GOTHIC2: A 3-arm multi-centre randomised placebo-controlled trial of Glycopyrrolate or Hyoscine Hydrobromide for the treatment of clozapine-Induced hypersalivation

PROTOCOL

V4.0, 03/05/2024

Trial Sponsor:
The University of Liverpool
Clinical Directorate
Thomson Yates Building
The Quadrangle, Brownlow Hill
Liverpool
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Trial Registry ID: ISRCTN36536677

CPMS ID: 58120

CTA Reference number: 04196/0065/001-0001

Research Ethics Ref: 23/LO/1002

Sponsor Ref: UoL001694

Funder Ref: NIHR131157

This project (ref. NIHR131050 is funded by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical research Council (MRC) and National Institute for Health Research (NIHR) partnership. The views expressed are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.

PROTOCOL APPROVAL

I, the undersigned, hereby approve this clinical trial protocol:

Authorised by Chief Investigator:

Signature: 

Date: 3 May 2024

Dr Inti Qurashi
Consultant Forensic Psychiatrist
Mersey Care NHS Trust

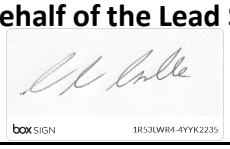
Authorised on behalf of Sponsor:

Signature: 

Date: May 3, 2024

Karen Jennings-Wilding
Senior Clinical Research Governance Manager
Clinical Directorate, University of Liverpool

Authorised on behalf of the Lead Statistician:

Signature: 

Date: 3 May 2024

Professor Carrol Gamble
Professor of Medical Statistics and Director
LCTC, University of Liverpool

General Information

This document describes the GOTHIC2 trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the Liverpool Clinical Trials Centre (LCTC) to confirm they have the most up to date version.

This protocol defines the participant characteristics required for trial entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority (HRA) guidance. Regulatory and ethical compliance information is located in section 17.

The Liverpool Clinical Trials Centre holds full registration status with the UK Clinical Research Collaboration registered Clinical Trials Unit (UKCRC CTU) network (www.ukcrc.org).

Randomisation: web access https://rand.lctc.org.uk/gothic2/

If there are any problems with the randomisation systems contact

LCTC via email on gothic2@liverpool.ac.uk

(Note that the LCTC is open from 0900 – 1700, Monday – Friday,

excluding public holidays and University of Liverpool closed days)

Clinical Queries

Clinical queries relating to this trial should be referred to the Chief Investigator,

Dr Inti Qurashi, via the LCTC: gothic2@liverpool.ac.uk

SAE Reporting

Where the adverse event meets one of the serious categories, an SAE form should be updated on the trial database **immediately and in no circumstances later than 24 hours** of becoming aware of the event by the responsible investigator and submitted to:

(See section 11 for more details).

Contact Details: Institutions

Sponsor:	**Trial Management, Monitoring and Analysis:**	**Statistics:**
The University of Liverpool Clinical Directorate Thompson Yates Building The Quadrangle, Brownlow Hill, Liverpool L3 5RB Tel: 00 44 (0) 7717 863747 Email: sponsor@liverpool.ac.uk	Liverpool Clinical Trials Centre Clinical Directorate Waterhouse Building 1-3 Brownlow Street Liverpool L69 3GL Tel: 0151 795 8577 Email: gothic2@liverpool.ac.uk	Liverpool Clinical Trials Centre Clinical Directorate Waterhouse Building 1-3 Brownlow Street Liverpool L69 3GL Tel: 0151 795 8577 Email: gothic2@liverpool.ac.uk

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**
Karen Jennings-Wilding Senior Clinical Research Governance Manager The University of Liverpool Clinical Directorate Thompson Yates Building The Quadrangle, Brownlow Hill, Liverpool L3 5RB Telephone Number: 0151 795 1780 E-mail: sponsor@liverpool.ac.uk	Dr Inti Qurashi Consultant Forensic Psychiatrist Mersey Care NHS Trust Parkbourn Liverpool L31 1HW Telephone Number: 0151 472 4045 E-mail: Inti.Qurashi@merseycare.nhs.uk

In cases where the CI is unavailable to respond to urgent queries the following individual/s will act as cover:

Medical Expert who will Advise on Protocol Related Clinical Queries:	**Medical Expert who will Advise on Protocol Related Clinical Queries (other than CI):**
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Medical Expert who will Evaluate SAE Reports:	**Medical Expert who will Evaluate SAE Reports (other than CI):**
Chief Investigator	Professor Richard J Drake Professor of Adult Psychiatry Institute of Brain, Behaviour & Mental Health The University of Manchester Oxford Road Manchester M13 9PL Telephone Number: +44 (0)7814 111 502 E-mail: richard.drake@manchester.ac.uk

Contact Details: Individuals

Medical Expert who will Evaluate SAE Reports (other than CI):	Medical Expert who will Evaluate SAE Reports (other than CI):
Professor James MacCabe Professor of Epidemiology and Therapeutics Institute of Psychiatry, Psychology & Neuroscience Kings College London de Crespigny Park London SE5 8AF Telephone Number: +44 (0)20 7848 0757 E-mail: James.maccabe@kcl.ac.uk	Dr Edward Silva Consultant Forensic Psychiatrist Rathbone Unit Mersey Care NHS Trust Parkbourn Liverpool L31 1HW Telephone Number: 0151 471 7949 E-mail: Ed.silva@merseycare.nhs.uk

Additional Contacts:

The contact details for the trial oversight committee members and participating sites are detailed in documents supplementary to the protocol and stored in the Trial Master File.

1 TABLE OF CONTENTS

2 GLOSSARY

ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse drug reactions
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
BBB	Blood-brain barrier
BNF	British National Formulary
CAG	Confidentiality Advisory Group
CANTAB	Cambridge Neuropsychological Test Automated Battery
CI	Chief Investigator
CIH	Clozapine-induced hypersalivation
CNS	Central Nervous System
CRF	Case Report Form
CR/TE	Child-resistant/tamper-evident
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DPA	Data Protection Act
DRS	Drooling Rating Scale
eCRF	Electronic Case Report Form
EME	Efficacy and Mechanism Evaluation
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GOTHIC1	A feasibility study of Glycopyrrolate in comparison to Hyoscine hydrobromide and placebo in the Treatment of Hypersalivation Induced by Clozapine
GOTHIC2	A 3-arm multi-centre randomised placebo-controlled trial of Glycopyrrolate or Hyoscine Hydrobromide for the treatment of clozapine-induced hypersalivation
GP	General Practitioner
Glycopyrrolate	Glycopyrronium bromide
HRA	Health Research Authority
IRAS	Integrated Research Application System
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
IPD	Individual Participant Data
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LAM	Lactational amenorrhoea method
LASS	Liverpool Anticholinergic Side-effects Scale
LCTC	Liverpool Clinical Trials Centre
LUNSERS	Liverpool University Neuroleptic Side Effects Rating Scale
MA	Marketing authorisation
MHRA	Medicines and Health Care Products Regulatory Agency
MRC	Medical Research Council

NHRS	Nocturnal Hypersalivation Rating Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR CRN	National Institute for Health Research Clinical Research Network
nIMP	Non-Investigational Medicinal Product
PAC-SYM	Patient Assessment of Constipation – Symptoms scale
PANSS	Positive And Negative Syndrome Scale for Schizophrenia
PBPP	Public Benefit & Privacy Panel for Health & Social Care
PI	Principal Investigator
PPIE	Public and patient involvement and engagement
PROM	Patient reported outcome measure
PSP	Personal and Social Performance scale
R&D	Research & Development
RA	Research assistant
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSE	Rosenberg Self-Esteem scale
RSI	Reference Safety Information
RVP	Rapid Visual Information Processing
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SPIRIT	Standard Protocol Item: Recommendations for Interventional Trials 2013
SS	Smoking status
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
USA	United States of America
USM	Urgent Safety Measure
VRM	Verbal Recognition Memory
WOCBP	Women of Child Bearing Potential

3 PROTOCOL OVERVIEW

Full Title:	A 3-arm multi-centre randomised placebo-controlled trial of Glycopyrrolate or Hyoscine Hydrobromide for the treatment of clozapine-induced hypersalivation
Acronym:	**GOTHIC2**
Phase:	III
Target Population:	Community and in-patients aged between 18 and 65 experiencing clozapine induced hypersalivation (CIH)
Sample size:	252 participants (84 per arm)
Inclusion Criteria:	1. Aged 18 to 65 years inclusive. 2. English speaking. 3. Prescribed clozapine for a minimum of three months. 4. Experiencing hypersalivation with a minimum score of 4 on the Drooling Rating Scale (DRS) and are either: (a) Currently not receiving treatment for CIH, OR (b) Receiving drug treatment for CIH and agreeable to a 48-hour washout period. 5. Has capacity and ability to provide written informed consent prior to study specific procedures.
Exclusion Criteria:	1. Medical conditions that could influence hypersalivation (e.g., Parkinson's Disease). 2. Neurological conditions that could affect cognitive functioning during the course of the study (e.g., unstable epilepsy). 3. History of an allergic reaction to hyoscine hydrobromide 4. History of an allergic reaction to glycopyrrolate. 5. Known contra-indications to hyoscine hydrobromide or glycopyrrolate as stated in the British National Formulary: a) Prostatic enlargement b) Myasthenia gravis c) Pyloric stenosis d) Paralytic ileus e) Glaucoma f) Hepatic Impairment 6. Known cautions to hyoscine hydrobromide or glycopyrrolate as stated in the British National Formulary: a) Chronic heart failure b) Stomach ulcer c) Ulcerative colitis

<table>
<tr><td></td><td colspan="2">d) Significant liver disease that in the opinion of the CI or PI is a contraindication
e) Down's syndrome
d) Arrythmia and/or history of myocardial infarction
e) Overactive thyroid gland
f) Unstable angina
7. Current prescription for potassium chloride, digoxin, amantadine, levodopa, Tricyclic antidepressants or Monoamine oxidase inhibitors.
8. Pregnant, trying to conceive or breastfeeding.
9. Sexually active heterosexual patients who are unable or unwilling to use contraception during the study (see section 10.4).
10. Participation in another drug study within the preceding 12 weeks (or within 5 half-lives of an IMP, whichever is longer) or use of other investigational drugs.
11. Active suicidal ideation as assessed within usual care.
12. Known sensitivity to any interventions or excipients.
13. Known history of intestinal obstruction.
14. Known history of urinary retention.
15. Severe renal impairment (eGFR <30 ml/min/1.73m2).
16. Known history of brain tumour or encephalitis.</td></tr>
<tr><td>Study Centres and Distribution:</td><td colspan="2">NHS Mental Health Trusts</td></tr>
<tr><td>Individual Participant Trial Duration:</td><td colspan="2">Duration of treatment and follow-up: 12 weeks (double blind)
Duration of optional open label follow-up: 12 weeks (unblinded)</td></tr>
<tr><td>Study Duration:</td><td colspan="2">Minimum 48-month study duration including a 33-month recruitment period</td></tr>
<tr><td rowspan="5">IMP/Intervention:</td><td colspan="2">Active 1:</td></tr>
<tr><td>IMP1:
Form:

Dose:

Route:</td><td>Hyoscine hydrobromide
Capsule

Week 1: 300 micrograms (1 capsule) twice daily.
Weeks 2-12: 300 micrograms (1 capsule) three times daily.

Oral</td></tr>
<tr><td colspan="2">Active 2:</td></tr>
<tr><td>IMP2:
Form:

Dose:

Route:</td><td>Glycopyrronium bromide (Glycopyrrolate)
Capsule

Week 1: 1 mg (1 capsule) twice daily.
Weeks 2-12: 1 mg (1 capsule) three times daily

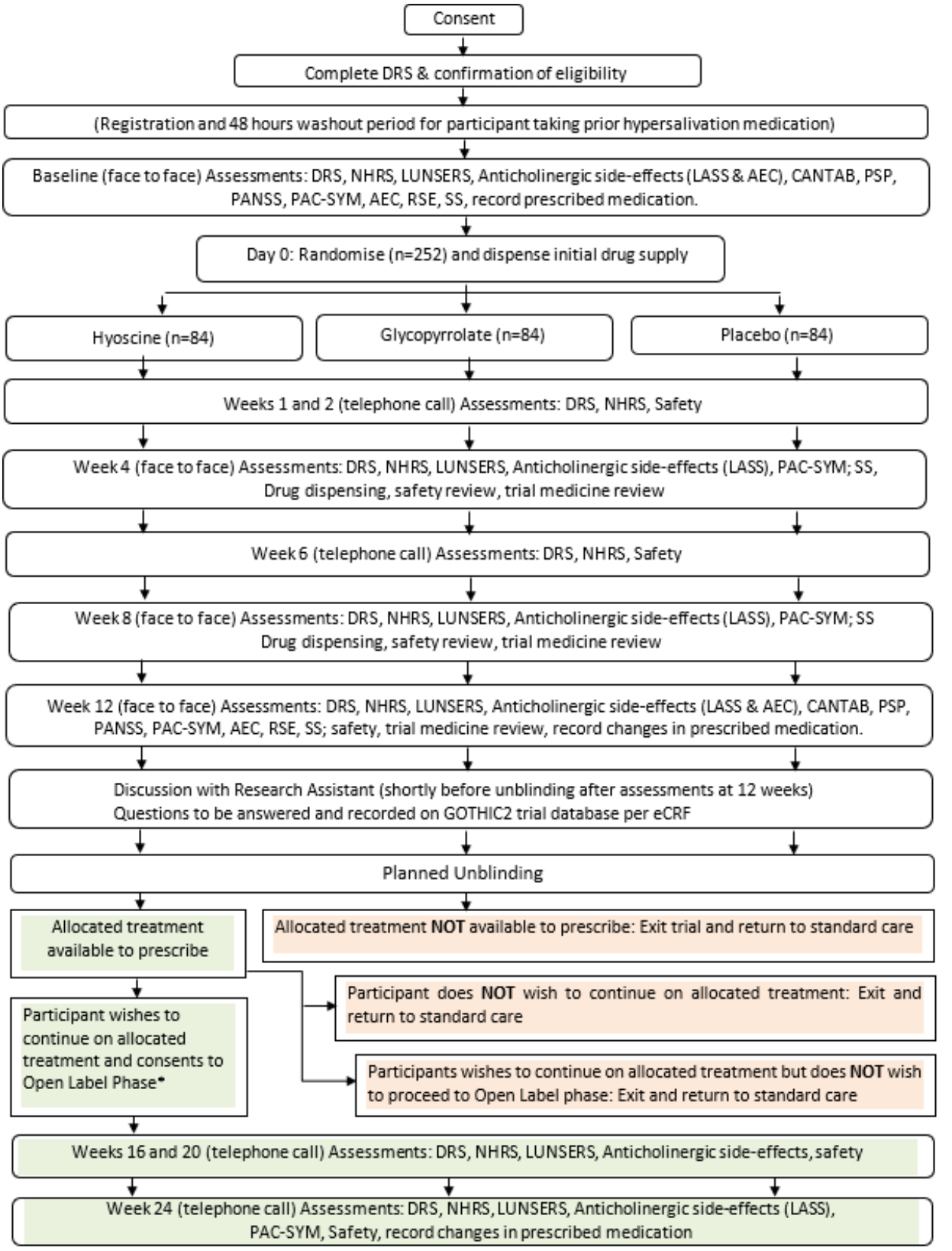
Oral</td></tr>
</table>

	Control:	
	Control: Form: Dose: Route:	**Matching placebo administered as per IMP** Capsule Week 1: 1 capsule twice daily. Weeks 2 – 12: 1 capsule three times daily Oral
Objectives:		
Primary objective	1. To ascertain efficacy of either hyoscine hydrobromide or glycopyrrolate in comparison to placebo in the treatment of CIH.	
Secondary objectives:	2. To establish which of glycopyrrolate or hyoscine hydrobromide, if any, is associated with fewer cognitive side-effects using a validated assessment measure. 3. To establish which of glycopyrrolate or hyoscine hydrobromide, if any, is associated with fewer ADRs.	
Exploratory objective:	4. To establish whether clozapine plasma levels are associated with CIH.	
Outcomes:		
Primary outcome:	Hypersalivation: Drooling Rating Scale	
Secondary Outcomes:	Neuroleptic side-effects: Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)	
	Anticholinergic side effects: Liverpool Anticholinergic Side-effects Scale (LASS)	
	Sustained attention and Verbal Recognition Memory (VRM): Cambridge Neuropsychological Test Automated Battery (CANTAB)	
	Nocturnal hypersalivation: Nocturnal Hypersalivation Rating Scale (NHRS)	
	Self-esteem: Rosenberg Self-esteem scale (RSE)	
	Hospital admission (whether for physical or psychiatric reasons)	
	Constipation: Patient assessment of constipation and symptoms (PAC-SYM)	
	Social functioning: Personal and Social Performance scale (PSP)	
	Symptoms of schizophrenia: Positive and negative syndrome scale (PANSS)	

	Effect and tolerability of treatment[1]: premature discontinuation of study treatment; Continuation at 12 weeks
	Discontinuation of clozapine
	Serious Adverse Events
Exploratory Outcome:	Clozapine plasma levels

[1] Premature discontinuation of study treatment and a decision to continue with study treatment post 12 weeks are included as global measures of the balance of both effect and tolerability.

3.1 Schematic of Trial Design



***Dispensing during this open label phase is generic brands sourced from NHS hospital stock**

DRS: Drooling Rating Scale *DRS is part of eligibility but not routinely performed at all sites hence consent taken before eligibility:* **PANSS**: Positive And Negative Syndrome Scale for schizophrenia; **NHRS**: Nocturnal Hypersalivation Rating Scale; **CANTAB**: Cambridge Neuropsychological Test Automated Battery; **PAC-SYM**: Patient Assessment of Constipation – Symptoms; **LASS**: Anticholinergic Side-effects Scale; **AEC**: Anticholinergic Effect on Cognition; **LUNSERS**: Liverpool University Neuroleptic Side Effects Rating Scale; **PSP**: Personal and Social Performance Scale for schizophrenia; **RSE**: Rosenberg Self-Esteem scale; **SS**: Smoking status

3.2 Trial lay summary

Schizophrenia is in most cases a long-term mental health condition that can cause a range of psychological symptoms. Clozapine is a medication used to treat schizophrenia when other medications have not helped. When patients begin taking clozapine they, in almost all cases, will be taking it for the rest of their lives. Clozapine is effective in up to 50% of people taking it but can cause side effects and one of the most distressing is excessive drooling, called clozapine-induced hypersalivation (CIH). CIH can cause serious physical health problems, including pneumonia, and psychological problems such as reduced self-esteem. Without treatment, CIH can lead patients to stop clozapine which almost always results in worsening schizophrenia symptoms and increases the risk of suicide and admission to a psychiatric hospital.

At the moment there is no proven treatment for CIH. The medication that is usually prescribed for CIH is called hyoscine hydrobromide (hyoscine), but the evidence that hyoscine can improve CIH is very weak. Also, hyoscine can cause unpleasant side effects such as bowel problems (constipation) and thinking problems (causing problems with attention and concentration). Some studies suggest that a different medication, called glycopyrrolate, might be helpful for CIH and may cause fewer thinking problems because it does not enter the brain like hyoscine does. However, it may still cause other side effects like constipation.

It is important to know which medications may improve CIH and what side effects are caused by them so patients can make an informed choice based on their mental illness symptoms and experience of side-effects.

We are conducting a clinical trial to find out if either of hyoscine or glycopyrrolate can improve CIH by comparing patients taking these medications with patients taking a dummy treatment (placebo). The placebo, hyoscine and glycopyrrolate will look, taste, smell and feel the same so that participants do not know which one they are receiving. This is important so we can be sure any differences in outcomes between the groups are only due to the treatment received. If both hyoscine and glycopyrrolate reduce CIH, we will compare the two medications to see which one causes fewer thinking and other side effects and assess patient preference.

GOTHIC2 will recruit 252 patients with CIH, both outpatients and inpatients, from NHS mental health Trusts.

There are two stages to the study. In the first 12-week stage, participants will be randomly assigned into one of three groups to receive either hyoscine, glycopyrrolate or placebo. Random assignment is the best way to ensure that the three treatment groups in GOTHIC2 are similar. Patients or the people responsible for their treatment and care will not know which treatment they are receiving to prevent bias. If the information is needed then it will be made available. We will regularly measure drooling, thinking, constipation and all side effects in order to see what effect the medication has. We will also measure how much clozapine is in the participants' blood to see if that is related to clozapine side effects. At the end of this stage the participant will be asked if (given the option) they would prefer to stay on the medication they have been taking or leave the trial. Participants who would like to continue on their treatment will continue to the second stage subject to its availability within routine care. All other participants will exit the trial at the end of the first stage.

If participants opt to continue (and the allocated treatment is available to prescribe) they will be asked to consent to a further 12 weeks. Participants will be followed up every four weeks to measure drooling, constipation and side effects in the same way as before. This stage of the trial is designed to obtain longer term information on safety and participant preferences about the study medication. This will be the first time this method has been used in a study of CIH and will be the longest funded trial of CIH medication that has been conducted. This trial will provide the first reliable evidence about which medication for CIH, if any, is helpful and will help patients with CIH to decide what medication is better for them, if both are effective at improving CIH, based on individual side-effects.

4 ROLES AND RESPONSIBILITIES

4.1 Sponsor

The University of Liverpool is the Sponsoring organisation and is legally responsible for the trial. They will formally delegate specific duties to the Chief Investigator and the Liverpool Clinical Trials Centre.

4.2 Funder

This trial is funded by NIHR EME (Efficacy and Mechanism Evaluation Programme).
Reference Number: NIHR131157.

Table 1: Trial Funding

Funder(s)	Financial and Non-financial Support Given	Role
NIHR Efficacy and Mechanism Evaluation Programme	Non-commercial financial support for delivery of project	The funders organised independent peer review of the study design, will approve protocol amendments, monitor trial progress, and appoint independent members of the trial oversight committees.

4.3 Chief Investigator (CI)

Dr Inti Qurashi is the CI for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the trial team.

4.4 Principal Investigators (PIs)

In each participating site a PI will be identified who will be responsible for identification, recruitment and data collection, along with follow up of trial participants and adherence to trial protocol at site. They will be responsible for safety reporting and processing any applicable safety information.

4.5 Clinical Trials Unit (CTU)

The Liverpool Clinical Trials Centre (LCTC) is part of the University of Liverpool. In collaboration with the CI, the LCTC will have overall management responsibility and will be responsible for trial management activities including (but not limited to) trial planning, budget administration and Trial Master File (TMF) management, safety reporting, data management, randomisation, statistical analysis, participating site initiation and monitoring and IMP management.

4.6 Other Third-Party Providers

Trial IMP will be procured, blinded and packaged by Sharp Clinical Services UK and distributed to sites in accordance with all applicable guidelines and as delegated by Sponsor.

Digital cognitive assessments will be measured using CANTAB (Cambridge Neuropsychological Test Automated Battery) on an interactive tablet device supplied pre-loaded by Cambridge Cognition.

4.7 Oversight Committees

This trial is subject to oversight from the following committees:

4.7.1 Trial Management Group (TMG)

A TMG will be formed comprising the CI, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management. The TMG will meet regularly, as defined in their terms of reference.

4.7.2 Trial Steering Committee (TSC)

The TSC will consist of an independent chairperson, two independent experts in the field of mental health (one of whom is Chair), an independent biostatistician, patient and public contributors and the CI. Other non-member individuals may be invited to meetings to provide trial progress reports and updates, or as observers. Representation from sponsor organisation will be as observer. The role of the TSC is to provide oversight for the trial and provide advice through its independent Chairperson. The TSC will consider recommendations of the Independent Data and Safety Monitoring Committee (IDSMC). The TSC assessment of IDSMC recommendations for the continuation or amendment of the trial will be communicated to the trial Sponsor and funder. The TSC will meet throughout the trial (at least annually) in accordance with their terms of reference/charter.

4.7.3 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC will consist of at least three independent members encompassing expertise in biostatistics and mental health.

The IDSMC will meet throughout the trial (at least annually), receive and review monitoring reports and interim analyses for the trial and provide recommendations on the conduct of the trial to the TSC in accordance with their terms of reference/charter.

5 INTRODUCTION

5.1 Background

Clozapine is the only effective antipsychotic for schizophrenia that has not responded to other medication. Clozapine has a high burden of adverse events including hypersalivation (excessive drooling) experienced by up to 80% of patients prescribed clozapine. It is described by patients as 'dribbling like a tap'. CIH leads to increased physical morbidity (skin infections, aspiration pneumonia and poor sleep due to nocturnal drooling) and increased psychological morbidity due to social stigma and reduced self-esteem. CIH leads to many patients stopping clozapine that almost always leads to relapse of schizophrenia and potentially long hospitalisation with increased NHS costs. Relapse increases the risk of self-harm and suicide.

There are no licensed drug treatments for CIH and the mechanism of CIH is unknown although it may be related to plasma clozapine levels. The usual treatment for CIH is hyoscine hydrobromide (hyoscine) but the evidence base for efficacy is weak. As hyoscine crosses the blood brain barrier (BBB), it can cause additional problems that are closely linked to worse long-term outcomes in schizophrenia such as worsening hallucinations and impaired cognition (e.g. verbal memory, attention and concentration). Hyoscine also has peripheral nervous system actions that increase the risk of constipation (already high with clozapine) and of life-threatening paralytic ileus. Recently an alternative treatment, glycopyrronium bromide (glycopyrrolate), has been used to treat CIH. Early evidence suggests that glycopyrrolate may be effective in treating CIH whilst being better tolerated in comparison to hyoscine because of its' reduced penetration of the BBB that minimises central nervous system anticholinergic adverse effects. It offers the hope of targeting the important problem of CIH without aggravating cognitive impairment or hallucinations. However, glycopyrrolate may also cause or worsen peripheral nervous anticholinergic side-effects.

Problem size and research context:

Approximately 39,000 patients are prescribed clozapine in the UK (1). CIH is experienced by 60 - 80% (2) and in a UK prevalence study of CIH, 92% of participants reported experiencing CIH with many cases reported as severe (3). Our published survey data is consistent with the prevalence reported in the literature with hypersalivation overwhelmingly the most frequently reported negative side effect, reported by 84% of patients (4) . It was described as 'dribbling like a tap' and 'I have to carry a towel with me wherever I go'. Patients report that CIH is demoralising (5) , leads to increased physical morbidity (skin infection, aspiration pneumonia, poor sleep) (6, 7) and increased psychological morbidity due to social stigma and reduced self-esteem.

In a UK cohort study of persons prescribed clozapine, 45% of patients discontinued clozapine within the first two years (8). Adverse drug reactions (ADRs) accounted for over half of discontinuations and CIH accounted for approximately 10% of ADRs reported by clinicians and patients. CIH was one of the four most common patient-cited reasons for discontinuation. Stopping clozapine, in nearly all cases, causes a rebound psychosis (8, 9) that is very difficult to treat leading to lengthy psychiatric hospitalisation (for in-patients), hospitalisation (for community patients) and increases the risk of self-harm, suicide and carer costs. Therefore, preventing discontinuation of clozapine would very likely be a cost- saving intervention given the relative costs of psychiatric admission compared to drug costs for CIH.

Public and Patient Involvement and engagement

Our Public and Patient Involvement and Engagement (PPIE) group have been closely involved in the

trial design of GOTHIC2, including the GOTHIC1 feasibility study, and highlighted the need for a better evidence base for the following reasons:

1. To establish an effective treatment for CIH. This is a critical, service-user informed question as there are no licensed pharmacological treatments for CIH and the medications currently used are poorly evidenced and may be causing more harm than benefit.
2. To assess effects of treatments for CIH on cognitive functioning and symptoms of schizophrenia to improve patient well-being. Community surveys indicate the highest degree of cognitive impairment in persons with schizophrenia occurs in those prescribed the highest level of anticholinergic drugs that cross the BBB (10). Some anticholinergics, such as glycopyrrolate, have minimal penetration of the BBB (11) and therefore are much less likely to cause CNS adverse effects (hallucinations, impaired cognitive functioning). Improving cognitive performance is associated with better treatment outcomes in schizophrenia (12). Establishing an effective treatment for CIH that does not impair cognitive functioning or cause/worsen hallucinations would be informative for treatment decisions for clinicians and patients when discussing risk/benefit analysis for medications for CIH.
3. To establish a tolerable treatment for CIH. All anticholinergics have peripheral nervous system actions (blurred vision, impaired micturition etc.) (13) and increase the risk of constipation (already high with clozapine (14)) and the risk of life-threatening paralytic ileus (15). Our proposal has been informed by PPIE on this issue and we will use several assessment measures to collect data on the widest range of potential ADRs.
4. To reduce the physical and psychological consequences of untreated CIH. CIH is demoralising (4), leads to increased physical morbidity (skin infection, aspiration pneumonia) (6, 7) and reduced quality of life due to social stigma and reduced self- esteem. Pneumonia is recognised as a prominent cause of mortality in persons prescribed clozapine and chronic aspiration of saliva may be a contributory factor (16) . Drooling at night (nocturnal hypersalivation) affects sleep quantity and quality (2). Our assessment measures will assess for sleep, nocturnal drooling and self-esteem.
5. To reduce the likelihood of patients discontinuing clozapine. CIH contributes to non- adherence with clozapine treatment (17) and the treatment cost of relapse is approximately £25K, more than four times that of a non-relapse case (18), and also incurs societal costs (e.g. increasing the risk of self- harm and the risk of suicide). We will be collecting data on clozapine discontinuation and hospital admissions.
6. Reducing the CNS anticholinergic load (as glycopyrrolate does not cross the BBB) has the potential not to worsen hallucinations in schizophrenia and may improve the ability of persons with schizophrenia to participate and benefit from psychosocial treatments improving rehabilitation outcomes in the longer- term (19).

5.2 Rationale

The health problem addressed:

Schizophrenia is typically diagnosed during adolescence or early adulthood and affects around 1% of the population and costs the UK economy more than £11 billion per year (1) of which inpatient admission costs form a major constituent (20). Approximately one third of patients do not respond to conventional antipsychotic treatment and are designated ‘treatment-resistant’. Direct treatment costs are 3-11 times greater for these patients than for treatment responsive schizophrenia (21).

Patients describe CIH as one of the most distressing side effects of clozapine (4) and a reason for discontinuation. Furthermore, aspiration pneumonia arising from nocturnal hypersalivation is implicated in the increased risk of pneumonia in clozapine-treated patients (22).

Existing relevant literature:

We searched the databases PubMed, Google Scholar, Cochrane library and Scopus (including EMBASE and MEDLINE) for all published peer-reviewed articles relating to treatments for clozapine-induced hypersalivation. We searched for all primary research, review articles, systematic reviews and qualitative articles for the period 1st January 1980 – 1st March 2020. We found the current evidence base to be weak, with few drug trials and no large randomised controlled trials. The available evidence does not assist patients, clinicians or carers when considering what medication to use for CIH that is a) effective; b) does not worsen cognition; c) is tolerable (i.e. one side-effect is not replaced by another).

A Cochrane review published in 2008 (23) of the efficacy of treatments for CIH concluded 'there are currently insufficient data to confidently inform clinical practice' and 'it seems reasonable to trial safe interventions for which there is a rationale'. The review identified 15 RCTs (n=984) of which 14 were conducted in China, thereby limiting their generalisability due to different study entry criteria. The trials had methodological issues including use of non-validated outcome measures, poor data reporting of adverse effects and none of the trials included either hyoscine hydrobromide (hyoscine) or glycopyrrolate. A more recent meta-analysis also found poor study quality and trials of medications that either are not available or not used in the NHS for CIH (9).

In the UK the most commonly used medication for CIH is hyoscine. Hyoscine is an antimuscarinic licensed for motion sickness and as a pre-operative drug to dry secretions but is not listed in the British National Formulary (BNF) as a licensed drug for CIH (24). The majority of studies in CIH are either open-label or small RCTs with no convincing evidence for any drug, including hyoscine, as an effective treatment (25). A recent small (n=14) placebo-controlled RCT of hyoscine for the treatment of CIH indicated hyoscine to be effective but the authors noted the need for a larger trial (26). However, hyoscine can cause a wide range of side-effects and the common ones include constipation, dizziness, drowsiness, headache, palpitations, urinary problems and rashes (24). Problematically, as hyoscine crosses the BBB it can cause or worsen cognitive impairment, which are important in schizophrenia as cognitive deficits are closely associated with poor long-term outcomes (27).

Glycopyrrolate is an antimuscarinic licensed in the UK to treat severe hypersalivation in children with chronic neurological conditions. It is widely used in the UK as a pre-anaesthetic agent and is commonly prescribed to treat hypersalivation in children with neurodevelopmental disorders (28) . It is well tolerated with weak penetration of the BBB (11, 29) that suggests that side effects involving cognitive impairment are less likely. Four placebo-controlled RCTs (n=289) of glycopyrrolate (three in children with neurological disorders, one in adults with Parkinson's disease) showed significant reductions in excess salivation as a result of glycopyrrolate treatment (30-33). In a mental health population, a placebo-controlled trial of glycopyrrolate for CIH (using a 2mg dose) showed a clinical improvement in hypersalivation but used an open crossover design with only a six-day intervention period (34). A small (n = 13) double-blind, randomised crossover study of glycopyrrolate and biperiden (an anticholinergic similar to hyoscine) in CIH reported a significantly greater improvement with glycopyrrolate (35). Furthermore, unlike biperiden, glycopyrrolate did not adversely affect cognitive functioning. While constipation can be an adverse effect of glycopyrrolate it appears to be well tolerated in an adult mental health population (3 6) , but this requires further exploration in a large, well-designed study.

There are no similar trials that have been or are being undertaken. A search (undertaken 28th July 2020)

of the World Health Organisation trial database (International Clinical Trials Registry Platform) using the terms clozapine, hyoscine, glycopyrr* identified studies exploring the prevalence of CIH(NCT04197037), risk factors for CIH (JPRN-UMIN000026822) and non-recruiting clinical trials exploring atropine (ACTRN12618000051246) and amitriptyline (IRCT201701136691N3) for CIH. Only one small study (led by the co-Chief Investigator) (26) exploring the use of glycopyrrolate or hyoscine for treatment of CIH was found and there have been no large-scale placebo-controlled trials of treatments for CIH.

Knowledge gap that this research addresses:

1. *Identify an effective treatment for CIH*: Establishing an effective and tolerable treatment for CIH that is less likely to add to the overall side- effect burden of patients and reduces avoidable morbidity is an important unmet research need.
2. *Establish treatment for CIH that does not worsen cognitive functioning and is tolerable*: If both hyoscine hydrobromide and glycopyrrolate are found to be effective treatments for CIH, then the efficacy, cognitive and ADR data from the trial will inform treatment choices for CIH patients based on individual circumstances (some patients will be more concerned about constipation rather than cognition, some concerned about hallucinations becoming worse). This would be a major step forward as the proposed study will provide high quality evidence to clinicians and will meet patient involvement in terms of answering their questions: 'What is an effective medication for drooling caused by clozapine?'; 'Is there a medication for drooling caused by clozapine that won't make my memory and attention worse?'; 'I already have constipation, is there a medication for CIH that won't, or is less likely, to make this worse?' ' What side-effects will I get and which of hyoscine hydrobromide or glycopyrrolate causes the fewer side-effects?' 'Is there a treatment for CIH that won't make my symptoms of schizophrenia worse?'
3. *Explores a potential mechanism of effect of clozapine*: It is unknown whether clozapine plasma levels are associated with CIH. If there is an association this provides an opportunity for patients to discuss clozapine dosing with their treating doctor. We will collect and analyse clozapine plasma levels in relation to CIH and other side-effects.
4. *Address methodological gap*: The proposal fills methodological gaps in the existing literature highlighted in the Cochrane review of pharmacological treatments for CIH (23) and will be the first adequately powered, placebo- controlledtrial of glycopyrrolate and hyoscine hydrobromide using validated outcome measures.

5.3 Risk and Benefits

This trial is categorised as Type A as per the risk-adapted approach to clinical trials adopted by the Medicines & Healthcare products Regulatory Agency (MHRA) as whilst there are no licensed drug treatments for CIH it is established clinical practice to treat CIH with hyoscine hydrobromide and more recently glycopyrrolate is also being prescribed.

Both hyoscine hydrobromide and glycopyrrolate are listed as potential drug treatments for CIH in a widely used prescribing manual for mental health prescribers (37).

More detail regarding management of risks associated with this trial are detailed in a separate Risk Assessment maintained in the TMF. The trial risk assessment is used to determine the intensity and focus of monitoring activity.

5.3.1 Potential Risks

Both hyoscine hydrobromide and glycopyrrolate have established and well-known safety profiles and are used routinely in the NHS. CIH leads to many patients stopping clozapine that almost always leads to relapse of schizophrenia and potentially long hospitalisation with increased NHS costs. Relapse increases the risk of self-harm and suicide.

A comprehensive list of contraindications, precautions and interactions for the trial interventions is available from the relevant Summary of Product Characteristics (SmPCs).

A summary of the more important risks and contraindications is as follows:

Hyoscine hydrobromide:
Drowsiness, dizziness, sedation and somnolence are commonly reported. As hyoscine hydrobromide crosses the BBB, it can cause additional problems that are closely linked to worse long-term outcomes in schizophrenia such as worsening hallucinations and impaired cognition (e.g. verbal memory, attention and concentration). Hyoscine hydrobromide also has peripheral nervous system actions that increase the risk of constipation (already high with clozapine) and of life-threatening paralytic ileus.

Glycopyrrolate:
Adverse reactions are common with glycopyrrolate due to its known pharmacodynamic anticholinergic effects. Irritability, flushing, nasal congestion, reduced bronchial secretions, dry mouth, constipation, diarrhoea, vomiting and urinary retention are very common. Common side effects include upper respiratory infection, pneumonia, urinary tract infection, agitation, drowsiness, epistaxis, rash and pyrexia.

Glycopyrrolate may also cause or worsen peripheral nervous anticholinergic side-effects (see Table 2: Anticholinergic side-effects).

Placebo:
Placebos are a pharmaceutically inert substance (typically a sugar pill) but have been known to cause unwanted side effects. Nausea, drowsiness and allergic reactions, such as skin rashes, have been reported generally as negative placebo effects but are not expected with this study.

5.3.2 Potential Benefits

1. To establish an effective treatment for CIH. This is a critical, service-user informed question as there are no licensed pharmacological treatments for CIH and the medications currently used are poorly evidenced and may be causing more harm than benefit.

2. To assess effects of treatments for CIH on cognitive functioning and symptoms of schizophrenia to improve patient well-being. Community surveys indicate the highest degree of cognitive impairment in persons with schizophrenia occurs in those prescribed the highest level of anticholinergic drugs that cross the BBB (10). Some anticholinergics, such as glycopyrrolate, have minimal penetration of the BBB (11) and therefore are much less likely to cause CNS adverse effects (hallucinations, impaired cognitive functioning). Improving cognitive performance is associated with better treatment outcomes in schizophrenia (12). Establishing an effective treatment for CIH that does not impair cognitive functioning or cause/worsen hallucinations would be informative for treatment decisions for clinicians and patients when discussing risk/benefit analysis for medications for CIH.

3. To establish a tolerable treatment for CIH. All anticholinergics have peripheral nervous system actions (blurred vision, impaired micturition etc.) (13) and increase the risk of constipation (already high with clozapine (14) and the risk of life-threatening paralytic ileus (15). Our proposal has been informed by PPIE on this issue and we will use a number of assessment measures to collect data on the widest range of potential ADRs.

6 AIMS

6.1 Objectives

6.1.1 Primary Objective

1. To ascertain efficacy of either hyoscine hydrobromide or glycopyrrolate in comparison to placebo in the treatment of CIH.

6.1.2 Secondary Objective(s)

2. To establish which of glycopyrrolate or hyoscine hydrobromide, if any, is associated with fewer cognitive side-effects using a validated assessment measure.
3. To establish which of glycopyrrolate or hyoscine hydrobromide, if any, is associated with fewer ADRs.

6.1.3 Exploratory Objectives

4. To establish whether clozapine plasma levels are associated with CIH.

6.1.4 Open Label Objectives

5. To increase knowledge of the safety profile of the active IMPs in the treatment of CIH.
6. To establish effectiveness of active IMPs over the open label phase.

6.2 Outcomes

Outcome	**Timing of measurement:** Stage 1: Blinded RCT Stage 2: Unblinded Open Label Phase (optional)	**Method of measurement**	**Objective**
Primary outcome			
Hypersalivation	Stage 1: Baseline, weeks 1, 2, 4, 6, 8, 12 Stage 2: weeks 16, 20, 24	Drooling Rating Scale (DRS)	1, 6
Secondary outcome(s)			
Neuroleptic side-effects	Stage 1: Baseline, weeks 4, 8, 12 Stage 2: 16, 20, 24	Liverpool University Neuroleptic Side- Effect Rating Scale (LUNSERS)	3, 6
Anticholinergic side effects	Stage 1: Baseline, weeks 4, 8, 12 Stage 2: 16, 20, 24	Liverpool Anticholinergic Side-effects Scale proforma (LASS)	2, 5
Sustained attention and Verbal Recognition Memory (VRM)	Stage 1: Baseline, week 12	Cambridge Neuropsychological Test Automated Battery (CANTAB)	2

Nocturnal hypersalivation	Stage 1: Baseline, weeks 1, 2, 4, 6, 8, 12 Stage 2: 16, 20, 24	Nocturnal Hypersalivation Rating Scale (NHRS)	1, 6
Self-esteem	Stage 1: Baseline, week 12	Rosenberg self-esteem scale (RSE)	2
Hospital admission (whether for physical or psychiatric reasons)	Stage 1: Up to 12 weeks Stage 2: Up to 24 weeks	Participant reported AE/SAE or medical records	3, 5
Constipation	Stage 1: Baseline, weeks 4, 8, 12 Stage 2: week 24	Patient Assessment of Constipation – Symptoms (PAC-SYM)	3, 5
Social functioning	Stage 1: Baseline, week 12	Personal and Social Performance (PSP)	2
Symptoms of schizophrenia	Stage 1: Baseline, week 12	Positive and Negative Syndrome Scale (PANSS)	3
Effect and tolerability of treatment	Stage 1: Up to 12 weeks	Premature discontinuation of study treatment and a decision to continue with study treatment post 12 weeks	3
Discontinuation of clozapine	Stage 1: Up to 12 weeks Stage 2: Up to 24 weeks	Participant reported/medical records	3, 5
Serious adverse events	Stage 1: Up to 12 weeks Stage 2: Up to 24 weeks	Participant reported/medical records	3, 5
Exploratory outcome			
Clozapine plasma levels	Stage 1: Baseline, week 12 (if available)	Clozapine dose and pre-dose blood sample	4

6.3 Internal Pilot

GOTHIC2 incorporates an internal pilot. Our Stop/Go criteria will be evaluated after 12 months of recruitment. Criteria have been informed by recruitment and retention rates observed in GOTHIC1 (36).

1. Consent rate of potential participants greater or equal to than 30%, continue; if less than 30% and a solution exists, then amend; if less than 30% and no solution exists, then stop.

2. Recruitment rate per site per month: if 1.25 or above, continue; if less than 1.25 and a solution exists then amend; if less than 1.25 and no obvious solution exists then stop.

3. Retention rate: if 80% or above continue; if less than 80% and a solution exists then amend; if less than 80% and no solution exists then stop.

7 TRIAL DESIGN

A randomised, double-blind, placebo-controlled, multicentre superiority trial with 1:1:1 allocation ratio to ascertain efficacy of hyoscine hydrobromide or glycopyrrolate in comparison to placebo in the treatment of CIH. Trial treatment duration is 12 weeks with an optional 12 week open-label follow up period.

7.1 Trial Setting

Potential participants will be identified and recruited from mental health Trusts in England (community and in-patients). Assessments will occur in NHS community-based clozapine clinics or, in-patient setting as this is standard care for these patients and provision has been made for the trial research assistants to make home visits if required (if participants are unable to attend the clozapine clinic).

7.1.1 Selection of Participating Sites

Criteria for the selection of sites will be determined by the TMG and will be described in a separate document 'Site Suitability Assessment' maintained in the TMF.

Sites fulfilling the trial-specific criteria will be selected to be recruitment sites for the trial and will be opened to recruitment upon successful completion of all global (e.g. REC and MHRA) and trial-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

- Positive Capacity and Capability Assessment by Research and Development (R&D) Department.
- Completed Research Site Agreement.
- Completion and return of 'Signature and Delegation Log' to LCTC (paper/electronic).
- All staff contributing to the trial must have valid certified GCP training throughout the conduct of the trial.

7.1.2 Selection of PIs

PIs will be required to demonstrate equipoise, relevant experience and commitment during early stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the trial in accordance with the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation.

A suitable co-investigator should be identified at each site to deputise in case of PI absence.

8 ELIGIBILITY CRITERIA

GOTHIC2 trial target recruitment is based on the sample size calculations described in Section 12. All participants must provide written, informed consent before any trial procedures occur (see Section 10.2 for more information regarding informed consent processes).

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. Waivers to eligibility are not permitted. All queries about participant eligibility should be directed to the Trial Manager (gothic2@liverpool.ac.uk) before randomisation.

8.1 Inclusion Criteria

1. Aged 18 to 65 years inclusive.
2. English speaking.
3. Prescribed clozapine for a minimum of three months.
4. Experiencing hypersalivation with a minimum score of 4 on the Drooling Rating Scale (DRS) and are either:
   (a) Currently not receiving treatment for CIH
   OR
   (b) Receiving drug treatment for CIH and agreeable to a 48-hour washout period
5. Written and informed consent obtained from participant (with capacity and ability) and agreement of participant to comply with the requirements of the trial prior to study specific procedures.

8.2 Exclusion Criteria

1. Medical conditions that could influence hypersalivation (e.g. Parkinson's Disease).
2. Neurological conditions that could affect cognitive functioning during the course of the study (e.g. unstable epilepsy).
3. History of an allergic reaction to hyoscine hydrobromide.
4. History of an allergic reaction to glycopyrrolate.
5. Known contra-indications to hyoscine or glycopyrrolate as stated in the British National Formulary:
   (a) Prostatic enlargement
   (b) Myasthenia gravis
   (c) Pyloric stenosis
   (d) Paralytic ileus
   (e) Glaucoma
   (f) Hepatic Impairment
6. Known cautions to hyoscine or glycopyrrolate as stated in the British National Formulary:
   (a) Chronic heart failure
   (b) Stomach ulcer
   (c) Ulcerative colitis
   (d) Significant liver disease that in the opinion of the CI or PI is a contraindication
   (e) Down's syndrome

(f) Arrythmia and/or history of myocardial infarction
(g) Overactive thyroid gland.
(h) Unstable angina

7. Current prescription for a) potassium chloride, b) digoxin, c) amantadine, d) levodopa e) Tricyclic antidepressants or f) Monoamine oxidase inhibitors
8. Pregnant, trying to conceive and/or breastfeeding.
9. Sexually active heterosexual patients who are unable or unwilling to use contraception during the study (see section 10.4).
10. Participation in another drug study within the preceding 12 weeks (or within 5 half-lives of an IMP, whichever is longer) or use of other investigational drugs.
11. Active suicidal ideation as assessed within usual care.
12. Known sensitivity to any interventions or excipients.
13. Known history of intestinal obstruction.
14. Known history of urinary retention.
15. Severe renal impairment (eGFR <30 ml/min/1.73m2).
16. Known history of brain tumour or encephalitis.

8.3 Co-enrolment Guidelines

To avoid potentially confounding issues, participants must not be recruited into other drug trials during their participation in GOTHIC2.

9 TRIAL INTERVENTIONS

Eligible patients will be randomised between hyoscine hydrobromide, glycopyrrolate and placebo. Both the IMPs and placebo are administered orally twice daily in the first week of treatment and then three times daily for 11 weeks. The trial is blinded so active and placebo bottles will be labelled with Annex 13-compliant labels.

IMP will be procured and packaged by Sharp Clinical Services UK in accordance with all applicable guidelines and as delegated by Sponsor.

9.1 Description of Non-Investigational Medicinal Product (nIMP)

Clozapine (any formulation/manufacturer, determined by local availability and prescribing practice) is classified as a nIMP for the GOTHIC2 trial.

9.1.1 nIMP Preparation, Dosage, Administration and Dose Modification

As nIMPs do not fall within the definition of investigational medicinal products, clozapine should be dispensed and destroyed in accordance with local legislations and requirements.

9.1.2 Stopping Clozapine Treatment

Participants who stop taking clozapine will discontinue trial treatment but continue follow-up as planned (see section 10.10.1).

9.1.3 nIMP Accountability

Clozapine dose and frequency prescribed to participants in GOTHIC2 will be recorded in the eCRF.

9.2 Description of the Interventions

9.2.1 Hyoscine hydrobromide (hyoscine)

Hyoscine hydrobromide (hyoscine) is authorised in the UK and the marketing authorisation holder is Dexcel®-Pharma Ltd. [MA No: PL 14017/0299]. This is an anti-muscarinic agent readily absorbed from the gastro-intestinal tract and the formulation is licenced for use for the prevention of travel sickness, though it is established (off licence) practice to treat CIH with hyoscine.

Brand name / Active ingredient:	Kwells / Hyoscine Hydrobromide
Formulation:	Capsule: Over-encapsulated Hyoscine Hydrobromide 300 mcg tablet with Lactose & Magnesium Stearate blend for oral administration
Dose: *	Week 1: 300 micrograms (1 capsule) twice daily Week 2-12: 300 micrograms (1 capsule) three times daily
Manufacturer:	Sharp Clinical Services UK

Packaging, storage:	Supplied in bottles with child-resistant tamper-evident (CR/TE) caps Do not store above 25°C
Supplier's name:	Sharp Clinical Services UK
Regulatory Status:	Market Authorised [MA No: PL 14017/0299]

* This is the dose range recommended in the BNF as off license use for hypersalivation and in the Maudsley Prescribing Guidelines (37) for the treatment of CIH and is consistent with current prescribing practice.

9.2.2 Glycopyrronium bromide (Glycopyrrolate)

Glycopyrronium bromide is authorised in the UK and the marketing authorisation holder is Dawa Limited. [MA No: PL 30684/0125]. It is an anti-muscarinic agent, and the therapeutic indication in the UK is for the symptomatic treatment of severe hypersalivation due to chronic neurological disorders of childhood onset in patients aged 3 years and older. In the UK it is used off-licence for the treatment of CIH.

Brand name / Active ingredient:	Glycopyrronium bromide
Formulation:	Capsule: Over-encapsulated Glycopyrronium bromide 1 mg tablet with Lactose & Magnesium Stearate blend for oral administration
Dose:**	Week 1: 1 mg (1 capsule) twice daily Week 2-12: 1 mg (1 capsule) three times daily
Manufacturer:	Sharp Clinical Services UK
Packaging, storage:	Supplied in bottles with child-resistant tamper-evident (CR/TE) caps. Do not store above 25°C.
Supplier's name:	Sharp Clinical Services UK
Regulatory Status:	Market Authorised [MA No: PL 30684/0125]

**This dosing schedule is based on findings from GOTHIC1 feasibility study (36) that showed it to be acceptable to study participants and informed by an evidence summary produced by The National Institute for Health and Care Excellence (38). NICE evidence summaries are for off-label or unlicensed medicines where there are no licensed alternatives. This evidence summary applies to patients with cerebral palsy.

9.2.3 Placebo

Brand name / Active ingredient:	Placebo
Formulation:	Placebo capsules filled with Lactose & Magnesium Stearate blend for oral administration
Dose:	Week 1: 1 capsule twice daily Week 2-12: 1 capsule three times daily

Manufacturer:	Sharp Clinical Services UK
Packaging, storage:	Placebo capsules are supplied in bottles with child-resistant tamper-evident (CR/TE) caps. Do not store above 25°C.
Supplier's name:	Sharp Clinical Services UK
Regulatory Status:	Unlicensed

9.3 Drug Storage and Supply

9.3.1 Trial supplies:

Supplies will be procured, packaged, labelled for trial use and distributed to sites in accordance with all applicable guidelines and as delegated by Sponsor to:

Sharp Clinical Services UK
Heads of the Valley Industrial Estate,
Unit 28 Heol Klockner,
Rhymney,
Tredegar NP22 5RL

9.3.2 Packaging:

The active trial IMP(s) and placebo capsules will be packaged in identical bottles with child-resistant tamper-evident (CR/TE) caps by Sharp Clinical Services UK, in accordance with the applicable regulations.

9.3.3 Labelling:

Bottles containing trial IMP(s) and placebo capsules will be labelled by Sharp Clinical Services UK with Annex 13-compliant labels. Unblinded, secondary tear-off labels will be used; the tear-off portion will be removed by local pharmacy in order to prevent disclosure of contents outside of pharmacy. Each bottle will be labelled and used for GOTHIC2 trial use only.

9.3.4 Shipment:

Shipments will be transported with temperature monitoring in a temperature-controlled vehicle. If IMP stock received from the distributor is unexpected, wrong, damaged or not within expiry dates, the stock should be quarantined and LCTC contacted for further actions (see 9.12).

9.3.5 Regulatory Release to Site:

QP release will be performed by Sharp Clinical Services UK. A separate document will be generated to detail how the drug will be distributed. A QP release certificate will be included with the first shipment to site.

9.3.6 Storage and Stability:

The IMP/Placebo should not be stored above 25°C. The storage area at site must have adequate control of the temperature in order to maintain stability and potency of study drug supplies. The storage area

must be equipped with calibrated thermometers which record daily maximum and minimum temperatures. Once dispensed to participants no further temperature monitoring will be performed.

9.3.7 Post-Trial Access to IMP:

After the 12-week trial treatment period participants will stop their blinded trial medication and will be given the option to either revert to usual NHS care, where they will receive the usual treatment provided by their treating psychiatrist, or to continue their allocated medication (if available to prescribe at their Trust) for a further 12 weeks in an unblinded, open label follow up period (see 9.15).

9.4 Preparation, Dosage and Administration

Prescribing and Dispensing

The allocated treatment will be dispensed by the local trial pharmacist after receiving a trial specific prescription. A 48-hour wash-out period is required prior to randomisation if a participant is on existing medication for CIH. There will be 3 dispensing visits for each participant's trial treatment:

NB. T4 and T8 visits must be planned to ensure participants do not run out of medication as minimal IMP overage (7 capsules) only exists in the first dispensing

Dispensing Visit	Timepoint	Administration
First dispensing	T0: Clinic / Home Visit	Participants will be dispensed 1 bottle with sufficient IMP/placebo for 4 weeks of treatment. Dosage (oral): Week 1: 1 capsule twice daily Week 2-4: 1 capsule three times daily
Second dispensing*	T4: Clinic / Home Visit	Participants will be dispensed 1 bottle with sufficient IMP/placebo for 4 weeks of treatment. Dosage (oral): Week 5-8: 1 capsule three times daily
Third dispensing*	T8: Clinic / Home Visit	Participants will be dispensed 1 bottle with sufficient IMP/placebo for 4 weeks of treatment. Dosage (oral): Week 9-12: 1 capsule three times daily

* The trial treatment may be dispensed to the participant in the hospital/clinic setting or may be collected by the delegated trial Research Assistant (or CRN support) for delivery to the participant during a home visit. Once dispensed to participants no further temperature monitoring will be performed.

9.5 Treatment Modifications

Participants in the trial should not be prescribed any other CIH treatment.

9.6 Dose modifications

Participants are prescribed two capsules per day in week one and three capsules per day from week two until end of treatment at week twelve. Should the treating clinician have any concerns about tolerance then the dose may be reduced in week one to one capsule per day and dose can be reduced in weeks 2-12 to one or two capsules per day. The reduction and reason for reduction should be recorded in the appropriate eCRF.

Participants who discontinue clozapine treatment should also discontinue trial treatment. The discontinuation of trial treatment, and reason, should be recorded in the appropriate eCRF.

9.7 Accountability Procedures

Drug accountability logs will be maintained by each site's pharmacy team throughout the trial; pharmacy will maintain an overall inventory of stock received, dispensed, returned, destroyed and quarantined.

If any stock expires at the trial site during the trial or any surplus stock remains at the trial site at trial closedown, this must be notified to the LCTC who will authorise destruction. Stock will be destroyed locally according to site policy and documented in the drug accountability records.

Additional accountability processes are provided in the GOTHIC2 Pharmacy Manual.

9.8 Assessment of Compliance

Participants will be invited to bring medicines with them during in-person visits for compliance and reconciliation checks, where possible. Participants will be provided with information regarding the dosing regimen.

9.9 Dosing Errors (Overdose and Under dose)

9.9.1 Prescription Errors

When a dosing error occurs that results in a serious adverse event due to an overdose, the investigator must complete and submit an SAE form to LCTC (see section 11.4) providing the following information, within 24 hours of being made aware of the event:

- Participant trial number.
- Date/s of dosing error.
- Trial treatment or nIMP.
- Week number (e.g. week 1, week 2 etc).
- Expected Dose.
- Actual Dose.
- Number of days affected by dosing error.
- Whether there have been any SAEs already reported as a result of the dosing error and relevant SAE numbers.

- Whether participant is aware of dosing error.
- Root cause analysis and corrective and preventive actions.

Whenever possible, any decision on unblinding will be made by CI/PI review dependent on clinical severity of overdose unless participant is being treated in an emergency situation and knowledge of the IMP is required to inform treatment (for unblinding procedures see section 9.14).

9.9.2 Missed Dose/s

Any missed doses will be recorded and participants will continue in the trial.

9.9.3 Accidental or Intentional Overdose

Patients with active suicidal ideation are ineligible for the trial. In the unlikely event of an accidental or intentional overdose, the participant will be advised to seek urgent medical attention. Where necessary, a 24/7 automated online code-break service will be available for unblinding information by the clinical team and/or casualty department (for unblinding procedures see section 9.14).

If an overdose is considered to be intentional the participant should be referred to appropriate care as per usual care pathways. Overdoses, beyond e.g. an extra dose being taken in error, that requires medical intervention and/or in opinion of the local PI has been taken with an intent to self-harm should be reported as a Serious Adverse Event.

9.9.3.1 Hyoscine hydrobromide (hyoscine)

Symptoms of overdosage are tachycardia, arrhythmia, blurring of vision and photophobia, urinary retention. Drowsiness is usual but paradoxical stimulation with hallucinations may occur.

Treatment: gastric lavage or induced emesis and symptomatic treatment.

9.9.3.2 Glycopyrronium bromide (glycopyrrolate)

The single-dose toxicity of glycopyrronium has been tested in a range of investigations, although only limited experimental details are available. Participants will be instructed to ensure an accurate dose is taken each time, in order to prevent the harmful consequences of anticholinergic reactions of glycopyrronium seen with dosing errors or overdose.

There is potential toxicity associated with glycopyrronium overdose. In an overdose of glycopyrrolate, standard localised protocols for managing overdoses should be followed and participants advised to seek medical advice.

9.10 Trial Restrictions

Contraception requirements are described in section 10.4.

9.11 Concomitant Medications/Treatments and Specific Restrictions

9.11.1 Medications Permitted

All medications other than those detailed in the current SmPC and below as prohibited medications are permitted.

9.11.2 Medications Not Permitted / Precautions Required

Medications for CIH should not be prescribed during the trial (e.g. hyoscine hydrobromide, glycopyrronium bromide, atropine drops), Patients with a current prescription for potassium chloride, digoxin, amantadine, or levodopa are excluded from the trial. These medications should not be prescribed during the period a participant is in the trial.

Refer to the SmPC(s) ('Special warning and precautions for use') for full information.

9.11.3 Data on Concomitant Medication

Dose and frequency data on clozapine use will be collected. Concomitant medication will be collected at baseline. Any changes in prescribed concomitant medication from baseline will be captured at week 12.

9.11.4 Specific Requirements / Restrictions

Patients taking hypersalivation medication will be discontinued from that medication for a minimum of 48 hours prior to randomisation. This is a sufficient washout period given the 4-hour half-life of the anticholinergics being trialled (39).

Following GOTHIC2 trial completion, a minimum two-week period is advised before a participant is considered for entry into another CTIMP.

9.12 Quality issues with IMP

If a quality issue is found to have occurred with the trial drugs at site or en route to site (e.g. temperature deviation), the trial drugs should be placed in quarantine. The Investigator must inform the Trial Manager gothic2@liverpool.ac.uk of any drug quality issues arising expeditiously.

9.13 Blinding

9.13.1 Details of Blinding

The two active IMP and placebo are each supplied as capsules, packaged and labelled so that they are indistinguishable from each other (section 9.3).

9.13.2 Who is blinded

Participants and site personnel (Clinicians, Research Assistants etc.), other than delegated pharmacy staff, will be blind to treatment allocations. For unblinding procedures see section 9.14.

Within LCTC knowledge of treatment allocation will be restricted to those who have an explicit need to know this information as a requirement to fulfill their role.

Members of the Trial Steering Committee will not see data summaries split by treatment group.

Members of the Independent Data and Safety Monitoring Committee will see data summaries split by treatment group and individual treatment allocations for assessment of safety events to be reviewed in the closed meeting session.

9.13.3 How the blind will be maintained

Blinding of the participant, research assistant and treating physician etc. is achieved by using the trial-specific labelling processes described in Section 9.3.

Randomisation confirmations, other than those issued to pharmacy, will not include information that will unblind the recipients. Hyoscine hydrobromide, glycopyrrolate and matching placebo are over-encapsulated to maintain blinding of participants and site teams with identical expiry dates.

9.14 Unblinding Process during Trial

9.14.1 Emergency Unblinding

This study will be conducted in a double-blind fashion. Hyoscine hydrobromide 300 micrograms, Glycopyrrolate 1mg and matching placebo are over-encapsulated and identical in appearance will be packaged in identical bottles.

In the event of an emergency in which knowledge of the investigational product is critical to the participants management, the blind for that participant may be broken.

Before breaking the blind of an individual participant's treatment, the investigator must be satisfied that it is an emergency and that knowledge of the treatment allocation is necessary, i.e., that it is needed to guide the appropriate clinical management of the participant and will alter the participant's immediate management. In many cases, particularly when the emergency is not investigational product-related, the problem may be properly managed by assuming that the subject is receiving an active product without the need for unblinding.

24 Hour Emergency Unblinding:

In the event of a medical emergency, where ingestion of anticholinergic medication may be relevant in informing the immediate treatment plan, an automated **online** code-break service will be available where the user logs in and enters the participant ID (randomisation number). No user name or password will be required in order to conduct the unblinding. There will be a series of questions to answer such as confirmation the person logging in to unblind is a medical professional, name and contact details, as well as the reason for unblinding etc. (this list is not exhaustive). A notification email alert will be sent to the CI and LCTC GOTHIC2 trial team each time a blind is broken. A limit will be set for a maximum of 3 unblinding requests per day.

Access to the online code break system can be found here: https://apps.lctc.org.uk/gothic2-unblind/

It is recommended that research staff at site contact the LCTC in the first instance (during office hours) if there is any uncertainty about what constitutes an emergency and whether unblinding can be avoided, e.g. if treatment can simply be stopped. Participants who are unblinded do not need to be withdrawn from the study and may continue to participate with follow up assessments. The IMP should be discontinued.

The reason for unblinding must be recorded on the online code break system.

9.14.2 Accidental Unblinding

If accidental/inadvertent unblinding occurs, this must be reported by email to the LCTC who will then respond to determine the following details:

- Date of unblinding;
- Detailed explanation of circumstances;
- Recipients of the unblinding information;
- Action to prevent further occurrence (if applicable)

9.14.3 Planned Unblinding at End of Trial Treatment

At the end of the 12-week trial period participants will be given the option of staying on the medication they have been taking (if available to prescribe at their Trust) or leave the trial.
The treatment allocation will be automatically revealed to clinicians and participants at the recruiting site when all relevant assessments have been completed and the data entered onto the trial database.
Please see section 9.15 for additional information.

9.15 Unblinded Open Label Follow-Up

At the end of twelve weeks of blinded treatment, participants will discuss with the RA whether s/he wishes to remain on the study intervention or stop. Participants will then be unblinded (see 9.14.3). Those participants who opt to continue with their trial treatment at the end of twelve weeks will proceed as follows:

- If in the placebo arm they will exit the trial and any onward treatment will be determined as routine care in discussion with their treating clinician.
- If allocated to one of the active IMPs and this is available to prescribe locally, participants will be asked to consent to the open label phase and they can remain on follow up to week 24.

The open label period is for a maximum of 12 weeks, with assessments at weeks 16, 20 and 24 from randomisation. Dispensing during this phase is sourced from usual NHS hospital stock. The doctor responsible for prescribing IMP for the first 12 weeks needs to ensure at the end of week 12 the patient has sufficient medication to last until review with their regular consultant psychiatrist (appointment to be arranged by the RA).

This may mean a prescriber writing a regular (non-trial) prescription for a small supply until their next review. This only applies to participants (who were not on placebo) who wish to continue on their medication into the open label phase of the trial.

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification and Screening

LCTC will provide a screening log for completion during the trial to document all patients who have been screened. This information is required for enrolling participants and for monitoring purposes.

Posters and leaflets will be available for display in clinical settings providing information about the trial to potential participants. The leaflet may also be stapled to the outside of the bag with clozapine medicines by the pharmacist to raise awareness of the trial.

There is also provision for potential advertising on social media, media boards and digital displays using the same poster and leaflet content.

10.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent must be obtained prior to trial participation (paper or eConsent).

Date(s) of informed consent processes (including date of provision of patient information, details of information provided (titles, version details), randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

The informed consent process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered.

In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent they do not have to give a reason.

10.2.1 Informed Consent Process

Written informed consent will be sought from potential participants or via an equivalent eConsent process.

Potential participants will initially be approached by a member of their treating team and asked if they would like to receive information about the trial. Potential participants will then be seen by a Research Assistant or member of the local research team.

An ethically approved written information sheet will be provided. This includes a detailed explanation of the trial and makes clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise.

After verbal and written information has been provided, the individual seeking consent will ensure that the potential participant has fully understood all the information and will ask if they are happy to agree to participation in the trial.

Where this is the case, written informed consent will be obtained by means of a dated signature on the consent form by the potential participant. This should be countersigned and dated by the person who obtained informed consent, i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

The original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:

- One copy provided to the potential participant for their information,
- One copy securely transferred to the LCTC
- One copy filed in the participant's medical records paper/electronic.

Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.

Potential participants must be consented prior to completing DRS assessment to confirm eligibility.

In addition, potential participants who are prescribed existing medication for the treatment of CIH must be consented before undergoing a 48-hour washout period prior to randomisation.

10.2.2 Loss of Capacity during Trial

For participants who have consented to the trial and then subsequently lose mental capacity, their original consent endures and new consent from a Legal Representative will not be required. They should be monitored for any signs of objection or distress during trial-specific procedures that would prompt a reconsideration of their continued participation. This would also be the case if their nominated relative raised concerns regarding their continued participation.

10.3 Eligibility Assessment and Confirmation

Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log and must not occur until fully informed consent is documented. Eligibility criteria are described in detail in Section 8.

Eligibility confirmation must be documented in the participant's medical notes and on the trial's Eligibility eCRF. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (i.e. randomisation). Protocol eligibility waivers are not permitted.

10.4 Contraception

The safety of hyoscine hydrobromide (hyoscine) or glycopyrrolate in pregnancy has not been demonstrated and the use of glycopyrrolate during pregnancy and breastfeeding is contraindicated.

Women of Child Bearing Potential (WOCBP) entering into this trial must agree to use a highly effective method of contraception preferably with low user dependency for at least 5 days following end of trial treatment after the last dose of hyoscine or glycopyrrolate.

Definition of WOCBP: fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an

alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly effective contraception for WOCBP is required. Some acceptable contraception methods are listed below;

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable*
- intrauterine device (IUD)*
- intrauterine hormone-releasing system (IUS)*
- bilateral tubal occlusion*
- vasectomised partner*

**These contraception methods are considered to be low user dependency.*

Male participants with a WOCBP partner should use a condom during treatment and at least until 5 days after the last dose of hyoscine or glycopyrrolate.

10.5 Baseline Assessments

Baseline assessments should be completed as per the Schedule of Assessments (Section 10.8).
Baseline assessments should be completed after confirmation of eligibility – note that this requires completion of the Drooling Rating Scale.

For participants who were receiving a prescribed medication for CIH a 48-hour washout period is required with the date of last administration of active treatment recorded on the randomisation eCRF.

Routine blood clozapine plasma level sample.

Routinely collected information e.g. medical history / relevant blood test results etc. can be transcribed from the patient's medical notes into the eCRF once appropriate consent has been obtained.

The patient can proceed to randomisation when all baseline assessments have been completed.

10.6 Randomisation

10.6.1 Randomisation Process

Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally by the LCTC to receive either hyoscine hydrobromide, glycopyrronium bromide (glycopyrrolate) or placebo in a ratio of 1:1:1. Randomisation should occur no later than 7 working days following:

a) Eligibility criteria have been fulfilled (and eligibility confirmed by a medically qualified person).
b) Informed written consent has been obtained (and appropriately documented) from the participant.
c) Baseline assessments have been completed.

A personal login username and password provided by the LCTC will be required to access the randomisation system. Designated research staff will be issued with their personal login and password upon completion of training in the use of the system. This training will be coordinated by the LCTC.

When the system requirements (i.e. consent, eligibility and 48-hour wash-out period for existing hypersalivation medication) are confirmed a unique trial number (randomisation number) will be displayed on a secure webpage. An automated email confirmation will be sent to the delegated pharmacy to confirm treatment allocation. Other designated personnel (e.g. RA, Principal Investigator (PI), Chief Investigator (CI), LCTC trial manager) will receive a separate email confirming that randomisation has taken place without revealing treatment allocation.

It is the responsibility of the PI or delegated research staff to inform LCTC and the pharmacy department at their site of impending randomisation to ensure there is sufficient supply of the trial treatments.

Following randomisation, participants should receive their randomised treatment allocation as soon as possible as described in Section 9.

10.6.2 Randomisation System Failure

In the event of a randomisation system failure, the site should contact the LCTC (Monday to Friday between 9:00 to 17:00 excluding Bank Holidays and University of Liverpool closed days) to try to resolve the problem. If the problem cannot be resolved the LCTC will perform central randomisation and randomise the participant using the back-up randomisation system.

10.7 Trial Treatment

Once the research team are made aware of the treatment allocation participants will receive their allocated treatment which should commence within 7 working days following randomisation. This will be administered as described in Section 9.

Care must be taken to maintain the appropriate level of blinding. Unblinding procedures and processes (i.e. in case of suspected reaction) are detailed in Section 9.14.

10.8 Schedule for Assessments and Follow-up

Where possible study visits will be scheduled to align with routine clozapine clinics within the participating site. If required face to face visits can be split over more than one appointment to mitigate intensity of participant burden.

10.8.1 Schedule of Assessments: Stage 1 (Blinded phase)

All assessments and follow up are to be conducted in line with the Schedule of Assessments below:

			Follow-Up Schedule						
Time (Weeks)		**T0**	**T1**	**T2**	**T4**	**T6**	**T8**	**T12**	
Visit Window (days)		*+7/-0 X [1,2]*	*-2 /+7 [3]*		*-4 /+0*	*-4 /+0*	*-4 /+0*	*-7 /+0*	
Visit in person (P) or by telephone (Tel)	**P**	**P**	**Tel**	**Tel**	**P**	**Tel**	**P**	**P**	
Trial Procedures	Screening	T0- Baseline						Completion	Premature Discontinuation
Written Informed Consent		**X**							
Assessment of Eligibility Criteria	**X**	**X**							
Review of Medical History	**X**	**X**							
Review of Concomitant Medications	**X**	**X**						**X**	
Assessment of Adverse Events			**(X)**	**(X)**	**(X)**	**(X)**	**(X)**	**(X)**	**(X)**
Pregnancy Test (Urine)		**(X)**						**(X)**	
Drooling Rating Scale (DRS)		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Confirmation of Full Eligibility		**X**							
Demographics	**X**								
Record clozapine dose and pre-dose clozapine plasma level (see footnotes)		**X**[4]						**(X)**[5]	
Nocturnal Hypersalivation Rating Scale (NHRS)		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Liverpool University Neuroleptic Side Effects Rating Scale (LUNSERS)		**X**			**X**		**X**	**X**	
Liverpool Anticholinergic Side-effects Scale proforma (LASS)		**X**			**X**		**X**	**X**	
Cambridge Neuropsychological Test Automated Battery (CANTAB)		**X**						**X**	
Personal and Social Performance Scale (PSP)		**X**						**X**	
Positive And Negative Syndrome Scale (PANSS)		**X**						**X**	
Patient Assessment of Constipation – Symptoms (PAC-SYM)		**X**			**X**		**X**	**X**	
Anticholinergic Effect on Cognition (AEC)		**X**						**X**	
Rosenberg Self-Esteem Scale (RSE)		**X**						**X**	
Smoking Status		**X**			**X**		**X**	**X**	
Randomisation		**X**[1]							
Trial Intervention: Dispensing		**X**[2]			**X**		**X**	**(X)**	
Trial Intervention: Medicine review					**X**		**X**	**X**	**(X)**
Trial Intervention: IMP accountability		**X**[2]	**X**	**X**	**X**	**X**	**X**	**X**	**X**

(X) As indicated/appropriate.

[1] within 7 working days of baseline assessments
[2] within 7 working days of randomisation
[3] In the event of potential T1 & T2 overlap (if undertaken at + 7 days) it is recommended T2 be postponed for another 7 days. There is flexibility within the schedule for this to happen as the next timepoint is the face-to-face visit at T4.
[4] Within last 3 months prior to baseline - routinely re-test if outside this timeframe, if option available at your Trust
[5] Routinely re-test at T12, if option available at your Trust

10.8.2 Schedule of Assessments: Optional Open label phase (Unblinded)

If the participant opts to continue on their trial medication (subject to availability to prescribe at their Trust) they will be unblinded (see 9.14.3 for planned unblinding) and all assessments and follow up are to be conducted in line with the Schedule of Assessments below:

Time (Weeks)	**T16**	**T20**	**T24**	
Visit Window	*+/- 7 days*			
Visit in person (P) or by telephone (T)	**Tel**	**Tel**	**Tel**	
Trial Procedures			Completion	Premature Discontinuation
Review of Concomitant Medications			X	
Changes in clozapine dose or CIH treatment	X	X	X	X
Assessment of Adverse Events	(X)	(X)	(X)	(X)
Drooling Rating Scale (DRS)	X	X	X	
Nocturnal Hypersalivation Rating Scale (NHRS)	X	X	X	
Liverpool University Neuroleptic Side Effects Rating Scale (LUNSERS)	X	X	X	
Anticholinergic Side-effects scale proforma (LASS)	X	X	X	
Patient Assessment of Constipation – Symptoms (PAC-SYM)			X	

(X) As indicated/appropriate.

10.8.3 Summary of Visits

Face to face Visits (Clinic or home):

Participants will be invited to attend clozapine clinics for treatment visits at:

T0 (baseline) and randomisation (within 7 working days of baseline assessments)
T4 -4/+7 days
T8 -4/+0 days
T12 -7/+0 days

Participants will be invited to attend clozapine clinics at 4, 6, 8 and 12 weeks from randomisation. If possible, these appointments should be arranged at the initial appointment when baseline

assessments and randomisation occur to fit in with routine clinic visits. If appropriate, these visits can be conducted as home visits by the research assistant, if preferable to the participant.

Note that these visits should occur as close to the intended date as possible. Visits should not occur later than intended due to quantity of IMP provided at each dispensing.

The following data should be collected and assessments/activities performed:

Screening

Assessment and potential eligibility criteria should take place at their routine care appointment at the site and the trial database screening log completed. This will provide a record of eligible participants and reasons why not initially potentially eligible.

48 hours washout period required for participants taking prior hypersalivation medication prior to attending for baseline assessments.

- Review of medical history.
- Review of concomitant medication.
- Demographics.

Baseline Visit (T0) (face to face):

At baseline, all procedures should be done ***before*** randomisation.

- Written informed consent & assessment of eligibility criteria.
- Review of medical history.
- Review of concomitant medication.
- Urine Pregnancy Test (for persons of childbearing potential).
- Complete DRS: Drooling Rating Scale.
- Confirmation of full eligibility.
- Record routine clozapine dose and pre-dose clozapine plasma level sample (if within 3 months prior to baseline - routinely re-test if outside this timeframe, if option available at your Trust)
- Assessments for participant/RA completion:
    - NHRS: Nocturnal Hypersalivation Rating Scale.
    - LUNSERS: Liverpool University Neuroleptic Side Effects Rating Scale.
    - LASS: Liverpool Anticholinergic side effects scale proforma.
    - CANTAB: Cambridge Neuropsychological Test Automated Battery.
    - PSP: Personal and Social Performance Scale.
    - PANSS: Positive And Negative Syndrome Scale.
    - PAC-SYM: Patient Assessment of Constipation – Symptoms.
    - RSE: Rosenberg Self-Esteem scale.
    - Smoking status.
- Assessments for RA completion with support from pharmacy if needed:
    - AEC: Anticholinergic Effect on Cognition.
- Date of last dose of CIH treatment for participants requiring a 48-hour washout period.
- Randomisation- date of randomisation defines T0.
- Provision of IMP: Dispensing of study drug (weeks 1-4).

T4: (face to face):

- Provision of IMP: Dispensing of study drug (weeks 5-8).
- Trial medicine review.
- Safety review (see section 11).
- Assessments for participant/RA completion:
  - DRS: Drooling Rating Scale.
  - NHRS: Nocturnal Hypersalivation Rating Scale.
  - LUNSERS: Liverpool University Neuroleptic Side Effects Rating Scale.
  - LASS: Liverpool Anticholinergic Side Effects Scale proforma.
  - PAC-SYM: Patient Assessment of Constipation – Symptoms.
  - Smoking status.

T8: (face to face):

- Provision of IMP: Dispensing of study drug (weeks 9-12).
- Trial medicine review.
- Safety review (see section 11).
- Assessments for participant/RA completion:
  - DRS: Drooling Rating Scale.
  - NHRS: Nocturnal Hypersalivation Rating Scale.
  - LUNSERS: Liverpool University Neuroleptic Side Effects Rating Scale.
  - Liverpool Anticholinergic Side Effects Scale (LASS) proforma.
  - PAC-SYM: Patient Assessment of Constipation – Symptoms.
  - Smoking status.

T12: (face to face): End of Stage 1 (blinded phase)

- Trial medicine review.
- Review of Concomitant medication: record any changes in prescribed medication.
- Safety review (see section 11).
- Urine Pregnancy Test (for persons of childbearing potential).
- Routine blood sample for clozapine plasma level (if additional measure available at your Trust).
- Assessments for participant/RA completion:
  - DRS: Drooling Rating Scale.
  - NHRS: Nocturnal Hypersalivation Rating Scale.
  - LUNSERS: Liverpool University Neuroleptic Side Effects Rating Scale.
  - LASS: Liverpool Anticholinergic Side Effects Scale proforma.
  - CANTAB: Cambridge Neuropsychological Test Automated Battery.
  - PSP: Personal and Social Performance Scale for schizophrenia.
  - PANSS: Positive And Negative Syndrome Scale.
  - PAC-SYM: Patient Assessment of Constipation – Symptoms.
  - RSE: Rosenberg Self-Esteem scale.
  - Smoking status.

- Assessments for RA completion with support from pharmacy if needed:
  - AEC: Anticholinergic Effect on Cognition.
- Consent to Open Label phase if applicable.
- Provision of Open Label phase IMP: Dispensing of study drug if applicable (see 9.15).

Additional considerations:

See section 9.14.3 for planned unblinding at end of 12-week trial treatment.

Research Assistants will need to arrange a handover to routine care appointment with the participants clinical team as close to the week 12 appointment as possible. If this is not available on the same date an interim prescription will need to be requested (see 9.15).

Telephone follow-ups:

Research Assistants will telephone participants at 1, 2 and 6 weeks from randomisation. Telephone appointments will be arranged and conducted by local research teams. For inpatients the Research Assistant will liaise with a ward nurse to arrange either a telephone review or a face to face assessment. The following information should be collected and recorded appropriately, i.e. using the correct eCRF:

- Safety review (see section 11).
- Assessments for participant/RA completion:
  - DRS: Drooling Rating Scale.
  - NHRS: Nocturnal Hypersalivation Rating Scale.

OPTIONAL: Stage 2 (Open Label Phase):

See section 9.15 for unblinded open label follow up.

Research Assistants will telephone participants at 16, 20 and 24 weeks from randomisation. Telephone appointments will be arranged and conducted by local research teams. For inpatients the Research Assistant will liaise with a ward nurse to arrange either a telephone review or a face to face assessment. The following information should be collected and recorded appropriately, i.e. using the correct eCRF:

T16 & T20: Telephone (+/-7 days)

- Review changes in clozapine dose or CIH treatment.
- Safety review (see section 11).
- Assessments for participant/RA completion:
  - DRS: Drooling Rating Scale.
  - NHRS: Nocturnal Hypersalivation Rating Scale.
  - LUNSERS: Liverpool University Neuroleptic Side Effects Rating Scale.
  - LASS: Anticholinergic Side Effects Scale proforma.

T24: Telephone (+/-7 days)

- Review of Concomitant medication: record any changes in prescribed medication.
- Review changes in clozapine dose or CIH treatment.

- Safety review (see section 11).
- Assessments for participant/RA completion:
  - DRS: Drooling Rating Scale.
  - NHRS: Nocturnal Hypersalivation Rating Scale.
  - LUNSERS: Liverpool University Neuroleptic Side Effects Rating Scale.
  - LASS: Anticholinergic Side Effects Scale proforma.
  - PAC-SYM: Patient Assessment of Constipation – Symptoms.

10.8.4 Guidance for different types of assessments

Trial specific Research Assistants (RAs) will be employed to work on the trial with CRN support. All staff conducting assessments need to be on each site Delegation Log for the regional area covered. Assessments will be paper or tablet based. Training will be provided on administration and delivery of the following trial-specific assessments:

Drooling Rating Scale (DRS)
The Drooling Rating Scale (DRS) is a semiquantitative assessment of the amount of drooling, and has been used in studies of drooling in cerebral palsy (40) and Parkinson's Disease patients (41). There are two questions: severity is rated on a five-point scale (never drools, dry to profuse-drooling off the body, and onto objects (furniture, books), whereas frequency is rated on a four-point scale (no drooling to constant drooling), forming a final score ranging from 2 - 9. The scale will be completed at all visit timepoints in face to face and telephone visits by the RA asking the participant questions. The scale can be easily administered without specialist training. The scale takes less than 1 minute to complete. *DRS has been used widely in the literature and is freely available, no permissions required.*

Nocturnal Hypersalivation Rating Scale (NHRS)
The NHRS is a validated five-item scale used to determine patient-reported hypersalivation. Scores range from no nocturnal hypersalivation (score=0) to being awoken at least three times per night due to hypersalivation (score=4) (42). The scale will be completed at all visit timepoints in face to face and telephone visits by the RA asking the participant questions. The scale can be easily administered without specialist training. The scale takes less than 1 minute to complete. *NHRS has been used widely in the literature and is freely available, no permissions required.*

Liverpool University Neuroleptic Side Effects Rating Scale (LUNSERS)
LUNSERS was developed by researchers at the University of Liverpool (43) to indicate the extent of side-effects experienced by patients medicated with neuroleptic drugs. It assesses a wide range of neuroleptics side-effects which is a secondary outcome and the scale is completed at T0 and 3 visit timepoints in stage 1, T4, T8 and T12 and a further 3 visit timepoints in stage 2, T16, T20 and T24. The scale can be completed by the participant or easily administered by members of various health care disciplines without specialist training. The scale contains 51 questions, each graded between 0 (not at all) up to 4 (very much) giving a score range of 0 to 204, LUNSERS takes less than 5 minutes to complete. *Copyright © The University of Manchester 1995. All rights reserved. Licence to use The Liverpool University Neuroleptic Side Effect Rating Scale has been granted by Oxford University Innovation Limited.*

Liverpool Anticholinergic Side-effects Scale Proforma (LASS – trial specific proforma)
This is an assessment tool developed as part of this trial to capture a novel severity of anticholinergic side-effects in both frequency and severity. The scale is completed at T0 and 3 visit timepoints in

stage 1, T4, T8 and T12 and a further 3 visit timepoints in stage 2, T16, T20 and T24. There are, to the best of our knowledge, no validated anticholinergic severity assessment scales. This would be a cross specialty scale that could potentially be used in many drug studies. The assessment will be completed in face to face and telephone visits by the RA asking the participant questions. The scale contains 20 questions, each graded between 0 (not at all) up to 4 (very much) giving a score range of 0 to 80. LASS can be easily administered without specialist training and takes less than 1 minute to complete.

Cambridge Neuropsychological Test Automated Battery (CANTAB)

Cognitive ability will be measured using the CANTAB® (44, 45) cognitive test battery for schizophrenia. CANTAB® assessments provide scientifically validated, highly sensitive, precise and objective measures of cognitive function, correlated to neural networks. The following assessments will be undertaken: 1. Screening test; 2. General memory and learning; 3. Working memory/executive functioning; 4. Visual memory; 5. Attention; 6. Verbal memory; 7. Decision making. CANTAB® is administered via pre-loaded tablet devices supplied by Cambridge Cognition and is completed by the participants. The RAs will complete online training in how to administer CANTAB available on Cambridge Cognition web-site using training videos and documents. Customer Support is available to deal with any queries or questions. The participant will complete the CANTAB® battery at T0 and T12 and completion takes approximately 45 minutes. *Licensing is provided with the purchase of CANTAB®.*

Personal and Social Performance Scale (PSP)

The Personal Social Performance (PSP) scale (46) assesses social functioning across four dimensions (socially useful activities, personal and social relationships, self-care, disturbing and aggressive behaviours). A single-item final score (ranging from 1 to 100) is obtained, with higher values indicating better performance. PSP has proven to be a validated and practicable instrument to describe the course of treatment of patients with schizophrenia in the short, medium, and long term of their disorder. With less than 15 minutes needed, the evaluation is very efficient and practicable for everyday clinical use. PSP will be captured at T0 and T12. The evaluation will be conducted by the RA, no specialist training is required. CI will provide overview and support where required.

PSP: Copyright © Blackwell Munksgaard 2000, managed by Wiley. *Licensing is provided by MAPI Research Trust with the purchase of PSP.*

Positive And Negative Syndrome Scale (PANSS)

PANSS has been widely used in clinical trials of schizophrenia and other disorders and is considered the “gold standard” for assessment of antipsychotic treatment efficacy (47). PANSS is also helpful when studying the effects of medication because it enables determination of which symptoms are being affected. GOTHIC2 will use the six-item Positive and Negative Syndrome Scale (PANSS-6) (48) PANSS is captured at T0 and T12. RAs will attend training events facilitated by a co-applicant (Drake) to learn how to facilitate the interviews. *Licensing is provided with the purchase of PANSS from Pearson Clinical.*

Patient Assessment of Constipation – Symptoms (PAC-SYM)

The PAC-SYM (49) is a validated tool that can be used to understand the severity of patient's constipation and help identify key symptom areas. PAC-SYM is a 12-point assessment where 0=absence of symptom, 1=mild, 2=moderate, 3=severe and 4=very severe. A total PAC-SYM score ranges from 0 to 48 with a low score indicating fewer symptoms and of lower severity. PAC-SYM will be captured at T0 and 3 visit timepoints in stage 1, T4, T8 and T12 and at T24 in stage 2. The participant will be asked to complete the PAC-SYM themselves but can be completed with the help of the RA. The scale takes less than 1 minute to complete. *Licensing is provided by MAPI Research Trust with the purchase of PAC-SYM.*

Anticholinergic Effect on Cognition (AEC)
AEC is a commonly used scale in drug research studies (50). The AEC tool classifies medication according to a 'traffic light' system, giving drugs an individual score of 0, 1, 2 or 3. A score of 0 means the medication has no anticholinergic effect on cognition, and a score of 3 means it has the most effect. This will be completed at T0 and T12 by the RA with support from pharmacy if needed and the score will be recorded on trial-specific eCRF by the RA. Completion takes about 10 mins and no training is necessary. *Permission to use AEC has been granted by Delia Bishara, Consultant Pharmacist, South London & Maudsley NHS Foundation Trust, on behalf of the Medichec developers.*

Rosenberg Self-Esteem Scale (RSE)
RSE is a 10-item scale that measures global self-worth by measuring both positive and negative feelings about the self. The scale is believed to be uni-dimensional. All items are answered using a 4-point Likert scale format ranging from strongly agree to strongly disagree. RSE is considered a reliable and valid quantitative tool for self-esteem assessment (51). RSE is captured at T0 and T12. The participant will be asked to complete the RSE themselves but can be completed with the help of the RA. The scale takes less than 2 minutes to complete. *RSE Copyright: No information*

Smoking Status
It is unknown whether CIH is related to plasma clozapine levels. A confounding factor is that there can be large changes in pre-dose plasma concentrations of clozapine between patients prescribed clozapine, on the same dose, exposed to tobacco smoke. Therefore, participant smoking status (and amount) will be recorded at baseline and week 12.

10.9 Sample Management

10.9.1 Sample Collection

A urine sample for a pregnancy test will be taken from females below 55 years of age at T0 and T12. These samples will not be stored and will be disposed of after use.

10.10 Intervention Discontinuation and Participant Discontinuation / Withdrawal

In consenting to the trial, participants agree to all trial activities including administration of trial intervention and treatment and follow-up assessments / visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

10.10.1 Premature Discontinuation of Trial Intervention

Participants may discontinue treatment for reasons including, but not limited to:

- Participant-led, i.e. request by the participant.
- Participant stops taking clozapine (discontinuation required).
- Unacceptable side effects (see Section 11 for Adverse Event reporting).
- Intercurrent illness preventing further treatment.
- Pregnancy.
- Clinician-led:

- Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion.
- Reasons of non-adherence or non-compliance with treatment or other trial procedures
- Participant meets an exclusion criterion (either newly developed or not previously recognised).

10.10.2 Premature Trial Intervention Discontinuation Procedures

Discontinuation from trial intervention should be reported to LCTC using the 'Change to or Discontinuation of Trial Intervention' CRF. This does not mean discontinuation of the trial altogether, and the remaining trial procedures, follow up assessment / visits and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn, see section 10.10.3). Data to be collected at the time of discontinuation will include the following:

- Assessment of Adverse Events.
- Drooling Rating Scale (DRS).
- Nocturnal Hypersalivation Rating Scale (NHRS).
- Reason for the premature trial intervention discontinuation should be documented on the appropriate CRF.
- The participant should be asked if are willing to remain in this trial for follow-up.
- LCTC should be informed if a participant requests to withdraw from this trial.

10.10.3 Participant Withdrawal from Trial

Participants are free to withdraw from the study at any time without providing a reason, though a reason should be recorded if the participant is willing to provide one. LCTC should be informed via email to gothic2@liverpool.ac.uk and via completion of a Withdrawal eCRF to be returned to LCTC/updated on trial database within 7 days.

If participants express a wish to withdraw from further trial activities, the research team at site should ascertain if this is for all elements of trial follow-up. The trial withdrawal form allows participants to specify which, if any, secondary outcome assessments can still be collected for the trial. In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable.

Where a participant decides that they do not want any further data to be provided for trial purposes, data already collected up to the point of withdrawal will still be used in trial reports and analyses, but no further data will be collected unless required by law (e.g. safety reporting regulatory requirements).

10.10.4 Participant Transfer

If a participant moves address but remains in the geographical area covered by the RA for that site they will continue to remain in the trial.

If the participant moves from the area and is able to transfer to another participating trial site, access to the participant's eCRFs will be made available to the new site. The participant remains the responsibility of the original site until the new site PI has signed the Transfer documentation.

10.10.5 Loss to Follow-up

A participant will be considered lost to follow up if they are not contactable over a four-week period by the site research team.

If a participant fails to attend/facilitate a required trial visit the following actions must be taken:

- Site research staff will attempt to contact the participant and reschedule the missed visit.
- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. min of 5 telephone calls and, if necessary, a headed letter to last known address). These attempts should be recorded in the patient medical notes.
- Standard contact routine: 4 phone calls in first 10 days, then a hard copy letter asking for contact within one week, then a final phone call attempt. If 4 weeks of no contact, then lost to contact. Consider conducting a case note review to identify participants who have not been in contact in case they have relapsed and been admitted to hospital (see section 11 for Safety Reporting).

  If the participant continues to be unreachable they should be considered withdrawn from the trial with a primary reason of lost to follow up and this should be recorded on the appropriate eCRF. The clinical team should be notified at this point.

10.11 Participant Reimbursement

Participants will be given a small financial recompense in shopping vouchers in recognition of their time participating in the trial. The maximum any participant will receive is £75. The baseline voucher will be given to participants at their baseline visit, subsequent vouchers will be provided in accordance with the below schedule:

Timepoint	Voucher Value
Baseline Completion	£25
Week 12 Completion	£25
Week 24 Completion	£25

10.12 End of Trial

The End of the Trial is defined to be the date on which all data for all participants is locked and data entry privileges are withdrawn from the trial database.

Trial closure activities will begin once all participant treatment and follow-up are complete. Alternatively, the trial may be closed prematurely by the TSC, on the recommendation of the IDSMC.

Site and trial closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely.

10.12.1 Trial Discontinuation

In the event that the trial is discontinued, sites will make arrangements for suitable ongoing care in the form of usual treatment offered.

11 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

For the purposes of this study, Adverse Reactions (AR) related to the trial interventions, hyoscine hydrobromide, glycopyrrolate and placebo and all Serious Adverse Events (SAEs) are reportable.

All SAEs will be recorded throughout the study and must be reported immediately (and within 24 hours of knowledge of the event) by entry into the trial database at the participating site via and signed off by the site PI. This includes SAEs related to IMPs and Clozapine (nIMP – see section 11.5.1).

Any trial specific SAE reporting exceptions are detailed in section 11.5.

Suicidal ideation may be anticipated within this patient population and will be monitored and clinically managed as per local site practices. Suicide ideation that meets the definition of serious will be reported as a serious adverse event. If the investigator considers that suicidal ideation is related to the investigational medicinal product (rather than a change arising from the participants mental disorder) and that it is one of the active medications, then the event is a suspected unexpected serious adverse reaction and must be reported as a SUSAR.

11.1 Terms and Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
Serious Adverse Reaction (SAR)	An adverse reaction which meets the definition of serious (see Section 11.4) is a SAR. A SAR event that has been assessed as 'expected' (see Section 11.8) according to the Reference Safety Information (see Table 5) will remain classified as a SAR only, however some Serious Adverse Reactions that are considered 'unexpected' will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).

Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is classed in nature as serious and "unexpected" (i.e. not listed within the Reference Safety Information (RSI) approved for the trial by the MHRA and current at the time of onset of the SUSAR).

11.2 Adverse Events of Special Interest

AEs of special interest (listed in Table 2 below) and AEs that meet the definition of seriousness (see section 11.4) are reportable by the site research team direct to the trial database.

Table 2: Anticholinergic side-effects

Mild or moderate anticholinergic effects	**Severe anticholinergic effects**
<u>Somatic symptoms</u>	**<u>Somatic symptoms</u>**
Reduced sweating	Faecal impaction/paralytic ileus
Blurred vision	Lower respiratory infections requiring treatment with antibiotics
New onset/worsening fatigue	New onset confirmed arrhythmia*
Tachycardia/palpitation	Urinary retention/urinary tract infection
Urinary hesitancy	Myocardial Infarction (heart attack)
<u>Neuropsychiatric symptoms</u>	**<u>Neuropsychiatric symptoms</u>**
Drowsiness	Ataxia
Nervousness, excitement	Delirium
Agitation	Epileptic seizures

*new onset confirmed arrhythmia participants will have to discontinue trial treatment (see 10.10.2).

11.3 Adverse Reactions

Non-serious adverse reactions related to trial treatment and ARs that meet the definition of serious (see section 11.4) are reportable by the site research team direct to the trial database.

11.4 Assessment of "Seriousness"

The assessment of seriousness of safety events must be performed by an appropriately delegated, medically qualified member of the site research team.

An Adverse Event or Adverse Reaction is assessed as serious if it:

- Results in death
- Is life-threatening
    - (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death)
- Requires hospitalisation or prolongation of existing hospitalisation
    - (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations

for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE)

- Results in persistent or significant disability or incapacity
    - (i.e. substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect
    - (in offspring of participants, or their partners, taking the IMP regardless of time of diagnosis)
- Is another important medical event
    - (these may not result in death, be life-threatening, overdose, secondary malignancy or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

11.5 Trial Specific SAE Reporting Requirements

SAEs must be entered into the trial database by the site research team within 24 hours of the site becoming aware.

11.5.1 Reporting requirements for Clozapine (nIMP)

The following events require to be onward reported to MHRA & REC for clozapine:

- A SUSAR that is a possible interaction between clozapine and a trial IMP.
- A SUSAR that might be linked to clozapine or one of the trial IMPs but cannot be attributed to only one of them.
- An AR associated with clozapine that in the opinion of the sponsor is likely to affect the safety of trial participants. This must be reported as an urgent safety measure (see 11.15).

The site research team must indicate on the SAE form if there is thought to be a possible interaction between clozapine and a trial IMP or if the SAR cannot be attributed to only one of them.

11.6 Severity of Adverse Events

All adverse events should be assessed for severity. The assignment of the severity/grading should be made by the investigator (or medically trained delegate) responsible for the care of the participant using the definitions in the table below.

Table 3: Severity Grading

Severity	Description
Mild	Does not interfere with routine activities
Moderate	Interferes with routine activities
Severe	Impossible to perform routine activities

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 11.4. Hence, a severe safety event need not necessarily be a "serious" safety event.

11.7 Assessment of "Causality" - Relationship to Trial Treatments

The assessment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

As the trial is blinded to investigators, assessment will be made against all possible interventions (i.e. active & placebo).

Table 4: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship to the IMP. N.B. An alternative cause for the AE should be given.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication) to the IMP. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship to the IMP (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship to the IMP and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship to the IMP and other possible contributing factors can be ruled out.

Events that are assessed as being possibly, probably or almost certainly related will be classed as "Related" (i.e. having a reasonable possibility of being a causal relationship), and events assessed as unrelated or unlikely will be classed as "Unrelated" (i.e. having no reasonable possibility of being related).

Assessment of causality should be made based on known safety profiles of the IMPs in question (e.g. SmPC(s)) or of other drugs in the same class).

In the case of discrepant views on causality between the treating investigator and others, the MHRA & REC will be informed of both points of view.

The causality assessment of the treating investigator will never be downgraded.

11.8 Assessment of "Expectedness"

There is no requirement for a reporting investigator to assess expectedness. Assessments of expectedness are sponsor's responsibility and are delegated to the LCTC and Medical Reviewer.

An event will be considered unexpected if it is not listed within the relevant document as detailed in the table below, which is current and approved for the trial at the time of the event's onset.

Table 5: Assessment of Expectedness

IMP/Intervention	Document to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Hyoscine (Hyoscine hydrobromide)	Kwells 300 microgram tablets - Summary of Product Characteristics (SmPC) Manufacturer: Dexcel® Pharma Ltd.	Section 4.8, Undesirable effects
Glycopyrrolate (Glycopyrronium bromide)	Glycopyrronium Bromide 1 mg Tablets - Summary of Product Characteristics (SmPC) Manufacturer: Dawa Ltd.	Section 4.8, Undesirable effects
Placebo	Matching placebo manufactured by Sharp Clinical Services	There is no RSI for the placebo. As there are no expected events for the placebo, all events thought to be related to the placebo will be SUSARs.

The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the RSI the event will be assessed as unexpected. Fatal or life-threatening events related to the IMP/Intervention by nature, are deemed unexpected (unless specified in the RSI as such).

11.9 Time Period for Active Monitoring of Safety Events

Active monitoring of safety events experienced by trial participants will be from the time of consent until 7 days from last administration of trial intervention.

IMPORTANT: Any serious adverse event occurring in a trial participant after the end of the "active monitoring" period must continue to be reported by sites to the LCTC if the PI becomes aware of them. Reporting should be in accordance with the timeframes and procedures described in section 11.13.

11.10 Notes on Safety Event Recording

The following events must be recorded for the purposes of the trial:

- An exacerbation of a pre-existing illness.
- An increase in frequency or intensity of a pre-existing episodic event/condition.
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration.
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the trial treatment.
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention.
- Injury or accidents.
- Pregnancy (See section 11.11 for more details).

Do not record:

- Non-related Adverse Events.
- Medical or surgical procedures - the condition which leads to the procedure is the adverse event.
- Pre-existing disease or conditions present before treatment that do not worsen.
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery.
- Overdose of medication **without signs or symptoms.**[1]
- The disease being treated or associated symptoms/signs unless more severe than expected for the participant's condition.

[1]*Note that although overdose of medication without signs or symptoms may be excluded from AE reporting it may still require investigation to ensure other protocol and regulatory requirements are met e.g. for IMP management and administration, or to ensure participant safety. If applicable, refer to appropriate part of Treatment section 9.9 (Overdose).*

***N.B.** If overdose occurred **with** resulting signs and symptoms that meet the protocol criteria for AE/AR/SAE/SAR/SUSAR then they should be reported accordingly (see section 11.4 for more information) and the overdose highlighted to the LCTC team.

The events above do not need recording as the trial is considered low risk. Both hyoscine hydrobromide and glycopyrronium are listed as potential drug treatments for CIH in a widely used prescribing manual for mental health prescribers (37). This is documented in the Risk Assessment.

11.11 Reporting of Pregnancy

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data)

should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc.

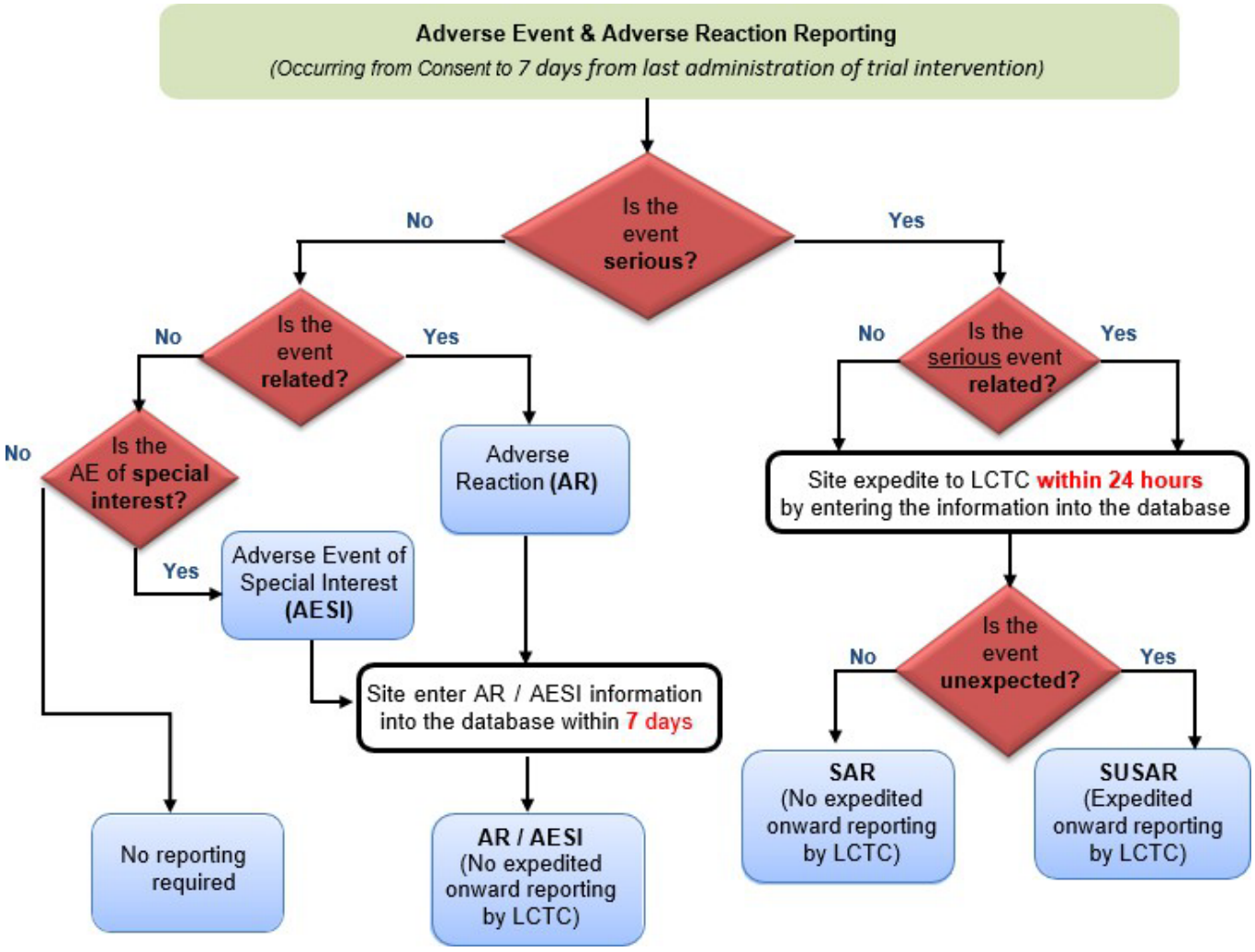
If pregnancy occurs within the active monitoring period described in section 11.9 this must be reported via the database to the LCTC, within 24 hours of the research team becoming aware. All pregnancies and outcomes reported to LCTC will be notified to the trial Sponsor and monitored by trial oversight committees.

11.12 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be reported via the database to the LCTC within 24 hours of becoming aware. Deaths occurring within the activemonitoring period described in section 11.9 are reportable.

11.13 Reporting Procedures

All safety events which are recorded for the trial should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine trial visits, from the participant's notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. SAEs are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below as an overview of reporting procedures for different types of safety events.


Adverse Event & Adverse Reaction Reporting
(Occurring from Consent to 7 days from last administration of trial intervention)
Is the event serious?
No
Yes
Is the event related?
No
Yes
Is the AE of special interest?
No
Yes
Adverse Event of Special Interest (AESI)
Adverse Reaction (AR)
No reporting required
Site enter AR / AESI information into the database within 7 days
AR / AESI (No expedited onward reporting by LCTC)
Is the serious event related?
No
Yes
Site expedite to LCTC within 24 hours by entering the information into the database
Is the event unexpected?
No
Yes
SAR (No expedited onward reporting by LCTC)
SUSAR (Expedited onward reporting by LCTC)

11.13.1 Site Responsibilities

Initial Reports

In addition to below requirements to report to the LCTC, safety events should also be reported to the site R&D team in accordance with local policy.

The site PI is responsible for ensuring that all adverse events (whether or not assessed as serious / related / expected) which the local research team becomes aware of are recorded on eCRFs for trial purposes and reported to LCTC. It is the responsibility of the PI/Co-PI as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events.

All adverse reactions (ARs) and adverse events of special interest (AESI) should be recorded in the database within 7 days of the site becoming aware of the event.

Events which are assessed as "serious" must **also** be recorded in the database **immediately and in no circumstances later than 24 hours from becoming aware**.

The assessments of seriousness and causality must be performed by an appropriately authorised medically qualified doctor. The following is considered the regulatory minimum reporting information and must be provided in initial reports:

- Participant study number.
- Study site identifier and name of reporting site staff member.
- Description of the event, including date of onset.
- For CTIMPs, suspect IMP.
- Seriousness assessment.
- Causality assessment.

N.B. In the absence of a delegated medically qualified doctor the SAE eCRF must be assessed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the SAE and make amendments as appropriate. The initial report shall be followed by detailed follow-up reports.

Follow-up Reports

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable. Where additional information on a SAE is received by site this must be entered into the database within 24 hours of becoming aware of the information.

Sites must respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event.

11.13.2 LCTC Responsibilities

The trial Sponsor, the University of Liverpool, have delegated to LCTC the duty of onward reporting of safety events to REC, MHRA, Sponsor, Host Organisation and company supplying trial intervention.

Safety events which are assessed as "serious", "related" and "unexpected", will be classed as SUSARs and will be onward reported in an expedited manner to MHRA and REC within the following timeframes:

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** of receipt at the LCTC. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.
- SUSARs that are not fatal or life-threatening – **within 15 days** of receipt at the LCTC.

Additionally, SUSARs will be reported to the trial Sponsor, Host Organisation and company supplying trial intervention within agreed timelines.

The PIs at all institutions participating in the trial will be notified of any SUSARs within a reasonable timeline as per LCTC Safety Processing Plan.

The LCTC will submit annual reports containing safety information to REC and MHRA.

Information on safety events will also be reported to TSC/IDSMC. Inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported safety events in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

11.14 Maintenance of Blinding during Safety Reporting

Systems for reporting safety events assessed as "related" (i.e. SAR and SUSAR) should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial.

Design of the trial's SAE eCRFs allow reporting investigators to assess causality without having to unblind the participant – i.e. the investigator will be asked to provide a causality assessment against all possible interventions that the participant may have received. Breaking the blind of investigators will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant.

Events that are assessed serious, unexpected and related to any of the possible interventions will be unblinded at the LCTC prior to onward reporting to Regulatory Authorities.

Unblinding procedures are detailed in Section 9.14.1.

11.15 Urgent Safety Measures (USMs)

An USM is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA via the usual amendment process.

The Sponsor/LCTC will notify the REC and MHRA immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and MHRA, further action will be agreed, which may include submission of a temporary halt, or permanent termination of the trial.

Following notification of a USM, onward reporting to the REC and MHRA is via the combined review service within the new IRAS ('My Studies – My Projects'; report type 'Urgent Safety Measures (USM)'). For USMs that are accepted, a substantial amendment should be submitted (using the Amendment Tool), identifying that the amendment is linked to an agreed USM. If the trial is temporarily halted it may not recommence until authorised to do so by the REC and MHRA. If the trial is halted or permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), the Sponsor/LCTC will notify the REC and MHRA within 15 days of the date of halt/termination.

11.16 Contact Details and Out-of-hours Medical Cover

This trial uses IMPs prescribed as standard NHS practice and inclusion in the trial presents no greater risk than that of standard clinical care for trial participants (hyoscine hydrobromide is standard for CIH and glycopyrrolate is increasingly used and cited as treatment option in Maudsley prescribing guidelines for CIH (Handbook of prescribing for psychiatrists)).

The active IMPs each have well established safety profiles and emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for participants. All participants will be provided with a contact card and copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

12 STATISTICAL CONSIDERATIONS

12.1 Sample Size

12.1.1 Sample Size Calculation

The trial is powered to detect the minimum clinically important difference of one point on the primary outcome measure, the Drooling Rating Scale (DRS), that measures frequency and severity of drooling. Our published pilot data (36) suggest a standard deviation of 1.8 at a given time point and a correlation between repeated measurements of r=0.56. Assuming six post baseline assessments at T1, T2, T4, T6, T8, and T12, a difference in treatment effect of 1 unit on the DRS, a standard deviation of 1.8 and correlation of 0.56, a total sample size of 213 participants (i.e. three arms of 71) is required to achieve 90% power with a 2.5% significance level adjusted to allow for both active treatments to be compared to placebo.

Allowing for 15% attrition requires a total of 252 participants (84 per arm).

12.2 Method of Randomisation

12.2.1 Allocation Sequence Generation

Randomisation will be undertaken by LCTC. The randomisation sequence will be generated using random variable block sizes. The open label period requires unblinding of participants, at 12 weeks and the risk of prediction of the randomisation sequence is mitigated by concealment of block sizes and stratification factors.

12.2.2 Concealment and Implementation of Allocation Sequence

Patient allocations will be irrevocably generated upon completion of the web-based randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial; this takes place after all baseline measurements have been completed.

12.3 Interim Analyses

There are no planned interim analyses for this trial.

Analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an IDSMC. These analyses will be performed at the LCTC. The IDSMC will be asked to give recommendations to the TSC on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

12.4 Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised below:

Analyses will be based on the intention to treat principle as far as is practically possible and corresponding with a treatment policy estimand. Baseline data will be analysed using descriptive statistics only and no formal hypothesis testing will be used. Means and standard deviations, or medians and ranges will be used depending on the underlying distribution of the data. Categorical data will be presented using frequency and percentages.

A p-value less than 0.025 will be used to determine statistical significance for each of the active arms against placebo for the primary outcome DRS. Testing of the cognitive function outcome between active arms will occur if statistical significance of each against placebo is demonstrated. A p-value of 0.05 will be used to declare statistical significance for the comparison of the cognitive function between active treatments. 97.5% and 95% confidence intervals will be used throughout as appropriate.

Primary outcome will be analysed using mixed models to allow for repeated measures. The model will include treatment group, baseline score and randomisation strata. A treatment interaction with the randomisation strata will be considered for inclusion in the model but the trial is not powered to detect this. Premature discontinuation of trial treatments and clozapine withdrawal will be analysed as logistic regression and as a time to event outcome using Cox Proportional Hazards model. Joint modelling will be used to consider time to withdrawal with the DRS. Linear regression will be used to determine relationship between DRS scores and plasma clozapine levels.

Missing data will be monitored throughout the trial and reasons for missing data will be recorded and used to inform ongoing trial conduct to reduce levels observed and within the analysis approach.

Such methods will be fully described in the SAP.

13 DATA MANAGEMENT

13.1 Source Documents

The case report form (CRF) will be considered the source document for data where the information cannot be obtained from the medical records and is recorded directly in the trial specific CRF.

The trial Source Data Checklist will document where the source data for the trial is routinely held. The investigator is required to confirm that the information held in the checklist is an accurate reflection of data collection practices at site. A copy of this checklist should be retained in the Investigator Site File.

13.2 Data Collection Methods

Data are to be entered into an electronic secure web-based trial specific system by approved members of the research team at site.

The following eCRFs are subject to expedited reporting and need to be entered into the trial database within timelines described in 11.13.1:

- Serious Adverse Event.

13.2.1 Questionnaires and Assessments

These are described in section 10.8.1. Assessments will be completed via tablet or paper version. The research team will enter data from these questionnaires and assessments into the electronic secure web-based trial-specific system. Any paper questionnaires and assessments will be stored in the ISF.

14 MONITORING

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan, based on the trial risk assessment, will be developed and agreed by the TMG and CI. This trial has been classed as Type A, low risk, and on-site monitoring will be triggered only.

Site monitoring visits may be 'triggered' in response to concerns regarding trial conduct, participant recruitment, outlier data or other factors as appropriate. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the trial protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- Source data verification.

15 CONFIDENTIALITY & DATA PROTECTION

This trial will collect and process Personal Data of participants. All data will be handled in accordance with applicable data protection legislation, including the UK General Data Protection Regulation (GDPR) and Data Protection Act (DPA) 2018.

The Data Controller organisations for this trial are the University of Liverpool and Mersey Care NHS Trust. The Data Processors for this trial include trial sites.

LCTC is part of the University of Liverpool, which is registered as a Controller with the Information Commissioner's Office.

Data will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.), thereby ensuring data minimisation and purpose limitation. At all times, this data will be handled confidentially and securely.

Data collected at sites and transferred to LCTC will include direct identifiers (e.g. participant names on Consent Forms and Special Category data (i.e. participant medical information on main CRFs). Medical data is subject to a duty of confidence under Common Law. Trial participants consent to the disclosure of their data to researchers as part of the trial's recruitment and consent process.

Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to LCTC by recruiting sites. This transfer of identifiable data is disclosed in the Participant Information. Main CRFs collecting medical data (i.e. Special Category) will be pseudonymised and labelled with a unique trial randomisation number. This data will be collected and stored separately to direct identifiers to ensure pseudonymisation.

Breaches of data protection principles or regulations identified by LCTC will be notified to the trial Sponsor and applicable Data Protection Officers. The following lawful bases for data processing are relied upon: public interest (personal data) and research purposes (special category data).

16 QUALITY ASSURANCE & CONTROL

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each site will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the site to be eligible to be initiated.
- The Trial Manager at the LCTC will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended the trial-specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual site.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG may monitor screening and consent rates between sites and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

16.1 Records Retention

All essential documents created for this trial will be retained for the trial-specific archive period as defined in the trial contracts. This archive period will begin on the official End of Trial date (defined in section 10.12 above).

The PI at each site is responsible for ensuring their site-specific records (trial files, data and source documents) are securely and confidentially retained during the full archive period. If a PI leaves their site (e.g. retires or changes employer) before the end of the archive period, they must transfer responsibility, in accordance with the local site processes and in compliance with the trial contract.

In addition to sites, each team who are delegated duties for the trial will be responsible for securely and confidentially retaining their own trial records for the whole archive period, unless their contracts with Sponsor permit different arrangements (e.g. provision of records to Sponsor for archiving).

17 REGULATORY & ETHICAL CONSIDERATIONS

17.1 Statement of Compliance

This trial will be run in accordance with all applicable legislation, including, but not limited to:

- Principles of GCP.
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended).
- UK GDPR & DPA 2018.
- UK Policy Framework for Health & Social Care Research.
- Human Tissue Act 2004.

17.2 Ethical Considerations

The trial will abide by the principles of GCP and Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone peer review and ethical and regulatory review by an independent REC and by MHRA.

17.3 Approvals

The protocol, participant information & consent materials and any proposed public-facing material will be submitted to an appropriate REC, the Health Research Authority (HRA) and MHRA and trial sites for approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

17.4 Non-Compliances

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and relevant regulatory and ethical e.g. MHRA and REC requirements are handled based on their nature and severity.

17.4.1 Protocol Deviations

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Protocol deviations and other non-serious breaches of GCP, etc. will be managed according to local site and LCTC procedures as appropriate.

17.4.2 Serious Breaches

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants. The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as 'serious' will be reported to MHRA and REC within 7 days by LCTC on behalf of the Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, MHRA or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

18 INDEMNITY

The University of Liverpool holds insurance against claims from participants for harm caused by their participation in this clinical trial. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements. As this is an investigator-initiated trial, the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply.

Clinical negligence is defined as: "A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

19 PUBLICATION AND DISSEMINATION

19.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG.

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

19.2 Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the GOTHIC2 Consortium which will also be named at the manuscript head.

19.3 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and results will be submitted to the MHRA, REC and funder. The trial results will be published regardless of the magnitude or direction of effect. A Lay Summary will be produced and made available via the HRA website.

19.4 Data Sharing

At the end of the trial, after the primary results have been published, the individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers.

IPD will only be shared with external researchers if the participants have consented to this onward disclosure in accordance with the Common Law Duty of Confidentiality, or if the external researchers obtain approval to waive this Common Law requirement (i.e. Section 251 Approval via the Confidentiality Advisory Group (CAG) / approval from the Public Benefit & Privacy Panel for Health & Social Care (PBPP)) or if the IPD has been fully anonymised prior to sharing.

All requests for access to the IPD will be assessed by the Sponsor and must be agreed by all Data Controller organisations. If a request is approved, it will be processed by LCTC.

20 AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
n/a	V1.0	28/11/2023	Original submitted version
	V2.0	16/01/2024	Full Study Title updated for clarification there are 3 possible trial interventions, hyoscine, glycopyrrolate or placebo (REC/HRA) Exclusion criteria 7, 8 & 10 updated (MHRA) Section 10.4 Contraception updated (MHRA) Section 11 Safety Reporting updated (MHRA)
	V3.0	25/01/2024	Section 10.4 Contraception: updated (MHRA instruction) Original approved version
1.	V4.0	03/05/2024	**Outcomes:** Clozapine plasma level analysis changed from a secondary to exploratory outcome. **Section 4.6 Other third party providers:** CANTAB added (per HRA data flow) **Section 10: Participant Timelines & Assessments** **Section 10.8 Schedule for Assessments and Follow-up:** Wording in italics added for clarification to reduce participant burden: Where possible study visits will be scheduled to align with routine clozapine clinics within the participating site. *If required face to face visits can be split over more than one appointment to mitigate intensity of participant burden.* **Section 10.8 & 10.9 Translational samples:** • Requirement at baseline (T0) changed from translational sample collection to data capture only of existing routine care measure for clozapine plasma level (if within 3 months of baseline) or routinely re-test if outside this timeframe. • Requirement at T12 changed from translational for clozapine sample collection and analysis to data capture for Trusts who routinely capture this measure more frequently than once a year (such as lead site, Mersey Care). This will provide useful data for a sub-set of participants. • All reference to translational sample collection and custodianship of samples deleted. **Section 12.1 Sample Size Calculation**: clarification provided. Secondary hypothesis deleted in line with request by funders in grant application to match contract (retained in original protocol in error).

			General updates: ISRCTN number: added Lancashire & South Cumbria NHS FT Trust logo: updated EndNote references: corrected Amendment History: updated

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