in a 1:1 ratio so that there are equal numbers in each group. We will ask patients to complete questionnaires at baseline (before the blinded treatment is given), then at 3 and 6 months after the treatment has been started. Patients will complete a daily log to report any side effects, changes to other medications they are taking, and any healthcare contacts during the trial.

At the end of the 6-month trial period for each patient, the Forensic Psychiatrist will be unblinded and decide on their treatment as part of standard care.

The trial hopes to prove that fluoxetine is effective and cost effective to use in patients exhibiting PSA symptoms so that the guidelines can be amended to allow fluoxetine to be prescribed in the community.

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
NIHR HTA	£2,400,080.55

ROLE OF TRIAL SPONSOR, FUNDER & CLINICAL TRIALS UNIT

The Trial Sponsor will be Nottingham Trent University (NTU), who are the employers of the non-medical Chief Investigator, Prof Belinda Winder. The medical Chief Investigator, Prof Donald Grubin, is a Visiting Professor at NTU.

The study will be conducted in collaboration with Swansea Trials Unit (STU), a registered Clinical Trials Unit (UKCRC registration number 58). STU will provide trial services including trial, data and pharmacovigilance management, trial location setup and close-down and overseeing trial monitoring, ensuring that all procedures are MHRA compliant. NTU will be responsible for all aspects of the qualitative work being done within this protocol, as well as conducting trial location visits for data collection. King's College London (KCL) will undertake the health economics analysis.

The study has been funded by the NIHR HTA (Ref 151549), who require regular update reports to confirm the progress of the study and expenditure.

ROLES AND RESPONSIBILITIES OF TRIAL COMMITTEES

Trial Steering Committee (TSC)

The trial will be overseen by a TSC chaired by a qualified UK-based person approved by the Funder. The TSC will comprise, as a minimum, an independent statistician, a Forensic Psychiatrist, a Forensic Psychologist, a Clinical Trials Pharmacist, a Health Economist, a representative from HM Prison and Probation Service (HMPPS) and at least one public representative. The TSC should meet approximately every six months or more frequently as required, receiving information from the Trial Management Group (TMG) and the Data Monitoring Committee (DMC) (see below) and will advise the Sponsor and the TMG. Observers from the Funder will be invited to all TSC meetings. The TSC will operate with agreed terms of reference.

The role of the TSC is to monitor and supervise trial progress towards interim and end objectives, to monitor and advise on scientific credibility and to consider and act upon the recommendations of the DMC.

Data Monitoring Committee (DMC)

An independent DMC chaired by an independent Forensic Psychiatrist will be convened for the duration of the trial. The committee will include a Forensic Psychologist an independent statistician and an independent Health Economist. The DMC will meet typically every six months, throughout the trial and receive unblinded reports of all adverse events from the STU trial team, as well as assessing progress in recruitment. The chair of the DMC may also call additional meetings as necessary. The DMC will have responsibility for advising the TSC and Sponsor on whether to continue the trial or suspend or terminate treatment for of a single patient or group of patients if patient safety is considered to be at risk. The DMC will operate with agreed terms of reference.

The role of the DMC is to assess the progress of the trial, monitor safety data and critical efficacy endpoints and to recommend whether the trial should be continued, modified, or stopped.

Trial Management Group (TMG)

The trial will be run by a TMG comprising the Lead Investigators, Trial Manager, Field Coordinator, Data Manager, Research Associates (RAs), Statistician, Health Economist, Pharmacy Advisor, Public Representative(s), STU representatives, a Sponsor representative and, where relevant, independent

personnel with expertise in the MMPSA pathway. The TMG will oversee the day-to-day trial management and should meet in person or by teleconference quarterly (or as required) for the duration of the study. The TMG will oversee and provide guidance on all aspects of regulatory approval, set-up, recruitment, protocol deviations, adverse events, data management, data analysis and dissemination. The TMG will report at agreed intervals to the TSC, the DMC and the study Sponsor.

The role of the TMG is to monitor all aspects of the trial conduct and progress, to ensure adherence to the approved protocol and to take appropriate action to safeguard the patients and the quality of the data.

Operational meetings

Key members of the TMG will meet by teleconference on a regular (weekly) basis to facilitate the setup of the trial and to discuss operational issues and safety reporting once recruitment has begun.

TRIAL FLOW CHART: A flowchart illustrating the trial can be found in Appendix 1.

KEYWORDS: SSRIs; sexual offending; sexual compulsivity; sexual preoccupation; problematic sexual arousal (PSA); prison; Randomised Controlled Trial (RCT).

1. BACKGROUND

Problematic sexual arousal (PSA) is an umbrella term encompassing sexual preoccupation (Mann et al., 2010), sexual compulsivity (Kalichman, 2013), hypersexual disorder (Krueger & Kaplan, 2002) nymphomania (Groneman, 1994), and sexual addiction (Carnes, 1994). It is widely recognized as a key factor contributing to both the occurrence and recurrence of sexual offending (Kingston et al., 2013; L. Marshall et al., 2001; Seto et al., 2023). PSA is characterised by persistent and intense sexual thoughts, physiological arousal, urges, and behaviours that are distressing and difficult to control, sometimes exhibiting paraphilic traits. While some individuals who commit sexual offences show PSA levels comparable to those convicted of nonsexual offenses or to general community samples (Blanchard G, 1990; Carnes, 1994; W. Marshall et al., 2009; W. L. Marshall et al., 2008), there exists a subgroup of people with a sexual offence who experience significantly higher levels of PSA (Ryan et al., 2017). This makes PSA an important target for interventions aimed at managing and preventing sexual offending.

Research has demonstrated that testosterone-lowering medications (anti-androgens and gonadotropin-releasing hormone (GnRH) agonists) are effective in reducing sexual urges and hypersexual behaviours in those with paraphilic and other sexual disorders (Darjee & Quinn, 2020; Thibaut, 2023; Thibaut et al., 2020). Furthermore, testosterone-lowering medication has been shown to reduce the risk of reoffending, with meta-analyses finding medium effect sizes (Hall, 1995; Lösel et al., 2005), especially when combined with psychological treatment (Kaplan & Krueger, 2010). Clinicians and researchers (Grubin, 2008, 2018; Morin et al., 2019) have postulated a promising role for these medications in treating sexual compulsivity in individuals convicted of sexual offences.

More recently, research has found that while psychotherapy alone has significant effects on reducing overall risk, intimacy deficits, general self-regulation and cooperation with supervision, taking medication (GnRH agonists, cyproterone acetate or a combination) in addition to psychotherapy produced greater improvements in these measures and also had a significant effect on increasing sexual self-regulation (Sauter et al., 2021). A further study followed 60 individuals convicted of a sexual offence for 20 years following treatment with a combination of a GnRH agonist and cyproterone acetate (Colstrup et al., 2020). The rate of a new sexual offences was 7.7 times higher among those who stopped treatment compared to those who continued it. Similar results have been found for the use of psychotherapy combined with leuprolide acetate (an anti-androgen), with sexual recidivism rates of 4.5% for a cognitive behavioural therapy only group and 0% for a cognitive behavioural therapy and medication group (Gallo et al., 2019).

A more recent double-blind, randomised controlled trial (RCT) of the effects of GnRH agonist medication (degarelix) on a sample of 52 Swedish men convicted of child sex offences and diagnosed with paedophilia demonstrated that individuals taking degarelix exhibited a reduction in overall risk, paedophilic disorder and sexual preoccupation 2- and 10-weeks post-medication (Landgren et al., 2020). This reduction was significantly larger than the reduction exhibited by the placebo group, though neither the treatment nor placebo group exhibited any significant improvements in self-regulation, empathy or self-reported risk. This RCT supports previous research suggesting a promising role for testosterone-lowering medications in reducing sexual compulsivity in individuals who have been convicted of a sexual offence (in this case a child sexual offence). However, a limitation of this study is the use of self-report measures in the form of a diary in which patients documented any ‘adverse events’ (AEs), as well as short follow-up periods (2 and 10 weeks).

Sauter et al (2024) conducted a retrospective study examining the impact of testosterone-lowering medication (TLM) on recidivism among individuals convicted of sexual offences. Participants included high-risk individuals treated with TLM (n=54) and a comparison group receiving psychotherapy only (n=79). Medications included GnRH agonists (83.3%), cyproterone acetate (16.6%), and some cases also included SSRIs (5.6%). Results showed that, despite the TLM group having a higher initial risk profile, they had significantly lower general recidivism rates (27.8% vs. 51.9%) and violent recidivism rates (1.9% vs. 15.2%) compared to the psychotherapy-only group. Differences in sexual recidivism were also lower, although not at a significant level (5.6% vs. 10.1%), perhaps due to the generally low base rate of sexual reoffending, which makes detecting statistically significant differences challenging. Nevertheless, the sexual recidivism rate in the TLM group was still lower than national and international estimates for sexual recidivism.

Overall, this research suggests that testosterone-lowering medication is effective in reducing PSA as well as both the risk and actual occurrence of sexual reoffending. Medication is likely to be particularly helpful for individuals who exhibit deficits in sexual regulatory functions (i.e. sexual compulsivity), and a combination of psychotherapy and medication is thought to be most effective in reducing the risk of sexual recidivism.

However, two meta-analyses from 2015 (Khan et al., 2015; Schmucker & Lösel, 2015) called into question the validity of these studies, noting differing samples (e.g. non-offending, adult offending and child offending), lack of matched control groups, the use of subjective outcome measures, short follow-up periods, studies not reporting recidivism rates and a lack of direct comparisons of different treatments. Researchers have advised that such methodological issues should be considered when interpreting individual studies (Darjee & Quinn, 2020). Furthermore, because of these methodological issues, as well as the serious side effects of testosterone-lowering medication, the use of these medications in correctional settings has been limited (Landgren et al., 2020).

More recent research has provided evidence for selective serotonin reuptake inhibitors (SSRIs) as an alternative treatment to testosterone-lowering medications. A number of research studies have been conducted into the use of various SSRIs (mainly sertraline and fluoxetine) for paraphilic behaviours and non-paraphilic PSA (Thibaut et al., 2020)). These studies have reported promising results for the role of SSRIs in the treatment of PSA, including a less severe side effect profile and cost-effectiveness. Furthermore, similar to testosterone-lowering medications, research has suggested that the use of SSRIs in combination with psychotherapy is most effective (Darjee & Quinn, 2020; Thibaut et al., 2020)

However, similar to the research into anti-androgens and GnRH agonists, three different meta-analyses conducted in the 2000s noted the lack of methodologically sound research, specifically referencing the small samples sizes, short follow-up periods, lack of control groups, lack of prospective studies, lack of reporting on recidivism, the use of self-report outcome measures and the lack of RCTs (Thibaut et al., 2020).

To date, there has been one RCT on SSRIs and PSA with a 12-week double-blind study on the use of Citalopram with a non-forensic sample of homosexual and bisexual patients diagnosed with sexual addiction (Wainberg et al., 2006). According to the WHO international clinical trials registry platform, there is a current open, randomised controlled phase II study, comparing naltrexone and fluoxetine treating compulsive sexual behaviour disorder (EudraCT 2019-004255-36) in adult males and females, the results of which are not yet available. As far as the authors are aware, no RCTs have been conducted on SSRIs with a sample of individuals convicted of a sexual offence(s).

In 2002, a systematic review of currently available evidence on the treatment of people with a sexual conviction was published. The review located 130 studies, only nine of which (with $n = 225$ patients in total) were of sufficient robustness to be included in their meta-analysis. None of these included comparison or control groups. This meta-analysis concluded there was preliminary evidence for the value of SSRIs in treating people with a sexual conviction, and their economic analysis demonstrated potential for the cost-effectiveness of this treatment. All-text searches of the Cochrane Library (in March 2022) using ‘SSRI’ and ‘fluoxetine’ yielded 148 and 196 results, respectively. A single Cochrane review was published in 2015 by Khan et al., which highlighted the lack of robust research on SSRIs and their effectiveness in treating sexual paraphilic disorders (Khan et al., 2015).

The World Federation of Societies of Biological Psychiatry 2020 guidelines for the pharmacological treatment of paraphilic disorders were produced following MEDLINE/PubMed searches (with SSRIs and hormonal treatments as search terms) and supplemented from other sources, including published reviews. The guidelines stated that while ‘not formally approved, SSRIs have already been included in clinical practice 'off label' for the treatment of paraphilic disorders with specific indications, although more research demonstrating effectiveness is also needed’ (Thibaut et al., 2020, p. 444). The authors highlight that there continues to be a lack of controlled studies, while acknowledging that there is some clinical evidence for fluoxetine reducing paraphilic sexual behaviour. The CI’s work in this area has included scoping and structured reviews of the literature, created training and contributed to policy for HM Prison and Probation service (HMPPS), NHS (England) and produced expert briefings for the National Organisation for the Treatment of Abusers (NOTA) and explanations of the research for patients and GPs (Elliott et al., 2018; Lievesley et al., 2014; Winder et al., 2017, 2023; Winder, Lievesley, Kaul, et al., 2014).

2. RATIONALE

There is a lack of robust quantitative evidence to support the use of SSRIs for the treatment of men with problematic sexual arousal convicted of a sexual offence. Consequently, this medication is only available for this purpose ‘off label’. There is, however, less strong evidence indicating that the SSRI fluoxetine may be effective in the treatment of PSA, and this is sufficient to support the implementation of an RCT. Successful

completion of the proposed double-blind, parallel-design RCT and acceptance of the primary hypothesis at a high degree of confidence will provide evidence to support the adoption of fluoxetine as a treatment for problematic sexual arousal.

Sexual offences reported to the police in England and Wales as of June 2024 were at their highest for any 12-month period (Crime in England and Wales - Office for National Statistics, 2024). Yet fewer than 1 in 6 women and 1 in 5 men who have experienced attempted rape, rape, attempted assault by penetration or assault by penetration report their abuse to the police (Rape Crisis, 2022). Sexual offending incurs tangible costs to society, with costs relating to contact child sexual abuse alone estimated to be £10.1 billion annually (Crime in England and Wales - Office for National Statistics, 2021.; Ministry of Justice, 2019).

While the aetiology of sexual offending includes both sexual and non-sexual factors (Seto, 2019; Seto et al., 2023), it is estimated that 45%–75% of adult males with a sexual conviction experience, and are motivated by, problematic sexual arousal (PSA) (Hamilton, 2020; Hocken et al., 2015; W. L. Marshall et al., 2008). Problematic sexual arousal can manifest through sexual preoccupation (intense and frequent sexual thoughts), heightened physiological arousal and sexual urges, and/or the need to orgasm an excessive number of times each day, every day(Kafka, 2010).

PSA is associated with adverse physical and mental health outcomes, including physical injury to the penis and hands, difficulties with emotional regulation, mood disorders, compulsive and addictive behaviours, loss of employment because of illegal and/or obsessive sexual behaviour, interpersonal difficulties and lower levels of life satisfaction and wellbeing (Långström et al., 2004). Problematic sexual arousal is a key criminogenic factor for sexual offending (Hanson & Morton-Bourgon, 2005) and reoffending (Hanson & Morton-Bourgon, 2004; Mann et al., 2010; Ozkan et al., 2020) and can be a barrier to effective psychological treatment of sexual offending, as it can affect focus and engagement in treatment programmes (Hamilton, 2020). At present, the primary treatment approach for people with a sexual conviction in the UK is psychological and this is most often based on the principles of cognitive behavioural therapy (Thibaut et al., 2020; Tyler et al., 2021; Winder, Lievesley, Kaul, et al., 2014). In England and Wales, the Healthy Sex Programme (HSP) is the only psychological intervention targeting offence-related sexual interests. It is designed for individuals with persistent sexual interests linked to offending, such as those involving children. The only evaluation of HSP has yielded mixed results regarding its effectiveness in reducing future risk (Freel & Wakeling, 2023). HSP does not specifically address PSA and no dedicated interventions currently exist for this issue, despite this being a key criminogenic factor for sexual reoffending and moreover a barrier to engagement in psychological interventions (Winder et al., 2017).

To address this treatment gap, in 2007, HMPPS commenced a pilot project offering Medication to Manage Problematic Sexual Arousal (MMPSA) to men with convictions for sexual crimes (Winder, Lievesley, Kaul, et al., 2014; Winder & Blagden, 2020). The MMPSA pathway was subsequently expanded to eight UK prisons, with Forensic Psychiatrists working within the healthcare department of each prison. These Forensic Psychiatrists could prescribe SSRIs, anti-androgens and GnRH agonists to adult men with sexual convictions, where they presented with PSA and had sought medical treatment to help them reduce their symptoms.

The proposal here is for an RCT for a medical pathway for men with PSA in prison, meaning that the initial cohort for the trial is men who have been convicted of a sexual offence and whose future behaviour is trackable via the Ministry of Justice. This focus on men who have harmed is essential to allow a full dataset to be produced, including abundant collateral information harvested from the HMPPS record, which will be analysed to provide secondary outcomes. It will enable recruitment in an environment in which PSA does not carry the same stigma as it does outside of custody and where its identification by prison staff will enable men to participate in the trial. Men who have been convicted of a sexual offence and who now face life under increased supervision even after custody will be motivated to participate in this trial, as the experiences and studies of this research team demonstrate they often have the wish to do something that could help others before they commit a first offence (i.e. to contribute to an RCT that may contribute to SSRIs being available in the community as a preventative medication).

This RCT would contribute to knowledge regarding the effectiveness of SSRIs for PSA. This would allow the prison service and the NHS to consolidate the pharmacological treatment pathway for men serving a custodial sentence for a sexual offence. This pathway remains under threat (from lack of financial resources) because the evidence base for the effectiveness of the treatment is not as robust as it needs to be. If the trial indicates that SSRIs are effective at reducing PSA, this finding will contribute to NICE guidelines, and it could be used as part of the evidence base to move SSRIs ‘on label’; this would in turn permit more medical professionals in the community to prescribe them as a treatment option to prevent and reduce PSA.

The proposed trial is timely, as similar community services are now being commissioned for individuals released from prison. These may also be developed as a preventative service for individuals living in the community without criminal convictions. Having a proven, approved and well-understood medical pathway for adult men with PSA could have a major impact on society, potentially significantly decreasing the number of sexual offences committed each year, with a substantive associated decrease in harm and cost to society.

2.1 Assessment and management of risk

SSRIs in general, and fluoxetine in particular, are frequently prescribed for the treatment of depression, obsessive–compulsive disorder, panic disorder and other conditions in both general practice and secondary psychiatric services. Their side-effect profile is well known, and mild at the starting dose of 20mg once a day. Allowing for a 4-week period before dose increase both allows time for side effects to settle and also reduces the likelihood of side effects at the next dosage increment.

Common side effects are nausea and indigestion, diarrhoea or constipation, loss of appetite, headache, dizziness, blurred vision, sleep disturbance, chills, joint pain, rash, palpitations, restlessness, erectile dysfunction and delayed ejaculation. SSRIs can also result in reduced libido, which in this clinical application is one of our aims. There are reports suggesting that in some individuals, libido does not return after the cessation of therapy. SSRIs are known to increase the risk of bleeding because of their effect on platelets, but this is a concern primarily in women post-partum (thrombocytopenia is rare). It is also taken into account in patients prescribed anticoagulants.

Although not contraindicated, it is advised that SSRIs are used with caution in patients with a history of mania or epilepsy (albeit they should not be prescribed if an individual is in a manic phase of a bipolar disorder or with poorly controlled epilepsy, both of which are part of the exclusion criteria for the study).

A more serious but rare risk is serotonin syndrome, in which there is pyrexia, confusion, agitation and potentially fitting and loss of consciousness. This can occur if doses are high, or if other medication is prescribed that raises cerebral serotonin concentrations. Serotonin syndrome is highly unlikely to occur at the dose prescribed, and the trial protocol excludes patients who are taking drugs that might raise serotonin levels; however, if serotonin syndrome did occur, it should be detected in the early stages given that all patients are in a prison environment. Medication would be stopped if these symptoms were observed.

There are claims that SSRIs may increase suicidal ideation in individuals under the age of 25. This is controversial, and in any case, when described, this has mainly been in children or adolescents. All the patients in this trial will be over the age of 18.

Withdrawal effects have also been described. Fluoxetine has less of a risk of this when compared with other SSRIs because of its longer half-life. In most cases, gradual reduction in dose over a few weeks is sufficient to manage this issue.

In individuals with PSA, as indicated by high levels of sexual preoccupation and sexual compulsivity, SSRIs are reported to make sexual thinking and behaviour easier to manage. This results in a reduction in sexually harmful behaviour (to themselves and others) and allows the individual to focus on non-sexual goals. This is the potential benefit that is being tested in this study.

Because SSRIs are regularly prescribed by prison psychiatrists attached to the MMPSA service, no extra resources or staff training are required. Furthermore, we will not exceed the maximum recommended dose of 60mg.

The risk of any of the side effects described above is no greater than that present in standard practice. Doses and dose increments are those found in normal clinical practice, and the population is similar to those treated with SSRIs for other conditions in the prison environment.

Fluoxetine has been extensively studied in clinical trials in adults (n = 9297) and is well tolerated; the most commonly reported adverse reactions are insomnia, headache, nausea and diarrhoea. Safety will be assessed during the trial at study visits. Each patient's notes will indicate they are on a clinical trial to raise safety awareness for all other medical contact. Their consultations with the prescribing psychiatrist at the prison clinic will continue so that any side effects can be monitored and responded to. A DMC will assess safety periodically during the trial without unblinding the investigators.

This trial is categorised as: Type A = No higher than the risk of standard medical care.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The primary research question is whether the SSRI fluoxetine reduces PSA in males serving a custodial sentence who are referred to the MMPSA service.

We will also investigate whether fluoxetine increases the physical and mental health and wellbeing of adult males referred to the MMPSA service compared to placebo. We will also conduct an economic analysis of the effectiveness of fluoxetine in improving the quality of life of these patients.

The research project will also include a qualitative study examining the experiences and knowledge of prison staff referring people in prison to healthcare for medication to manage PSA. It will also examine barriers to and catalysts for referral by conducting interviews with prison staff. Thie qualitative study will begin at sites soon after the trial opens at those sites and run for approximately 12 months (or when 30 participants have been recruited). The outcome of this study may inform the recruitment processes and delivery of the RCT and may be used to produce recommendations for NHS (England) and HMPPS regarding the MMPSA pathway.

Most outcomes will be measured at three time points (baseline, three months after medication initiation, six months after medication initiation). For details of each step of the research pathway, please see Appendix 1. Clinical measures and side effects will be collated by the prescribing psychiatrist at each consultation and recorded on a Case Report Form (CRF) for the trial by a member of the trial team. Sexual Compulsivity Scale (SCS) scores, wellbeing measures, quality of life measures (patient-reported outcome measures – PROMs), anxiety and depression measures and paedophilic interest measures will be collated by a member of the research team or other authorised member of staff involved in the trial and analysed by the trial statistician.

All study designs including quantitative, qualitative and economic studies will be registered with the Open Science Framework.

3.1 Primary objective

The primary objective of this trial is to determine whether fluoxetine prescribed over 6 months is effective in reducing PSA in adult males referred to the MMPSA service when compared with placebo according to the trial-adapted **Sexual Compulsivity Scale** (**SCS**).

3.2 Secondary objectives

1. To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg daily) for reducing PSA in adult males referred to the MMPSA service at 3 months compared to placebo according to the trial-adapted **Sexual Compulsivity Scale** (**SCS**).
2. To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg daily) for improving wellbeing in adult males referred to the MMPSA service at 3 and 6 months compared to placebo according to the **Warwick–Edinburgh Mental Wellbeing Scale** (**WEMWBS**) for wellbeing.
3. To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg daily) for improving anxiety and depression in adult males referred to the MMPSA service at 3 and 6 months compared to placebo according to the **Hospital Anxiety and Depression Scale** (**HADS**) for anxiety and depression.
4. To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg daily) for reducing paedophilic and /or hebophilic interests in adult males referred to the MMPSA service at 3 and 6 months compared to placebo according to the **Problematic Sexual Interest Questionnaire (PSIQ).**
5. To assess the cost-effectiveness of fluoxetine compared to placebo using QALYs derived from the **EQ5D-5L** and the **SCS** at 3 and 6 months.
6. To understand the timing and motivations for change, prior help-seeking, and the service, treatment, and personal factors (including views on mandatory use, expectations, and expected continuation/discontinuation) that influence engagement with MMPSA collected in the Treatment Considerations questions in the PROMs booklet at baseline.
7. To understand participants' experiences, side-effects, wellbeing, and engagement over time while taking MMPSA, and how these factors influence continuation, perceptions of helpfulness, and evolving

views on voluntary versus mandatory use collected in the Experience and Impact section of the PROMs booklet at 3m and 6m.To understand the triggers for and/or barriers to referring someone for medication and understand any systemic or individual barriers to people continuing with a referral.

3.3 Outcome measures/endpoints

The primary outcome to measure is the efficacy of fluoxetine in reducing PSA in adult males referred to the MMPSA service as measured by the trial-adapted SCS. Secondary outcomes will measure the effect of fluoxetine on wellbeing and paedophilic intent in adult males referred to the MMPSA service and the cost-effectiveness of fluoxetine treatment. We will also investigate the processes around referrals to the MMPSA pathway using staff interviews. A summary of objectives and outcomes can be found in Table 1.

3.4 Primary endpoint/outcome

The primary clinical outcome is the trial-adapted SCS (Winder, Lievesley, Kaul, et al., 2014; Winder et al., 2017, 2023) at 6 months after medication is first commenced.

The SCS was developed to assess persistent, intrusive and poorly controlled sexual thoughts and behaviour. It has ten items scored from 1 (not at all like me) to 4 (very much like me), so the minimum possible score is 10 and the maximum possible score is 40. In HMPPS, an individual is referred for medication to manage their PSA if their total score is 15 or higher or if they score 3 or 4 on any one of the 10 SCS items. A reduction in SCS indicates a reduction in PSA. This scale has been reported as being valid and reliable for this population (Winder, Lievesley, Kaul, et al., 2014), and it is currently used as part of the MMPSA pathway evaluation by both prescribing Forensic Psychiatrists and this research team (Winder et al., 2017). This trial has adapted the SCS to change the timeframe of the questions being asked for the baseline, 3- and 6-month visits.

Objectives	Outcome measures	Timepoint(s) of evaluation
Primary Objective: To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg daily) for reducing PSA in adult males referred to the MMPSA service compared to placebo.	SCS	6 months
Secondary Objectives		
To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg daily) for reducing PSA in adult males referred to the MMPSA service compared to placebo.	SCS	3 months
To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg daily) for improving wellbeing in adult males referred to the MMPSA service compared to placebo.	WEMWBS	3 and 6 months
To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg daily) for improving anxiety and depression in adult males referred to the MMPSA service compared to placebo.	HADS	3 and 6 months
To determine the efficacy of fluoxetine (dose 20mg / 40mg / 60mg daily) for reducing paedophilic and /or hebophilic interests in adult males referred to the MMPSA service compared to placebo.	PSIQ	3 and 6 months
To assess determine the cost-effectiveness of fluoxetine compared to placebo in adult males referred to the MMPSA service	SF-SUS, EQ-5D-5L	3 and 6 months
To understand the timing and motivations for change, prior help-seeking, and the service, treatment, and personal factors (including views on mandatory use, expectations, and expected continuation/discontinuation) that influence engagement with MMPSA.	Treatment Considerations	Baseline
To understand participants' experiences, side-effects, wellbeing, and engagement over time while taking MMPSA, and how these factors influence continuation, perceptions of helpfulness, and evolving views on voluntary versus mandatory use.	Experience & Impact	3 and 6 months
To identify the triggers for referring someone for medication and understand any systemic or individual barriers to people completing a referral.	Qualitative	First 12 months of recruitment

Table 1. *Summary of objectives and outcomes for the trial.*

3.5 Secondary endpoints/outcomes

All **PROMs**, including the primary outcome measure described above, will be gathered at baseline, then at three and six months after medication is first commenced. Each outcome measure is listed below.

- The **Warwick–Edinburgh Mental Wellbeing Scale** (**WEMWBS**), which has been reported as being valid and reliable for this population in previous research (Kelley et al., 2022; Tennant et al., 2007) and is currently used as part of the MMPSA pathway evaluation by this research team, will be used to assess wellbeing. It consists of 14 positively phrased Likert items. The scoring range for each item is from 1–5 and the total score is from 14–70, with higher scores indicating greater wellbeing.
- The **Hospital Anxiety and Depression Scale** (**HADS**), which has been reported as being valid and reliable for this population in previous research (Winder, Lievesley, & Elliott, 2014; Zigmond & Snaith, 1983))and is currently used as part of the MMPSA pathway evaluation by this research team, will be used to assess anxiety and depression. This scale provides separate scores for anxiety and depression, with the minimum possible score for each sub-scale being 0, and the maximum being 21. Scores between 0–7 are interpreted as normal, 8–10 as mild, 11–15 as moderate, and 16 or over as severe.

- The **Problematic Sexual Interest Questionnaire (PSIQ)** will be used to measure paedophilic and /or hebophilic interests. The questionnaire has been adapted from the validated Pedophilic Fantasies, Desires, and Activities Questionnaire (PFDAQ; (Stoléru et al., 2020)). The authors have granted permission for it to be adapted for use in the prison setting and initial validation of the PSIQ will be done in a separate study with relevant approvals. Further validation and concurrent validation of the PSIQ will be undertaken during the trial.
- The **Treatment Considerations** and the **Experience and Impact** sections of the PROMs booklet will be used to understand referral behaviours by patients and their experiences of the MMPSA pathway.

Licences and permissions will be obtained for each measure. PROMs will be scored as per manualised instructions.

Clinical measures: Data collection forms developed by Grubin (2008) concerning masturbation, sexual preoccupation and ability to distract from sexual thoughts in the week before assessment will be used for this trial. Each item is scored on a ten-point Likert scale (Low–High). Data will be obtained by the prescribing psychiatrist as part of a clinical interview and will be triangulated with SCS scores. These measures are currently used by the prescribing Forensic Psychiatrists at each prison treatment site. We will also collect adaptive functioning (as assessed by the OASys Screening tool).

Compliance and psychological interventions: Record of any psychological interventions the individual has completed or is currently participating in. People in prison receive medication and healthcare through separate and different processes to psychological interventions, and there is very little, if any, interconnection between the two systems. The programmes department in prison will have a record of which psychological interventions a patient has participated in, is currently participating in, or is on the waiting list for. This information will be accessed, with appropriate consents from patients, through each prison's online records system.

Measure of compliance with medications: Healthcare staff administering standard care medications will complete patients' medication charts as per usual practice, detailing the extent of acceptance and refusal (with reasons, if known). The trial location PI or delegate along with the research team will collect concomitant medications in a log, and this will be cross-referenced with a daily log given to patients for them to record any medication they have been prescribed. We will also measure levels of fluoxetine in the patient's saliva samples at months three to six inclusive to provide objective evidence of compliance.

Economic evaluation: All health economics (HE)-related outcome measures will be gathered at baseline and at 3 and 6 months after medication is first commenced. Each HE outcome measure is listed below.

- **Secure Facilities Service Use Schedule** (**SF-SUS**) (adapted) will record the services used by patients for the economic evaluation (Barrett & Byford, 2007; Fonagy et al., 2020).
- The **EuroQol 5-Dimension** (**EQ-5D-5L**) five-level version will measure health-related quality of life (Nathan et al., 2019).

The economic evaluation will consider the cost-effectiveness of fluoxetine compared to treatment as usual in the treatment of PSA with the purpose of providing information to decision-makers in the criminal justice and healthcare systems. It will take a service perspective, including costs to the criminal justice system and health and social care services. Service-use data for the economic evaluation will be collected using a modified version of the SF-SUS (Barrett & Byford, 2007) that has been adapted for use in prisons. The SF-SUS collects information on patients' use of all services in prisons, including healthcare, psychological interventions, work (paid and voluntary), peer-mentoring roles, education and time spent in segregation. Data are collected from prison records and can also be collected in the daily log and during trial visits with the patient. Information on contact with the prescribing clinician regarding the dosage of fluoxetine will be collected from clinical records and the daily log completed by the patient. Despite the challenges of estimating costs in prison-based settings, every effort will be made to use the service-use data to apply a unit cost to each service-use item, so that an individual total cost per patient can be calculated.

The primary economic evaluation will be a cost-utility analysis using quality-adjusted life years (QALYs) as the primary outcome. QALYs will be calculated using utility data collected from the EQ5D-5L, which is a preference-based measure consisting of five questions with five levels of response; these are converted into utility-index scores ranging from 0 to 1, where a higher score indicates a better quality of life. While the EQ-5D is the preferred outcome measure of NICE (National Institute for Health and Care Excellence 2013) and

has been used in studies of similar populations (Nathan et al., 2019), we will also undertake a secondary cost-effectiveness analysis using the primary outcome measure, the SCS.

Sentence data: We will collect information about each patient's length of sentence, date of sentencing and release date, the reason for their conviction, the number and type of previous convictions, relevant reoffending risk measures, the prison security level, and whether they have completed any of their sentence in a therapeutic community.

Safety data: We will also monitor side effects and any illnesses or other medical conditions as documented in clinical notes and the daily log. These will be collected from consent and monitored at every trial visit until the final assessment at 6 months. Any illnesses reported by the patient to staff will be recorded on the **Adverse Event Log** and assessed by a medic named on the **trial delegation log** in accordance with Section 9 of the protocol. Any unexpected events will be followed up and reported during the course of the trial.

3.6 Exploratory endpoints/outcomes

There will also be a qualitative study that will analyse barriers to, and catalysts for, referring people in prison for medication to manage PSA, and to understand systemic or individual barriers to people referring patients or completing a referral. That study will commence as soon as the trial location is open to trial recruitment and will comprise interviews with approximately 30 prison staff who are in a position to refer people in prison for medication to manage PSA. Interview questions will include knowledge of the medication, signs that a patient is struggling with PSA and other behaviours that might relate to problematic sexual arousal (such as rule transgression, sexualised or violent behaviour, excessive time spent in cells, exhibitionist behaviour and quality of social interactions with others).

4. TRIAL DESIGN

The main study is designed as a double-blind randomised controlled superiority trial with two arms. Eligible consenting patients will be randomised to receive either fluoxetine or placebo, with follow-up assessments at 3 months and 6 months (see Appendix 1). PROMs and HE outcomes will be collected at baseline, 3- and 6-month assessments.

A qualitative study will be embedded within the RCT. This aims to analyse barriers to and catalysts for referring people in prison for medication to manage PSA and to understand systemic or individual barriers to people being referred or completing a referral. This aspect of the study will commence soon after the trial location is open to trial recruitment.

The first 12 months after recruitment begins will consist of a pilot to determine whether the trial protocol is suitable and if recruitment to the RCT is achievable.

4.1 Pilot phase (12 months)

Following Avery et al. (2017) and the Consolidated Standards of Reporting Trials (CONSORT) (Eldridge et al., 2016) extension to pilot trials, an internal pilot will be completed to assess the feasibility of the trial. The pilot will focus on the uncertainties around the processes of the main study to ensure that these are run smoothly over its life. Given the Co-CI's close involvement with the MMPSA pathway delivering fluoxetine, we anticipate that the uncertainties of the RCT will relate to recruitment, protocol adherence, robustness, and completeness of outcome data, follow ups and reporting.

Detailed and systematic reporting of pilot data will inform the decision-making process for stopping, amending or proceeding with the main study. Additionally, the pilot will inform the design, management and reporting of the main study and systematically track and document design modifications during the pilot trial to inform the decision about whether trial data can be pooled into the main study.

Internal pilot enrolment will start in all trial locations for 12 months to determine the viability of recruitment, randomisation, treatment and follow-up assessments. It is likely that issues, for example with recruitment or data collection, will vary across prisons, and solutions may be specific to the individual environment.

We will use red/amber/green (RAG) categories to assess recruitment throughout the pilot (12m). At least eight trial locations to be used in the assessment. Current sites of interest include HMP Grendon, HMP Whatton,

HMP Hull, HMP Isle of Wight, HMP Usk, HMP Leyhill, HMP North Sea Camp and HMP Frankland. These trial locations have been aggregated into three groups based on security status, number of treatment places and number of prisoners. Any trial locations identified since the trial was funded will not be factored into the assessment, as the assessment plan below was pre-agreed with the Funder.

- Group A comprises HMP Whatton and HMP North Sea Camp.
- Group B comprises HMP Hull, HMP Usk and HMP Grendon.
- Group C comprises HMP Isle of Wight, HMP Frankland, HMP Leyhill.

Average progression for patient recruitment will be calculated per trial location per month for the 42 months of data collection and aggregated per group, per quarter, following the progression criteria set out in Table 2.

Progression Criteria	Red	Amber	Green
Trial recruitment	<70%	≥70%	100%
Recruitment rate/group/quarter	<70%	>70%	100%
Number of trial locations opened	<70%	≥70%, <100%	100%
Total patients recruited	>70%	≥70%, <100%	100%
Completed intervention (based on trial recruitment numbers)	>70%	≥70%, <100%	100%
Protocol adherence	<80%	≥80%, <100%	100%
Data collection	>70%	≥70%, <100%	100%
Follow-up	>70%	≥70%, <100%	100%

Table 2. *Progression criteria per group, per quarter.*

Table 3 overleaf shows proposed recruitment by month for each trial location during the internal pilot phase. The TSC and TMG will consider a rolling version of the table with aggregated numbers so that RAG criteria can be considered by trial location and as a total from month seven onwards.

Supplementary data will also be gathered during the pilot and reported on, and this may inform the stop–go decision, but their primary function will be to inform the design and delivery of the main study. These data will include:

1. Safeguarding issues.
2. Patient and Public Involvement (PPI) group engagement.
3. Continuity of treatment between sites.
4. Dissemination.
5. Barriers to recruitment.

Supplementary quantitative and qualitative data will be reported using RAG criteria. Thresholds will not be set for classification of supplementary data – they will be assessed by the CIs and discussed with the Funder.

Table 3. Progression (RAG) criteria per site, per month, for the internal pilot as agreed by funder as part of the application. Any new trial locations taking part have not been added in below as the table was pre-agreed as part of the funding arrangement.

G: Green; A: Amber; R: Red.

RECRUITMENT MONTH	1			2			3			4			5			6		
Site	G	A	R	G	A	R	G	A	R	G	A	R	G	A	R	G	A	R
HMP Whatton	2	1	1	2	1	1	2	1	1	1	0	0	2	1	1	2	1	1
HMP Frankland	0	/	/	1	0	0	0	/	/	1	0	0	0	/	/	1	0	0
HMP Hull	1	0	0	0	/	/	1	0	0	0	/	/	1	0	0	0	/	/
HMP Isle of Wight	1	0	0	0	/	/	1	0	0	0	/	/	1	0	0	0	/	/
HMP Usk	0	/	/	0	/	/	0	/	/	1	0	0	0	/	/	0	/	/
HMP Leyhill	0	/	/	0	/	/	1	0	0	0	/	/	0	/	/	0	/	/
HMP North Sea Camp	0	/	/	1	0	0	0	/	/	0	/	/	1	0	0	0	/	/
HMP Grendon	1	0	0	0	/	/	0	/	/	1	0	0	0	/	/	1	0	0

(Table 3 continued)

RECRUITMENT MONTH	7			8			9			10			11			12			13 (if required)		
Site	G	A	R	G	A	R	G	A	R	G	A	R	G	A	R	G	A	R	G	A	R
HMP Whatton	2	1	1	2	1	1	2	1	1	2	1	1	2	1	1	2	1	1	2	1	1
HMP Frankland	0	/	/	1	0	0	0	/	/	1	0	0	0	/	/	1	0	0	0	/	/
HMP Hull	1	0	0	0	/	/	1	0	0	0	/	/	1	0	0	0	/	/	1	0	0
HMP Isle of Wight	0	/	/	0	/	/	1	0	0	0	/	/	0	/	/	0	/	/	0	/	/
HMP Usk	1	0	0	0	/	/	0	/	/	0	/	/	0	/	/	0	/	/	1	0	0
HMP Leyhill	1	0	0	0	/	/	0	/	/	1	0	0	1	0	0	0	/	/	1	0	0
HMP North Sea Camp	0	/	/	1	0	0	1	0	0	0	/	/	0	/	/	1	0	0	0	/	/
HMP Grendon	0	/	/	0	/	/	0	/	/	0	/	/	1	0	0	0	/	/	0	/	/

5. TRIAL SETTING

The RCT will take place within the healthcare centres of at least eight HMPPS sites with established services for prescribing MMPSA, working with NHS England and their Welsh counterparts, along with HMPPS staff. Other prisons offering the MMPSA pathway may also be considered for inclusion as trial locations.

Each of the prisons house adult males who have been convicted of sexual offences or have a sexual element to their offence. All but one of the selected prisons will be operated by HMPPS, simplifying the management of the project. The prisons for the RCT were chosen because they all currently provide access to fluoxetine for the treatment PSA. The provision of fluoxetine is managed under the MMPSA pathway, which will provide referrals to the RCT and enable the prescription of fluoxetine and placebo. The management of the delivery of medication will be trial location specific, and it will be driven by local security considerations and procedures that will consider not only the needs of the prison but also of each individual patient. As such, those on the RCT will be provided with treatment (fluoxetine or placebo) using well-established protocols with which they and the prison staff are familiar; there will be no special measures required to deliver the RCT medication.

Site staff involved in the trial will receive training from the trial team in accordance with their proposed role. Staff with full involvement require in depth training whereas other staff may only need an awareness of the trial. The trial handbook will elaborate on the training proposed.

The prisons likely to host the RCT are HMP Whatton, HMP Frankland, HMP Hull, HMP Isle of Wight, HMP Usk, HMP Leyhill, HMP North Sea Camp, HMP Ashfield and HMP Grendon. New sites, including non-HMPPS prisons, may be added with Funder permission if issues are identified with the set-up process or early recruitment during the pilot, or if general recruitment is lower than expected (several more MMPSA treatment sites have been set up in the Southwest of England since the trial was funded). These prisons provide a broadly representative sample of prisons in England and Wales, as they include those categorised as High Security, Category B, Category C, and open prisons, and Therapeutic Communities. This means that the RCT will have access to patients across a wide range of prisons at various stages of their sentence.

The qualitative study will take place in the same trial locations as the RCT and will involve interviewing prison staff.

6. PATIENT ELIGIBILITY CRITERIA

The target population for the RCT is 196 eligible men aged 18+ with a conviction who present with PSA and are referred to the MMPSA service to ensure that at least 118 complete the full 6 months of the trial. The sample of men eligible to enrol in the RCT will be resident in one of the trial locations in the RCT that prescribe fluoxetine as part of the existing medical treatment pathway. NHS (England) and HMPPS already fund MMPSA clinics (including the services of a Forensic Psychiatrist).

PSA will be diagnosed by the Forensic Psychiatrist or other specialist attached to each trial location following standard practice (which includes using the SCS) prior to the patient being confirmed as eligible for the trial.

The trial locations are spread throughout the UK prison estate and represent people at every stage of their custodial journey. Demographic information will be collated for each patient so that equality, diversity and inclusion information can be reported for consented patients, and this will allow examination of any differences between the demographics of the patients and those of the UK prison population as a whole.

6.1 Inclusion criteria (RCT)

The inclusion criteria for the RCT are as follows.

- Male.
- Aged 18+ years.
- Currently detained at one of the prison sites running the trial and referred to the MMPSA service

- Total SCS score of 15+ or a score of 3 or 4 on any one item.
- **Diagnosis of PSA made by a Forensic Psychiatrist or other relevant specialist.**
- **Clinician determination that it is appropriate to prescribe fluoxetine.**
- Understands written and verbal English sufficiently to have the trial explained to them.
- Has the capacity to give informed consent.
- Agrees to use appropriate contraceptive methods during the trial and for 6 months after.

Criteria in bold MUST be assessed by a medically qualified person.

6.2 Exclusion criteria (RCT)

Those meeting any of the following will be excluded from participating in the RCT.

- Current pharmacological treatment with an SSRI/anti-androgen/GnRH agonist.
- Contraindication to SSRIs.
- Major mental illness (e.g. schizophrenia or other psychotic disorders) if acutely unwell and therefore unable to give informed consent.
- Current manic or hypomanic episode; known bipolar I disorder; history of antidepressant-induced mania or hypomania.
- Patients with epilepsy.
- Currently prescribed medication that interacts with the 5-HT system, meaning it has serotonin effects.
- Currently on prophylactic medication that has an impact on sexual arousal.
- Known congenital long QT syndrome, known clinically significant arrhythmia, known cardiac disease and/or electrolyte disturbance predisposing to QT prolongation, and those requiring concomitant QT-prolonging medicinal products that cannot be discontinued or substituted.
- Clinically significant bleeding disorders or recent major gastrointestinal bleeding within the previous 3 months.
- Known significant hepatic impairment or known electrolyte disturbance (e.g., hypokalaemia, hypomagnesaemia) that may predispose to arrhythmia.
- Currently prescribed testosterone/oestrogen supplement therapy.
- Imminent risk of harm to self (specifically, on an open Assessment, Care in Custody and Teamwork) or to others (psychiatrist judgement of imminent risk) e.g., current suicidal ideation with intent/plan, recent suicide attempt within a defined timeframe, or acute safeguarding risk requiring urgent escalation is deemed too high to be randomised to placebo.
- Planned release date is within 9 months (including shortened sentences).
- Prison transfer to a prison where MMPSA is not available within the next 9 months is highly likely or actually planned.

6.3 Eligibility criteria (qualitative study)

Those eligible to participate in the qualitative study must be adults (18+) working in one of the FASAR trial sites. Eligible roles include prison officers, healthcare staff, psychologists, and programme facilitators. Individuals will be excluded if they are unable to give informed consent, are acting as the Single Point of Contact (SPOC) for the FASAR trial or have received FASAR-specific training at trial sites.

7. TRIAL PROCEDURES

This trial will adopt a Co-Principal Investigator (Co-PI) role framework whereby we will require one medically qualified PI and, if necessary, one other PI role can take operational responsibility for the trial.

The medical PI (typically the Forensic Psychiatrist or GP) is the only role who can confirm eligibility and conduct safety reviews of AEs, whereas a non-medical PI (if identified as necessary) will be responsible for the day-to-day running of the trial within the trial location and will liaise closely with the RAs to ensure

that trial procedures are followed and that the relevant documents are completed in a timely and accurate manner. The non-medical PI may be the MMPSA Treatment Manager, Forensic Psychologist or another member of staff at the trial location with sufficient oversight of the key processes. **All medical decisions must be made by a medical practitioner at the trial location authorised to do so on the trial delegation log.**

Patients will be recruited only from prison sites that currently offer MMPSA and that have been opened as trial locations (it is not possible for patients to travel between prisons). To maximise referrals and therefore recruitment to the RCT, NTU research staff may organise 'roadshows' throughout the duration of the study if recruitment is slower than expected. Members of the research team will travel to the trial locations and advertise and explain the MMPSA pathway as well as the RCT to staff and patients. The team will also organise staff-specific training on MMPSA, how to identity someone who may be appropriate for MMPSA and how to make referrals. The team may also opt to make use of prison radio, prison journals, libraries and prison newsletters to give information about the MMPSA pathway and the RCT throughout the duration of the trial using ethically approved wording or documentation where the trial is specifically mentioned.

A Patient and Public Involvement (PPI) group have been involved to discuss how to maximise referrals and recruitment at all participating prison sites. Any individual who chooses not to participate in the RCT will be asked if they would be willing to provide their reason(s) for this so that any issues can be raised with the trial team and PPI group and addressed quickly.

The process for consenting patients into the trial is two-fold. First, we need consent to access their records. If they are potentially eligible, we proceed with the second step and give them detailed information about the trial. If they agree to the trial's requirements, we receive consent from them.

For the qualitative study, participants will be recruited from the site prisons via a global (all-staff) email invitation. Additional recruitment methods may include posters in staff areas, direct contact via line managers or team leads, and presentations or briefings at staff meetings to raise awareness of the study and encourage participation.

7.1 Patient identification and consent to screen

Potential patients will be drawn from the population of adult males serving a custodial sentence. If they present with symptoms of PSA, they can self-refer (or a member of staff can refer them with their permission) for the MMPSA service at one of the trial locations.

All routine referrals will be submitted as per local guidelines where they are reviewed by the MMPSA Treatment Manager, MMPSA Single Point of Contact (SPOC), Psychologist or other qualified delegated person at the site. Where trial-specific activities are involved, this protocol will refer to these persons/roles as the FASAR SPOC. The delegation log must have all FASAR SPOCs listed and the roles they have been allocated. All must have received relevant training.

As part of the standard care process, the patient will be asked to complete the SCS to assist with determining whether they are eligible for the MMPSA pathway (as part of standard care). The FASAR SPOC may also decide to mention that there is a clinical trial they may be eligible for if they appear to be potentially eligible at first glance. If the FASAR SPOC does tell them about this research in the prison, the patient must be told that they may be eligible for the trial but that in order to officially check, we need them to consent to the trial team accessing the relevant information on the prison databases, systems and files. If they want to know more, the patient should be given the **Consent to Screen Information Sheet (CSIS)** to read. This sheet will only have high level information about the trial because we don't want to go into detail at this point in case they are not eligible. The types of checks will be listed on the **CSIS** so that they are aware of which data items we need to check, namely:

- Total SCS score of 15+ or a score of 3 or 4 on any one item.
- Not receiving medications that would be a contraindication for taking fluoxetine.
- No medical conditions that make them ineligible for the trial.
- Parole hearing/release date in no less than 9 months (including shortened sentences).
- Pre-planned prison transfer to a prison where MMPSA is not available within next 9 months.

The FASAR SPOC should also emphasise to the patient that non-prison staff such as Research Associates (RAs) from Nottingham Trent University (NTU) may also be involved in completing screening checks using their electronic records and that we will need consent for them to be allowed access.

If the patient consents to being screened, they must sign the **Consent for Screening Consent Form (CSCF)** which should be countersigned by a delegated member of the trial team. If the patient is unable to sign for themselves an independent witness can sign on their behalf.

7.2 Screening

7.2.1 Phase 1 screening (before discussing with the patient)

Once consented for screening, the patient must be added to the **Trial Enrolment Log** by the FASAR SPOC or RAs before screening checks can be started by persons delegated to do so on the delegation log. Eligibility will be documented on an **Eligibility Case Report Form** (**CRF**) for each patient. As different roles will have access to different systems, we require the initials of the person responding to each screening criterion to be recorded on the form. The **Enrolment Log** will be updated with the eligibility outcome and consent decision in due course.

PSA will be diagnosed by the Forensic Psychiatrist attached to each trial location following established protocols developed by the Co-CI and including the SCS questionnaire as part of standard care. The diagnosis must be within the last 3 months to be acceptable for inclusion into the trial. The SCS result recorded by the Forensic Psychiatrist will be used for eligibility assessment for the trial. The raw data from the SCS questionnaire will be captured retrospectively on the **Screening – SCS Confirmation CRF** for patients who consent to the trial but not for those who are not eligible or do not consent.

7.2.2 Phase 2 screening (during discussions with the patient)

If initial screening indicates that the patient is still currently eligible for the trial. The FASAR SPOC, Forensic Psychiatrist or other delegated person can discuss the trial in full with the patient using the **Patient Information Sheet (PIS).** The patient will be offered the chance to take the PIS away to their cell to read it in their own time and then ask questions.

If the patient is not initially eligible, the **Enrolment Log** should be updated and the patient told that they do not meet the criteria required.

During initial discussions about the trial with the patient, the patient will be asked:

a) Whether the patient is willing to use contraceptives if the opportunity for sex with a female arises while they are in the trial and for 6 months after.

b) Whether they understand what it would mean to be in the placebo arm (i.e. the possibility of no SSRIs for 6 months).

c) Whether they will agree to providing saliva samples at 4 time points (months 3-6 inclusive) to allow the trial to confirm that they have taken the trial medicine.

The person discussing the trial with the patient must decide whether the patient has the capacity to consent based on the full information provided. This should be confirmed by the Forensic Psychiatrist or other qualified medical specialist prior to confirming full eligibility.

Full eligibility checking should be started by the FASAR SPOC or delegate as soon as the patient has met the criteria listed in Section 7.1. The Forensic Psychiatrist will be informed of any potential trial patients so that they can also discuss the trial with them in full at their appointment where they will also re-check the patient's medical status, medications and capacity to consent as part of their role as a medic (required for a drug trial). The Forensic Psychiatrist must discuss the medication options (fluoxetine and placebo) with the patient in terms of safety so that the patient is fully aware of what side effects they may experience. The patients also need to understand the requirement to remain in the trial if they think that they are on placebo, although the right to withdraw will also be covered.

At the end of the appointment the Forensic Psychiatrist or medically qualified delegate must make a final eligibility decision for the patient and record this in the patient's records and the **Eligibility CRF**, which requires the medic's signature. The FASAR SPOCs and RAs should be notified ASAP of the eligibility decision. If the patient is eligible, arrangements should be made to receive consent if not already taken by the Forensic Psychiatrist. If they are not eligible, the **Enrolment Log** must be updated and the patient informed that they cannot take part in the trial.

7.3 Consent for the trial

At each site, there will be nominated persons responsible for discussing the trial and receiving consent from eligible patients e.g. a Forensic Psychiatrist, Forensic Psychologist, FASAR SPOC or RA. The

person(s) delegated responsibility to participate in the informed-consent process must be duly authorised, trained and competent to participate according to the ethically approved protocol, the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki (2024). The **Delegation Log** will list all trial location staff authorised by the (co-)PI to receive consent from a patient. Evidence of their trial-specific training must be recorded on a **Trial Location Training Log** as part of site training and initiation (or subsequent training if they get involved in the trial at a later date).

Informed consent must be obtained prior to the patient undergoing activities that are specifically for the purposes of the trial and are out-with standard routine care at the participating trial location (including the collection of identifiable patient data).

The PI(s) (typically the Forensic Psychiatrist) takes responsibility for ensuring that all vulnerable patients are protected and participate voluntarily in an environment free from coercion or undue influence.

This patient population may include people who cannot read or write or who have mild cognitive impairment. As such, appropriate alternative methods for supporting the informed-consent process can be employed. Moderate and severe cognitive impairment is an exclusion criterion for this trial. This may include allowing a witness to sign on a patient's behalf (in the case of problems with reading or writing) or allowing someone to date the form on behalf of the patient. The trial cannot support the provision of translators, so only patients with an understanding of verbal English should be approached. The capacity to consent means that the patient:

- can understand the purpose and nature of the research.
- can understand what the research involves, and its benefits (or lack of benefits), risks and burdens.
- can understand the alternatives to taking part.
- is able to retain the information long enough to make an effective decision.
- is able to make a free choice.
- is capable of making this decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity).

A standard consent procedure will be used with patients, in which the trial is explained verbally in simple terms, checking frequently for understanding. They will then be given a copy of the **PIS** to provide further information which they may take back to their cells and read in their own time and at their own speed. The PIS has a two-page summary section at the start to introduce the general concept of the trial to help understanding the requirements before the details are listed. They will usually be given up to a week to consider the invitation to participate and ask questions of the trial team or the RAs, but this can be extended if the relevant staff are not easily available. Prison staff will be given the contact details of the RAs in case a patient has non-medical questions.

If the patient is willing to proceed, a meeting will be set up to repeat the trial explanation and seek informed consent. The patient **Informed Consent Form** (**ICF**) will be initialled by the patient for each consent statement and a signature provided by the patient and person receiving consent. This person must be on the **Delegation Log** as being authorised to receive consent for the trial at that site. The person receiving consent does not need to be medically qualified, but there must be a medical decision of eligibility in the patient's notes before consent can be taken by a non-medic.

The **Enrolment Log** will be updated to reflect the consent decision. If the patient does not consent, the **Enrolment Log** will be completed to reflect this, along with any reasons provided for their decision. The **Enrolment Log** will be used to provide the number of potential patients available for the trial, showing how many were not eligible and why, how many consented and how many declined. The **Enrolment Log** must be emailed to the Trial Office at FASAR@swansea.ac.uk by the PI or their delegate, or an RA, every time a new person is added, or on a monthly basis as a minimum.

The right of a patient to refuse participation without giving reasons must be respected. Where possible, we will ask for any reasons for not wanting to take part that we can adapt the trial and enhance recruitment. Responding to this question will be optional.

Where a patient is able to consent but later becomes incapacitated, the management of these patients will be modified in accordance with the nature of the incapacitation. Typically, the original consent given endures the loss of capacity, providing that the trial has not significantly altered (there may be clinical justification under such circumstances for cessation of any further clinical intervention while data collection for follow-up purposes continues).

At the point of consent, the patient will be given a **Trial Membership Card** which will have key information on it. The patient will be advised that they should show the card when reporting any illnesses or symptoms of concern so that the prison staff are aware of the need to complete relevant trial documentation and alert the medical PI, FASAR SPOC and RAs to the situation.

For the qualitative study, interested individuals will receive a **Participant Information Sheet** outlining the study's purpose, procedures, and ethical considerations. Those who wish to take part will provide written informed consent, either in person or electronically, using a standardised **consent form** in line with approved ethical procedures.

7.4 Reimbursement

As per HMPPS requirements following their ethical review, no reimbursement of time to take part in the trial for patients will be offered.

We will offer £20 in e-vouchers for staff participating in interviews (approx. 30-40 mins) as part of the qualitative element of the trial.

7.5 Randomisation scheme

Patients will be randomised on a 1:1 basis, stratified by site. The randomisation service will be provided by Sealed Envelope Ltd. (https://www.sealedenvelope.com) in consultation with the statistician based at STU.

As randomisation is not time-sensitive, we do not anticipate trial locations being significantly affected if the web-based system unexpectedly failed. However, a backup randomisation service will be provided in exceptional situations by STU by emailing FASAR@swansea.ac.uk with a **randomisation request form**.

7.5.1 Method for implementing the randomisation/allocation sequence

After confirmation of patient eligibility and consent, the RA or other delegated person at the trial location will enter relevant patient data via the secure web-based randomisation system available 24 hours a day run by Sealed Envelope Ltd. When the data have been entered and validation rules have been met, the randomisation system will stratify patients according to the trial location they are recruited from, and a unique patient randomisation code will be generated. The system will provide an immediate confirmatory email to nominated trial location staff, the person randomising, the RAs and the Trial Office. The treatment allocation will not appear on the email, only the randomisation code.

Only the manufacturer (Sharp Clinical Services (UK) Ltd) and distributor of the medication (over-encapsulated fluoxetine or placebo tablets) will be aware of the treatment allocation, as all prison and healthcare staff and the trial RAs will be blinded. Sharp Clinical Services (UK) Ltd will have the code break list and prepare medication packs and labels which will not include the medication name to maintain the blind. A dispenser or other equivalent role at trial location pharmacies will dispense the blinded medication once the patient's name has been added to the label as required by prison sites. Trial location pharmacy staff will receive, store and dispense medication as it arrives from the distributor with no manipulation of boxes or their contents required unless it is to remove strips where a "dispense at the hatch" or 7-day allowance in cell is permitted for the patient. The psychiatrist will provide a trial-specific prescription at the start of the trial, then at weeks 4 and 8 which will reflect any changes to dose required. Trial medication will be provided to the trial location in time for the next scheduled dosing round in accordance with Section 8.8.

7.6 Blinding

All patients and prison, psychology and healthcare staff will be blinded to the trial allocation. Additionally, all trial team staff will also be blinded except for key STU staff involved with Investigational Medicinal Product (IMP) management and unblinded reporting for DMC and TSC meetings. Trial locations and Pharmacy staff with IMP-related questions will be advised to email COPE.MMSA@ntu.ac.uk with any queries that could potentially unblind the main trial team at STU or NTU. An unblinded section of the Trial Master File (TMF) will be set up by unblinded staff at NTU with restricted access until the end of the trial, when the section can be merged with the trial TMF held at STU. This section will hold unblinded reports, IMP-related information and pharmacy-related communications that the main trial team are not permitted to see during the trial.

Dosage and regimen of placebo and fluoxetine will be matched. There will be no discernible difference in appearance, weight, texture or smell between the over-encapsulated fluoxetine and the encapsulated placebo tablets.

The trial statistician will be blinded until the database has been locked at the end of the trial and the **Statistical and Health Economics Analysis Plan** (**SHEAP**) has been finalised. They will only be responsible for providing blinded data reports up to this time. An independent statistician at NTU will review the randomisation allocations at intervals to ensure that they follow the specification in the protocol and will assist in the production of unblinded reports for oversight committees (TSC and DMC).

All AEs will be reported blinded to the TMG. Unblinded Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will only be reported to independent members of the DMC. DMC discussion of unblinded SAEs and SUSARs will only involve independent members who may also invite the unblinded statistician to discuss the findings with them.

7.6.1 Unblinding

Final unblinding of all patients will take place after the creation of a locked analysis dataset and the finalisation of the **SHEAP**.

All patient allocations will be unblinded as each completes their 6m visit so that the Forensic Psychiatrist is aware of what they were given and can continue treatment accordingly. This information will be provided by the unblinded trial team staff who will link the Trial ID and the allocation and provide this to the trial location staff who will know the patient's name and can match it to the Trial ID of the patient. Any patient ending their participation in the trial early for any reason will also be unblinded to allow appropriate ongoing treatment by the Forensic Psychiatrist.

The Forensic Psychiatrist or other delegated person can let the patient know which treatment they had received in the trial during a follow up appointment to review their standard care medication requirements after the trial ends for them at 6m. It is important that a safety review of the patient is done by a qualified person as the patient is informed of their allocation at the 6m end of trial time point in case there are concerns about their response to what they were taking and how they feel about it.

Patients will be given a **trial certificate** as evidence of their participation in the trial which will also have their treatment allocation on it. The patient may ask for this to be uploaded onto their prison record to evidence their participation.

7.6.2 Emergency unblinding

Emergency unblinding (24/7) will be managed by Sealed Envelope Ltd. Training will be provided on how to request an unblind within the system. Researchers with access to Sealed Envelope can initiate an unblind with permission from the PI or delegate but are not unblinded themselves during the process. An unblinding email is sent to one nominated individual at the trial location for action.

The randomisation allocation should only be broken for valid medical or safety reasons, e.g. in the case of an SAE of importance. All emergency unblinding of SUSARs will be at the discretion of the trial location psychiatrist or other delegated person when clinically indicated for patient safety. If an emergency unblind occurs, STU will notify the Sponsor, relevant regulatory authorities and independent members of oversight committees. The unblinded staff at STU will manage all communication to reduce the number of Trial Office staff becoming aware of the allocation for that patient.

Details of the request must be documented using an **Unblinding Form** and stored in the Investigator Site File (ISF). A copy of the form must be emailed to the Trial Office at FASAR@swansea.ac.uk for filing in the TMF. This form does not have the allocation recorded on it, only the details of the reason for the unblind. Any unblinded documentation, e.g. the unblinding email, should be filed in the confidential section of the ISF by an unblinded person.

The actual allocation must **NOT** be disclosed to the patient and/or other study personnel unless necessary.

In the event that the web-based unblinding system is not available, trial locations should email a completed **Unblinding Form** the Trial Office at FASAR@swansea.ac.uk to trigger an unblind manually. Unblinded staff at STU will have access to Sealed Envelope Ltd to facilitate the unblind.

If emergency unblinding is delayed, **the treating clinician should treat the patient as if the active drug has been given.**

7.7 Trial assessments

Appendix 2 describes the data being collected and the timepoints for those assessments.

7.7.1 Patient characteristics

Key data variables will be accessed at baseline using the relevant prison databases (including OASys and P-NOMIS). Demographic variables will include age, ethnicity, nationality, religion, sexual orientation, relationship status, qualifications, adaptive functioning measures, sexual reoffending risk measures such as OSP and Risk Matrix 2000s (RM2000s) and variables pertaining to institution history, offence history and psychological intervention history.

7.7.2 Patient reported outcome measures (PROMs)

PROMs outcomes will be measured at three time points: baseline, 3 months after baseline and 6 months (primary outcome) after baseline. PROMs will be scored as per manualised instructions. The SCS and clinical measures of PSA will be administered at the three time points by the RA or other delegated person(s) at trial visits. While the SCS is collected by the Forensic Psychiatrist as part of their clinical review and will be used to screen the patient, a baseline SCS will be given to the patient to complete by the RA or delegate for the trial. The trial SCS to be completed at baseline, 3m and 6m has been adapted from the routinely used SCS by adding a timeframe within which patients can consider their more recent symptoms and feelings.

PROMs collected from the patient at baseline, 3m and 6m will include:

- Sexual Compulsivity Scale (SCS) score (SC Kalichman, 2013) The SCS has been amended (with Dr Kalichman's permission) by the trial team. The revised version specifically asks about how the participant has felt in the last 30 days, to align with the other PROMs. Question 10 has also been slightly amended to reflect the trial population.
- The Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)© (Tennant et al., 2007) score.
- Hospital Anxiety and Depression Scale (HADS) score (Zigmond & Snaith, 1983).
- Problematic Sexual Interests (PSIQ) score (novel questionnaire designed for this trial) (paper to be published).
- Treatment Considerations. (baseline) To understand the timing and motivations for change, prior help-seeking, and the service, treatment, and personal factors (including views on mandatory use, expectations, and expected continuation/discontinuation) that influence engagement with MMPSA.
- Experience and Impact (follow up). To understand participants' experiences, side-effects, wellbeing, and engagement over time while taking MMPSA, and how these factors influence continuation, perceptions of helpfulness, and evolving views on voluntary versus mandatory use.

7.7.3 Health economics

We will also collect data on:

- Secure Facilities Service Use Schedule (adapted for this trial) from Barrett & Byford 2007 (Fonagy et al., 2020).
- EuroQol 5-Dimension 5-level version (Herdman et al., 2011)
- Psychological or other interventions the individual has completed or is currently participating in.

7.7.4 Medication and illnesses

Any possible side effects documented in clinical notes and patient daily log will be collected from the point of consent and monitored at every patient appointment until the final trial visit at 6 months. Any illnesses and medication reported by the patient since the previous visit will be recorded and assessed in accordance with Section 9 of the protocol. Any unexpected events will be followed up and reported during the course of the trial. As patients will most likely be continuing/starting fluoxetine treatment after the trial, we will not follow up on persisting side effects that were not classified as serious during the 6 months of the trial.

7.7.5 Other data

- Clinical measures concerning masturbation, sexual preoccupation and ability to distract from sexual thoughts in the week before assessment, collected at baseline, 3m and 6m.
- Measure of adherence with medications using saliva tests (Soares et al., 2021) to be taken at months 3, 4, 5 and 6.

As RAs may be at trial locations for patient visits they may opt to conduct ad hoc checks on other patients at trial locations using electronic records e.g. adverse event checks.

7.8 Long-term follow-up assessments

No long-term assessments beyond 6 months will be conducted in this trial. We may seek separate consent from each patient to be contacted in the future about additional research projects when they reach their 6m visit and complete the trial. This consent will be optional and will not affect their participation in this trial.

7.9 Qualitative assessments

The qualitative study embedded within this RCT will analyse barriers to and catalysts for referring people in prison for medication to manage PSA; this will help to understand systemic or individual barriers to people being referred or continuing with a referral. This qualitative study will commence soon after the trial opens at a trial location and will run for approximately 12 months.

It will comprise interviews with 30 prison staff across all trial locations who are in a position to refer people in prison for medication to manage PSA. Interview questions will include knowledge of the medication, signs that a prisoner is struggling with PSA, other behaviours that might relate to problematic sexual arousal (such as rule transgression, sexualised or violent behaviour, excessive time spent in cells, exhibitionist behaviour and quality of social interactions with others). A sample of 30 participants for the study will allow a broad dataset from which to explore consistent themes that will be analysed thematically to provide practical guidance relating to the referral and recruitment process.

Data will be analysed using reflexive thematic analysis (TA). Reflexive TA is highly regarded for its flexibility in working with qualitative data to identify, analyse, and interpret patterns that offer detailed insights into participants' experiences (Braun & Clarke, 2022).

Data collection will commence in the pilot stage of the research programme to inform recruitment strategies for the project. Data may be collected remotely (where staff prefer to be interviewed via a remote platform) or in person, either at NTU or in prison. Data will be stored on NTU Secure Drive, in compliance with the General Data Protection Regulation (GDPR). The qualitative study will start as soon as trial locations are open to trial recruitment and run for approximately 12 months. Anonymous documentation relating to the qualitative study will be filed separate to the TMF, including material requiring ethical approval and Interview transcripts to maintain confidentiality, and a file note will be written in the STU TMF to indicate where those files will be held at NTU.

We will aim to produce recommendations for NHS (England) and HMPPS regarding the medication to manage sexual arousal pathway for people serving a custodial sentence for a sexual offence.

7.10 Withdrawal criteria

A patient may terminate their participation in the trial at any time without giving a reason and with no personal disadvantage. Withdrawal can occur as follows:

- **At any time:** Patient withdrawal of consent; withdrawal of patient by the CI, PI or delegate at site; early termination of the trial at the request of the TSC/Sponsor.
- **After receipt of first dose:** To be considered by DMC in case of potential SAE attributable to the IMP.

Where possible, a patient will be withdrawn from only the treatment itself and will be invited to attend trial follow-up visits to obtain outcome data in accordance with the planned analysis, but they will have the option to decline this.

The Sponsor has the right to terminate this study at any time. In terminating the study, the Sponsor and the CI will ensure that adequate consideration is given to the protection of the patients' interests.

If the study is terminated, patients who are already enrolled will be encouraged to attend all subsequent visits so that safety information may be collected. If it is not possible for a patient to attend all subsequent visits, the patient will be asked at least to undergo safety assessments until the 6-month visit.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform the CI. The Sponsor will also promptly inform the relevant regulatory authorities of any urgent safety measures or the suspension/termination and of the reasons for this action.

Patients will usually be withdrawn from treatment if they do not follow the dosing regimen prescribed (see Section 8.13). If this has been identified by reviewing the daily log, the RA or delegated trial location staff should discuss the adherence issue with the CIs as soon as possible, providing reasons why the deviation has occurred where possible. The patient may need to be withdrawn if they are not taking the trial medication they have been allocated in sufficient quantities to see a clinical effect. Patients should be alerted to this possibility when they are informed about the trial, and trial visits should ensure where possible that dosing can be adhered to wherever possible. Non-adherence measured using the saliva samples will only be identified at the end of the trial. The statistician will be alerted to these patients so that they can be accounted for in the analysis.

The patient must remain free to withdraw from the trial at any time without giving reasons and without prejudicing their future treatment. They must be provided with a contact point where they may obtain further information about the trial. Data collected up to the point of withdrawal will be retained for analysis. Any intention to use such data will be outlined in the consent literature. Where a patient is required to re-consent or new information needs to be provided to them, it is the responsibility of the PI or other delegated person to ensure that this is done in a timely manner.

Participants for the qualitative study may withdraw their consent up to two weeks after their interview. They will be given information on how to do this and advised they will not need to repay the voucher they have received if they choose to do so.

7.11 Storage and analysis of clinical samples

We will use saliva samples to measure the levels of fluoxetine in the patients' bodies at months 3, 4 5 and 6 so that we capture fluoxetine levels once the dose titration has been completed (approx. week 8) and the patient's body has the appropriate dosing. Patients will be made aware of this requirement prior to consent and will be informed that fluoxetine is the only substance being tested for and that the test will be done at CatSci Ltd laboratory (https://catsci.com/). The sample will not be used by any prison, interventions or healthcare staff.

Saliva (drool or spit) will be collected in a pre-labelled tube, and the tube will be sealed prior to posting to the designated laboratory along with relevant sample forms containing the patient's Trial ID and the date of the sample.

Once the sample arrives at the labs it will be frozen, and batch tested at the end of the trial to determine whether patient given fluoxetine had sufficient levels in their bodies to be considered compliant with the trial prescription. A selection of placebo patient samples will also be included in the analysis to check the reliability of the testing. Results will be held in a separate database and sent to unblinded STU staff who will provide relevant advice on compliance for the analysis. The database will be merged with the main trial database for final analysis once both are locked. Residual samples will be disposed of by the laboratory.

7.12 End of trial

7.12.1 End of patient participation at 6m

Once patients complete the 6m data and sample collection visit, they have completed the trial and can be returned to standard care. As the Forensic Psychiatrists will not know what they had been prescribed for the trial, the trial team will notify them of the treatment allocated so that they can:

a) continue treatment with no dose change if they had been allocated fluoxetine.

b) Change of medication if previously on fluoxetine but different medication needed.

c) restart dose titration if they had been allocated the placebo and are now due to start fluoxetine.

The Forensic Psychiatrists will be notified by letter and any other messaging system deemed important by each site, of the patient completing their 6m visit and a copy of the notification must be stored with the patient's medical records.

7.12.2 Premature end of patient participation prior to 6m

Some patients may opt to withdraw from the trial or have a medical decision to withdraw them prior to the final visit at 6m. A withdrawal CRF must be completed to reflect the nature of the withdrawal and reason(s) why if given.

The patient should return to standard care as soon as possible. Any SAEs or SARs will still need to be followed up to resolution.

7.12.2 End of the trial

The end of trial data collection is defined as the last follow-up data collection point (i.e. last patient, last visit) for the last patient recruited and retained in the trial.

The end of the trial itself will be defined as one year after the database has been locked to allow adequate time for analysis.

The authorising REC, and the MHRA will be notified by the Sponsor or delegate of the end of the study within 90 days of completion of the trial or within 15 days in the case of an early termination.

8. TRIAL TREATMENTS

Sharp Clinical Services (UK) Ltd have provided a simplified Investigational Medicinal Product Dossier (IMPD) for this trial based on fluoxetine (Flamingo Pharma (UK) Ltd), the placebo (microcrystalline cellulose, (Sharp Clinical Services (UK) Ltd), the material needed to over-encapsulate them and the blister packs.

8.1 Intervention – Fluoxetine 20mg capsules

Appearance: Capsule form. The original form from Flamingo Pharma (UK) Ltd is a blue and white capsule marked with 'R9' and are provided in a blister pack made from clear PVC film with a backing of aluminium foil.

Dose: Each capsule tablet contains fluoxetine hydrochloride equivalent to 20mg fluoxetine.

Expiry: Capsules have a shelf life of three years.

IMPD info: The SmPC for fluoxetine within the IMPD is dated 08-Apr-2022.

The IMPD states that as more than one campaign is necessary during the trial, other brands of fluoxetine may be used if the brand above is not available.

8.2 Placebo - Microcrystalline cellulose

Appearance: The placebo is a Swedish Orange, size 0 gelatin capsule containing a Microcrystalline Cellulose fill and will be manufactured by Sharp Clinical Services (UK) Ltd.

Expiry: Capsules have a shelf life of four years.

8.3 Encapsulation

Both fluoxetine and placebo will be identically over-encapsulated using standard bovine hard gelatin capsules size 0, Swedish orange (Capsugel ®) to conceal the tablet identity, matching appearance, texture, smell and weight.

The simplified IMPD states that encapsulation of the Fluoxetine 20mg capsule is not expected to have any significant effect on the dissolution profile of the drug product. Gelatin shells are an immediate release capsule therefore comparative dissolution testing is not deemed necessary.

Microcrystalline Cellulose has been chosen to back-fill the capsules.

The expiry of the over-encapsulated capsules for fluoxetine and the placebo will have the lowest expiry date of the input materials used.

There is a known nitrosamine risk with Fluoxetine. Microcrystalline cellulose may contain nitrite, which can contribute to nitrosamine formation in drug products. A summary of the drug product nitrosamine risk assessment should be provided. This should have considered the key areas of potential risk with the overencapsulation process and addition of microcrystalline cellulose. Where a risk of presence/formation of a nitrosamine impurity is identified, the risk assessment should be submitted in full for assessment and additionally include information about the potential risk to trial participants, the risk mitigation steps taken and any control limits introduced.

8.4 Blister packs

Fluoxetine 20mg capsules and matching placebo capsules will be blister packed in PVC/PVDC (250/60) film with a 20micron foil seal.

8.5 Regulatory status of the drug

The Marketing Authorisation (MA) Holder for fluoxetine is Flamingo Pharma (UK) Ltd, MA number PL 43461/0053. It was first authorised on 21 Feb 2018 and the current SmPC in use was updated 08-Apr-2022.

Fluoxetine is used off-licence in this trial, although it is licensed and marketed in the UK for the treatment in adults of conditions including major depressive episodes/disorders, obsessive-compulsive disorder and bulimia nervosa.

Sharp Clinical Services (UK) Ltd (www.sharpservices.com, based in Tredegar, UK) will be responsible for the over-encapsulation and the provision of a matching placebo. They will also produce the packaging for both to ensure that both are identical in appearance and packaging. The simplified IMPD they have provided (dated 31-Jul-2025) will be used for this trial.

8.6 Product Characteristics

No Investigator Brochure is required for this trial. A simplified IMPD will be provided by Sharp for fluoxetine and placebo. Section 4.8 of the SmPC for fluoxetine will be used for Reference Safety Information (RSI) in this trial.

Should a new version of the fluoxetine SmPC be issued during the Development Safety Update Report (DSUR) period, a documented risk assessment will determine whether the RSI used for the trial requires updating. Any update will consider the impact on the DSUR. A modification will be submitted and authorised before any new RSI is implemented.

8.7 Drug storage, supply and destruction

Sharp will be contracted to produce a specific number of over-encapsulated fluoxetine and matching placebo tablets. At least two campaigns of IMP production will be necessary due to expiry dates.

Sharp will provide blister packs of 7 over-encapsulated capsules (fluoxetine or placebo). There will be 4 blister packs put into one carton. Medication will be ordered in two stages per patient: baseline at the point of randomisation and a follow up shipment which will be triggered no later than week 12 to ensure there is no gap in medication for the trial. Each shipment will have 9 cartons to allow sufficient medication for a possible maximum dose of 60mg at week 8 for each patient.

Fluoxetine when not over-encapsulated has a shelf life of 36 months from manufacture. Any adjustments to this due to the over-encapsulation process will be factored in when ordering campaigns from the manufacturer. The fluoxetine SmPC does not detail any special requirements for storage for the original tablet and blister pack.

Sharp will be responsible for the distribution of cartons of blinded IMP to sites triggered by a randomisation notification from Sealed Envelope. They will assign kits based on specified kit codes provided via Sealed Envelope.

The kits and blister strips will be labelled as per CTIMP requirements and will have a space for inserting the patient's name added by the site on receipt. This is a requirement for prisons receiving trial medication.

Site pharmacies will be notified of a patient consenting by the NTU research team. The site will be told the name of the patient and their Trial ID. Once the patient has been randomised, the site pharmacy will be contacted again with the kit codes assigned at randomisation so that they can place an order with Sharp. The site pharmacies will receive a copy of the randomisation email as a second source of this information. On receipt of the trial medication, the site will notify NTU@swansea.ac.uk of the trial medication arriving. The trial **Pharmacy Manual** will describe the process for receiving, checking and storing trial medication and for adding the patient's name to the trial label on the boxes. The Pharmacy staff do not need to know which medication someone has been allocated but they do need to match the kit codes and Trial ID on the shipment from Sharp with the patient's name to ensure that it goes to the correct person. Any queries during this process should be directed to COPE.MMSA@ntu.ac.uk.

Per patient deliveries of blinded kits will have two shipments of 9 cartons, one at baseline and one at approx. week 13 to reduce possible wastage of medication.

The trial team will advise the pharmacy if the patient is still in the trial prior to the baseline kit running out at week 15 to allow enough time for the second order to be placed, shipped and received.

Any unused trial medication should be returned to the trial location Pharmacy who will follow local regulations for the destruction of medication. The destruction of unused IMP must be documented on trial forms which must be sent to FASAR@swansea.ac.uk in real time.

8.8 Dosage schedules

Patients will begin at 20mg as their first dose as soon as possible after randomisation and the trial prescription being issued. The actual date of dose 1 will depend on how long it takes to ship the blinded medication to the trial location and for the trial location pharmacy to receive and process it in accordance with trial requirements. At the point when the patient is first called for their medication, we will identify this as Week 1. They will begin at 1 tablet (i.e. 20mg) daily. Week 4 will be planned as 4 weeks after dose 1 is dispensed.

At 4 and 8 weeks after dose 1 (+/- 2 weeks according to when routine follow up visits occur), the Forensic Psychiatrist or other delegated person will conduct assessments to determine whether the dose needs to be increased as outlined in Section 8.9.

Any patients deemed to be at high risk of taking multiple medication doses are given a daily dose and not permitted to have medication in their cell.

8.9 Dosage modifications

Dosing will be reviewed at Weeks 4 and 8 to determine whether the current dose needs to be increased by 20mg. The maximum dose permitted per prescription is 60mg. Therefore, patients can only be prescribed 20mg, 40mg or 60mg of blinded medication. The psychiatrist will be blinded to the treatment allocated so the assessments will be based on medical opinion and feedback from the patient.

Tablets will be prescribed by the psychiatrist and dispensed in accordance with the risk assessment performed for each patient. Patients may be offered one of the following options:

1) 28d course of tablets provided to be kept in their cell.
2) 7d course of tablets provided to be kept in their cell.
3) Daily dispensing by attending the Pharmacy Dept or other dispensing location at the trial location (if the patient is deemed high risk and cannot be given medication to keep in their cell).

In the event of a lockdown, it should be possible for medication to be brought to the patient's cell. A missed dose due to lockdown can be recorded by the patient in their daily log. If a dose is missed due to issues at the trial location e.g. lockdown or lack of access to healthcare, Pharmacy resources, etc, the RAs should be informed as soon as possible in case there is the potential for a longer-term issue with medication not being available.

Treatment may be stopped for a patient if there is a medical need (adverse reaction or need to introduce a contraindicated medication with a higher medical need), if they transfer to a prison not offering the MMPSA pathway or if compliance is an issue.

If a patient has stopped taking the IMP allocated for more than 5 days, they cannot restart it and should be withdrawn from taking the trial treatment as potential benefit will be difficult to prove. In such

instances, where feasible, the patient can still continue to complete trial questionnaires and the daily log if they wish to.

8.10 Treatment discontinuation

There may be instances whereby the IMP may need to be stopped, either as a planned tapering of dose or immediate cessation. Discontinuation criteria include:

- Any clinically relevant sign or symptom that, in the opinion of the Investigator (or delegated medically qualified clinician), warrants stopping the IMP **- Immediate cessation**.
- Any serious or intolerable adverse event that prevents continued IMP administration **- Immediate cessation**.
- Any change in compliance with inclusion or exclusion criteria that is clinically relevant and affects participant safety **- Immediate cessation**.
- Development of seizures **- Immediate cessation**.
- Suspected or confirmed serotonin syndrome **- Immediate cessation**.
- Severe cutaneous reactions, rash with systemic features, or hypersensitivity reactions where no alternative aetiology is identified **- Immediate cessation**.
- Clinically significant cardiac arrhythmia or other clinically significant ECG abnormality **- Immediate cessation**.
- Clinically significant drug–drug interaction requiring cessation of fluoxetine **- Immediate cessation**.
- Emergence of mania or hypomania.
- Any intercurrent illness or condition that significantly alters the risk–benefit balance of continued IMP exposure.
- Treatment failure or lack of tolerability where continued IMP use is not clinically appropriate.

In non-emergent discontinuation scenarios, fluoxetine should be tapered in accordance with SmPC recommendations, with a defined tapering schedule (e.g. gradual dose reduction over at least 1–2 weeks).

Where discontinuation is required, the participant will be asked whether they want to withdraw from the trial in full or only from treatment (and continue to participate in saliva sample collection and questionnaire completion)

The responsibility for clinical review lies with the Forensic Psychiatrist care reviews for SSRIs at the start of treatment. Any adverse events that may be related to the IMP dose at any time during the patient's 6 months in the trial should be immediately directed to the Forensic Psychiatrist for urgent consideration. Changes to dose must be reflected in an amended prescription and the Trial Office must be immediately notified of the change and the justification for it.

Where possible, the Forensic Psychiatrist should assume that the patient is taking fluoxetine rather than the placebo and avoid the need for unblinding wherever possible (see Section 7.6.2).

8.11 Known drug reactions and interaction with other therapies

The long elimination half-lives of both fluoxetine and norfluoxetine (metabolite) should be borne in mind when considering pharmacodynamic or pharmacokinetic drug interactions (e.g. when switching from fluoxetine to other antidepressants).

8.11.1 Contraindicated combinations

Irreversible, **non-selective monoamine oxidase inhibitors** (e.g. iproniazid): Some cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with an irreversible, non-selective monoamine oxidase inhibitor (MAOI). These cases presented with features resembling serotonin syndrome (which may be confounded with [or diagnosed as] neuroleptic malignant syndrome). Cyproheptadine or dantrolene may benefit patients experiencing such reactions. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. Therefore, fluoxetine is contraindicated in combination with an irreversible, non-selective MAOI. Because of the two-week lasting effect of the latter, treatment of fluoxetine should only be started two weeks after discontinuation

of an irreversible, non-selective MAOI. Similarly, at least five weeks should elapse after discontinuing fluoxetine treatment before starting an irreversible, non-selective MAOI.

Metoprolol used in cardiac failure: Risk of metoprolol AEs, including excessive bradycardia, may be increased because of an inhibition of its metabolism by fluoxetine (see Section 4.3 of the RSI).

8.11.2 Non-recommended combinations

Tamoxifen: Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65%–75% reduction in plasma levels of one of the more active forms of the tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including fluoxetine) should whenever possible be avoided.

Alcohol: In formal testing, fluoxetine did not raise blood alcohol levels or enhance the effects of alcohol. However, the combination of SSRI treatment and alcohol is not advisable.

MAOI-A including linezolid and methylthioninium chloride (methylene blue): Risk of serotonin syndrome including diarrhoea, tachycardia, sweating, tremor, confusion or coma. If concomitant use of these active substances with fluoxetine cannot be avoided, close clinical monitoring should be undertaken, and the concomitant agents should be initiated at the lower recommended doses.

Mequitazine: Risk of mequitazine AEs (such as QT prolongation) may be increased because of an inhibition of its metabolism by fluoxetine.

8.11.3 Combinations requiring caution

Phenytoin: Changes in blood levels have been observed when combined with fluoxetine. In some cases manifestations of toxicity have occurred. Consideration should be given to using conservative titration schedules of the concomitant drug and to monitoring clinical status.

Serotoninergic drugs (lithium, tramadol, triptans, tryptophan, selegiline (MAOI-B), St. John's Wort [Hypericum perforatum]): There have been reports of mild serotonin syndrome when SSRIs were given with drugs also having a serotoninergic effect. Therefore, the concomitant use of fluoxetine with these drugs should be undertaken with caution, with closer and more frequent clinical monitoring.

QT interval prolongation: Pharmacokinetic and pharmacodynamic studies between fluoxetine and other medicinal products that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicinal products cannot be excluded. Therefore, co-administration of fluoxetine with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine), anti-malaria treatment particularly halofantrine and certain antihistamines (astemizole, mizolastine), should be undertaken with caution.

8.11.4 Buprenorphine-containing medicinal products

Fluoxetine should be used cautiously when co-administered with buprenorphine-containing medical products, as the risk of serotonin syndrome, a potentially life-threatening condition, is increased.

Drugs affecting haemostasis (oral anticoagulants, whatever their mechanism, platelet anti-aggregants including aspirin and NSAIDs): risk of increased bleeding.

Clinical monitoring, and more frequent monitoring of INR with oral anticoagulants, should be made. A dose adjustment during the fluoxetine treatment and after its discontinuation may be suitable (see Sections 4.4 and 4.8 of the RSI).

Cyproheptadine: There are individual case reports of reduced antidepressant activity of fluoxetine when used in combination with cyproheptadine.

Drugs inducing hyponatremia: Hyponatremia is an undesirable effect of fluoxetine. Use in combination with other agents associated with hyponatremia (e.g. diuretics, desmopressin, carbamazepine and oxcarbazepine) may lead to an increased risk (see Section 4.8 of the RSI).

Drugs lowering the epileptogenic threshold: Seizures are an undesirable effect of fluoxetine. Use in combination with other agents which may lower the seizure threshold (for example, tricyclic antidepressants (TCAs), other SSRIs, phenothiazines, butyrophenones, mefloquine, chloroquine, bupropion, tramadol) may lead to an increased risk.

Other drugs metabolised by CYP2D6: Fluoxetine is a strong inhibitor of CYP2D6 enzyme; therefore, concomitant therapy with drugs also metabolised by this enzyme system may lead to drug interactions, notably those having a narrow therapeutic index (such as flecainide, propafenone and nebivolol) and those that are titrated, but also with atomoxetine, carbamazepine, tricyclic antidepressants and risperidone. They should be initiated at or adjusted to the low end of their dose range. This may also apply if fluoxetine has been taken in the previous five weeks.

8.12 Concomitant medication

If a patient is currently being prescribed (or is due to be prescribed) any of the contraindicated medications listed in Section 8.10, they should not be considered for the trial.

All medications prescribed at the start of the trial will be recorded, along with any changes to medication (additions, changes and removals) until the final 6-month visit.

Any medical care requiring prescribed medication for the patient should consider the possibility that the patient may have been allocated fluoxetine prior to that care being given.

8.13 Trial restrictions

No dietary restrictions or requirements apply.

Fluoxetine has no or negligible influence on the ability to drive and use machines. Although fluoxetine has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive medicinal product may impair judgement or skills. Patients should be advised to avoid operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients will be asked to take the relevant precautions to avoid making someone pregnant. This restriction will only apply to patients on Release on Temporary License (ROTL) who may be given day release if eligible.

8.14 Assessment of compliance with treatment

We will determine adherence by counting tablets in packs for those patients permitted to have medication in their cells. For those getting a daily dose dispensed at a dispensing hatch, the dispenser will record whether the patient completely swallows the medication on a **trial dispensing form**.

Patients need to have taken 75% of their medication in accordance with the instructions provided to be considered as adhering to the protocol.

The RA will compile information on reasons for drop-out or treatment non-adherence. If there has been a protocol deviation, the trial location will be asked to report this on a **Protocol Deviation Form** and to email it to the Trial Office at FASAR@swansea.ac.uk for internal review (see Section 13.5).

Non-compliant patients whose access to IMP is stopped can still be included in trial data collection if they agree to continue to provide data.

8.15 Name and description of each Non-Investigational Medicinal Product (NIMP)

Not applicable.

9. PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a patient to an IMP which is related to any dose administered to that patient. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as ARs. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	Any untoward medical occurrence that: • results in death. • is life-threatening. • requires inpatient hospitalisation or prolongation of existing hospitalisation. • results in persistent or significant disability/incapacity. • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the patient or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An AE that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • In the case of a product with a marketing authorisation, this could be in the SmPC for that product, so long as it is being used within its licence. If it is being used off label, an assessment of the SmPC's suitability will need to be undertaken. • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

Table 4: Definition of adverse events in clinical trials

9.2 Operational definitions for (S)AEs

The risk of major adverse unexpected events is anticipated to be low, as fluoxetine has a marketing authorisation for use in adults with major depressive episodes and/or obsessive–compulsive disorder. There is therefore wide experience with drug exposure, and it has been found to be well tolerated. The available **Summary of Product Characteristics (SmPC)** describes all essential information for the use of the medicine, and the qualitative and quantitative information on benefits and risks.

Expected AEs and ARs from the IMP are listed below and will be reported on an **Adverse Event** (**AE**) **Log**. There is no requirement for the reporting of AEs and ARs to Sponsor, REC or MHRA in an

expedited manner in this trial. AEs will be reported at regular intervals to the TMG (which includes a Sponsor representative) and oversight committees for review. AEs are not efficacy endpoints and are being reported solely for safety in this trial.

Anticipated SAEs will be recorded for the duration of the trial on an **AE Log** and **SAE Form** but will not be considered as SUSARs unless they are deemed related to the IMP and the severity and/or frequency of the event is considered to be unexpected, e.g. a rare event occurring frequently.

As no blood or urine testing is being undertaken for this trial due to the prison setting and an unwillingness from patients to provide samples that could be used for drug testing by staff, safety reporting will be based on routine medical assessments following information from the patient or prison staff related to their health and wellbeing.

Table 5 lists the undesirable effects for fluoxetine listed in the SmPC dated 17 December 2020; as such, these are not considered unexpected if they occur at the frequency recorded in the table.

9.3 Assessing AEs

Safety reporting will be the responsibility of a medically qualified person such as the Forensic Psychiatrist who will usually be the medical PI for the trial. There may also be delegated personnel such as the trial location GP who can undertake this role. The trial team will have RAs at trial locations who can assist with the identification of AEs (e.g. reviewing the daily log at months 3 and 6) and can ensure that the relevant paperwork is completed and submitted in a timely manner, but they will not be expected to undertake any medical reviews of the events identified other than flagging potentially serious AEs to the site's authorised medics for assessment.

The RAs, FASAR SPOCs or other delegated person will be responsible for adding the data onto the trial database in a timely manner. The delegated medic must sign any relevant documentation such as an **SAE form** as soon as possible. This form must be uploaded to the REDCap database as confirmation of the signature is required. Given the security issues around access to the REDCap database we will not ask the Forensic Psychiatrist to log into the system to sign the documents electronically. The Sponsor/CI may delegate responsibility for the safety reporting procedures for the trial to STU.

All patients will be asked about new or unexpected symptoms at each assessment visit (baseline, weeks 4 and 8) and at each trial visit (months 3 and 6). Patients will also be encouraged to report any illnesses or feelings of being unwell in a daily log that will be collected by the RA at each trial visit and flagged for review by a qualified delegated medical person if deemed potentially serious. If a patient develops a medical condition of concern during the evening/night-time, there will be a process at trial locations to ensure that they can indicate their medical concerns to a relevant nominated staff member, e.g. duty governor, who will consider whether urgent medical attention is needed, which would be part of standard care at sites. The patient will be given a **membership card** for the trial so that the prison staff are aware of the need to alert the relevant member of the trial team or RA or, if delegated, to record the incident on trial documentation and to ensure that due diligence regarding the medical event is followed for this trial.

Details of AEs will be recorded from consent until the 6-month follow-up visit. All AEs will be recorded on an **AE Log** and added to the database as soon as possible by the RA, FASAR SPOC or other delegated person. All AEs will be assessed for (a) seriousness and (b) causality in relation to the IMP (see Appendix 3). Any medical person responsible for assessing AEs (e.g. psychiatrist, GP) should exercise medical judgement in deciding whether an AE/AR is serious (see Table 4 above). The medical person will then grade all AEs in relationship to the study treatment (i.e. did the trial intervention cause the event/reaction) according to their clinical judgement as follows:

- **Unrelated:** where the AE is not considered to be related to the IMP.
- **Possibly:** although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- **Probably:** the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP.
- **Definitely:** the known effects of the investigational medicinal product or its therapeutic class, or based on challenge testing, suggest that the IMP is the most likely cause.

Table 5 overleaf summarises a list of reported side effects of fluoxetine for consideration when assessing possible causality.

Please note that three of the side effects highlighted in yellow below are desirable outcomes for this trial, namely erectile dysfunction, ejaculation disorder and sexual dysfunction, and care should be taken to make sure these are recorded when reported by the patient.

Note: *neither the CI nor Sponsor can downgrade a PI causality assessment*; *but upgrading of an event is possible. In the event of differing opinions during assessment*, *BOTH must be provided on reports.*

Expectedness

If an event is judged to be possibly, probably or definitely related, i.e. an AR/SAR, an evaluation of expectedness will be needed from a medical person. They should refer to the known side effects derived from the RSI in Table 5 of this protocol to determine if the event is expected.

There are also events that are more common in the patients involved in this trial than would be expected due to the setting of the trial, but not necessarily related to the medication which are listed here:

- (Attempted) suicide.
- Self-harm.
- Trauma due to an assault.

These events may be reported as SAEs where the seriousness category applies but would be considered expected due to the environment of the trial rather than the medication itself.

AE reporting, including of SUSARs, will be carried out in accordance with the applicable regulations.

All trial locations involved in the trial will inform the Trial Office of any SAEs within 24 hours of knowledge of the event to ensure that appropriate safety reporting procedures are followed by the Sponsor.

Table 5. Known undesirable effects of fluoxetine taken from the SmPC dated 17 December 2020.

	Very common	Common	Uncommon	Rare	Unknown
Blood & lymphatic system disorders				-Thrombocytopenia -Neutropenia -Leucopenia	
Immune system disorders				-Anaphylactic reaction -Serum sickness	
Endocrine disorders				-Inappropriate antidiuretic hormone secretion	
Metabolism & nutrition disorders		Decreased appetite[1]		Hyponatraemia	
Psychiatric disorders	Insomnia[2]	-Anxiety -Nervousness -Restlessness -Tension -Libido decreased[4] -Sleep disorder -Abnormal dreams[3]	-Depersonalisation -Elevated mood -Euphoric mood -Thinking abnormal -Orgasm abnormal[5] -Bruxism -Suicidal thoughts & behaviour[6]	-Hypomania -Mania -Hallucinations -Agitation -Panic attacks -Confusion -Dysphemia -Aggression	
Nervous system disorders	Headache	-Disturbance in attention -Dizziness -Dysgeusia -Lethargy -Somnolence[6] -Tremor	-Psychomotor hyperactivity -Dyskinesia -Ataxia -Balance disorder -Myoclonus -Memory impairment	-Convulsion -Akathisia -Buccoglossal syndrome -Serotonin syndrome	
Eye disorders		Vision blurred	Mydriasis		
Ear & labyrinth disorders				Tinnitus	
Cardiac disorders		-Palpitations -Electrocardiogram QT prolonged (QTcF≥450msec)[8]		Ventricular arrhythmia including torsades de pointes	
Vascular disorders		Flushing[7]	Hypotension	-Vasculitis -Vasodilitation	
Respiratory, thoracic & mediastinal disorders		Yawning	-Dyspnoea -Epistaxis	-Pharyngitis -Pulmonary events (inflammatory processes of varying histopathology and/or fibrosis)[10]	
Gastrointestinal disorders	-Diarrhoea -Nausea	-Vomiting -Dyspepsia -Dry mouth	-Dysphagia -Gastrointestinal haemorrhage[11]	Oesophageal pain	

	Very common	Common	Uncommon	Rare	Unknown
Hepato-biliary disorders				Idiosyncratic hepatitis	
Skin & subcutaneous tissue disorders		-Rash[8] -Urticaria -Pruritus -Hyperhidrosis	-Alopecia -Increased tendency to bruise -Cold sweat	-Angioedema -Ecchymosis -Photosensitivity reaction -Purpura -Erythema multiforme -Stevens-Johnson syndrome -Toxic Epidermal Necrolysis (Lyell Syndrome)	
Musculoskeletal, connective tissue & bone disorders		Arthralgia	Muscle twitching	Myalgia	
Renal & urinary disorders		Frequent urination[9]	Dysuria	-Urinary retention -Micturition disorder	
Reproductive system & breast disorders		-Gynaecological bleeding[11] -Erectile dysfunction -Ejaculation disorder[10]	Sexual dysfunction	-Galactorrhoea -Hyperprolactinaemia -Priapism	Postpartum haemorrhage[17]
General disorders & administration site conditions	Fatigue[12]	Feeling jittery Chills	-Malaise -Feeling abnormal -Feeling cold -Feeling hot	Mucosal haemorrhage	
Investigations		Weight decreased	-Transaminases increased -Gamma-glutamyl transferase increased		

[1] *Includes anorexia.*
[2] *Includes early morning awakening, initial insomnia, middle insomnia.*
[3] *Includes nightmares.*
[4] *Includes loss of libido.*
[5] *Includes anorgasmia.*
[6] *Includes complete suicide, depression suicidal, intentional self-injury, self-injurious ideation, suicidal behaviour, suicidal ideation, suicide attempt, morbid thoughts, self-injurious behaviour. These symptoms may be due to underlying disease.*
[7] *Includes hypersomnia, sedation.*
[8] *Based on ECG measurements from clinical trials.*
[9] *Includes hot flush.*
[10] *Includes atelectasis, interstitial lung disease, pneumonitis.*
[11] *Includes most frequently gingival bleeding, haematemesis, haematochezia, rectal haemorrhage, diarrhoea haemorrhagic, melaena, and gastric ulcer haemorrhage.*
[12] *Includes erythema, exfoliative rash, heat rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash macular-papular, rash morbilliform, rash papular, rash pruritic, rash vesicular, umbilical erythema rash.*
[13] *Includes pollakiuria.*

[14] Includes cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorhagia, menorrhagia, metrorrhagia, polymenorrhea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage.
[15] Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, ejaculation delayed, retrograde ejaculation.
[16] Includes asthenia.
[17] This event has been reported for the therapeutic class of SSRIs/serotonin and noradrenaline reuptake inhibitors (SNRIs).

9.4 Recording and reporting of SAEs, SARs and SUSARs

From trial locations to the Trial Office (STU)

All AEs reported verbally or recorded in the daily log will be added to the database as soon as possible. Data will be entered by the RA or another authorised delegated person.

If the AE is considered serious (as per the definitions in Section 9.1), then an **SAE Form** must also be completed with whatever information is available at that time and emailed to the Co-CIs and the Trial Office at FASAR@swansea.ac.uk by trial location staff no later than 24 hours of awareness of the event (see Appendix 3 for details). The RAs may assist with the paperwork for the reporting process but cannot make any medical decisions. The Trial Office will acknowledge receipt of the forms within 2 working days.

Initial reports should be submitted as soon as the following minimum criteria are met:

- A suspected SAE/SAR is identified.
- A patient is identified (Trial ID).
- An AE has occurred that is assessed by a qualified delegated person as potentially serious.
- A recognised reporting source is identified (e.g. Forensic Psychiatrist, GP, FASAR SPOC, RA).

It is critical that a potential SAE is notified to the trial as quickly as possible by emailing a partially complete **SAE Form** to FASAR@swansea.ac.uk, even if there is not much detail about the event at that point. Following the initial report, all SAEs should be followed up with additional **SAE Forms** until the event has resolved or an outcome has been reached. The medical Co-PI or medical person delegated to oversee safety reporting may be asked to provide further information by the trial office. The medical Co-PI is also responsible for reporting AEs internally as required in line with local prison procedures.

If the patient is admitted to a hospital wing or transferred to an NHS hospital for their condition, the medical PI (or medically qualified delegate) and FASAR SPOC or RA should maintain oversight of the situation and continue to complete **SAE forms** as required.

If a patient withdraws from the trial, any pre-recorded SAEs or SARs should still be followed up to a medical conclusion. This will be explained to the patient in the **PIS**.

From the Trial Office to other parties

SAEs will be reported to the Sponsor within 24 hours of knowledge of the event from the trial location by delegated prison staff or research staff. These events will be reported on an **SAE Form** with any subsequent **follow-up SAE Forms** will be forwarded immediately. Events will be followed up until the event has resolved or an outcome has been reached.

All SAEs assigned by the medical person as being both suspected as related to IMP treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the MHRA. The Sponsor is responsible for informing the MHRA, the REC and Marketing Authorisation Holder of SUSARs within the required expedited reporting timescales. This task is delegated to the CI for FASAR but STU may assist with this task.

The Sponsor is responsible for ensuring that all SAEs, SARs and SUSARs (except those specified in this protocol as not requiring reporting) are reported in the appropriate timescale to the MHRA and REC (see Appendix 4 for details).

For FASAR, the above tasks are delegated to the CI but can be delegated to STU for action.

Once an **SAE Form** is sent by the site, the medical Co-CI (or medical delegate) will complete a clinical review (assessment of causality and expectedness) within 24 hours of receipt. The assessment will be notified to the trial location and the Trial Office in accordance with the **Clinical Review Form**.

Only SUSARs should be expedited to the MHRA and REC. They will be reported according to the following timelines:

- Fatal and life threatening SUSARs should be reported as soon as possible, but not later than 7 days after awareness of the reaction. Additional relevant information must be sent within 8 days of the initial report.
- Non-fatal or non-life-threatening SUSARs should be reported as soon as possible, but not later than 15 days after awareness of the reaction.

A copy of the **SUSAR report** should be provided to the Sponsor.

In addition to reporting to the REC and MHRA, SUSARs will also be reported to all members of the TMG and the DMC. The CIs shall ensure that all trial location investigators receive regular safety updates of SAEs and SUSARs that occur in relation to the IMP in the trial.

Interruption and suspension of dosing will be managed as per Section 8.9.

9.5 Responsibilities

Medical PI responsibilities (e.g. Forensic Psychiatrist, GP)

- Checking for AEs and ARs when patients attend for clinical assessments or trial visits.
- Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the RSI approved for the trial.
- Ensuring that all SAEs are recorded and reported to the Trial Office within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that SAEs are chased with the Trial Office if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that AEs and ARs are recorded on an AE Log and that the RAs enter the data onto the trial database.

Chief Investigator (medical Co-CI) responsibilities (as Sponsor delegate)

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning the seriousness of SAEs, their causality and whether the event was anticipated (in line with the RSI) where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning whether an event/reaction was anticipated or its expectedness was in line with the RSI.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the trial **Monitoring Plan**.
- Reviewing Medical Dictionary for Regulatory Activities (MedDRA) coding for all SAEs and SARs proposed by STU.
- Preparing the clinical sections and final sign off of the **DSUR**.

Sponsor Responsibilities

The Sponsor retains responsibility for the oversight of the trial but will delegate tasks to the CI and the Trial Office.

Trial Steering Committee (TSC)

In accordance with the Terms of Reference for the TSC, the committee is responsible for periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC)

In accordance with the Terms of Reference for the DMC, the committee is responsible for periodically reviewing overall safety data to determine patterns and trends of events or to identify safety issues that would not be apparent on an individual-case basis.

AEs will be reported at agreed intervals to the DMC, usually as part of a meeting report.

Trial Management Group (TMG)

The TMG will ensure that all aspects of regulatory approval are in place and will review a line listing of all recorded AEs produced by the statistician.

The TMG will report at agreed intervals to the TSC, the DMC and the study Sponsor. The medical CI will ensure that **DSURs** and **Annual Progress Reports (APRs)** are completed and SUSARs are reported within required regulatory timelines.

9.6 Notification of deaths

All deaths that occur during the trial between consent and the final assessment at six months will be recorded and assessed for expectedness and causality by the trial location medical Co-PI, as will any deaths that fall outside the 6-month period but stem from an ongoing (S)AE during the trial and are unresolved at six months. A completed SAE Form must be emailed to the Trial Office at FASAR@swansea.ac.uk within 24 hours of knowledge of the event.

Only deaths that are assessed to be caused by the IMP will be reported to Sponsor, the MHRA and REC within seven days of notification. Deaths that do not constitute a SAR or SUSAR will be recorded and reported in the DSUR and APR.

9.7 Pregnancy reporting

There will be no pregnancy reporting requirements for this trial, as requested by the approving REC.9.8 Overdose

Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose have included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias (including nodal rhythm and ventricular arrhythmias) or ECG changes indicative of QTc prolongation to cardiac arrest (including very rare cases of torsades de pointes), pulmonary dysfunction and signs of altered central nervous system status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare.

Monitoring of cardiac and vital signs is recommended, along with general symptomatic and supportive measures. No specific antidote is known. Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage. In managing overdosage, consider the possibility of multiple drug involvement. An extended time for close medical observation may be needed in patients who have taken excessive quantities of a tricyclic antidepressant if they are also taking, or have recently taken, fluoxetine.

9.9 Reporting urgent safety measures

When an immediate hazard to the health and safety of a research patient(s) has been identified, an Urgent Safety Measure (USM) will be implemented to protect a clinical trial patient against any immediate hazard to their health or safety. In such instances changes in trial conduct will be implemented before approval from an ethics committee or regulatory body is sought. Examples of when USMs may be required include an increase in the intensity or frequency of expected events and reactions judged to be clinically important, unexpected reactions that occur during or following a patient's trial completion or new safety findings.

The Co-CI and Co-PIs may take immediate safety measures to protect research patients against any hazard to their health or safety without prior authorisation from the REC or Sponsor. The Sponsor, CI and Trial Office must be alerted to a USM as soon as possible by completing and emailing an **Urgent Safety**

Measures Form to the Trial office at FASAR@swansea.ac.uk. Where possible, the CI should be contacted for advice on the immediate action to be taken beforehand.

USMs might include an urgent change to a trial procedure(s), a temporary halt to the trial at one trial location or trial-wide, a permanent halt to the trial or the addition of new trial procedures yet to be reviewed by the REC or regulatory body.

Subsequent to implementing a USM, the trial location must immediately notify the CI and Trial Office of the action taken, completing and emailing an **Urgent Safety Measures Form** to FASAR@swansea.ac.uk.

USMs must be reported immediately to the Sponsor (by email), REC (by email) and to the MHRA (by telephone, +44 20 3080 6456) to a medical assessor, ideally within 24 hours of measures being taken and no later than three days from the date that measures were taken. See Appendix 4 for further information on how to proceed when contacting the MHRA for advice or to submit a substantial modification in response to a USM.

The MHRA website should always be checked for the current information.

9.10 The type and duration of the follow-up of patients after adverse reactions

Any ARs reported within the specified time period (baseline to 6-month visit) should be followed up to conclusion where possible, especially those categorised as serious. Any AEs/ARs presenting after the 6-month visit has concluded when the medication will be continued / started for patients as part of standard care will not be recorded for the trial.

9.11 Development Safety Update Reports (DSURs)

An annual **DSUR** will be submitted to the MHRA and REC listing all SARs and SUSARs. The CI (or delegate) is responsible for submitting this report on the anniversary of the Clinical Trial Authorisation (CTA) approval.

10. STATISTICS AND DATA ANALYSIS

Data cleaning and preparation processes will be carried out prior to final analysis. A **statistical and health economics analysis plan (SHEAP)** with be produced separately, see Section 10.3 for more details.

All patients enrolled will be followed up and included unless they withdraw from the study before the administration of the first dose. An intention to treat (ITT) analysis will be carried out. Per protocol analysis of the primary outcome may also be carried out alongside the ITT analysis if deemed necessary by the TSC.

The primary data analysis will use analysis of covariance (ANCOVA) to adjust for important covariates such as baseline measurements and age. The analysis will be conducted evaluating the intervention having been used for six months. For secondary outcomes, similar analyses will be conducted, adjusting for multiple testing using the Hochberg correction. All analyses will first be carried out on an ITT basis for patients with available outcome data. Analysis of secondary-outcome data will be performed, evaluating the intervention having been used for three and six months.

10.1 Sample size calculation

A sample size of 118 individuals at six months after medication initiation randomised in a 1:1 ratio as described above has > 95% power to detect a medium-to-large effect size of 0.67 (based on this group's analysis of the current evaluation of the MMPSA) at the 0.05 significance level. We aim to recruit 196, allowing for a 40% loss between baseline and trial completion.

10.2 Planned recruitment rate

Recruitment for the trial will be conducted through referrals to the MMPSA pathway at participating sites, as described in Section 7. At present, there are an estimated 70 individuals prescribed MMPSA across all trial locations (with 350 patients over the last five years). The current evaluation of the MMPSA, conducted by the PI and colleagues reported that 86% of referrals were prescribed fluoxetine as opposed to anti-androgens.

All potential patients meeting inclusion/exclusion criteria and providing informed consent will be subjected to randomisation.

10.3 Statistical and Health Economics Analysis Plan (SHEAP)

A version-controlled **SHEAP** will be produced and agreed to prior to the completion of recruitment to address the research question and to generate a CONSORT compliant report. All analysis will be by ITT and detailed in the **SHEAP**. Patients will be analysed 'as randomised', i.e. according to the group to which they were originally allocated. Outcome data obtained from all patients will be included in the data analysis, regardless of protocol adherence.

The finalised **SHEAP** will contain as a minimum the following items:

- Short synopsis of the trial background, research question and study objective.
- Study methods.
- Presentation of data for analysis.
- Statistical principles.
- Analysis strategy for primary outcome, secondary efficacy and safety outcomes and mechanistic analyses.
- Modifications made and reasons.
- Statistical software to be used.

Any changes between the methods in the protocol and the **SHEAP** will be explained in the **SHEAP** and an assessment made of the need for a protocol modification. Additionally, any protocol modification will require a review of the **SHEAP** to determine if changes are needed. These reviews will be documented in the TMF.

To address the question of whether fluoxetine is effective at reducing PSA in comparison to a treatment-as-usual placebo, an ANCOVA adjusting for baseline SCS scores will be used. Adjusting for baseline SCS scores will adjust for chance differences in randomisation, ensuring that potential group differences in baseline SCS scores do not impact the analysis. Using ANCOVA will also have greater statistical power by using the pre-test as a covariate, assuming a degree of correlation between pre- and post-medication scores.

Similar analyses will be used to analyse secondary outcomes, adjusting for multiple testing using the Hochberg correction. We will investigate bias due to missing data by looking at the fraction of missing information and include transparent adjustments for potential confounders (e.g. site). All analyses will first be carried out as ITT for patients with available outcome data. In line with previous research, analyses will also be carried out with patients who followed the protocol for the full 6 months to address the active treatment effects of the intervention. Predictors of missingness will be included in analyses or multiple imputation used as appropriate.

Safety reporting will be conducted to determine whether the medication is safe by assessing all AEs reported by patients. The statistician and researchers will remain blinded until preliminary analyses are complete. We will complete an analysis of the fidelity of treatment delivery and will also record inadvertent unblinding, trial-related AEs and reasons for drop-out.

10.3.1 Summary of baseline data and flow of patients

Baseline comparability of the randomised group will be assessed in terms of age, SCS and site. Baseline values will be used as covariates to adjust for comparisons between treatment arms.

10.3.2 Primary outcome analysis

SCS score at 6 months following commencement of treatment will be analysed using analysis of covariance, adjusted for covariates including baseline SCS and demographic variables.

10.3.3 Secondary outcome analysis

Plans for the secondary outcome analyses are detailed in the SHEAP.

10.4 Subgroup analyses

A series of sub-group analyses will be conducted on the primary outcome based on a range of participant characteristics and will be detailed in the SHEAP.

10.5 Adjusted analysis

Efficacy analysis will be adjusted by age, baseline test values and other baseline covariates listed in Section 10.3.1. Safety analysis will not be adjusted.

10.6 Interim analysis and criteria for the premature termination of the trial

No interim analysis is planned. Interim analysis on safety will be conducted if requested by the TSC/DMC. Decision criteria based on safety as part of a guideline for early stopping or other adaptations will be set by the TSC with input from the DMC.

10.7 Patient population

All randomised patients will be included in trial analyses and analysed according to treatment allocated. Patients randomised who do not complete the study will, as far as possible, be included in trial analyses.

10.8 Procedure(s) to account for missing or spurious data

Every attempt should be made to minimise missing data, encouraging patients to engage with the trial at all data collection timepoints even if they are no longer taking the interventional medication. Patterns and the level of missing data will be examined. Multiple imputation will be considered to account for a small amount of missing data.

10.9 Other statistical considerations

Every attempt will be made to ensure that the **SHEAP** is adhered to. Any deviations from the **SHEAP** will be reported to the TSC and DMC.

10.10 Economic evaluation

The economic evaluation will consider the cost-effectiveness of fluoxetine compared to treatment as usual in the treatment of PSA with the purpose of providing information to decision-makers in the criminal justice and healthcare systems. It will take a service perspective, including costs to the criminal justice system and health and social care services. Service use data for the economic evaluation will be collected using a modified version of the SF-SUS, adapted for use in the recruiting prisons (Barrett & Byford 2007).

Resource use data as set out in will be collected using the modified SF-SUS (15) at will be collated for baseline, covering the six months preceding the visit, and at six months follow-up for the 6-month period between baseline and follow-up. The different elements of the SF-SUS will be completed from different data sources, which was the approach used in similar studies in UK prisons (16):

- By a trained researcher from computer records including (P-NOMIS and OASys) for prison name, wing, time in segregation, and time in employment or training.
- Participant daily log for health-related contacts such as GP, nurse, substance misuse services, and mental health services and for programmes and interventions, both individual and group based (each day participant completes tick box to record if they had any appointments or programmes/interventions).
- and in research visits with the trial participant, which will occur at baseline and six months only and only for infrequent services such as admission to hospital or hospital wing, outpatient appointments, and visits to accident and emergency. It has been used in similar studies in UK prisons (16).
- Trial medication, and prescribing time will be recorded in the participant daily log and the details of the prescribing clinician from clinical records separately.

Despite the challenges of estimating costs in prison-based settings, every effort will be made to use the service-use data to apply a unit cost to each service-use item so that an individual total cost per patient is calculated.

The primary economic evaluation will be a cost–utility analysis with QALYs as the primary outcome. QALYs will be calculated using utility data collected from the EQ5D-5L, which is a preference-based measure consisting of five questions (on mobility, self-care, usual activities, pain, anxiety/depression) with five levels of response (unable, severe, moderate, slight, no problems), which are then converted into utility-index scores ranging from 0 to 1, where a higher score indicates a better quality of life. While the EQ-5D is the preferred outcome measure of NICE (National Institute for Health and Care Excellence 2013) and has been used in studies in similar populations (Nathan et al. 2019), we will also undertake a secondary cost-effectiveness analysis using the primary clinical outcome measure, the SCS.

The economic evaluation will compare costs and outcomes together, producing ICERs to summarise the incremental cost per unit change in outcome (Drummond et al. 2015). Uncertainty around the ICER and the willingness to pay for improvements in outcome will be examined via bootstrapped replications of costs and outcomes (Barber & Thompson 2000) and through the calculation of cost-effectiveness acceptability curves (Fenwick & Byford 2005).

10.11 Qualitative analysis

The qualitative study will be analysed with reflexive thematic analysis (TA). Reflexive TA is a widely used and adaptable qualitative research method that enables the interpretation and exploration of patterns or themes within a dataset (Braun & Clarke. 2022).

11. DATA MANAGEMENT

11.1 Data collection tools and source document identification

Following patient consent, trial data will be gathered through review of medical records by the FASAR SPOC, RAs and Forensic Psychiatrist at each trial location at baseline (post consent), 3 months after dose 1 taken, and 6 months (primary outcome) after dose 1 taken. PROMs will be scored as per manualised instructions.

There will be two **Data Management Plans (DMPs)** for this trial:

- STU DMP – to cover the trial database which holds pseudo-anonymised data (Trial ID, case report form data, daily log data) and saliva test results.

- NTU DMP – to cover the storage of signed consent forms, qualitative data collection and analysis and the storage of patient identifiers to arrange site visits and to facilitate the patient's name being added to medication boxes by sites.

Both DMPs will set out the modes of collection, storage and access for the trial.

11.2 Source data

As required by GCP, source data are contained in source documents (original records or certified copies).

Source data allows not only reporting and analysis but also verification of data collected for the purposes of quality control, audit or inspection. Several attributes are considered of universal importance to source data and the records that hold those data. The data and records must be accurate, legible, contemporaneous, original, attributable, complete, consistent, enduring and available when needed.

Completed paper **Case Report Forms (CRFs), PROMs questionnaires** and the **daily log** will be filed with the patient's trial file by the RA or other delegated person. These source data will be entered into the trial database at the end of each trial visit within a site-agreed timespan. They will be coded with the patients' Trial ID and will not include their names or any other identifiable information. This database will be hosted on a Swansea University server with backup and restoration procedures in place.

The ISF containing original signed **informed consent forms** and any **paper data collection forms** will be kept in separate physical locations within secure premises at NTU. Trial paperwork will be transported from trial locations to NTU by the RAs using lockable briefcases. Access to the ISF will be restricted to researchers working on the trial, Sponsor representatives and representatives of regulatory authorities who will assess compliance with regulatory requirements to ensure the protection of trial patients and the reliability of trial data.

Patient data held at STU will be anonymised using unique Trial IDs. A list of the Trial IDs will be kept securely within the ISF at each trial location and will be updated as new patients consent to the trial. A confidential and secure minimal identifiable data set to link patients' names with their Trial ID will be stored separately from the ISF held at the prison in a pre-agreed secure location. Patient names are required by the NTU staff and research staff to allow trial visits and electronic record checking but STU will never hold these names in the trial database. Only electronic data containing anonymised information will be saved on Swansea University computers in password-protected files with access restricted to those who can be unblinded.

11.2.1 Source documents

Source documents for the RCT will include any medical records held at the trial location, prescriptions and pharmacy-related documents, and any paper-based data collection. A **source data location list** will be developed for each site.

11.2.2 Access to source data

Direct access to source data will be granted to authorised representatives from the Sponsor, the host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections, in line with patient consent.

At the end of the trial the trial location may authorise the paper files relating to the trial to be transferred to the NTU office for long term archiving. A file note describing the trial and the location of the trial documentation should be held at the trial location to allow requests for archived paperwork to be submitted if required.

11.3 Case Report Forms (CRFs)

A **CRF** is a form on which individual patient data required by the trial protocol are recorded. It may be a printed or electronic document (**eCRF**). This trial will collect trial data using paper **CRFs** in line with prison security policy to limit the use of external electrical equipment/system access in restricted areas. The CRF

data are used to perform statistical analysis for the trial. The **CRFs** will be reviewed and signed off by the trial statistician before use.

The **CRFs** for this trial will have questions designed to capture the items listed in Section 7.7, as well as safety reporting and IMP tracking.

Data from the paper **CRFs** will be input into the trial database at the earliest possible time following collection.

11.3.1 CRFs as source documents

Electronic file access in the prison setting is highly restricted. As such, we will prioritise data collection using paper **CRFs** which will be considered source documents. If the CRF is to be transferred to the Sponsor, it is necessary for the trial location to retain the original copy to ensure that the PI has the original account of what has occurred during the trial at their site.

11.4 Data handling and record keeping

GCP requires that Sponsors operating such systems validate the system, maintain SOPs for the use of the system, maintain an audit trail of data changes ensuring that there is no deletion of entered data, maintain a security system to protect against unauthorised access, maintain a list of the individuals authorised to make data changes, maintain adequate backup of the data, and safeguard the blinding of the trial and archiving of any source data (i.e. hard copy and electronic).

If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data. The Sponsor should use an unambiguous patient identification code that allows identification of all the data reported for each patient. Sponsors are responsible for ensuring compliance with the requirements outlined above when tasks are subcontracted. There should be no loss of quality when an electronic system is used in place of a paper system.

The trial electronic database will be managed and operated as required by GCP. The trial location investigator or delegate will record all study data using the trial-specific electronic database provided by STU. The investigator will ensure the accuracy, completeness and timeliness of the data entered on to the eCRFs. All data will be handled and stored in accordance with the Data Protection Act or other applicable legislation.

Data will be checked according to the **DMPs**, and queries will be generated and sent to the trial location investigator for response using the electronic database. Corrections resulting from these queries will be confirmed and sent back to STU. The queries and their responses will be stored in the audit trail of the electronic database.

For the qualitative study, data may be collected remotely (where staff prefer to be interviewed via a remote platform) or in person, either at NTU or in prison. Data will be stored on the NTU secure drive, in compliance with the GDPR and as per the **DMPs**.

11.5 Archiving

The sponsor is the custodian of all research data generated during this trial. However, this role will be delegated to the non-medical CI who will maintain oversight and STU who will maintain an archive for both the paper TMF and the electronic trial database for a period of 25 years following trial closure. Both parties will ensure an archive succession plan is in place.

For the qualitative study, data will be stored on the NTU secure data drive and securely deleted in line with the **DMP.**

The TMF at STU will not be merged with the files held at NTU relating to the qualitative work at the end of the trial. The STU TMF will be archived for 25 years. Trial locations will be asked to archive their ISF locally but may give permission to allow the trial files to be transferred to NTU (sponsor and trial office) as required. Destruction of the TMF and individual ISFs will require authorisation from the Sponsor.

Site data will be stored at NTU for 25 years. Identifiable information will be permanently deleted once coded an checked for the qualitative study and patient identifiers will be deleted once no longer needed for trial processes. Access to anonymised trial data will be controlled by the CI and STU who will ensure that access is granted in a secure, compliant and transparent manner through robust procedures and controls. The same process will be true of NTU and the identifiable data they will hold independently of STU.

12. MONITORING, AUDIT AND INSPECTION

A **Monitoring Plan** for the RCT will be developed and agreed by the TMG, Sponsor, CI and STU based on the trial risk assessment. Monitoring of this trial to ensure compliance with GCP and scientific integrity will be conducted by NTU and STU trial team via a combination of central and on-site monitoring as per the data and trial monitoring plans. This may include 100% central monitoring of all primary outcome data, remote trial location initiation and closedown visits for all trial locations as a minimum, and one monitoring visit during the recruitment period to complete 100% source data verification (SDV) on primary outcome data in accordance with the trial **Monitoring Plan**. Patient enrolment, consent, eligibility, allocation to treatment groups and adherence to trial intervention will all be considered in the **Monitoring Plan**.

Triggered trial location monitoring may occur if large numbers of protocol deviations or safety issues are raised at any one trial location. The **Monitoring Plan** will outline the requirements of triggered central and on-site monitoring.

PIs and trial location involved in the trial will permit trial monitoring, audits and regulatory inspection(s). In the event of an inspection, the trial location will enable direct access to representatives of the Sponsor and regulatory authorities as detailed in the contract.

The qualitative data will be managed by NTU delegated staff who will ensure that all data confidentiality and storage requirements are met, and data destruction is completed as required.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review and reports

The trial will be conducted in accordance with the principles of GCP. Recruitment will not begin until all required approvals are in place for an individual site.

Health Research Authority (HRA) approval will be sought for the trial, alongside a favourable ethical opinion from an appropriate NHS REC, the NTU Ethics Committee. HMPPS permission will be sought for all prisons as sites. Where required, local NHS capacity and capability or private healthcare confirmation will be obtained.

All patient facing documents and the trial protocol will be submitted for review and approval to all required organisations within England and Wales. Potential Scottish trial locations will have local requirements followed for approvals to be given.

A CTA will be sought from the MHRA.

Substantial modifications will not be implemented until a favourable opinion has been received from the HRA, REC or MHRA as appropriate. Non-substantial modifications will be sent to the HRA using the appropriate template. Trial locations will be notified of the outcome of the modification via the Trial Office prior to implementation.

An APR and DSUR will be sent by the CI to the REC and MHRA respectively within 30 days of the anniversary of the favourable opinion or CTA as appropriate until trial end. The CI will notify the REC and MHRA within 30 days of the end of the trial (or 15 days if the trial terminates early).

Within 12 months of trial end, the CI will submit a final report to the REC and MHRA, using the appropriate template and indicating the results of the trial, including details of any publications or abstracts.

All correspondence and submission details will be filed in the TMF held at STU.

We have ethical approvals from the HRA, HMPPS and NTU for the ongoing evaluation and follow-ups of the current MMPSA pathway at the prison treatment sites. (**Long term evaluation: NRC Ref: 2013-092**; **Title: Evaluation of the use of pharmacological treatments with individuals who have been convicted of a sexual offence. HRA 17/NE/0335**; **IRAS 228963**). These ethical approvals, while not covering the trial or qualitative studies in this research project, demonstrate that the research team have successfully navigated this sensitive area of research for 12 years, and that the assessments being completed by the psychiatrist and research team have previously been approved as sound.

13.2 Peer review

The Detailed Description of the Project, which summarised the principles of the trial, has received an independent and expert peer review by the NIHR HTA as the Funder of the trial.

The Sponsor has also conducted a proportionate governance and risk assessment of the proposed protocol prior to accepting the role of research sponsor.

13.3 Public and Patient Involvement

Patients will receive a brief **information sheet** explaining the possibility of being eligible for the trial as part of the "consent to be screened" process. If they are deemed potentially eligible and can be told about the details of the trial, a full **PIS** explaining the trial will be given. All patient-facing documents will be written with input from the PPI group and an expert in learning disabilities. The PPI group meet regularly and will provide ongoing advice to the trial for any patient-facing information, data collection tools and trial processes. We also have a dedicated PPI person who is part of the research team and a member of the TMG. He will provide advice and review documents for suitability and correctness. As the trial progresses, the group will comment on trial progress and amendments and support the trial reporting process with opinions and helping us to write lay summaries of our findings.

13.4 Regulatory compliance

The trial will be conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (2024), the principles of GCP and in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2025 and all subsequent amendments, the UK Policy Framework For Health and Social Care Research (2017) and other regulatory requirements as appropriate.

The Protocol will be submitted for approval by an NHS REC and to the MHRA for a CTA prior to the trial commencing. Trial location permissions will be gained from each prison prior to being initiated.

Special consideration should be given to potential variation in procedures at trial locations due to security measures; something that might be routine at one trial location could be additional to routine care at another trial location.

Before any trial location can enrol patients into the study, the CI or designee will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, the CI or designee, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The CI will work with trial locations so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study.

13.5 Protocol compliance

The trial location PI is responsible for the overall conduct of the trial at the site and compliance with the protocol and any subsequent modifications. Accidental protocol deviations can happen at any time. In the event that a PI or delegate has deviated from the protocol, the nature of and reasons for the deviation will

be adequately documented on a **Protocol Deviation Form** and reported to the CI (via the Trial Office) and Sponsor within 24 hours of awareness.

In accordance with the principles of GCP, prospective, planned deviations or waivers to the protocol are not allowed under the UK Clinical Trial regulations and will not be used.

Deviations from the protocol that are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. All such instances will be investigated. Protocol amendments and reporting of the events will occur as required. The TMG will monitor protocol deviations and any resulting Corrective and Preventive Actions (CAPAs) taken; reports to the Sponsor and oversight committees on these deviations will also be submitted.

13.6 Notification of serious breaches to GCP and/or the protocol

A 'serious breach' is a breach that is likely to effect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial; or
- the scientific value of the trial.

The CI (via the Trial Office) and the Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

The Sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial, or the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of the serious breach.

13.7 Data protection and patient confidentiality

At sites

- Sites will maintain key documents such as enrolment logs, AE Logs, etc. under the control of a PI. The RAs will oversee the completion of these documents and will always require access at the site.

At Nottingham Trent University (NTU)

- Paper records will be transported from trial locations (after a research visit) to NTU by the RA using a lockable briefcase.
- Paperwork will be kept in a locked cabinet in secure premises at NTU at all times when the record is not in use for a study visit. Access to the records will be restricted to researchers working on the study, Sponsor representatives and representatives of regulatory authorities required to audit the conduct of the research study.
- Identifiable data including the link between the patient names and the Trial ID will be stored separately from other data electronically at NTU and backed up regularly.
- The qualitative interviews data and recordings will be stored and regularly backed up on a NTU server.
- All data files at NTU will be password protected.
- The qualitative folder will have restricted access to NTU trial team members only. STU and KCL trial team members will not have access unless absolutely necessary.
- Staff interview data will be pseudo-anonymised.
- Analysis of interviews will be done by NTU staff.

At STU

- The trial database will be stored on a dedicated, secure and backed up Swansea University server.
- All electronic files at STU will be stored in a secure location and only authorised personnel will have access.

- The TMF will have restricted access by trial team members.
- Patient data will be anonymised on the database by the use of Trial IDs.
- Analysis will be conducted by the study team on anonymised data.

13.8 Financial and other competing interests for the CI, PIs at each trial location and committee members for overall trial management

At the time of writing the protocol, no financial conflict or any other relevant connection or shared interest was declared for the CI, known trial location PIs, committee members or anyone involved in the trial management. Declarations confirming the absence of any conflict of interest will be signed for independent members of the oversight committees.

13.9 Indemnity

The Sponsor, NTU, has arranged appropriate insurance and indemnity to meet the potential legal liability for harm to the patients arising from the design or management of the trial for negligent harm. In addition, many trial health professionals hold substantive or honorary NHS contracts, which provide them with appropriate protection from NHS clinical negligence arrangements.

13.10 Modifications

Throughout the trial, the TMG will decide whether any modifications to the trial are required. The Trial Manager will complete the Modification Tool and submit to the Sponsor for approval. For substantial modifications to the CTA, a valid notice of modification to the MHRA will be submitted for review. For substantial modifications to the REC approval or the supporting documents, a valid notice of modification to the REC will be submitted for review. Substantial modifications will also be submitted to the HRA and HMPPS. Details of amendments will be made available to participating R&D offices where relevant for impact review and contract revision as required (agreement of which should not delay implementation). A modification can be implemented once all relevant approvals are obtained.

Non-substantial modifications will be submitted as per current processes and also emailed to HMPPS and any other relevant party not automatically included in the Integrated Research Application System (IRAS)-based processes online.

The Sponsor/CI is responsible for providing details of modifications and approvals, including copies of revised documents, to all participating investigators and study teams. This role will be completed by the Trial Manager. The Trial Manager will maintain records of all modifications and version control of all trial documents.

The Trial Manager will communicate changes to relevant collaborators and update trial registries, e.g. International Standard Randomised Controlled Trials Number (ISRCTN).

13.11 Post-trial care

Patients randomised to placebo will be reassessed by the Forensic Psychiatrist at the end of their participation in the trial. The Forensic Psychiatrist will be told the treatment the patient has been given for the trial and will decide whether they should:

a) continue with treatment if the patient has been allocated fluoxetine

b) start a course of fluoxetine treatment if the patient has been given the placebo

c) consider an alternative treatment regimen if fluoxetine is no longer deemed appropriate.

13.12 Access to the final trial dataset

The CI and trial statistician will have access to the final dataset. Should PIs or others require access to the final dataset, this will require approval by the TMG, TSC and Sponsor and will only be made available following trial completion and publication. A **data sharing agreement** may be required.

14. DISSEMINATION POLICY

14.1 Dissemination policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. A **Publication Plan** will be developed to clarify the rules on authorship and to plan the relevant key outputs for the trial.

Patients in the trial will be told by the Forensic Psychiatrist what they had been given for the trial when they are reassessed after the 6-month trial visit to consider whether a change to their standard prescription is needed. The findings of the trial can be disseminated within prisons using anonymised data using communication channels such as prison newsletters.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be agreed upon by the CI, PIs, and members of the TMG and will follow the guidance provided by the International Committee of Medical Journal Editors. The **Publication Plan** will provide further details on this.

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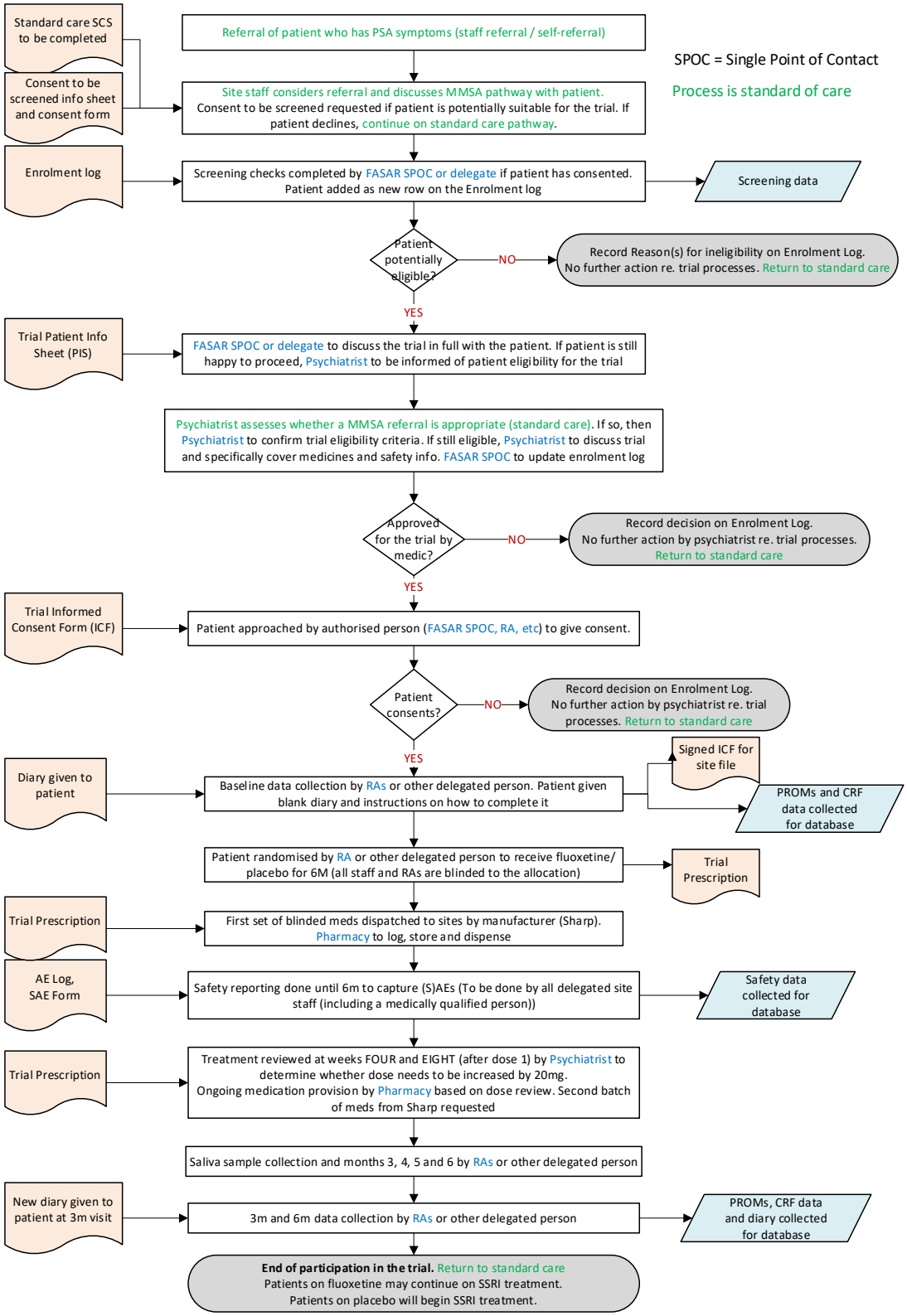
APPENDICES

Appendix 1 – Trial flowchart (one page)

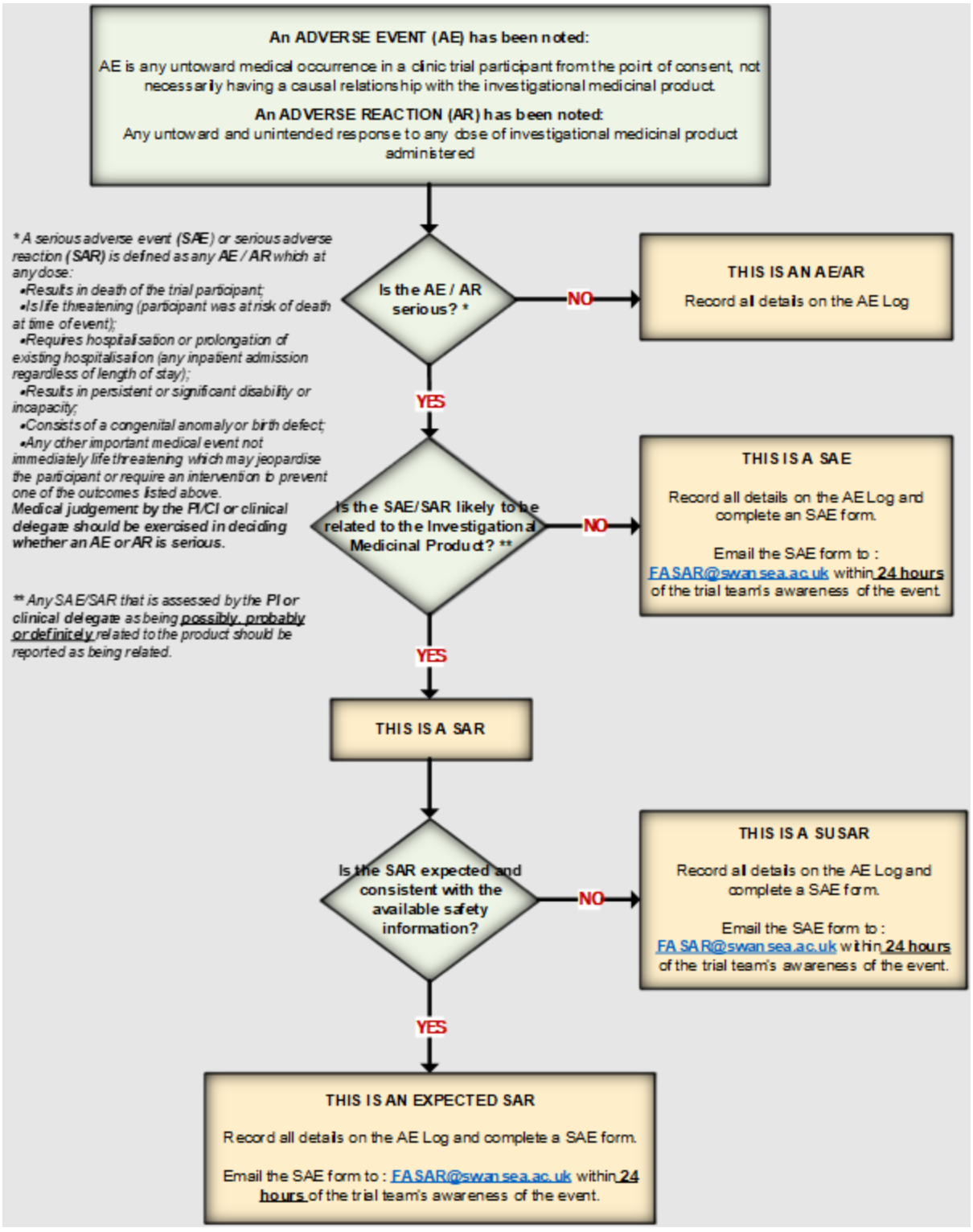


Appendix 2 – Schedule of procedures

Data items	Consent to screen	Screen	Consent to RCT	Baseline data collection	Random-isation	Dose 1	Time period after dose 1						Ad hoc
							4 weeks	8 weeks	3 months	4 months	5 months	6 months	
Consent decision	X		X										
Key demographics		X											
SCS score		X*		X					X			X	
Concomitant medication		X				X	X	X	X			X	
Psychological interventions		X											
Mental health assessments		X											
Clinical measures concerning masturbation, sexual preoccupation and ability to distract from sexual thoughts				X			X	X	X			X	
PROMs booklet completion				X					X			X	
Saliva sample collection									X	X	X	X	
Randomisation					X								
Dosage on prescription						X	X	X					
Patient daily log (issued at baseline and 3m, collected at 3m and 6m)									X			X	
Safety reporting						X	X	X	X			X	X
Withdrawal													X

*SCS completed as part of standard care by psychiatrist and will be used for eligibility only. The trial will rely on an adapted SCS questionnaire within the PROMs booklet for analysis.

Appendix 3 – Safety reporting – Decision framework to be used for assessment of Adverse Events



Safety Reporting Flowchart

Appendix 4 – Safety reporting – Decision framework for expedited reporting to regulatory authorities

A related SAR, SUSAR or USM has been reported to the trial office: Trial locations have reported an event as per the: - Decision Framework to be used for the Assessment of Adverse Events in the FASAR trial. (Appendix 3) - Framework for Reporting Urgent Safety Measures in the FASAR trial All **SUSARs** require expedited reporting as do **all USMs**.

Trial locations will report all events to the Trial Office (email FASAR@swansea.ac.uk).

On receipt of notification of an event, the Trial Office will notify the CI or independent reviewer within 24 hours of STU awareness of an event indicating that a response is required within 24 hours. Should the event indicate a possible SUSAR, this will be highlighted within 24 hours of awareness.

Expedited reporting to the MHRA, the REC and the Sponsor will occur via the Trial Office.

The **Trial Manager** (or delegate) has the responsibility to:

- ensure that the medical CI or independent reviewer is aware of the need for an assessment, indicating the time frame for reporting;
- complete all expedited reporting to the MHRA within 7 days (fatal or life threatening) or 15 days (all others) of awareness of the event;
- liaise with site(s) for missing information and complete the regulatory forms as required;
- forward updated information to the medical CI or Independent Reviewer;
- remain vigilant of the timeframe for reporting of an event;
- file reports and relevant communication in the TMF.

USMs must be reported immediately to the Sponsor (by email), REC (by email) and to the MHRA (by telephone, +44 20 3080 6456) medical assessor, ideally within 24 hours of measures being taken and no later than 3 days from the date that measures were taken. The MHRA website should always be checked for the current information:

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#urgent-safety-measures

Information you will be asked for on the MHRA call:

- The IRAS ID and/or the ISRCTN number of:
  - the trial for which USM action has been taken
  - sponsor ongoing trials with the same IMP
- The affected IMP(s) – commercial or developmental names.
- Nature of the safety concern and whether it has been reported as a SUSAR.
- Which USMs have been taken and when.
- The number of UK patients who are currently receiving the IMP, the number of patients who received it and the number affected by the USM.
- Contact details in case of further questions.

After discussing the USM with the MHRA assessor via phone, you must provide the MHRA with written notification of the measures taken and discussed with the medical assessor, within 3 days from the date the measures were taken.

As the trial covered by the USM has gone through the Combined Review process, then the written notification of the USM should be submitted via IRAS.

Notification of a substantial amendment (Amendment tool plus any updated document including the changes agreed with the medical assessor) is also required. The substantial amendment covering the changes made as part of the USM should be submitted within approximately two weeks of notification to the MHRA.

Any potential reason for delay to submission of the substantial amendment should be discussed and agreed with the medical assessor at the time of initial notification or through a follow up call.

The USM-related substantial amendment must not include changes different from those required as an urgent safety measure. This is due to the fact that unrelated changes may result in rejection.

Please submit your substantial amendment using MHRA Submissions via the Human Medicines Tile. Please select 'Clinical Trial' as the Regulatory Activity and 'CT - Amendment' from the Regulatory sub activity dropdown list.

As the trial has gone through the Combined Review process, then the substantial amendment should be submitted via IRAS. More information on how to submit a substantial amendment is found via IRAS.

If you are not able to report a USM to the MHRA via the phone, please send an email to clintrialhelpline@mhra.gov.uk within 3 days of taking urgent measures. The subject of the email should be 'USM for trial IRAS ID/ISRCTN number'. Please explain in the email the USM implemented, the reason and why you did not report it via phone. An MHRA assessor will contact you and provide advice regarding further actions.