PROTOCOL FULL TITLE

Olanzapine for young PEople with aNorexia nervosa: An open-label feasibility study to test recruitment, treatment acceptance, adherence, safety and outcome measures assessment and patients' experience to prepare for a definitive randomised placebo-controlled trial (OPEN)

SHORT TRIAL TITLE: OPEN

PROTOCOL VERSION NUMBER AND DATE: V1.3; 02/DEC/2022

RESEARCH REFERENCE NUMBERS

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SIGNATURE PAGE

Trial Statistician
Signature: Date:14/12/2021

Name (please print): Dominic Stringer
Position: Research Fellow (Statistician)

For and on behalf of the Chief Investigator:

Date:
31/01/2021

Signature:
Name: Dr Hubertus Himmerich
.....

KEY TRIAL CONTACTS

Chief Investigator	**Dr Hubertus Himmerich** Address: Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, 103 Denmark Hill, London SE5 8AF, UK, Telephone: +44 (0)20 7848 0187, Email: hubertus.himmerich@kcl.ac.uk (Chief Investigator [CI], UK) This trial has been applied for to the National Institute for Health Research (NIHR) in response to the call "19/76 Antipsychotics for anorexia nervosa." This call was a joint call between the NIHR (UK) and the National Health and Medical Research Council (NHMRC; Australia). Therefore, it has a part that takes place in the UK where Dr Himmerich is the CI and an Australian part.
CO-SPONSORS	King's College London and South London and Maudsley NHS Foundation Trust KCL, lead sponsor: Professor Reza Razavi Vice President & Vice Principal (Research) King's College London Room 5.31, James Clerk Maxwell Building 57 Waterloo Road London SE1 8WA +44 (0)207 8483224 reza.razavi@kcl.ac.uk SLAM Co-Sponsor Mr Dunstan Nicol-Wilson South London and Maudsley NHS Foundation Trust R&D Department Room W1.08 Institute of Psychiatry, Psychology & Neuroscience (IoPPN) De Crespigny Park London SE5 8AF 020 7848 0339 slam-ioppn.research@kcl.ac.uk
Funder(s)	**National Institute for Health Research** (NIHR); Evaluation, Trials and Studies Coordinating Centre; University of Southampton, Alpha House, Enterprise Road, Southampton SO16 7NS, Email: alan.marshall@nihr.ac.uk (Funder UK)

Key Protocol Contributors	**Chief Investigator, Co-Applicants, Prof Sloane Madden**
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i. LIST of CONTENTS

GENERAL INFORMATION	Page No.
TITLE PAGE	1
RESEARCH REFERENCE NUMBERS	1
SIGNATURE PAGE	2
KEY TRIAL CONTACTS	3
i. LIST of CONTENTS	5
ii. LIST OF ABBREVIATIONS	6
iii. TRIAL SUMMARY	7
iv. FUNDING	9
v. ROLE OF SPONSOR AND FUNDER	9
vi. ROLES & RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES, GROUPS AND INDIVIDUALS	10
vii. PROTOCOL CONTRIBUTORS	10
viii. KEYWORDS	12
ix. TRIAL FLOW CHART	13
SECTION	
1. BACKGROUND	15
2. RATIONALE	18
3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS	21
4. TRIAL DESIGN	28
5. TRIAL SETTING	28
6. PARTICIPANT ELIGIBILITY CRITERIA	28
7. TRIAL PROCEDURES	30
8. TRIAL TREATMENTS	39
9. PHARMACOVIGILANCE	42
10. STATISTICS AND DATA ANALYSIS	44
11. DATA MANAGEMENT	49
12. ETHICAL AND REGULATORY CONSIDERATIONS	51
13. DISSEMINATION POLICY	53
14. REFERENCES	54
15. APPENDICIES	60

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AFP-AN	Adolescent Focused Therapy for Anorexia Nervosa
AN	Anorexia Nervosa
AR	Adverse Reaction
BMI	Body Mass Index
CA	Competent Authority
CI	Chief Investigator
CBT-ED	Cognitive Behavioural Therapy for Eating Disorders
CRF	Case Report Form
CRO	Contract Research Organisation
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
ED	Eating Disorder
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraVIGILANCE	European database for Pharmacovigilance
FPT	Eating-Disorder-Focused Focal Psychodynamic Therapy
FT-AN	Family Therapy for Anorexia Nervosa
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MANTRA	Maudsley Anorexia Nervosa Treatment for Adults
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PI form	Participant Information form
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Public and Patient Involvement
PREMs	Patient Reported Experience Measures
PROMs	Patient Reported Outcome Measures
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSCM	Specialist Supportive Clinical Management
SSI	Site Specific Information

SUSAR	Suspected Unexpected Serious Adverse Reaction
TAU	Treatment as Usual
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

iii. TRIAL SUMMARY

Trial Title	Olanzapine for young PEople with aNorexia nervosa: An open-label feasibility study to test recruitment, treatment acceptance, adherence, safety, outcome measures and patients' experience to prepare for a randomised placebo-controlled trial	
Internal ref. no. (or short title)	OPEN	
Clinical Phase	Feasibility Study	
Trial Design	Open treatment of 55 patients, with olanzapine for 12 months. Participants will be examined at baseline, and at 8 weeks, 16 weeks, 6 months and 12 months after start of treatment.	
Trial Participants	Adolescent and young adults (12-24 years old) with AN not responding to TAU, according to NICE, within the first month of treatment	
Planned Sample Size	55	
Treatment duration	12 months	
Follow up duration	12 months	
Planned Trial Period	20 months	
	Objectives	Outcome Measures
Primary	Feasibility: Recruitment and treatment.	Number of patients recruited and treated in different settings (adolescent/adult, inpatient/daycare/ outpatient) who - agree to take olanzapine (un-blinded, real-life conditions) - adhere to olanzapine - complete all study assessments and questionnaires at the five assessment points
Secondary	Test the feasibility of data collection processes for the following data: • Baseline measures • Body weight and BMI • Psychopathology	Completeness, levels of missing data and measurements for the below measures: Baseline measures: • Demographics • Clinical examination measures: • Body weight • Body height • Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) Psychopathology measures:

	• Health economy and quality of life • Drug adherence • Drug safety To use qualitative methods to assess willingness to participate in a blinded, placebo-controlled RCT	• Eating Disorder Examination-Questionnaire (EDE-Q) • Depression Anxiety Stress Scales (DASS); adolescents: Revised Children's Anxiety and Depression Scale (RCADS) • Revised Beliefs about Voices Questionnaire (BAVQ-R; A/a>15 years) • Self-Regulation of Eating Behaviour Questionnaire (SREBQ) General psychopathology measures: • Yale-Brown Obsessive Compulsive Scale (Y-BOCS); adolescents: Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) • Columbia Suicide Severity Rating Scale (C-SSRS) Health economy and quality of life measures: • EQ-5D-Y™ • Child, Adolescent and Adult Service Use Schedule (CAA-SUS) • Eating Disorders Symptom Impact Scale (EDSIS) Drug adherence measures: • Olanzapine plasma level • Pill count Drug safety measures: • Physical examination • Laboratory parameters (Electrolytes and salt/water balance, kidney function, liver function, blood count/bone marrow, plasma glucose and lipid profile) • Epworth Sleepiness Scale (ESS) • UKU-Side Effect Rating Scale (UKU-SERS) CONSORT data: • Screen failure information Withdrawal information
Exploratory	• TAU • Patient experience of	• TAU (types of TAU elements, frequency, length, setting, concomitant medications, co-morbidities) • Patients experience of recruitment and treatment (acceptability and reasons for adherence or non-adherence)

	recruitment and treatment • Exploratory analysis of change in measures over time to inform a future definitive study design	• Exploratory analysis of change in measures listed in secondary objective above over time
Intervention	Olanzapine	
Formulation, Dose, Route of Administration	Tablets, dose: between 2.5 and 10 mg/d, oral administration.	

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
National Institute for Health Research (NIHR); Evaluation, Trials and Studies Coordinating Centre; University of Southampton, Alpha House, Enterprise Road, Southampton SO16 7NS; Email: alan.marshall@nihr.ac.uk	£361,578.52

v. ROLE OF TRIAL SPONSOR AND FUNDER

The NIHR is the funder of this feasibility study. The roles and duties of the funder and the sponsor have been agreed on in the
"RESEARCH CONTRACT BETWEEN SECRETARY OF STATE FOR HEALTH AND SOCIAL CARE AND KING'S COLLEGE LONDON".
The research team will carry out the research for the cosponsors which are King's College London (KCL) and South London and Maudsley (SLAM) KCL and SLAM will have overall responsibility for the initiation and management of the trialThe funder of the UK arm of the study is the NIHR and the funding for the Australian side of the study is the NHMRC. The UK study will be sponsored by King's College London and SLAM while the Australian twin study will be sponsored by the University of Sydney.
The trial design has been delineated in the application of the NIHR in response to the call "19/76 Antipsychotics for anorexia nervosa." It has been reviewed in a 2-stage review process and agreed for funding.

The CI, Dr. Hubertus Himmerich, who is employed by KCL will ensure for the cosponsors the implementation of the trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Trial Management Committees

- Trial Steering Committee (TSC)

  The TSC will be chaired by a very experienced psychiatrist and will also include an independent statistician and patient representative.

- Data Monitoring (and ethics) Committee (DMEC)

To safeguard the interests of trial participants, monitor data collection and safety of OPEN, , the DMEC will receive and review information on the progress and accruing data of OPEN and provide advice on the conduct of the trial to the TSC. Its independent members will be an adult and an adolescent consultant psychiatrist, two PPIs, and a statistician. The chief investigator and the trial manager will attend the open session of the DMEC meetings. The DMEC will be chaired by a very experienced consultant psychiatrist.

- Trial Management Group

The TMG will meet regularly and plan the day-to-day running of the trial. The TMG will consist of the CI and members of the research team including the site clinicians, the researchers, the trial manager, the trial statisticians, and the PPI.

Individuals responsible for the trial management

In the UK, -individuals with managerial responsibility include the CI and the UK co-applicants (see next section), the researcher, and the qualitative researcher which will be appointed after approval of the study.

vii. Protocol contributors

Chief Investigator and Lead Applicant, UK:

- Dr Hubertus Himmerich: Conducted clinical and preclinical studies, e.g., randomized controlled trial (RCT) on olanzapine vs. clozapine, longitudinal obesity study (N=450); Consultant Psychiatrist at an inpatient unit for anorexia nervosa (AN)

Co-Applicants, UK:

- Dr. Dasha Nicholls: Reader in Child Psychiatry at Imperial College London, Consultant Child and Adolescent Psychiatrist, Past Chair of the Eating Disorders Faculty of the Royal College of Psychiatrists: Provided scientific expertise on the treatment of children and adolescents with anorexia nervosa
- Dr. Mima Simic: Consultant Child and Adolescent Psychiatrist; Head of the CAMHS Eating Disorders Service at SLaM: Provided clinical expertise on the treatment of children and adolescents with anorexia nervosa

- Prof Ulrike Schmidt: Leading expert for the development of novel therapies and treatment pathways for people with AN: Contributed to study design, provided scientific and managerial expertise and advise on PPI
- Prof Janet Treasure: Leading expert for family work and carer involvement in AN, chief investigator in large studies for AN with up to 760 participants: Clinical and scientific advice, involve adult patients and carers
- Prof Sabine Landau: Statistician: Renowned expert, has been active in AN research: contributed expertise and knowledge in medical statistics and trial design
- Dr. Dilveer Sually: Experienced trial coordinator: Has been involved in trial proposal development using trial experience, education and qualifications
- Miss Jessica Bentley: PPI with lived experience of AN: advise on all aspects of trial cycle drawing on lived experience and a science background
- Dr. Vanessa Lawrence: Senior Lecturer in Qualitative Social Sciences, expert in qualitative methods to develop and evaluate complex interventions in the field of mental health: Advised on the qualitative research aspects of this study
- Professor Allan Young: Professor in Mood Disorders, KCL; world-leading expert in psychopharmacological research and specifically clinical studies: give advice on study design, psychopharmacology, assessment and clinical data evaluation

Co-Applicant and Chief Investigator, Australia:

- Prof Sloane Madden: Associate Professor, University of Sydney; leads the largest public eating disorders service in Australia, will recruit adolescent and adult patients for the Australia arm of the study

Further Contributors:

- Professor Sarah Byford, KCL: Health economist with strong track record in eating disorders research
- Miss Aylin Unlu: 2nd PPI
- Prof Evelyn Attia, Columbia University, New York, USA: Advice and access to data for this proposal
- Dr. Aditya Sharma, Clinical Senior Lecturer and Honorary Consultant in Child and Adolescent Psychiatry, Newcastle University: Psychopharmacological advice
- Ms. Hiba S. Mutwalli, BSc, MSc, ANutr, dietitian, and Ms. Sevgi Bektaš, psychologist. Both are PhD students of Dr Himmerich and Prof Treasure. Both will help with recruitment, data evaluation and publication
- Ms. Briana Applewhite, BSc, MSc: Researcher assisting in writing study protocol, ethics applications and preparation of study alongside trial manager
- Ms. Olena Said, PhD: Trial manager and research worker assisting in writing the study protocol and supporting trial documentation, regulatory applications and study set up and execution.

PPI contribution:

PPI made significant contributions to the ideas, decisions and drawing up of this proposal and will continue to guide the study until publication and presentation of the results:

- Trial team includes two patients with lived experience of AN. One has a professional background in science (Miss Bentley, co-applicant). She has helped review the literature, design the study, conduct a chart review on olanzapine-treated inpatients, develop questionnaires assessing patient and carer views on medication for AN [2,3], and facilitate a workshop at the National Carers Conference 2017
- Miss Bentley and Dr Himmerich facilitated a workshop with patients, carers and professionals at the Eating Disorders International Conference (EDIC) 2018 to discuss the topic of this study proposal.

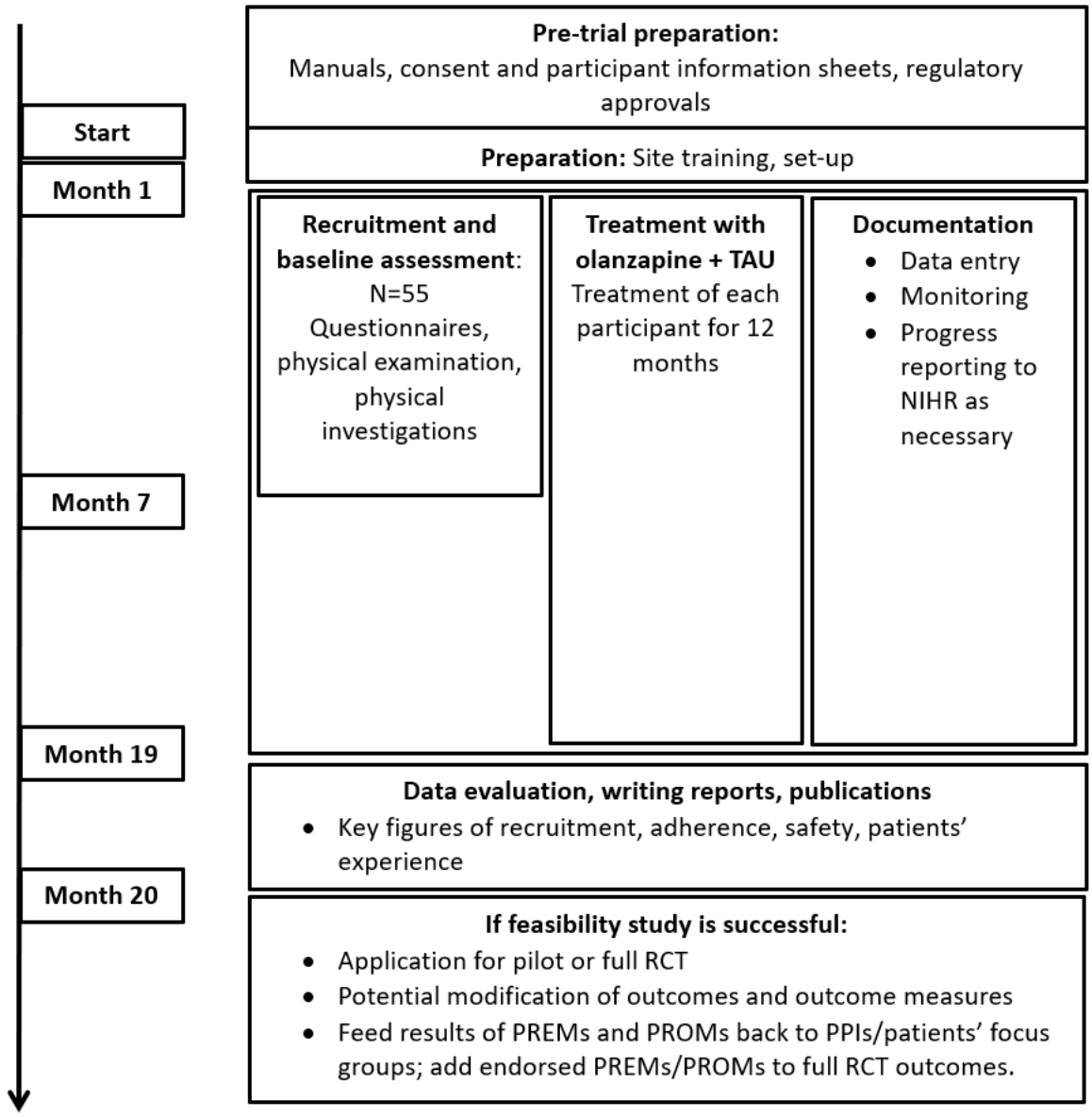
- 36 patients with AN and 37 carers have completed the respective questionnaire. From their answers, we identified important outcome parameters: anxiety, mood, and sleep disturbances [38].
- Two independent focus groups of 18 inpatients and 8 inpatients, respectively, with AN to discuss the study and willingness to take part in a trial on olanzapine treatment
- Spoken and recorded feedback from five service users who had previously taken olanzapine
- 2 PPIs from the Research Design Service London gave feedback for this application.

viii. KEY WORDS

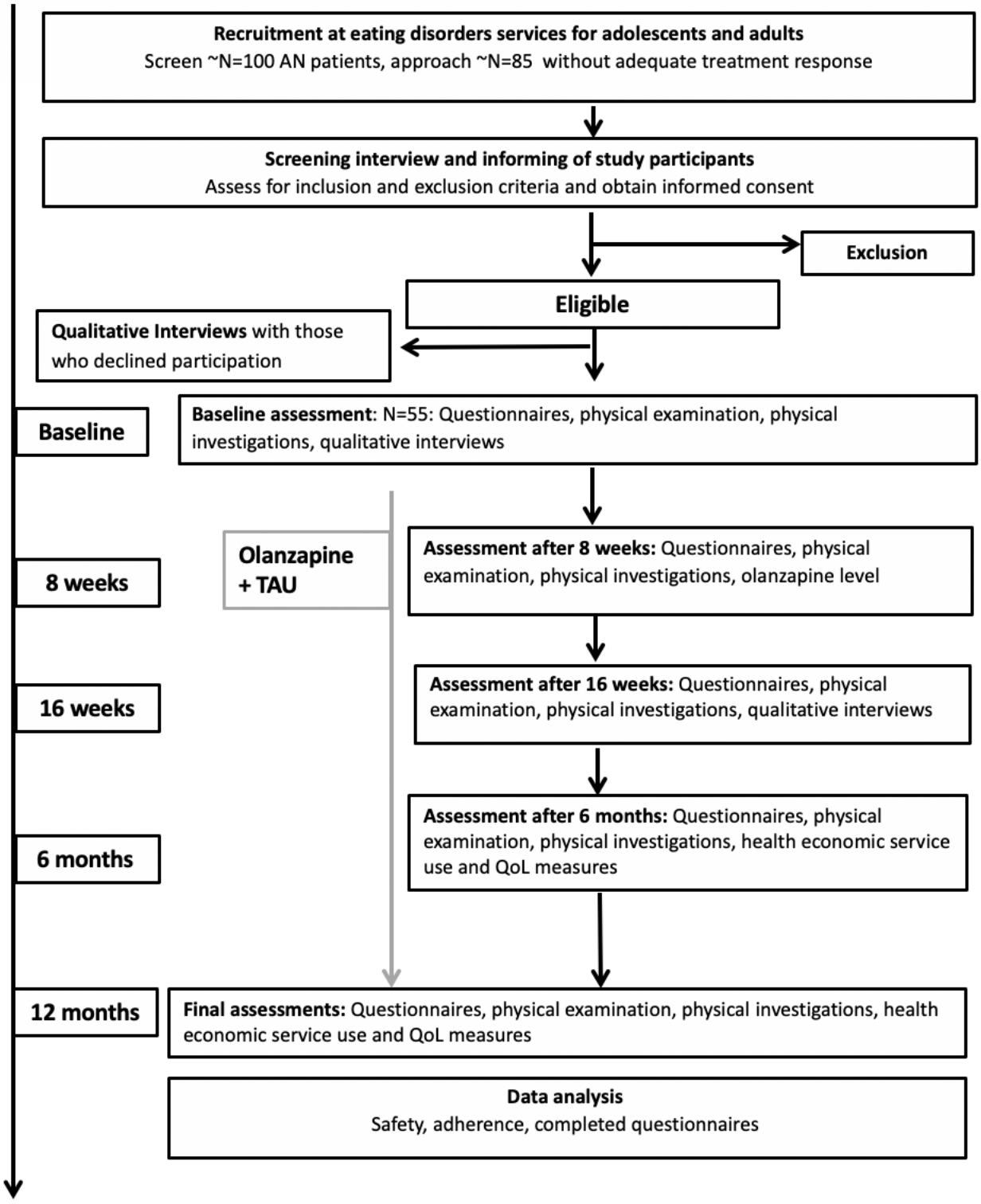
Eating disorders, Anorexia nervosa, Antipsychotics, Psychopharmacology, Olanzapine, Feasibility.

ix. TRIAL FLOW CHARTS

Flow chart 1: Time schedule of the trial



Flow chart 2: Time schedule of study participants



1. BACKGROUND

1.1 Need for research to improve the treatment of anorexia nervosa

Anorexia nervosa (AN) is a serious mental disorder associated with high mortality, morbidity, and treatment costs.
NICE (2017) guidelines state there is very limited evidence for the pharmacological treatment of AN and does not recommend the use of psychotropic drugs for the promotion of weight gain.
In NHS clinical practice, however, antipsychotics are routinely prescribed off-label despite the considerable uncertainty of the balance of benefits and harms associated with these drugs.
There is a need to improve treatment for patients AN, and antipsychotics may offer a decisive improvement in patient therapy. However, there is insufficient data available regarding the efficacy and safety of antipsychotics in this patient group to recommend the use of any antipsychotic for the treatment of AN at present [1]. Moreover, published studies regarding treatment with antipsychotics for AN do not cover changes in general psychopathology, health economic and quality of life-related aspects of this therapy.
As stated in the HTA call 16/97, AN is a major health problem specifically in young women. Common comorbid conditions, such as depression, anxiety, and substance use disorders, add significantly to the burden, and the impact on families and carers is devastating. The above statement can be substantiated by the current scientific literature which shows that the prevalence of AN is approximately 1-4% among women [2]. The peak incidence is at an age between 14 and 17 years [3]. AN is frequently associated with depressive disorder [4], anxiety disorders [5], obsessive-compulsive disorder (OCD) [6], and autism spectrum disorder [7].
Moreover, the course of AN is often chronic and this can lead to persistent disability [8]. A recent longitudinal cohort study showed that only about 30% of patients with AN had recovered after 9 years [9]. The dietary deficit is often accompanied by significant physical health issues, such as growth retardation, osteopenia, amenorrhoea, and renal insufficiency, and also changes in laboratory parameters, cardiac arrhythmia and disturbances of the thyroid function [10]. The most common causes of death in patients with AN are sudden cardiac death associated with ventricular arrhythmias and suicide [11-13]. Mortality rates are nearly six times higher for people with AN than in the general population, and in people aged 15-24 years old, the mortality risk from AN is higher than for other serious diseases in adolescence, including asthma or type 1 diabetes [8,14].

1.2. Studies of antipsychotics in AN

We systematically reviewed clinical trials on antipsychotics in AN using PubMed/Medline and the Web of Science®.
With regard to first-generation antipsychotics (FGA), studies on the use of haloperidol, sulpiride and pimozide for the treatment of AN have been published. Cassano, et al. [15] investigated the effectiveness of haloperidol in 13 severely affected patients with AN. They were given between 1 and 2 mg of haloperidol per day for 6 months in addition to standard treatment. The study was not placebo-controlled. A significant increase in weight, as well as favourable changes in the scores of the Eating Disorder Inventory (EDI), the Eating Attitude Test (EAT) and the Clinical Global Impression and Improvement Scale (CGI-I) were seen after 6 months. Mauri, et al. [16] reported a 9-patient case series of patients with severe, refractory restrictive AN, which meant having a body mass index (BMI) below 13 kg/m2. Patients received between 3.5 and 9.5 mg of haloperidol per day for the duration of their inpatient treatment (up to 4 months). An increase in BMI and subjective clinical improvements in body image disturbance and drive for thinness were observed. However, no comparison data were reported. Neither double-blind,

placebo-controlled cross-over studies on sulpiride [17] nor pimozide [18] reported any significant changes in ED psychopathology.
Studies on the second-generation/atypical antipsychotics (SGA) quetiapine [19,20] and risperidone [21] looked at a wide range of psychological parameters, such as depressive, psychotic, obsessive-compulsive and anxiety symptoms, as well as ED psychopathology; however, they did not find statistically significant superiority of the drug in question in any of these domains when compared with placebo. Ruggiero, et al. [22] investigated amisulpride in comparison to fluoxetine and clomipramine. Patients with AN on amisulpride gained significantly more weight than patients on fluoxetine and clomipramine. However, as fluoxetine and clomipramine have not been shown to be beneficial in AN, and as there was no placebo condition, this study result is difficult to interpret.
A retrospective case-controlled study by Frank, et al. [23] reviewed the treatment and outcome of 106 adolescent inpatients with AN, 22 of whom had been treated with aripiprazole (1–5 mg daily). Those who received aripiprazole were compared with controls across a variety of different parameters, including weight gain, food avoidance and length of admission. It was found that the those taking aripiprazole had a statistically significant greater increase in weight gain. In addition, two case series [24,25] comprising a total of nine patients with AN reported weight gain under aripiprazole.
Five RCTs investigating SGAs examined olanzapine as an active treatment. In 2007, Brambilla, et al. published a double-blind, placebo-controlled, multi-centre trial that looked at the effectiveness of olanzapine in the treatment of AN [26]. The trial involved 35 outpatients with AN. Half of the patients received 1 month of 2.5 mg and then 2 months of 5 mg olanzapine daily, with the other half receiving placebo. Outcome parameters included the results of interviews including the Hamilton Depression scale (HAM-D) and the Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS), in addition to weight. Patients with the binge-purging subtype of AN gained weight significantly during olanzapine treatment. The olanzapine group also exhibited significant improvements in psychopathology, specifically in the HAM-D and in the cluster of compulsive symptoms of the YBC-EDS. Bissada, et al. [27] published the results of another RCT with olanzapine in AN. This study involved 34 patients who received either 2.5–10 mg olanzapine daily or placebo for 10 weeks. It was shown that olanzapine led to more rapid weight gain, with a greater proportion of patients reaching their target BMI, and a faster decrease in obsessive symptoms, as measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Olanzapine did not have any significant effect on the symptoms of depression, anxiety or compulsions. Kafantaris, et al. [28] investigated olanzapine in a small RCT with 15 young patients with AN (age range 12–21 years). The treatment group received between 2.5 and 10 mg of olanzapine daily for 10 weeks. There were no significant differences in weight gain, ED symptoms or the results of general psychopathology assessments between the groups, as measured using the Eating Disorder Examination Questionnaire (EDE-Q), YBC-EDS, HAM-D and the Brief Psychiatric Rating Scale (BPRS). Attia, et al. [29] conducted an RCT with 17 patients with AN in an outpatient setting published in 2011. The participants were >16 years old. Half of the patients were given 2.5–10 mg of olanzapine daily and the other half received placebo for 8 weeks. The results revealed a significantly greater increase in body weight in the patients on olanzapine, but no differences in the scores of several psychopathological scales measuring ED and general psychopathology. The largest RCT on olanzapine treatment for AN was published in 2019 by Attia, et al. [30] and included 152 outpatients with AN, aged between 16 and 65 years with a BMI of 14-18.5 kg/m2. The treatment group received between 2.5 and 10 mg of olanzapine daily for 16 weeks. Significantly higher weight gain was found in the olanzapine group (6.7 kg), compared with the placebo group (4.2 kg) after 16 weeks. Evelyn Attia, the PI of this RCT, has agreed to offer advice and collaborate with us in this proposed project. She has also provided her data to help us with an approximate sample size estimation for a potential RCT on olanzapine in AN. However, there was no significant difference between groups with respect to ED or general psychopathology.
In summary, the RCTs demonstrating statistically significant changes were those involving olanzapine only. Even though a single open trial by Cassano, et al. [15] showed that haloperidol may have a role in treatment of AN, and a retrospective case-controlled study by Frank, et al. [23] made a similar argument

for the use of aripiprazole, no RCT data are available for haloperidol or aripiprazole. Thus, we have decided to test olanzapine in this feasibility study. However, all previous studies of olanzapine in AN have shortcomings, including small samples, a focus mainly on weight gain, rather than changes in psychopathology and the quality of life of patients and carers, and a lack of economic measures. The discussed studies do not allow generalisability across outpatient, day-care and inpatient settings.
Studies investigating olanzapine in patients with AN [26-30] used doses between 2.5 and 10 mg/d. Thus, in our proposed study, we will initiate olanzapine treatment at 2.5 mg/d and continue on this dose or increase the dose slowly to up to 10 mg/d. However, in clinical practice in Adolescent Psychiatry, the starting dose is often 1.25 mg/d. Therefore, we will allow for adolescent patients to start with 1.25 mg/d and maintain this dose. This will be a clinical decision. This dosage is within the British National Formulary (BNF) limits. As the BNF cites caution for people with a slower metabolism and female patients, we propose a slow up-titration schedule (1.25 or 2.5 mg/d increments each week for adolescents and 2.5 mg/d for adults up to a maximum of 10 mg/d for both adolescents and adults). Olanzapine does not come in the form of 1.25mg/d tablets in the UK, so clinicians will be instructed to half the 2.5mg/d tablet and give to patients on initial dosages . This is the dose range we would also apply in an RCT.
We will recommend same down-titration increments after 12 months to improve patient safety. However, it will be a clinical decision outside our study whether patients continue or stop olanzapine treatment.

1.3. Meta-analyses of antipsychotics in AN

A meta-analysis by Kishi, et al. [31] included eight of the above-mentioned RCTs on olanzapine, quetiapine, risperidone, pimozide and sulpride, comprising a total of 221 patients with AN. The pooled data did not show an advantage of antipsychotic treatment over placebo treatment for the outcomes of weight gain, ED psychopathology, depressive symptoms, or anxiety.
De Vos, et al. [32] analysed treatment with antipsychotics, antidepressants and hormonal therapy, in comparison to placebo, when used in addition to psychotherapy. In total, they analysed 18 RCTs involving 869 patients with AN. Among these RCT were five on antipsychotics, four on olanzapine and one on sulpiride. The results showed no statistically significant effect on weight gain for antidepressants or antipsychotics as a group when compared to placebo.
A third meta-analysis on the effects of antipsychotics in AN was performed by Dold, et al. and published in 2015 [33]. It focused on the use of SGAs in AN and included seven RCTs of 201 patients. These comprised four RCTs on olanzapine, two RCTs on quetiapine and risperidone. The results revealed no statistically significant between-group differences for mean BMI change following pooling of the SGAs or when examining the individual drugs. Furthermore, the SGAs failed to differentiate significantly from placebo with regard to the total scores of the Yale-Brown-Cornell Eating Disorders Scale (YBC-EDS) and the Eating Disorders Inventory (EDI). It was concluded that pharmacological treatment of AN with SGAs cannot be generally recommended, although certain individuals or subgroups of patients may benefit from antipsychotic medication.
In an own meta-analysis performed in preparation for this proposal [34], we focused on adherence, drop-out rates and metabolic side effects during treatment with antipsychotics in AN. Only 10 studies had appropriate data on drop-out rates. The pooled dropout rate in the intervention arm from psychopharmacological trials was 28% in people with AN. Personal reasons or factors associated with the study were the most common reason for dropout, not adverse events or metabolic effects.
In summary, meta-analytic research has not found a statistically significant therapeutic effect of FGAs or SGAs as a group. However, the currently available meta-analyses were performed before the latest and largest trial on olanzapine [30] could be taken into account. Thus, even the latest meta-analysis of Dold, et al. is outdated. Compared to personal reasons, drug-related factors such as side effects seem to play a lesser role in the discontinuation of antipsychotic treatment under trial conditions. This suggests

an urgent need to consider and fully examine potential individual and patient-related factors that influence dropout rates in psychopharmacological trials and treatment compliance.

2 RATIONALE

2.1. Clinical considerations on the use of antipsychotics in AN

According to the scientific literature summarised above, olanzapine is the SGA with the highest likelihood to restore weight. It may also treat important psychological and emotional symptoms in patients with AN in a safe way, because:

- Olanzapine is known to have a beneficial influence on anxiety [35,36] and sleep [37]. From a survey of 36 patients with AN and 37 carers, we learned that anxiety and sleep disturbances are important problems for patients with AN [38].
- It has been shown to increase appetite [39], and in patients with schizophrenia, clozapine and olanzapine cause the most weight gain among antipsychotic agents [40,41]. However, clozapine can have severe side effects [42].

We reviewed the medical records of 12 recent inpatients with AN, who received olanzapine within one year. These patients showed a statistically significant increase in weight (4.6 kg) and Body Mass Index (BMI) (1.8 kg/m^2) over 8 weeks [43]. See **Figure 1**.

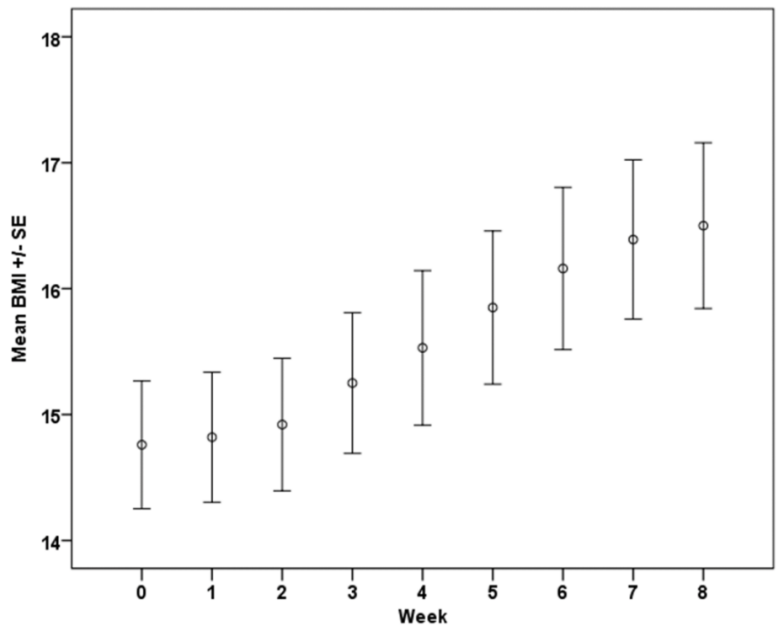


Figure 1 shows the significant increase in BMI in 12 difficult-to-treat AN inpatients treated at our Eating Disorders Unit at the Bethlem Royal Hospital over the course of 8 weeks [43]. Increase in weight: 4.6 kg, increase in BMI: 1.8 kg/m^2.

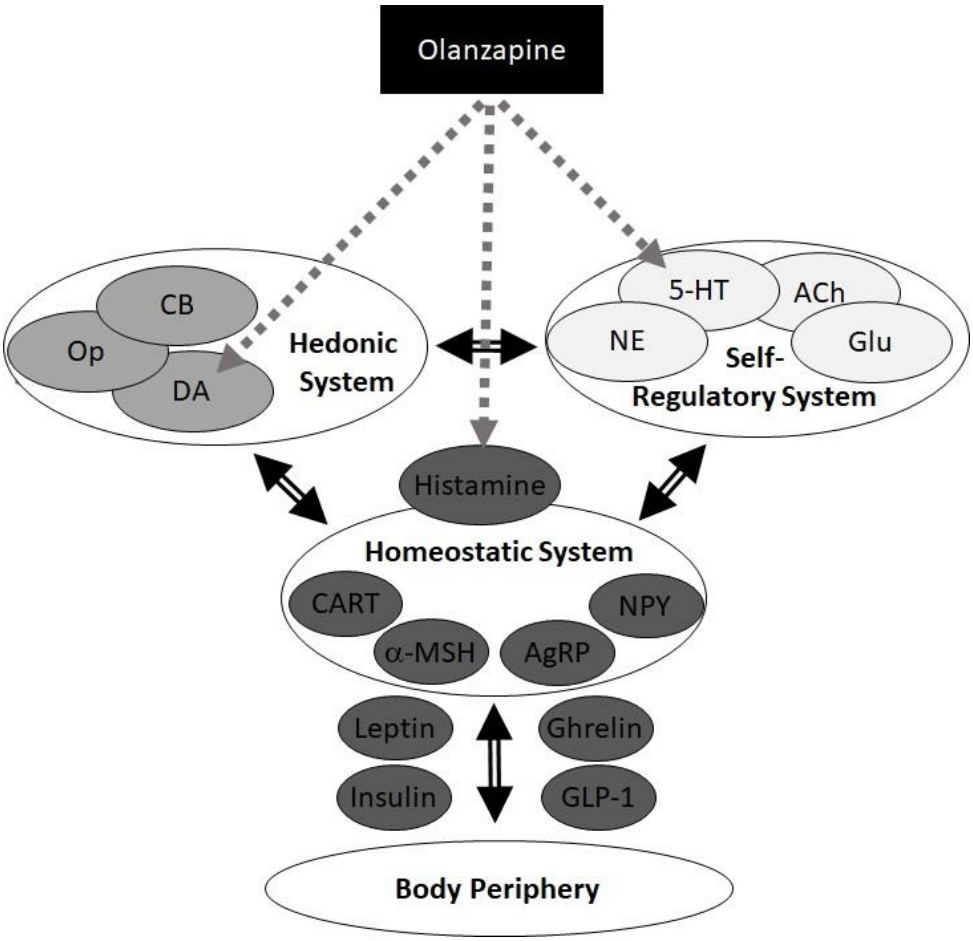
2.2. Pharmacodynamic and pathophysiological considerations on the use of olanzapine in AN

The current scientific literature has increased our understanding of how medication could be beneficial for patients with AN on a molecular, functional and behavioural level: Eating behaviour and appetite control include a complex integration of several neural circuits including those related to

- Self- and social regulation, learning and memory,
- Hedonic aspects associated with the desire to eat and pleasure during food consumption and satiation, and
- Homeostatic regulation, which integrates peripheral signals of food consumption and energy stores with central systems of appetite control [1,44].

These neural circuits - the self-regulatory, the hedonic and the homeostatic system - are both anatomical and functional entities. Possible drug targets for the treatment of AN may therefore include signal molecules and receptors of the self-regulatory system, such as serotonin, norepinephrine and glutamate, the hedonic system, including opioids, cannabinoids and dopamine, and the hypothalamic homeostatic system, including histamine, ghrelin, leptin, insulin and glucagon-like peptide-1 [1,44].
Olanzapine is an SGA that acts on a wide variety of neurotransmitter receptors. It binds mainly to dopamine and serotonin receptors, acting as an antagonist. More specifically, olanzapine binds to D_2 receptors, attaches to the serotonin $(5\text{-HT})_{2A}$ receptor, and its antagonistic effect on histamine H_1 receptors has been discussed as a major driver of weight gain [39]. Blocking H_1 receptors may also help to reduce anxiety and sleep symptoms, which are commonly reported in AN [1,35-37]. **Figure 2** depicts the interplay of the hedonic system, the self-regulatory system, the homeostatic system and the neurotransmitters related to these systems which are influenced by olanzapine.

Figure 2: Schematic and simplified depiction of the interplay of the hedonic system, the self-regulatory system, the homeostatic system, the body periphery and the molecular target location of olanzapine to treat AN. Abbreviations: Anorexia nervosa (AN), opioids (Op), cannabinoids (CB), dopamine (DA), serotonin (5-HT), norepinephrine (NE), acetyl-choline (ACh), glutamate (Glu), neuropeptide Y (NPY), agouti-related peptide (AgRP), melanocyte-stimulating hormone (α-MSH), cocaine and amphetamine regulated transcript (CART), glucagon-like peptide-1 (GLP-1). Figure modified from our review article [1].



2.3. Preparation for this trial

Our team started preparations for this trial in 2016, when the call was first advertised by the NIHR HTA.

We have:

- Recruited two PPIs, had two independent focus groups, spoke to service users individually, recorded statements, developed questionnaires with PPIs to assess patient and carer views, conducted a survey and evaluated the results [38].
- Reviewed the literature on psychopharmacological treatment in eating disorders [1], shared decision making (SDM) in the pharmacotherapy of eating disorders [45], dropouts during drug trials in eating disorders [34] and PRN medication in AN [46]
- Performed an audit on olanzapine in AN [43]
- Discussed the topic at various conferences, e.g. National Carers Conference 2017 (London), EDIC
- 2018 (London), EPA 2019 (Warsaw) and WFSBP 2019 (Vancouver)

2.4. Assessment and management of risk

Intervention: After a systematic review of RCTs and meta-analyses concerned with antipsychotics in AN [15-34], reviewing the literature on the mechanisms of action of medications to treat AN [2], performing focus groups with patients with AN, a survey among patients and carers [38] and an audit on the effects of olanzapine in our service [43] and discussing the topic at various conferences, we decided that olanzapine is the antipsychotic with the highest likelihood to restore weight and treat important psychological symptoms in patients with AN in a safe way. In adolescent patients, olanzapine should be started with 1.25 or 2.5 mg/d. This will be a clinical decision. In adolescents, the start dose will be 2.5 mg/d. We propose a slow up-titration schedule of 1.25 or 2.5 mg/d increments each week for adolescents and 2.5 mg/d for adults up to a maximum of 10 mg/d for both adolescents and adults (fur further details see section 3 “Background and Rationale”). Patients can also stay on the initial dose of 1.25 or 2.5 mg/d.
Treatment as usual (TAU): In this project, we propose to add olanzapine to TAU. TAU is currently defined by the NICE Guidelines on eating disorders (issued in 2017) and the CCQI guidelines of the QED. TAU includes:

- Treatment provided by specialist services
- Psychoeducation and psychological treatment (e.g. AFP-AN, CBT-ED, FPT, FT-AN, MANTRA, SSCM)
- Monitoring of weight, mental and physical health
- Family members’ or carers’ involvement
- Dietary advice

TAU does not necessarily include psychopharmacological medication. However, we do not know whether it can be expected that all services that will potentially become study centres of this project, will apply TAU as defined above, and if so whether they provide it at the same frequency, intensity or in comparable settings (e.g. group or 1:1 setting, family therapy or carers’ workshops). For the purposes of this trial, there will not be any specific requirements for TAU, the treatment will be provided per local practice Therefore, we will use a checklist to document the types of TAU elements patients received, their frequency, length and setting.
One reason for the NIHR HTA call for a study testing antipsychotics in young people with eating disorders is the discrepancy between EDs treatment guidelines and clinical practice. Whereas treatment guidelines such as NICE do not recommend psychopharmacological treatment, between 80% and 90% of patients with EDs are taking psychopharmacological drugs. Instead of taking medications without EDs indication and without monitoring, this open-label feasibility study will test olanzapine in a well-defined patient group. Olanzapine is a medication approved for the treatment of schizophrenia, and its risk profile is well-known. However, if olanzapine is added to psychotherapy, it might lead to a slightly increased risk of adverse events.

Despite being licensed for Schizophrenia, Olanzapine is already in use in patients with treatment-resistant anorexia nervosa [43], it has been tested successfully in randomized-controlled trials [30], and it is

recommended for weight gain in people with anorexia nervosa with category grade B evidence by the WFSBP guidelines on the pharmacological treatment of eating disorders World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders [98]. We will manage the risk by excluding patients with a specifically high risk. People with pregnancy, women of child bearing potential not willing to do a pregnancy test and not willing to adhere to contraceptive measures as specified under section 8.10 (Trial restrictions), people with serious self-harm, suicidality, psychotic disorder, serious medical comorbidities which are contraindications for olanzapine, current alcohol or illicit drug use disorder, on major tranquilliser or opioids, QTc interval >450 ms (two ECG measurements), alerting liver function tests or white cell count [47], on other medication at stable dose for <4 weeks, on medication interacting with olanzapine are considered as high risk. We will use appropriate guidance and instructions for QTc measurement in the same standardised way throughout the trial. The instructions will cover things like the same level of activity before ECG measurements (e.g., sitting or lying after two minutes rested), that if both readings are significantly different, then rather than take an average, redo with a different machine. We will also take consideration of factors such as age, gender, potassium levels, family history, and cardiac examination results.

We will also monitor potential side effects with physical examinations, regular determination of routine laboratory parameters, pregnancy tests, olanzapine concentration measurements and using UKU side effects questionnaire.

We have chosen a daily dose for olanzapine between 2.5 mg and 10 mg which is lower than the typical dose to treat patients with schizophrenia.

This is a feasibility study designed to inform a future definitive RCT only and not ascertain or verify safety or efficacy of olanzapine in this population.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The research question of the study has already been defined by the call HTA 19/76 “For young people with anorexia nervosa, is it feasible to conduct a trial to examine the benefits and harms of prescribing atypical antipsychotics to those who have not responded to first-line treatments?” We have chosen olanzapine as the most promising medication to test in this patient group, and we have defined study aims accordingly.

3.1 Primary objective

The primary objective of this feasibility study is to assess the **feasibility** of carrying out such a trial to inform a future definitive RCT. This includes

- To assess the proportion of patients in different settings (adolescent/adult, inpatient/daycare/ outpatient) who
  - agree to take olanzapine (un-blinded, real-life conditions)
  - adhere to olanzapine
  - complete all study assessments and questionnaires at the five assessment points.

3.2 Secondary objectives

Secondary objectives are to test the feasibility of data collection procedures (completeness and summary statistics) for the following measures:

- Measures at baseline (demographics, smoking, alcohol, and substance abuse)
- Body weight and BMI
- Eating disorder psychopathology
- General psychopathology
- Health economic and quality of life assessment completed by both participants and their carers
- Drug adherence (to examine different methods to measure adherence (questionnaire, pill count, olanzapine plasma level)
- Drug safety (to examine the quality of reporting of adverse events)

Also to use qualitative methods to assess willingness to participate in a blinded, placebo-controlled RCT

3.2.1 Exploratory Objectives

- Treatment as usual (TAU)(to examine and document what TAU means in practice)
- Assess patients experience of recruitment and treatment (to use qualitative methods to study patients' experience of recruitment and treatment, acceptability and reasons for adherence and non-adherence)
- Explore change in the measures as listed in section 3.2 to inform a future definitive RCT.

For further information on the primary, secondary, and exploratory objectives see next section on outcome measures.

3.3 Outcome measures/endpoints

3.3.1. Feasibility of questionnaires and assessments

We will assess the applicability of potential future RCT outcomes, assessment measures and completion of assessments. Questionnaires not completed in >25% will not be included in a potential application for a randomized pilot study or full RCT following this feasibility. This feasibility study includes full assessments at baseline, after 8 weeks, after 16 weeks, after 6 months and after 12 months. The assessments will be conducted by the researcher with the support of the patients' clinical service teams. Qualitative interviews will take place at baseline and after 16 weeks. Furthermore, patients who refuse to enter the study will also be offered the opportunity to participate in a qualitative interview aimed at understanding their reasons for refusing to participate in the OPEN study. They will be conducted by the qualitative researcher; see flow chart.
During study-related activities, the intake of olanzapine and the study assessments, 12- to 15-year-old children will be accompanied by a trusted adult, which may be a parent, carer or a clinical staff member entrusted with the clinical care of the patient.

3.3.2. Body weight and BMI

Patients' weight and height will be measured objectively and BMI calculated during the assessments at baseline, 8 weeks, 16 weeks, 6 months, 12 months.

3.3.3. ED psychopathology

ED psychopathology, general psychopathology, health economic outcomes and quality of life will be measured using questionnaires. Scores for adults and adolescents are comparable for some questionnaires, e.g., the Epworth Sleepiness Scale (ESS) and the Epworth Sleepiness Scale - Child Adolescent (ESS-CHAD) but not all. If not comparable, scores will be converted into binary outcomes, e.g., scores of the Depression Anxiety Stress Scales (DASS) and Revised Children's Anxiety and Depression Scale (RCADS).

Eating Disorder Examination-Questionnaire (EDE-Q): The EDE-Q is a questionnaire assessing key behavioural features and associated psychopathology of eating disorders [49]. It includes four subscales: Restraint, weight concern, shape concern, eating concern
Revised Beliefs about Voices Questionnaire (BAVQ-R; A/a>15 years): The BAVQ-R is a self-report measure of patients' beliefs, emotions and behaviour about auditory hallucinations [50]. We have chosen this questionnaire as people with AN often report experiencing an internal voice. This so-called "anorexic voice" comments on the individual's eating, weight and shape and instructs the individual to restrict or compensate [51]. This questionnaire will provide information about patients' emotional and behavioural reactions to these auditory hallucinations. This will allow conclusions not only about the content and form, but also about the meaning given to these auditory hallucinations [50].
The Self-regulation of Eating Behaviour Questionnaire (SREBQ): The SREBQ is a self-reported measure of the patients' capacity for management of behaviour, thoughts, feelings, attention and environment in the pursuit of personal goals and measuring change in response to self-regulation interventions in adults [52]. The questionnaire will give additional information on food cravings, dietary restraint and the capacity for self-regulation in patients with AN [53].

3.3.4. General psychopathology

As AN has been found to be associated with depressive disorder [4], anxiety disorders [5], OCD [6] and autism spectrum disorder [7], shows an overlap with schizophrenia on a symptomatic and genetic level [53,64], and because we are testing olanzapine, an antipsychotic drug [55], we decided to include scales measuring general psychopathology related to the mentioned disorders.
Depression Anxiety Stress Scales (DASS): The DASS [56] is a 42-item instrument designed to measure the three related negative emotional states of depression, anxiety and stress. Over 20 years, it has been vastly used in research and has been evaluated in large clinical samples to investigate symptoms of depression, anxiety and stress (e.g. [56,57]).
For adolescents, we will use the Revised Children's Anxiety and Depression Scale (RCADS): The RCADS is a 47-item questionnaire that measures the frequency of various symptoms of anxiety and low mood. This questionnaire is commonly used in studies involving adolescents. Therefore, we use it in addition to the DASS. The RCADS produces a total anxiety and low mood score, and separate scores for each of the follow sub-scales [58]: Separation anxiety, social phobia, generalised anxiety, panic, obsessive compulsive, total anxiety and low mood.
Yale-Brown Obsessive-Compulsive Scale (Y-BOCS): The Y-BOCS [59] is a clinician-administered 10-item scale designed to measure the severity and type of symptoms in people with OCD. The symptoms assessed are obsessions and compulsions. The Y-BOCS is sensitive to changes in OCD symptoms. Therefore, it has been extensively used in clinical studies in over 30 years (e.g. [60,61]). The Y-BOCS version for adolescents is the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS).
Columbia Suicide Severity Rating Scale (C-SSRS): The C-SSRS is a suicidal ideation rating scale created to evaluate suicidality in adolescents and adults (12 years and up) [62]. It rates an individual's degree of suicidal ideation and has been used successfully in research in adolescent as well as adult populations (e.g. [63,64]).

3.3.5. Health economic and quality of life assessment

EQ-5D™: The EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. It consists of a descriptive system, which comprises five dimensions: Mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In the 30 years since its development, it has been successfully used in several thousand national and international studies (e.g. [65,66,67] to measure quality of life. EQ-5D-Y, a version adapted for youths will be used for the OPEN study [67].

Adult Service Use Schedule (AD-SUS): The AD-SUS has been developed and employed in several mental health trials (such as [68]) Information about the study participants' use of services will be collected in interviews with a researcher at baseline, at 6- and the 12-month follow-ups. At baseline, information will cover the previous 3 months. At each of the follow-up interviews, service use since the previous interview will be recorded; in this way, the entire period from baseline to the final follow-up will be covered. The AD-SUS contains a researcher- and a self-completed section. Both sections together will cover: The number and duration of contacts with various services and professionals, the use of psychological therapies, and the use of non-trial pharmacological therapies including sleeping tablets, mood stabilisers and painkillers. In the OPEN study, the Child and Adolescent and Adult Service Use Schedule (CAA-SUS) will be used. The CAA-SUS a questionnaire designed specifically for the OPEN study, which incorporates features of CA-SUS and AD-SUS will be applied to take the health and social care perspective.

Eating Disorders Symptom Impact Scale (EDSIS): The EDSIS has been developed as a measure to assess the specific caregiving burden of both AN and bulimia nervosa [69]. Subscales of the EDSIS are related to: Nutrition, dysregulated behaviour, guilt and social isolation.

3.3.6. Drug adherence measures

Olanzapine plasma level: We will perform therapeutic drug monitoring and measure olanzapine levels at week 8 after the start of olanzapine treatment. [70]. An independent physician will have immediate access to olanzapine levels, and feedback to the study team if the level exceeds the upper normal limit.
Pill count: We will use the pill count as an indirect measure of adherence. Thus, the number of dosage units that have been taken/not taken will be counted. We are, however, aware that the removal of a dosage unit does not mean that the medication has been taken, that it does not characterize the adherence pattern, and that it is unable to identify causes of adherence or non-adherence. Therefore, we will use pill count in addition to the olanzapine plasma level [71].

3.3.7. Drug safety measures

Adverse effects: In OPEN, we will measure possible adverse effects in a structured and standardised manner. As there are no existing guidelines concerning the use of antipsychotics in AN, we decided on the clinical outcome measures of adverse effects based on the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia [72].

- Physical examination:
  - Weight
  - Blood pressure (BP) and pulse
  - Body temperature
- Electrocardiogram (ECG): A QTc interval of > 450 ms confirmed by a second ECG measurement or an otherwise seriously abnormal ECG [47] will be an exclusion criterion for this study. We will only exclude patients if two separate readings are >450ms.
- A QTc interval >500 ms in the ECG or rises by more than 60 msec from baseline or other severe cardiac side effects will stop study participation of this patient.
- A QTc interval >500 ms in the ECG or rises by more than 60 msec from baseline or other severe cardiac side effects in more than one patient in the feasibility study will lead to a stop of the study after the feasibility phase.
- Laboratory parameters: Routine laboratory parameters in patients with AN often show alterations, including electrolytes, liver enzymes, kidney parameters, leukocyte count, haemoglobin and others. Additionally, medical problems secondary to AN, or due to the treatment itself may lead to further laboratory abnormalities [10]. Furthermore, olanzapine may lead to changes in metabolic parameters, including cholesterol, plasma glucose and blood fats [73]. Therefore, the following parameters will

be determined at baseline, 8 weeks, 16 weeks (end of trial medication) and at the 12-month follow-up.
  - Electrolytes and salt/water balance
  - Kidney function
  - Liver function
  - Blood count/bone marrow
  - Plasma glucose (fasting or random) or glycated hemoglobin (HbA1c) and lipid profile
  - Pregnancy test in women and female adolescents
- UKU-Side Effect Rating Scale (UKU-SERS): The UKU-SERS [74] is a general rating scale for the registration of unwanted side effects of psychotropic medication. UKU is an acronym for the Danish name “Udvalg for Kliniske Undersøgelser” (Task force for clinical investigations). UKU was a task force of the Scandinavian College of Neuropsychopharmacology (SCNP) working with the development of rating scales and methodological issues in relation to psychopharmacological research. It covers a broad range of different possible side effects and has been widely used in clinical studies since its development and publication in 1987 (e.g. [75,76].
- Epworth Sleepiness Scale (ESS): The ESS is a self-administered questionnaire that provides a measurement of the general level of daytime sleepiness [77]. Since its development, it has been used in several thousand clinical studies (e.g. [78-79]). Sleepiness is a frequent symptom in patients with AN, because starvation results in a fragmentation of sleep and a reduction of slow wave sleep, and thus abnormalities in sleep efficiency and sleep architecture [80,81]. On the one hand, daytime sleepiness is a common side effect of antipsychotics, and specifically olanzapine is known to induce moderate somnolence [82], on the other hand, it has been shown to lead to an improvement of sleep [37] and may thus reduce AN-associated daytime sleepiness.

Table 1 provides a synopsis and schedule of all assessment tools used in OPEN. We have listed many outcome parameters. However, given the multiple comorbidities of AN which were explicitly mentioned in the HTA call 16/97 and the number of potential side effects of olanzapine [55], this multitude of parameters makes sense from a clinical perspective.

3.4 Primary endpoint/outcome

Primary objective: **feasibility**

Primary endpoints: Assessing the proportion of patients in different settings, examining different methods to measure adherence (questionnaire, pill count, olanzapine plasma level). Important measurement time points are the baseline and 12 months after baseline.

Summary statistics will be presented on the following for feasibility and may include estimation of confidence intervals:

Patients approached, screened and included in the study

Adherence, completed physical assessments (including BMI measurement) and questionnaires

Willingness to take part in an RCT

Elements that constitute TAU

Summary statistics on psychopathology, general psychopathology and quality of life assessments and change in BMI will also be reported.

3.5 Secondary endpoints/outcomes

The secondary objective is feasibility (completeness and summary statistics) of recording the following measures at baseline:

Demographics and the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

And of the following measures at baseline (where applicable), 8 weeks, 16 weeks, 6 months, and 12 months post-baseline:

Height, weight, BMI, ED psychopathology questionnaires- (RCADS, EDE-Q, BAVQ-R, SREBQ), General psychopathology assessments and questionnaires-(DASS, RCDADS, Y-BOCS, C-SSRS), Health economic and quality of life assessments (EQ-5D-Y, CAA-SUS, , EDSIS,) olanzapine plasma levels (8 weeks only), Physical examination measures, ECG, laboratory parameters, ESS, ESS-CHAD and quality of adverse events reporting (UKU-SERS).

Also to assess willingness to participate in an RCT (blinded, placebo-controlled).

3.6 Exploratory endpoints/outcomes

3.6.1. Treatment as usual

It is unclear whether TAU can be defined according to current guidelines. Therefore, we will use a checklist to document the types of TAU elements patients received, their frequency, length and setting. We will also record Concomitant Medications to document the different medications patients are taking for their anorexia as well as their various co-morbidities and to explore whether any commonly taken additional medications affect the action of olanzapine in this population (drug-drug interactions).

3.6.2. Patients experience of recruitment and treatment

Patient experience of recruitment and treatment, acceptability and reasons for adherence and non-adherence will be ascertained in qualitative interviews which will be performed, transcribed and analysed.

3.6.3 Change in measures over time

Change in the measures as listed in section 3.5 will be explored/described to inform a future definitive study design.

3.7 Schedule of events

Synopsis and schedule of OPEN outcomes/assessment tools in the feasibility study. The superscript numbers indicate, who will perform the scheduled assessments: [1]Reserecher, [2]The study participant's clinical treatment team, [3]Qualitative Researcher. * if procedure is performed on the day of the Screening visit, it does not need to be repeated; items highlighted in green are standard care procedure.

Methods/Assessments	Screening	Baseline Assessment (≤ 7-10 days following Screening)	Assessment at 8 weeks (±7 days)	Assessment at 16 weeks (±7 days)	Assessment at 6 months (±7 days)	Assessment at 12 months (±7 days)
Informed Consent	X[1]					
Clinical Examinations						
- Inclusion/Exclusion Criteria	X[1]					
- Psychiatric and physical examination	X[1,2]		X[1,2]	X[1,2]	X[1,2]	X[1,2]
- Weight, height, blood pressure (BP), body temperature	X[1,2]	X[1,2*]	X[1,2]	X[1,2]	X[1,2]	X[1,2]
- Laboratory parameters (Electrolytes and salt/water balance - Kidney function, Liver function Blood count/bone marrow, Fasting glucose and lipid profile)	X[1,2]		X[1,2]	X[1,2]	X[1,2]	X[1,2]
- Electrocardiogram (ECG)	X[1,2]		X[1,2]	X[1,2]	X[1,2]	X[1,2]
- Concomitant Medications	X[1]	X[1*]	X[1]	X[1]	X[1]	X[1]
- Serum Pregnancy Test	X[1,2]		X[1,2]	X[1,2]	X[1,2]	X[1,2]
IMP dispensing		X[1,2]	X[1,2]	X[1,2]	X[1,2]	
Screening for Drug or Alcohol Abuse Disorders						
- Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)		X[1]				
Treatment as Usual						
- Treatment elements checklist		X[1]	X[1]	X[1]	X[1]	X[1]
Adherence measures						
- Olanzapine plasma level			X[1,2]			
- Pill count			X[1,2]	X[1,2]	X[1,2]	X[1,2]
AE recording/reporting			X[1]	X[1]	X[1]	X[1]
- UKU Side Effects Rating Scale			X[1]	X[1]	X[1]	X[1]
Eating Disorders Psychopathology						
- Eating Disorder Examination-Questionnaire (EDE-Q)		X[1]	X[1]	X[1]	X[1]	X[1]
- Revised Beliefs about Voices Questionnaire (BAVQ-R)		X[1]	X[1]	X[1]	X[1]	X[1]
- Self-regulation of Eating Behaviour Questionnaire (SREBQ)		X[1]	X[1]	X[1]	X[1]	X[1]
General Psychopathology						
- Depression Anxiety Stress Scales (DASS/RCADS)		X[1]	X[1]	X[1]	X[1]	X[1]
- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS/CY-BOCS)		X	X	X[1]	X[1]	X[1]
- Columbia Suicide Severity Rating Scale (C-SSRS)		X[1]	X[1]	X[1]	X[1]	X[1]
Rating and Documentation of Side Effects						
- Epworth Sleepiness Scale (ESS/ESS-CHAD)		X[1]	X[1]	X[1]	X[1]	X[1]
Health Economy and Quality of Life						
- EQ-5D-Y™		X[1]			X[1]	X[1]
- Child, Adolescent and Adult Service Use Schedule (CAA-SUS)		X[1]			X[1]	X[1]
- Eating Disorders Symptom Impact Scale (EDSIS)		X[1]			X[1]	X[1]
Qualitative Research						
- Patient experience: Interview with those who consent to trial participation		X[3]				
- Patient experience: Interview with those who declined to participate in trial		X[3]				
- Experience of treatment and the trial (including adherence/nonadherence)				X[3]		
Questions on RCT						
- Willingness to take part in an RCT (double-blind)		X[1]			X[1]	X[1]

4 TRIAL DESIGN

The design of this feasibility study is open treatment of 55 patients with olanzapine for 12 months. Participants will be examined at baseline, and at 8 weeks, 16 weeks, 6 months and 12 months after start of treatment. This is a one-arm open treatment design, there is no placebo and no comparator.

5 TRIAL SETTING

This a multicentre trial. There are no specific site requirements other than what is standard in NHS eating disorders services.

- A medical doctor to prescribe olanzapine and to perform the physical examination.
- The facility to take blood for routine laboratory parameters and to determine olanzapine plasma levels.
- An ECG to measure QTc time.

The researcher employed for this study and the CI will keep a list of sites participating in the trial. Recruitment at specialist CAMHs and adult eating disorder units in inpatient/outpatient settings at NHS sites to ensure generalisability (different treatment setting, degree of severity, chronicity).

The consultant psychiatrist involved in the clinical treatment of patients will inform the trial team about a potential patient and ask the patient whether they can be contacted online if necessary. Obtaining informed consent and inclusion into the study will take place on site by a member of the research team.

6 PARTICIPANT ELIGIBILITY CRITERIA

Patient group: 55 adolescent and young adults (of all sexes/genders) with AN not responding to TAU, according to NICE, for at least a month of treatment. Our age range starts from 12 years as, in a comparable published trial [28] and a published study proposal [83] in adolescent patients with AN, the minimum age was 12 years for safety reasons. According to olanzapine's SmPC, olanzapine is currently not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. However, as stated in the NIHR HTA call 16/97 "Antipsychotics for anorexia nervosa", olanzapine is widely used in people with AN between 12 and 24 years even though it is not licensed and studies testing its safety are lacking. One purpose of this feasibility is to test, whether a study investigating the safety of olanzapine in this patient group is feasible. The main concern when prescribing olanzapine in adolescents with schizophrenia is weight gain and the consequences of weight gain such as lipid disturbances. In people with AN, however, this weight gain is the intended therapeutic effect, as weight gain is necessary for patients' medical safety and to be able to take part in psychotherapeutic measures.

6.1 Inclusion criteria

- Adolescent or young adults (12-24 years old).
- Receiving inpatient, day care or outpatient treatment
- Diagnosed with AN, or atypical AN, according to DSM-5.

- Patients have gained <2 kg within at least one month of TAU. Outpatients should have attended ≥4 therapeutic sessions. 2 kg within the time frame of at least one month appears most appropriate to predict further therapy response or non-response to the current treatment according to our systematic review and meta-analysis on early response and treatment outcome prediction [84].
- The patient can read and write in English.
- Written Informed consent to participate

6.2 Exclusion criteria

Exclusion criteria:

- Serious self-harm, suicidality, psychotic disorder, serious medical comorbidities (as detailed below) which are contraindications for olanzapine
- Current alcohol or illicit drug use disorder
- On major tranquilliser or opioids
- QTc interval >450 ms (two separate ECG measurements) [47]
  - A QTc interval >500 ms in the ECG or rises by more than 60 msec from baseline or other severe cardiac side effects will stop study participation of this patient.
  - A QTc interval >500 ms in the ECG or rises by more than 60 msec from baseline or other severe cardiac side effects in more than one patient in the feasibility study will lead to a stop of the study.

  Alerting liver function tests or white blood cell count [47]

    - Bilirubin >40 μmol/L
    - Alkaline phosphatase >200 U/L
    - AST >80 U/L
    - ALT >90 U/L
    - GGT >90 U/L
    - WBC <2.0 x10^9/L
    - MCV >120 fL

- On other psychopharmacological medication at stable dose for <4 weeks
- On medication interacting with olanzapine
- Pregnancy
- Of childbearing potential and unwilling to have pregnancy tests.
- Objecting to taking effective contraceptive measures as specified under section 8.10. on trial restrictions. The participant information and consent sheet include a section on pregnancy and appropriate birth control measures.
- Breast feeding
- Insufficient understanding of the Trial/lack of capacity to agree to the Trial procedures as assessed by the responsible clinician
- Hypersensitivity to Olanzapine or to any of its excipients
- Taking part in another pharmacological trial for AN
- Involvement in research that includes contraindications for treatment with olanzapine

Serious self-harm means one of the following:

- Recent (within the last 12 months) self-harm with suicidal intent

- Recent self-harm with the risk to a person's own life (e.g., drug intake, deep cutting, burning, swallowing sharp items)
- Recent self-harm which could lead, or has led, to long lasting impairment of one's health and functioning

Serious medical comorbidities which are contraindications for olanzapine mean one of the following:
- Coronary heart disease
- Cerebrovascular disease
- Parkinson's disease, parkinsonism or dementia
- Hepatic or renal impairment

We will examine and document all physical and mental comorbidities that are not exclusion criteria. For example, mood disorders, obsessive-compulsive disorder, anxiety disorders and personality disorders are common co-morbidities which are not exclusion criteria.

In order to determine inclusion and exclusion criteria, to detect serious physical or mental illnesses, and to find out current medications or potentially needed medication, a full psychiatric and medical history taking, physical examination and assessment will take place when screening potential participants, including:
- Body weight and height
- Blood pressure and pulse rate, lying and standing
- Body temperature
- Muscle strength
- Skin
- Signs of infection and nutritional deficiency
- Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) for study participants >15 years old; all participants will be screened for alerting levels of GGT and MCV as indicators of alcohol use; alcohol and drug use is a health risk for people on olanzapine [85]

7 TRIAL PROCEDURES

7.1 Recruitment

Recruitment will take place at specialist CAMHs and adult eating disorder units in inpatient, outpatient, and day care settings.

7.1.1 Participant identification

Psychiatrists in the participating ED services will identify patients in their care for potential eligibility, approach them and inform them the study. If patients agree, their verbal agreement will be documented in the patient notes, and their contact data will be forwarded to the researcher of the OPEN study. The researcher will inform the patient and the medical doctor or psychiatrist who is responsible for the patient's treatment in detail about the study and the necessary screening. Thus, the aims of the participant identification process are to find and approach potential participants and bring the clinicians and the potential participants in contact with the study team. We will also recruit participants by advertising posters in each of the trial sites. This will open the study to a diverse pool of candidates and minimize the potential of selection bias by consultant psychiatrists.

In light of the COVID-19 pandemic, contingency plans will be put in place to ensure the study will be completed in the scheduled time frame and the patient safety not jeopardized. In addition to the hard copies of consent and PI forms, all consent forms and PI forms will be made available online for use as appropriate in the event that such measures become necessary Trial assessments will take place in person adhering to social distancing guidelines, and qualitative assessments will take place virtually or in-person based on the participants preference. The Trial Management Group (TMG) Trial Steering Committee (TSC), and the Data Monitoring and Ethics Committee (DMEC) will all meet for sessions virtually to ensure the safety of the members.

Qualitative interviews will examine the decision-making process among an estimated 30 participants who either agree or decline to participate in the trial. After consent to participate in OPEN has been obtained or declined, participants will be given a participant information sheet for the qualitative interview and asked for verbal consent to be contacted by the qualitative research assistant who will follow up with a phone call to answer questions and schedule one-off appointments.

7.1.2 Screening

The aim of the screening process is to ascertain whether inclusion and exclusion criteria are met. In accordance with the inclusion and exclusion criteria outlined in section 6.1. and 6.2., the clinical research team will update the eCRF with the following information about the potential participant after informed consent is obtained:

- Age
- Gender
- Diagnosis of AN
- Level of nonresponse to TAU (at least one month of treatment; weight gain <2 kg within at least one month of TAU; outpatients should have attended ≥4 therapeutic sessions.
- Potential serious self-harm, suicidality, psychotic disorder
- Serious medical comorbidities which are contraindications for olanzapine
- Current alcohol or illicit drug use disorder
- Use of major tranquilliser or opioids
- QTc time
- Liver function tests or white cell count
- Use of other medication at stable dose for <4 weeks
- Use of medication potentially interacting with olanzapine
- Pregnancy test, willingness to take further pregnancy tests after 8 weeks, 16 weeks, 6 months, and 12 months and to take contraceptive measures as specified in section 8.10. on trial restrictions (females of childbearing potential only)
- Breast feeding
- Capacity of the adult participant or the adolescent participant and their legal representatives to agree to the study

For definition of serious self-harm and serious medical comorbidities see section 6.1. and 6.2.

To obtain this information and thus determine inclusion and exclusion criteria, a full psychiatric and medical history taking, physical examination and assessment will take place. See section 6.1. and 6.2. To obtain this information is included in the standard care for a patient with AN if pharmacological treatment is considered.

7.1.3 Payment

Patients will be paid £10 for consenting to take part in the study and £10 for completing the study after one year. This covers travel costs and other costs. However, we do not expect patients to travel specifically for the study. Participant payment of £20 will be offered to those who decline to enter the trial to support participation in qualitative interviews. Differential incentive payments for qualitative research can be offered to advance the goals of a study (Persad et al, 2019).

7.2 Consent

The CI will have overall responsibility for the conduct of research. The CI will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol and principles of Good Clinical Practice (GCP) and Declaration of Helsinki.
Informed consent will be obtained prior to the participant undergoing the baseline assessments.
Written consent will be taken by the members of the research team at each site. The Patient Information and Consent forms will be given to the participants and ample time will be given for the participants to review and complete the forms and for any questions to be answered. One copy of the signed consent forms will be given to the patient, one copy will be kept in the patient medical notes and one copy will be filed in the Site File. .

The right of a participant to refuse participation without giving reasons must be respected, and the participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. This contact point will be the researcher and the CI.

Data and samples collected up to the point of withdrawal will only be used after withdrawal if the participant has consented for this. This is explained in the information sheet and specified in the consent form. Patients under 16 years old will be required to assent to take part in the trial and a consent from a parent/legal guardian will be obtained. Participants who turn 16 years old during the study will be required to consent, and it is the responsibility of the PI to ensure this is done in a timely manner. The PI will take responsibility for ensuring that all participants are protected and participate voluntarily in an environment free from coercion or undue influence.

We will only include patients who can read and write in English.

Before asking patients to participate in the trial, the potential adult participant or the potential adolescent participant and their parents or legal representatives will have a discussion with their medical doctor or consultant psychiatrist about the therapeutic effects and potential side effects of the treatment with olanzapine. They will explain the following common and very common side effects for olanzapine according to the BNF: Anticholinergic syndrome; appetite increased; arthralgia; asthenia; eosinophilia; fever; glycosuria; oedema; sexual dysfunction. Psychiatrists will receive training on how to explain these common and very common side effects once trial sites are open to adhere to uniform of clinical explanations with the participants. These side effects are also outlined in the consent form and patient information form in both an electronic and physical copy.

Participants will be informed that the use in this study is off-label. Patients and their families or legal representatives will receive a leaflet about olanzapine and about the study. The leaflet will be approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements. They will have the opportunity to ask questions.

All members of the research team who will have contact with study participants will have received adult and child safeguarding training.

The capacity assessment during the screening process will be conducted by the clinical teams on site and include an assessment that the potential adult participant or adolescent participant and their parents/legal representatives have the ability to:

- understand the information of the participant information sheet, particularly regarding the effects and potential side effects of olanzapine, the procedures at each study visit and the participant's right to withdraw from the study at any time with no negative implications to their clinical care;
- understand the purpose and nature of the research
- understand what the research involves, its benefits (or lack of benefits), risks and burdens
- understand the alternatives to taking part
- are able to retain the information long enough to make an effective decision.
- Weigh up the options (taking olanzapine or not, taking part in the study or not) and are able to make a free choice
- are capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
- are capable of communicating their decisions.

Mental capacity will be assumed lacking if, in a specific circumstance, a person is unable to decide for him or herself because of impairment or a disturbance in the functioning of their mind or brain. This trial will include children (under the age of 16 years of age), young people (between the ages of 16 and 17) and adults. Therefore, the legal framework and ethical considerations for involving young people in research which are set out in the Department of Health Reference Guide to Consent for Examination or Treatment (2009) apply. Olanzapine is considered to be of significant value of children and young people with AN. The protection of participating children is fully considered.

These aspects of the Capacity assessment are to be documented in the CRF at each study visit.

Where a participant becomes incapacitated during the trial, the patient will be withdrawn from the study.

7.3 The randomisation scheme

This is an open-label feasibility trial. Participants will not be randomized. All participants will be treated with olanzapine and will know this.

7.4 Blinding

This is an open-label feasibility trial. Participants will not be blinded. All participants will be treated with olanzapine and will know this.

7.5 Emergency Unblinding

This is an open-label feasibility trial. Participants will not be blinded. Therefore, there is no need to unblind them.

7.6 Baseline data

7.6.1. Screening data

At baseline, we will enter the screening data of those participants who consent to take part in the trial into the database. This screening will take approximately 3 hours. These data include:

Screening Data:

- Inclusion/Exclusion Criteria
- Psychiatric and physical examination
- Laboratory parameter checks to ensure normal ranges throughout the study (Electrolytes and salt/water balance - Kidney function, Liver function, Blood count/bone marrow, Plasma glucose (fasting or random) or glycated hemoglobin (HbA1c) and lipid profile- see below values of concern)
- Body temperature
- Electrocardiogram (ECG)
- Screening for Drug or Alcohol Abuse Disorders
- Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

7.6.2. Standardized assessments:

We will obtain the following baseline data using standardized questionnaires and assessments:

Psychopathology

- Eating Disorder Examination-Questionnaire (EDE-Q)
    - Depression Anxiety Stress Scales (DASS/RCADS)
- Revised Beliefs about Voices Questionnaire (BAVQ-R)
- Self-regulation of Eating Behaviour Questionnaire (SREBQ)
- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS/CY-BOCS)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Rating and Documentation of Side Effects

- Epworth Sleepiness Scale (ESS/ESS-CHAD)
- UKU- Side Effects Rating Scale (UKU-SERS)

Health Economy and Quality of Life

- EQ-5D-Y™
- Child, Adolescent and Adult Service Use Schedule (CAA-SUS)
- Eating Disorders Symptom Impact Scale (EDSIS)

Laboratory Parameters (*values of concern*) [47]

- Electrolytes and salt/water balance
    - K+ <3.5--<3.0 2
    - Na+ <135--<130 3
    - Mg++ 0.5-0.7--<0.5 4
    - PO4-- 0.5-0.8-- <0.5 5
- Kidney function
    - Urea >7-- >10

- Liver function
  - Bilirubin >20-->40
  - AlkPase >110-->200
  - AsT >40-- >80
  - ALT >45-->90
  - GGT >45-->90
- Blood count/bone marrow
  - WCC <4.0-<2.0
  - Neutrophil count <1.5-<1.0
  - Hb <11-<9.0
  - Acute Hb drop (MCV and MCH raised - no acute risk)
  - Platelets <130- <110

- Plasma glucose or HbA1c and lipid profile [96]
  - Total cholesterol 5mmol/L or less
  - LDL cholesterol 3mmol/L or less
  - Triglycerides <1.7mmol/L

7.6.3. Further Assessments
Treatment as Usual
- Treatment elements checklist

Qualitative Research
- Qualitative interviews to explore the perceived risks and benefits of taking olanzapine and participating in the trial.

Questions on RCT
- Willingness to take part in an RCT (double-blind)

For the justification of these data, see section 3. These selections of these assessments are the results of applying four times for this study to the NIHR HTA at stage 1 and two times at stage 2 and incorporating the feedback of the reviewers during six rounds of review into the trial design.

7.7 Trial assessments

Trial assessments will take place 8 weeks, 16 weeks, 6 months, and 12 months after baseline with an appointment of approximately 3 hours and will take place in person at trial sites. They include:

Clinical Examinations
- Psychiatric and physical examination
- Weight, height, blood pressure (BP), body temperature
- Laboratory parameters
- Body temperature
- Electrocardiogram (ECG)

Treatment as Usual check
- Treatment elements checklist
- Concomitant Medications

Adherence measures
- Olanzapine plasma level
- Pill count

Psychopathology
- Eating Disorder Examination-Questionnaire (EDE-Q)
- Depression Anxiety Stress Scales (DASS/RCADS)
- Revised Beliefs about Voices Questionnaire (BAVQ-R)
- Self-Regulation of Eating Behaviour Questionnaire (SREBQ)
- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS/CY-BOCS)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Rating and Documentation of Side Effects
- Epworth Sleepiness Scale (ESS/ESS-CHAD)
  - UKU- Side Effects Rating Scale (UKU-SERS)

Health Economy and Quality of Life
- EQ-5D-Y™
- Child, Adolescent and Adult Service Use Schedule (CAA-SUS)
- Eating Disorders Symptom Impact Scale (EDSIS)

Qualitative Research
- Experience of treatment and the trial, including motivation for adherence/nonadherence (after 16 weeks only)
- Carers/parents will be given an opportunity to contribute at the 16 week qualitative interview with the participants' consent.

Questions on RCT
- Willingness to take part in an RCT (double-blind; after 6 and after 12 months only)

For the justification of these data, see section 3. Section 3.7. provides an overview of all assessments and when they will take place.

7.8 Long term follow-up assessments
Beyond the trial assessment 12 months after baseline which is described above, no long-term follow-up assessments are planned.

7.9 Qualitative assessments
Patient experience of recruitment and treatment: Patient experience of recruitment and treatment, treatment acceptability and reasons for adherence or non-adherence will be ascertained in qualitative interviews which will be performed, transcribed, and analysed.

We will conduct individual qualitative interviews in a subgroup (N=30) of young people with AN who either agree (N=20) or decline (N=10) to participate in the OPEN feasibility study. Interviews will be

conducted virtually or face-to-face based on the participants preference. Interviews will examine the decision-making process and the perceived risks and advantages of taking olanzapine within the study. Those who are recruited to OPEN will be interviewed at baseline and after the 16-week assessment point about their experiences of olanzapine treatment, participating in the study, including beliefs about side effects, acceptability and adherence, the perceived burden of completing outcome measures and attitudes towards randomisation in a future clinical trial. We will interview people who have adhered to olanzapine as well as people who have dropped out. Patients who decline to participate in the main study but have consented to take part in the interviews will participate in one interview at baseline. The qualitative researcher will aim for 'empathic neutrality', posing open and non-leading questions that invite participants to recount their experiences of the study and treatment from their perspective.
Purposive sampling will be conducted based on gender, age, recruitment source, BMI at baseline and adherence to explore a range of perspectives.
Qualitative data will be analysed using the Framework Approach [85] to facilitate analysis within and between individual cases and groups of participants. The thematic framework will draw on a priori issues around the acceptability of the intervention and design study, but also be responsive to emergent themes. Dr Lawrence will supervise a qualitative researcher who will get in contact with approached and recruited patients. All qualitative interviews in the UK will be carried out by the UK qualitative researcher (TBA). Qualitative data evaluation will be performed in cooperation with the qualitative research in Australia. Dr Lawrence and Prof Madden will consult with each other about the qualitative research performed in both countries.

7.10 Withdrawal criteria

The physician responsible for a patient can withdraw a patient from a trial or a certain aspect of the trial any time for appropriate medical reasons, be they individual adverse events or new information gained about a treatment. Trial participants also have the liberty to withdraw their consent at any time and for any reason.

A patient should stop olanzapine treatment if they show:

- If they show a QTc interval >500 ms in the ECG
- If they show rises by more than 60 msec from baseline [47] in the ECG
- Severe cardiac problems
- Serious Adverse Events (SAE) - An SAE will be a withdrawal criterion if it is deemed to be related to the treatment with olanzapine by the Principal Investigator
- Serious Adverse Reaction (SAR)
- Suspected Unexpected Serious Adverse Reaction (SUSAR)

However, should a patient stop olanzapine, the patient is not necessary withdrawn from the study, every effort should be made to continue to obtain follow up data as long as the participant is willing.

The whole trial will stop in case of:

- A QTc interval >500 ms in the ECG or rises by more than 60 msec from baseline or other severe cardiac side effects in more than one patient
- Serious self-harm or suicidal behaviour in more than one patient. Serious self-harm is defined as the following:
  - Recent (within the last 12 months) self-harm with suicidal intent
  - Recent self-harm with the risk to a person's own life (e.g., drug intake, deep cutting, burning, swallowing sharp items)

- Recent self-harm which could lead, or has led, to long lasting impairment of one's health and functioning

7.11 Storage and analysis of clinical samples

No biological samples will be collected or stored for this trial. Laboratory parameters will only be determined as clinical routine laboratory parameters to ensure safety of the treatment as this is usually done in clinical practice.

7.12 End of trial

The trial will end after the database is locked following the 12 months-assessment of the 55th patient included into the study.

7.13 Safeguarding, Confidentiality and Distress Risk Management

7.13.1 Distress Risk Management

All of the questionnaires used in this study are routinely used in research studies and/or in the clinical setting. Similarly, clinical and qualitative interviews do include routinely used elements and approaches in research and/or clinical setting. Although the risk of major distress occurring during an interview (in association with the research study) is minimal considering the participants are known patients under specialist eating disorder services and based on previous research using similar procedures, there is a possibility that some of the questionnaires or the interview processes result in increased distress in the participants.

To minimise the risk, the participants will be given information about the study procedures (including but not limited to the questionnaires, the physical health checks and the qualitative interviews) in the participant information sheet and they will be provided with an opportunity to discuss their further concerns or queries with a clinician.

All the interviews and questionnaires are being completed at usual NHS clinical sites, by or in the presence of a research clinician. The Chief Investigator is a consultant psychiatrist with experience of working with vulnerable people. They and other research clinicians on the team will overview all procedures and be available during the sessions.

Members of the research team will remain sensitive to signs of participant distress and will terminate the procedure if the participant wishes to stop. Researchers will also check the participant`s mental state and safety upon completion of the interview process at each encounter. A clinician will always be available on site to support if necessary. If there are ongoing concerns due to participant distress, the research team will liaise with the participant`s clinical team to ensure there is ongoing clinical support available and if necessary, to discuss whether it is appropriate for the participant to remain in the study.

7.13.2 Safeguarding Management

Considering the specific vulnerabilities of the participants of this study, additional steps will be taken to ensure physical and mental safety of the participants throughout the trial. Firstly, all participants will be in the care of a GP and under an NHS specialist eating disorder team. Notably, for recruitment of

participants to this study, the psychiatrists in the participating ED services will be identifying patients in their care for potential eligibility and informing them of the study. Participants who do not want to remain in the care of their specialist team will be withdrawn from the study and their GP informed. This will be explained to the participants in the participant information sheets and consent forms.

Similarly, consent for the research team to be in contact with the patient`s care teams (including the ED specialist services and their GP) will be explicitly obtained from all patients at screening.

On the patient information sheets, the contact details of the trial manager are being shared with the participants as a contact person, aside from their clinical teams, that could be contacted by participants to discuss any concerns.

In case of a participant disclosing information relevant to their health and safety such as risk to self (eg. self-harming or suicidal risk), risk from others, or the safety of others, or any such information regarding the participant becoming apparent to the research team during the course of the study, the following steps will be taken and will be reflected on the patient information sheet and consent forms:

- Participants will be informed that all information is confidential, regardless of the participant's age, but there will be limits to confidentiality when there is a risk to self, from others, or to others. It will be explained to all participants that confidentiality might be broken when it is in the best interest of the participant or the public, or required by law. For participants under the age of 16, the threshold for disclosing risk to parents will take into consideration what is appropriate to the best interests of the child. As part of the study, the participants are being asked to comply with contraceptive measures and take regular pregnancy tests, if applicable. Participants will be explained that in case of a pregnancy, they will be withdrawn from the study and this information will be shared with themselves, their clinical team, and potentially with their parents/carers in case of a participant under the age of 16. In case of a safeguarding concern becoming apparent during the research process, the researcher will liaise with the participant`s clinical team to raise the concern with them and to ensure that the local safeguarding process is being completed.

- In all cases of concern around a participant`s health and safety, the researcher will liaise with the participant`s responsible clinician at the ED services to assess the participant and advise on further actions, including whether the participant is able to remain in the study. Regardless of the participant`s situation with regards to the study, they remain a patient under the specialist ED team, therefore, the local risk management policies of the relevant trust shall apply and be overseen by the clinical team of the patient.

8 TRIAL TREATMENTS

8.1 Name and description of treatment

This trial will use the atypical antipsychotic olanzapine as the treatment. Olanzapine is a dopamine D1, D2, D4, 5-HT2, histamine- 1-, and muscarinic-receptor antagonist. In this study, olanzapine will be used as tablet or as a dispersible tablet, of 2.5, 5, 7.5 or 10 mg. Olanzapine is UK-licensed and commercially

available on the UK market. Any brand/manufacturer of Olanzapine with a marketing authorisation in the UK can be used.

8.2 Regulatory status of the drug

Olanzapine has a marketing authorisation in the UK. It will be used in its marketed presentation and packaging. For this trial, the product will not be further processed, e.g., by repackaging or by trial labelling.
Olanzapine is indicated and approved for:

- Treatment of schizophrenia
- Acute treatment of manic or mixed episodes associated with bipolar I disorder
- Maintenance treatment of bipolar disorder

These indications apply to adult patients.

8.3 Product Characteristics

Olanzapine is an atypical antipsychotic used in and approved for the treatment of schizophrenia and bipolar disorder. Olanzapine is currently widely used for the treatment of AN even though it is not approved in this indication. This feasibility study will use it in this indication in order to inform the feasibility of a future definitive RCT. Apart from its use in AN which is not a current indication for olanzapine all BNF standards apply for this trial.

8.4 Drug storage and supply

Drug storage and supply will follow the policies of the involved NHS Mental Health Trusts and the pharmacies serving the patients. There are no specific requirements for this feasibility study apart from the guidelines and legislation that apply for the use of olanzapine in the UK.
Olanzapine will be sourced locally by the research site pharmacy at market price.
For this trial, there are no special arrangements for prescription, storage and dispensing of olanzapine.

8.5 Preparation and labelling

- No labelling of Olanzapine will be required since it is a feasibility study, and the study drug will be used from commercial stock and according to its SmPC.

8.6 Dosage schedules

In this feasibility study, we will initiate olanzapine treatment at 1.25 mg/d or 2.5 mg/d in adolescent patients and continue this dose or increase the dose slowly to up to 10 mg/d. *In adults, the start dose will be 2.5 mg/d.* Patients can maintain this dose if it is deemed sufficient. This will be a clinical decision. This dosage is within the British National Formulary (BNF) limits.

8.7 Dosage modifications

The study will follow a slow up-titration schedule (1.25 or 2.5 mg/d increments each week for adolescents and 2.5 mg/d for adults up to a maximum of 10 mg/d for both adolescents and adults). This is the dose range we would also apply in an RCT. Olanzapine does not come as a 1.25mg/d tablet so clinicians will be instructed the halve the 2.5mg/d tablet in initial dosages.
The same down-titration increments apply after 12 months to improve patient safety. However, it will be a clinical decision outside our study whether patients continue or stop olanzapine treatment.

8.8 Known drug reactions and interaction with other therapies

The current recommended therapeutic elements to treat AN are psychotherapy, diet counselling and physical monitoring. Thus, there is no specific combination or concomitant medication to be expected in the patient group of this study.
The following combinations are, in principle, known to lead to potential drug interactions:

- Diazepam: May potentiate orthostatic hypotension.
- Alcohol: May potentiate orthostatic hypotension. Alcohol dependence is an exclusion criterion of this trial. Patients will be advised not to drink alcohol during the trial.
- Carbamazepine: Increased clearance of olanzapine.
- Fluvoxamine: May increase olanzapine levels.
- CNS Acting Drugs: Caution should be used when taken in combination with other centrally acting drugs and alcohol.
- Antihypertensive Agents: Enhanced antihypertensive effect.
- Levodopa and Dopamine Agonists: May antagonize levodopa/dopamine agonists.
- Lorazepam (IM): Increased somnolence with IM olanzapine.
- Other Concomitant Drug Therapy: When using olanzapine in combination with lithium or valproate, we will refer to the Drug Interactions sections of the package insert for those products.

Fluoxetine is available in a fixed combination with olanzapine (Symbyax®). This combination is indicated for the treatment of depressive episodes associated with bipolar I disorder or treatment resistant depression. In adolescents, the daily dose should be below 12 mg. However, in this trial 10 mg olanzapine is the maximum daily dose.

8.9 Concomitant medication

Caution is advised for the drugs listed in the previous section as concomitant medication. However, there is no contraindication for the monotherapy with olanzapine. Additionally, blood concentration of olanzapine will be monitored throughout the study. Contraindications according to the BNF apply to elderly patients who will not be included in this trial and to patients who receive olanzapine as intramuscular application which is not envisaged in this trial either.

8.10 Contraception Guidelines

Contraception needs to be used and the duration for use.
A woman is considered of childbearing potential (WOCBP), i.e., 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 post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, more than one FSH measurement is required. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
For females of childbearing potential who may participate in the study, the following methods of contraception, if used properly and used for the duration of the study, are considered sufficient:

- Oral, patch or injection combined or progestestogen only contraceptives. Hormonal contraception must be associated with inhibition of ovulation
- Intrauterine device
- Surgical sterilization

- Vasectomized partner provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Sexual abstinence. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Periodic abstinence, i.e., calendar, symptothermal, or post-ovulation methods are not an acceptable form of contraception for this study.
Male participants will be required to use condoms. Male participants not willing to follow the contraception advice will be excluded.
The duration of contraception required is defined as until the end of the study.

8.11 Assessment of compliance with treatment

Compliance will be assessed by

- Measurement of the olanzapine plasma level 8 weeks after baseline
- Pill count, self-reported by the patient at 8 weeks, 16 weeks, 6 months, and 12 months after baseline.

Noncompliance to the protocol trial procedures will be documented by the investigator. Noncompliance will not lead to withdrawal from the trial. This is a feasibility study which will find out the rate of compliance or noncompliance as well as the rate of participation in assessments and assessment completion.
Compliance and non-compliance are part of the qualitative research aspect of this feasibility study.

9 PHARMACOVIGILANCE

9.1 Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

- **Adverse Event (AE)**: Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
- **Adverse Reaction (AR):** Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
- **Unexpected Adverse Reaction (UAR)**: An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

  The summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)

- **Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** Any adverse event, adverse reaction, or unexpected adverse reaction, respectively, that**:**
  - results in death;
  - is life-threatening;

- required hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect.

- **Important Medical Events (IME) & Pregnancy:** Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will also be reported. In case of a pregnancy, study medication will stop. The pregnant study participant will be followed up until 12 months after baseline.

9.2 Recording and reporting of SAEs, SARs AND SUSARs

Reporting Responsibilities

All SAEs will be reported immediately to the Chief Investigator and to the Sponsor (excepting those specified in this protocol as not requiring reporting)

All SAEs will be reported to the main REC where in the opinion of Chief Investigator (CI) the event was:
- related – that is, it resulted from administration of any of the research procedures, and
- unexpected – that is, the type of event is not listed in the protocol as an expected occurrence,

within 15 days of the CI becoming aware of the event.

Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

The active monitoring period for (S)AEs will end 13 months after baseline which is after down-titration of study medication. Following the active monitoring period, the CI will report any related or unexpected SAEs that he becomes aware of. Where a participant withdraws consent for further processing of data, this does not preclude the reporting of SAEs. The participant information sheet will include a section explaining this to the participant.

9.3 Premature Termination of the Trial

The trial may be prematurely discontinued by the Sponsor, Chief Investigator on the basis of new safety information or for other reasons given by the Data Monitoring & Ethics Committee / Trial Steering Committee regulatory authority or ethics committee concerned.
If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Research Ethics Committee will be informed within 15 days of the early termination of the trial.

9.4 Adverse events that do not require reporting

Routine hospitalizations for examinations related to AN standard care will be recorded but do not require reporting.

Additionally, the following known adverse reactions associated with taking olanzapine do not require reporting:

somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, plasma glucose or HbA1c and triglyceride levels, glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia, dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases, rash, asthenia, fatigue pyrexia, arthralgia, increased alkaline phosphatase, high gamma glutamyl transferase, high uric acid, high creatine phosphokinase and oedema.

9.5 Overdose

Overdoses of 500 mg olanzapine tablets at once or 30 mg daily for at least one week have been reported. Therefore, we will define 500 mg olanzapine taken at once or 30 mg overdose for at least one week as overdose [87-93]. Overdoses will be observed from reported pill counts, patient comments and plasma level measurements. In case of an overdose, study medication will stop for this participant. However, they can remain in the study until 12 months after baseline. An overdose will be fully reported and described in an SAE report form.

9.6 Reporting urgent safety measures

If any urgent safety measures are taken the CI will immediately and, in any event, no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the circumstances giving rise to those measures.

9.7 The type and duration of the follow-up of participants after adverse reactions.

Any SUSAR will be reported to the REC irrespective of how long after administration of Olanzapine the reaction has occurred until resolved.

Table of reporting responsibilities

	Who	When	How	To Whom
SAE (related or unexpected)	Chief Investigator	Within 15 days of CI becoming aware of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Main REC with a copy to the sponsor and DMEC Chair
Urgent Safety Measures	Chief Investigator	Immediately Within 3 days	By phone Notice in writing setting out reasons for the urgent safety measures and the plan for future action.	Main REC Main REC with a copy sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC with a copy to the sponsor
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to the sponsor

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

According to the guidance given by the NIHR Research Design Service London, https://www.rds-london.nihr.ac.uk/resources/justify-sample-size-for-a-feasibility-study/, a reasonable sample size can be

between 30 and more than 50 [94,95]. According to the call, our proposed feasibility study should cover: Willingness to accept and adhere to the intervention; a demonstration that adherence can be measured; estimated numbers of young people potentially eligible for recruitment; key parameters of a potential future trial to include a justification of the choice and timing of an appropriate primary outcome measure. Given the variety of parameters, a figure at the upper end of the recommended range seemed plausible to us. We also have also carried out a sample size calculation for this feasibility study based on estimating the feasibility parameter "rate of adherence": Assuming that 70% of patients took olanzapine for at least 16 weeks, a sample size of 55 patients can estimate a 95% confidence interval for this parameter with 12.2% margin of error (i.e., expected CI from 57.8% to 82.2%; for a more extreme attrition rate of 50% the margin of error increases to 13.3%).

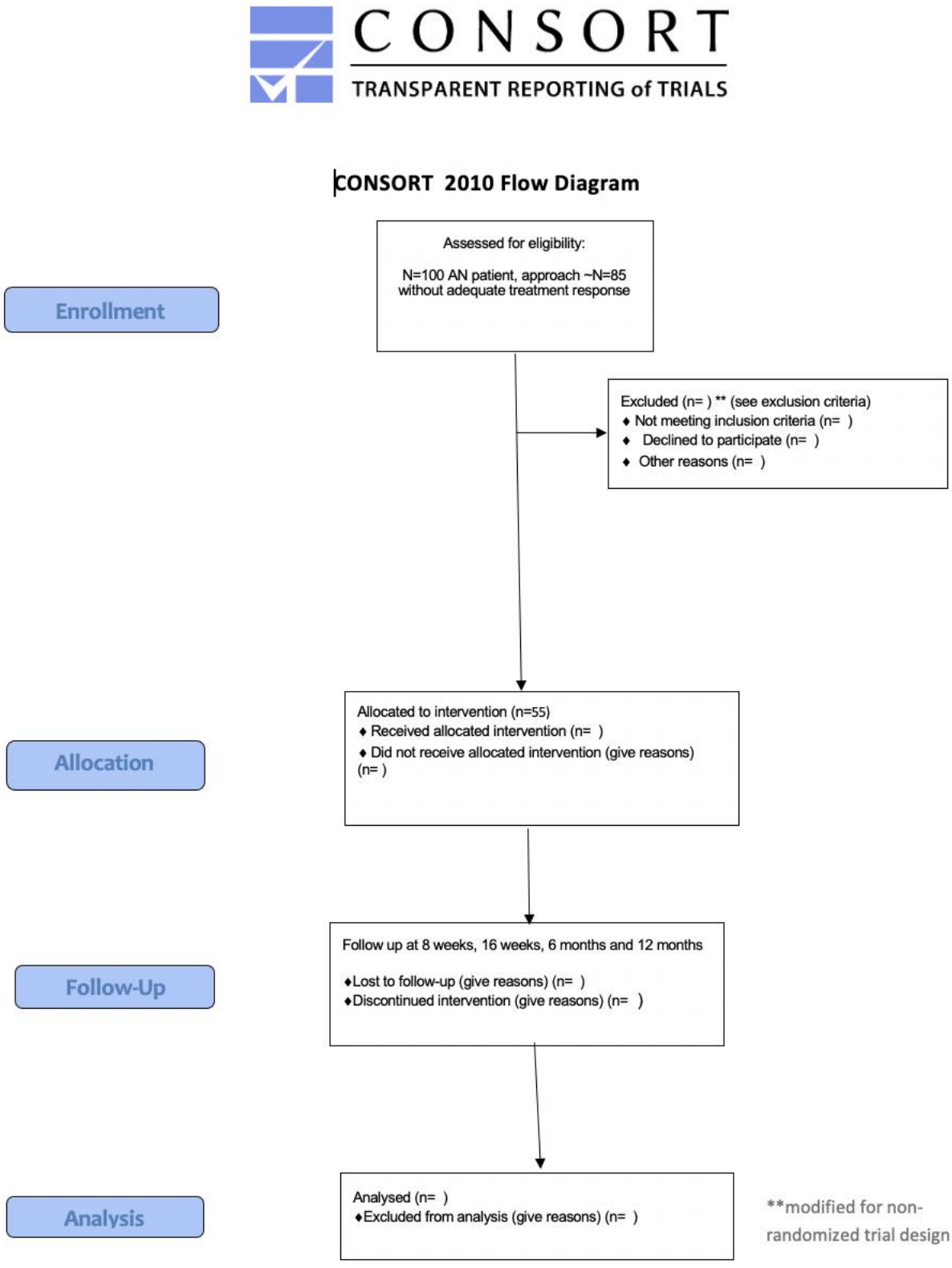
10.2 Planned recruitment rate

This is a feasibility study to test recruitment. In the months 2 to 7 of the project, we are aiming to recruit 55 patients

10.3 Statistical analysis plan

The statistical analysis plan will include a mixed-methods analysis utilizing summary statistics and qualitative analysis of the feasibility outcomes.

10.3. 1 Summary of baseline data and flow of patients



10.3.2 Primary outcome analysis

The main outcome is feasibility.

Summary statistics will be presented on the following for feasibility and may include estimation of confidence intervals:

- Patients approached, screened, and included in the study
- Adherence, completed physical assessments (including BMI measurement**)** and questionnaires

10.3.3 Secondary outcome analysis

Descriptives (including completeness) will be reported for the following measures: demographics, alcohol, smoking and substance use, body weight and BMI, ED psychopathology, general psychopathology, health economic and quality of life assessments, laboratory parameters (kidney function, liver function, blood count, plasma glucose, HbA1c and lipid profile), drug adherence and safety.

The safety outcomes will include:

- Summary statistics on “concerning” and “alerting” laboratory and ECG parameters according to [47]
- Descriptives of other safety parameters
- Summary of reported AEs and SAEs

10.3.4 Exploratory analyses

- We will also perform exploratory analyses looking at change over time in measures listed in Section 10.3.3 to inform a future definitive study design. Such analyses will use appropriate longitudinal modelling approaches; further details will be covered in the Statistical Analysis plan.

- Elements that constitute TAU will be described.

- Patient experience of recruitment and treatment, acceptability and reasons for adherence and non-adherence will be ascertained in qualitative interviews which will be performed, transcribed and analysed.

10.3.5 Qualitative analysis

We will conduct individual qualitative interviews in a subgroup (estimated 30 individuals) of young people with AN who either agree or decline to participate in the OPEN feasibility study. There are two main aims of the qualitative interviews: deciphering the barriers of inclusion for the study and also follow up interviews with questions concerning reflections of their participation. Interviews will examine the decision-making process and the perceived risks and advantages of taking olanzapine within the study. At the point of recruitment, participants will be asked why they agreed or refused to take part in the study. We will also ask for their permission to share their details for subsequent publications. Those who are

recruited to OPEN will be interviewed after the 16-week assessment point about their perceptions prior to participation and their subsequent experiences of olanzapine treatment and the study design, including the perceived burden of completing outcome measures and attitudes towards randomisation in a future clinical trial. We will interview people who have adhered to olanzapine as well as people who have dropped out. The qualitative researcher will aim for 'empathic neutrality', posing open and non-leading questions that invite participants to recount their experiences of the study and treatment from their perspective.

Purposive sampling will be conducted based on gender, age, recruitment source, BMI at baseline and adherence to explore a range of perspectives. A further 10-15 interviews with health care professionals across settings will explore the perceived challenges and facilitators to recruitment and retention. Qualitative data will be analysed using the Framework Approach [85] to facilitate analysis within and between individual cases and groups of participants. The thematic framework will draw on a priori issues around the acceptability of the intervention and design study, but also be responsive to emergent themes.

All qualitative interviews will be carried out by the UK qualitative researcher (TBA2).

Two PhD student studying at King's College London under the supervision of Dr Himmerich and Dr. Treasure, will assist Dr Lawrence will the qualitative data collection and analysis.

10.4 Subgroup analyses

We do not plan any subgroup analyses.

10.5 Adjusted analysis

We do not plan any adjusted analyses.

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

We do not plan any interim analyses.

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

The trial manager will monitor the integrity and completeness of the data weekly and approach clinical services for missing information. Trial statisticians will also monitor integrity and completeness of the data periodically and report discrepancies to the trial manager, at least prior to every DMC meeting.

We do not plan to impute or otherwise handle missing data in the analyses. Instead, missing data in this feasibility study will inform the potential application for a full RCT about risks to data completeness and integrity.

10.8 Other statistical considerations

Throughout data collection and analysis, we will consider whether each clinician participating in the study followed exact protocol when carrying out assessments on participants. To ensure that correct protocol is being followed throughout the trial, clinicians will be asked to submit reports to the CI after each assessment period (baseline, 8 weeks, 16 weeks, 6 months, 12 months). Consultants will also be asked to send copies of blood test results of participants to the CI after the 5 assessment periods to confirm

eligibility for continuing to take Olanzapine. Researchers will also be required to enter all data following assessment to eliminate collection and data entry errors.

10.9 Economic evaluation

Three questionnaires will be utilized in order to assess the health economic impact and quality of life of patients with Anorexia. We will test whether patients and carers complete the questionnaires to evaluate for feasibility. The EQ-5DTM will be given to all 55 participants in the study. The EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. It consists of a descriptive system, which comprises five dimensions: Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the 30 years since its development, it has been successfully used in several thousand national and international studies (e.g. [65,66]) to measure quality of life. The 3-level version has been shown to be suitable for adolescents as well as adults [67]). Specifically, the EQ-5D-Y will be used in the study.
Adult Service Use Schedule (AD-SUS): The AD-SUS has been developed and employed in several mental health trials (such as [68]) Information about the study participants' use of services will be collected in interviews with a researcher at baseline, at 6- and the 12-month follow-ups. At baseline, information will cover the previous 3 months. At each of the follow-up interviews, service use since the previous interview will be recorded; in this way, the entire period from baseline to the final follow- up will be covered. The AD-SUS contains a researcher- and a self-completed section. Both sections together will cover: The number and duration of contacts with various services and professionals, the use of psychological therapies, and the use of non-trial pharmacological therapies including sleeping tablets, mood stabilisers and painkillers. In the OPEN study , the Child and Adolescent and Adult Service Use Schedule (CAA-SUS) will be used. The CAA-SUS a questionnaire designed specifically for the OPEN study, which incorporates features of CA-SUS and AD-SUS will be applied to take the health and social care perspective.
Eating Disorders Symptom Impact Scale (EDSIS): The EDSIS has been developed as a measure to assess the specific caregiving burden of both AN and bulimia nervosa [69]. Subscales of the EDSIS are related to: Nutrition, dysregulated behaviour, guilt, and social Isolation.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

A web-based electronic data capture (EDC) system will be designed, using the InferMed Macro 4 system. The EDC will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit (KCTU) for the duration of the project. It will be hosted on a dedicated server within KCL.

Participant age will be entered on the EDC, initials, date of birth, NHS number, email addresses, participant names and addresses, and full postcodes will not be entered into the EDC. No data will be entered into the EDC system unless a participant has signed a consent form to participate in the trial. Source data will be entered centrally by the coordinating study team typically within 5 days of data collection by authorized staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. A full audit trail of data entry and any subsequent changes to entered data

will be automatically dated and time stamped, alongside information about the user making the entry/changes within the system.

Patient self-reported measures will be collected via Qualtrics, a cloud-based subscription software platform for experience management and entered into the EDC by authorized research staff.

The CI will undertake appropriate reviews of the entered data for the purpose of data cleaning and will request amendments as required. No data will be amended independently of the study site responsible for entering the data.

At the end of the trial, the site PI will review all the data for each participant and provide electronic sign-off that all the data are complete and correct. At this point, all data can be formally locked for analysis.

The InferMed Macro 4 system also includes an e-Case Report Form (eCRF) database in order to enter individual patient data throughout the protocol. The system can be programmed to perform validation checks, such as range checks to prevent data entry errors. Missing data codes are routinely programmed into all fields, for ease of analysis. A standard feature of InferMed MACRO data entry system is the built-in audit trail on all data fields, the automatic saving of data as you leave a form, and the ability to maintain a record of 'source data verification' checks.

For the qualitative interviews, audio recordings and transcription of the interviews will be handled by a 3rd party company specialized in transcription services. There will be a data handling agreement in place to ensure the data protection and confidentiality of each of the participants. Information on the Data Use Agreement will be included in the Participant Information Sheet and must be signed by participants before taking part in the study.

11.2 Data handling and record keeping

The CI or delegate will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorized research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorized to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g., Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance.

All data input into Qualtrics will be downloaded and stored on a password-protected computer at KCL with access from delegated research personnel only.

Data will be locked before data analysis takes place to ensure data integrity. Data collected on the data collection forms will be stored in an electronic database in which the participants will be identified by a specific study number. The participants name and any other identifying factors will be stored in a separate database linked only by the study number. This information will be collected with the consent of the participants and their parent(s) in the case of the adolescent participants to enable follow-up to be undertaken. There will be a data handling agreement in place by the sponsor and the 3rd party transcription service (Clear Voice) to safeguard participant information.

11.3 Access to Data

Direct access will be granted to authorised representatives within the research team, in the UK and Australia, the sponsor, host institution, 3rd party transcription service, and the regulatory authorities to permit trial-related monitoring, audits and inspections in line with participant consent. We will also keep a list of the individuals authorized to make changes to data.

The Investigators will permit trial-related monitoring, audits, and REC review by providing the Sponsors and REC direct access to source data and other documents (e.g., participants' case sheets, blood test reports, X-ray reports, histology reports etc.).

During the trial, the data will be put into a shared database (managed by KCTU and shared with the University of Sydney). The data generated from the UK study will not be accessible by colleagues at the University of Sydney, however KCL will receive pseudonymised from the Australian sister study.

11.4 Archiving

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate for the purpose of archiving. The CI will appoint named individuals within the research team to be responsible for archiving the documents which are, or have been, contained in the trial master file and, access to those documents shall be restricted to those appointed individuals. At the end of the trial, all trial data will be stored and archived in line with Sponsor requirements.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Research Ethics Committee (REC) review & reports

As OPEN is a feasibility study in adolescents and adults testing a medication that will be prescribed off-label, it raises issues about informed consent, off-label prescription of olanzapine, and protection of participants.

Informed consent: In case of subjects over 16 years old, informed consent will be obtained from the patient, in the case of subjects under 16 years old informed consent will be obtained from the parents or guardian, and informed assent from the subjects by the treating clinician and a researcher of our feasibility study together. They will make sure and document that the informed consent is voluntarily expressed, and patients have the capacity to do so. The patient will be adequately informed using materials and a Patient Information sheet, which will be approved by the ethics committee.

- Off-label prescription: Olanzapine is approved for the treatment of schizophrenia, but not for AN. Therefore, it needs to be prescribed off-label. Therefore, this feasibility study has safety measures in place to monitor potential side effects including physical examinations, ECG, laboratory parameters and several side effects scales: and ESS/ESS-CHAD.

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Mental Capacity Act 2005. All correspondence with the

REC will be retained in the Trial Management File and an annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given. The CI will submit final results, including any publications/abstracts, to the REC within one year after the end of the trial.

We will apply for approval by completing the Integrated Research Application System (IRAS) research application form to obtain Research Ethics Committee (REC) and Health and Care Research Approval (HRA).

12.2 Peer review

The trial has been peer reviewed a total of 4 times before submission and approval by the NIHR. In February 2017, we applied for the first time in response to the NIHR HTA call 16/97 "Antipsychotics for anorexia nervosa". In this application, we applied for a complete randomised-controlled trial (RCT) including a feasibility study and a main RCT with an in-pilot study. The final time, we applied for a feasibility study only in accordance with the current call 19/76 "Antipsychotics for anorexia nervosa".

12.3 Public and Patient Involvement (PPI)

Prior to the commencement of research, we've recruited two PPIs, had two independent focus groups, spoke to service users individually, recorded statements, developed questionnaires with PPIs to assess patient and carer views, conducted a survey and evaluated the results [38].

The PPI made significant contribution to the ideas, decisions and drawing up of this proposal and will continue to guide the study until publication and presentation of the results.

12.4 Regulatory Compliance

This protocol and related documents will be submitted for review to Health Research Authority (HRA), and the London Westminster Research Ethics Committee (REC).

12.7 Data handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

- Participant data will be pseudo-anonymised.
- All pseudo-anonymised data will be stored on a password protected computer.
- All trial data will be stored in line with the Data Protection Act and archived in line with sponsor requirements.

12.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The research team does not declare any conflict of interest.

Funding to conduct the trial is provided by the National Institute for Health Research (NIHR).

12.9 Indemnity

The lead sponsor, King's College London, will take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting. King's College London also provides cover under its No Fault Compensation Insurance, which provides for payment of damages or compensation in respect of any claim made by a research subject for bodily injury arising out of participation in a clinical trial or healthy volunteer study (with certain restrictions). The co-sponsor, South London and Maudsley NHS Foundation Trust, take responsibility for arranging the initiation and management of this research, and will take responsibility for ensuring that appropriate standards, conduct and reporting are adhered to regarding its facilities and staff involved with the project.

12.10 Amendments

If the CI wishes to make a substantial amendment to the REC application or the supporting documents, the CI will submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. Any substantial amendments will be notified to the NHS R&D office to assess whether the amendment affects NHS permissions.

12.11 Post trial care

During this trial, participants will receive olanzapine for 1 year. Following the trial, clinicians will make a shared decision with the patient whether olanzapine will be continued or not. If the clinician and patient decide to end the use of the drug, the dosage will be tapered down gradually for 3-4 weeks before treatment is discontinued completely.

12.12 Access to the final trial dataset

The final trial dataset will be available for access to the CI, statistician, junior statistician, researchers, trial manager, KCTU and the investigators. The trial will allow site investigators to access the full dataset if a formal request describing their plans has been approved by the steering committee.

13 DISSEMINATION POLICY

13.1 Dissemination policy

At the conclusion of the trial, there will be a registration with an appropriate trial registry. It is intended that the results of the study will be presented at national/international conferences, charities, as well as service user & carers meetings. Trial design and results will be published in open access peer reviewed journals, as well as KCL/NHS press offices, scientific journals, and the NIHR HTA Journal. The trial results will be shared with and published in collaboration with the research team at University of Sydney. Interested participants will be routinely informed about the study and updates related.

13.2 Authorship eligibility guidelines and any intended use of professional writers

Everyone who is listed as an author should have made a substantial, direct, intellectual contribution to the work. For example (in the case of a research report) they should have contributed to the conception, design, analysis and/or interpretation of data. Everyone who has made substantial intellectual contributions to the work should be an author. All applicants and co-applicants will be cited as authors.

Everyone who has made other substantial contributions should be acknowledged. The CI will act as the corresponding author who takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process. All authors should participate in writing the manuscript by reviewing drafts and approving the final version.

14 REFERENCES

1. Himmerich H, Treasure J. Psychopharmacological Advances in Eating Disorders. Expert Rev Clin Pharmacol 2018;11:95-108.
2. Keski-Rahkonen A, Mustelin L. Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences, and risk factors. Curr Opin Psychiatry 2016;29:340-5.
3. Javaras KN, Runfola CD, Thornton LM, Agerbo E, Birgegård A, Norring C, Yao S, Råstam M, Larsson H, Lichtenstein P, Bulik CM. Sex- and age-specific incidence of healthcare-register-recorded eating disorders in the complete Swedish 1979-2001 birth cohort. Int J Eat Disord 2015;48:1070-81.
4. Miniati M, Benvenuti A, Bologna E, Maglio A, Cotugno B, Massimetti G, Calugi S, Mauri M, Dell'Osso L. Mood spectrum comorbidity in patients with anorexia and bulimia nervosa. Eat Weight Disord Eat Weight Disord 2018;23:305-11.
5. Godart NT, Flament MF, Perdereau F, Jeammet P. Comorbidity between eating disorders and anxiety disorders: a review. Int J Eat Disord 2002;32:253-70.
6. Cederlöf M, Thornton LM, Baker J, Lichtenstein P, Larsson H, Rück C, Bulik CM, Mataix-Cols D. Etiological overlap between obsessive-compulsive disorder and anorexia nervosa: a longitudinal cohort, multigenerational family and twin study. World Psychiatry 2015;14:333-8.
7. Koch SV, Larsen JT, Mouridsen SE, Bentz M, Petersen L, Bulik C, Mortensen PB, Plessen KJ. Autism spectrum disorder in individuals with anorexia nervosa and in their first- and second-degree relatives: Danish nationwide register-based cohort-study. Br J Psychiatry 2015;206:401-7.
8. Schmidt U, Adan R, Böhm I, Campbell IC, Dingemans A, Ehrlich S, Elzakkers I, Favaro A, Giel K, Harrison A, Himmerich H, Hoek HW, Herpertz-Dahlmann B, Kas MJ, Seitz J, Smeets P, Sternheim L, Tenconi E, van Elburg A, van Furth E, Zipfel S. Eating disorders: the big issue. Lancet Psychiatry 2016;3:313-5.
9. Eddy KT, Tabri N, Thomas JJ, Murray HB, Keshaviah A, Hastings E, Edkins K, Krishna M, Herzog DB, Keel PK, Franko DL. Recovery From Anorexia Nervosa and Bulimia Nervosa at 22-Year Follow-Up. J Clin Psychiatry 2017;78:184-9.
10. Himmerich H, Schönknecht P, Heitmann S, Sheldrick AJ. Laboratory parameters and appetite regulators in patients with anorexia nervosa. J Psychiatr Pract 2010;16:82-92.
11. Sachs KV, Harnke B, Mehler PS, Krantz MJ. Cardiovascular complications of anorexia nervosa: A systematic review. Int J Eat Disord 2016;49:238-48.
12. Zerwas S, Larsen JT, Petersen L, Thornton LM, Mortensen PB, Bulik CM. The incidence of eating disorders in a Danish register study: Associations with suicide risk and mortality. J Psychiatr Res 2015;65:16-22.
13. Steinhausen HC. The Outcome of Anorexia Nervosa in the 20th Century. Am J Psychiatry 2002;159:1284-93.

14. Smink FR, van Hoeken D, Hoek HW. Epidemiology, course, and outcome of eating disorders. Curr Opin Psychiatry 2013;26:543-8.
15. Cassano GB, Miniati M, Pini S, Rotondo A, Banti S, Borri C, Camilleri V, Mauri M. Six-month Open Trial of Haloperidol as an Adjunctive Treatment for Anorexia Nervosa: A Preliminary Report. Int J Eat Disord 2003;33:172-7.
16. Mauri M, Miniati M, Mariani MG, Ciberti A, Dell'Osso L. Haloperidol for severe anorexia nervosa restricting type with delusional body image disturbance: a nine-case chart review. Eat Weight Disord 2013;18:329-32.
17. Vandereycken W. Neuroleptics in the short-term treatment of anorexia nervosa. A double-blind placebo-controlled study with sulpiride. Br J Psychiatry 1984;144:288-92.
18. Vandereycken W, Pierloot R. Pimozide combined with behaviour therapy in the short-term treatment of anorexia nervosa. A double-blind placebo-controlled cross-over study. Acta Psychiatr Scand 1982;66:445–50.
19. Court A, Mulder C, Kerr M, Yuen HP, Boasman M, Goldstone S, Fleming J, Weigall S, Derham H, Huang C, McGorry P, Berger G. Investigating the effectiveness, safety and tolerability of quetiapine in the treatment of anorexia nervosa in young people: a pilot study. J Psychiatr Res. 2010;44:1027-34.
20. Powers PS, Klabunde M, Kaye W. Double-blind placebo-controlled trial of quetiapine in anorexia nervosa. Eur Eat Disord Rev 2012;20:331-4.
21. Hagman J, Gralla J, Sigel E, Ellert S, Dodge M, Gardner R, O'Lonergan T, Frank G, Wamboldt MZ. A double-blind, placebo-controlled study of risperidone for the treatment of adolescents and young adults with anorexia nervosa: a pilot study. J Am Acad Child Adolesc Psychiatry. 2011;50:915-24.
22. Ruggiero GM, Laini V, Mauri MC, Ferrari VM, Clemente A, Lugo F, Mantero M, Redaelli G, Zappulli D, Cavagnini F. A single blind comparison of amisulpride, fluoxetine and clomipramine in the treatment of restricting anorectics. Prog Neuropsychopharmacol Biol Psychiatry. 2001;25:1049-59.
23. Frank GK, Shott ME, Hagman JO, Schiel MA, DeGuzman MC, Rossi B. The partial dopamine D2 receptor agonist aripiprazole is associated with weight gain in adolescent anorexia nervosa. Int J Eat Disord 2017;50:447-50.
24. Trunko ME, Schwartz TA, Duvvuri V, Kaye WH. Aripiprazole in anorexia nervosa and low-weight bulimia nervosa: case reports. Int J Eat Disord 2011;44:269–75.
25. Frank GK. Aripiprazole, a partial dopamine agonist to improve adolescent anorexia nervosa-A case series. Int J Eat Disord 2016;49:529-33.
26. Brambilla F, Garcia CS, Fassino S, Daga GA, Favaro A, Santonastaso P, Ramaciotti C, Bondi E, Mellado C, Borriello R, Monteleone P. Olanzapine therapy in anorexia nervosa: psychobiological effects. Int Clin Psychopharmacol 2007;22:197-204.
27. Bissada H, Tasca GA, Barber AM, Bradwejn J. Olanzapine in the treatment of low body weight and obsessive thinking in women with anorexia nervosa: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2008;165:1281-8.
28. Kafantaris V, Leigh E, Hertz S, Berest A, Schebendach J, Sterling WM, Saito E, Sunday S, Higdon C, Golden NH, Malhotra AK. A placebo-controlled pilot study of adjunctive olanzapine for adolescents with anorexia nervosa. J Child Adolesc Psychopharmacol 2011;21:207-12.
29. Attia E, Kaplan AS, Walsh BT, Gershkovich M, Yilmaz Z, Musante D, Wang Y. Olanzapine versus placebo for out-patients with anorexia nervosa. Psychol Med 2011;41:2177-82.
30. Attia E, Steinglass JE, Walsh BT, Wang Y, Wu P, Schreyer C, Wildes J, Yilmaz Z, Guarda AS, Kaplan AS, Marcus MD. Olanzapine Versus Placebo in Adult Outpatients With Anorexia Nervosa: A Randomized Clinical Trial. Am J Psychiatry 2019;176:449–56.
31. Kishi T, Kafantaris V, Sunday S, Sheridan EM, Correll CU. Are antipsychotics effective for the treatment of anorexia nervosa? Results from a systematic review and meta-analysis. J Clin Psychiatry 2012;73:757–66.

32. de Vos J, Houtzager L, Katsaragaki G, van de Berg E, Cuijpers P, Dekker J. Meta analysis on the efficacy of pharmacotherapy versus placebo on anorexia nervosa. J Eat Disord 2014;2:27.
33. Dold M, Aigner M, Klabunde M, Treasure J, Kasper S. Second-Generation Antipsychotic Drugs in Anorexia Nervosa: A Meta-Analysis of Randomized Controlled Trials. Psychother Psychosom. 2015;84:110–6.
34. Kan C, Eid L, Treasure J, Himmerich H. A Meta-Analysis of Dropout and Metabolic Effects of Antipsychotics in Anorexia Nervosa. Front Psychiatry 2020;11:208.
35. Tollefson GD, Sanger TM. Anxious-depressive symptoms in schizophrenia: a new treatment target for pharmacotherapy? Schizophr Res 1999;1(35 Suppl):13-21.
36. Temmingh H, Stein DJ. Anxiety in Patients with Schizophrenia: Epidemiology and Management. CNS Drugs 2015;29:819-32.
37. Kluge M, Schacht A, Himmerich H, Rummel-Kluge C, Wehmeier PM, Dalal M, Hinze-Selch D, Kraus T, Dittmann RW, Pollmächer T, Schuld A. Olanzapine and clozapine differently affect sleep in patients with schizophrenia: results from a double-blind, polysomnographic study and review of the literature. Schizophr Res 2014;152:255-60.
38. Dessain A, Bentley J, Treasure J, Schmidt U, Himmerich H: Patients' and Carers' Perspectives of Psychopharmacological Interventions Targeting Anorexia Nervosa Symptoms. In: Himmerich H, Jáuregui Lobera I (Hrg.): Anorexia and Bulimia Nervosa, InTech Open, London, 2019.
39. Himmerich H, Minkwitz J, Kirkby KC. Weight Gain and Metabolic Changes During Treatment with Antipsychotics and Antidepressants. Endocr Metab Immune Disord Drug Targets 2015;15:252-60.
40. Tek C, Kucukgoncu S, Guloksuz S, Woods SW, Srihari VH, Annamalai A. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. Early Interv Psychiatry 2016;10:193-202.
41. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686-96.
42. Citrome L, McEvoy JP, Saklad SR. Guide to the Management of Clozapine-Related Tolerability and Safety Concerns. Clin Schizophr Relat Psychoses 2016;10:163-77.
43. Himmerich H, Au K, Dornik J, Bentley J, Schmidt U, Treasure J. Olanzapine treatment for patients with anorexia nervosa. Can J Psychiatry 2017;62:506-7.
44. Treasure J (2011). Neuroimaging of Eating Disorders: Commentary. In: Shenton ME, Turetsky BI (Eds.). Understanding Neuropsychiatric Disorders: Insights from Neuroimaging. Cambridge: Cambridge University Press. pp. 510-6.
45. Himmerich H, Bentley J, Lichtblau N, Brennan C, Au K. Facets of shared decision-making on drug treatment for adults with an eating disorder. Int Rev Psychiatry. 2019;31:332-46.
46. Tyrrell-Bunge E, de Carvalho AF, Scott C, Tomlin S, Treasure J, Himmerich H. A three level-intervention to reduce PRN medication on a specialist eating disorders ward for adult female patients with anorexia nervosa. Psychiatr Danub. 2018;30:107-8.
47. https://www.kcl.ac.uk/ioppn/depts/pm/research/eatingdisorders/resources/GUIDETOMEDICALRISKASSESSMENT.pdf
48. Mazure CM, Halmi KA, Sunday SR, Romano SJ, Einhorn AM. The Yale-Brown-Cornell Eating Disorder Scale: development, use, reliability and validity. J Psychiatr Res 1994;28:425-45.
49. Luce KH, Crowther JH. The reliability of the Eating Disorder Examination-Self-Report Questionnaire Version (EDE-Q). Int J Eat Disord 1999;25:349-51.
50. Chandwick P, Lees S, Birchwood M. The revised Beliefs About Voices Questionnaire (BAVQ-R). Br J Psychiatry 2000;177:229-32.

51. Pugh M, Waller G. Understanding the 'Anorexic Voice' in Anorexia Nervosa. Clin Psychol Psychother 2017;24:670-676.
52. Boekaerts, M., Maes, S. and Karoly, P. (2005) 'Self-regulation across domains of applied psychology: Is there an emerging consensus?', Applied Psychology, 54(2), 149–154.
53. Kliemann, N. et al. (2016) 'Development and validation of the Self-Regulation of Eating Behaviour Questionnaire for adults', International Journal of Behavioral Nutrition and Physical Activity, 13(1), 1–11
54. Kouidrat Y, Amad A, Lalau JD, Loas G. Eating disorders in schizophrenia: implications for research and management. Schizophr Res Treatment. 2014;2014:791573.
55. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR; ReproGen Consortium; Psychiatric Genomics Consortium; Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium , Duncan L, Perry JR, Patterson N, Robinson EB, Daly MJ, Price AL, Neale BM. An atlas of genetic correlations across human diseases and traits. Nat Genet 2015;47:1236-41.
56. Meltzer HY, Fibiger HC. Olanzapine: A new atypical antipsychotic drug. Neuropsychopharmacology 1996;14:83-5.
57. Brown TA, Chorpita BF, Korotitsch W, Barlow DH. Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. Behav Res Ther 1997;35:79-89.
58. Marshall AJ, Evanovich EK, David SJ, Mumma GH. Separating Common from Unique Variance Within Emotional Distress: An Examination of Reliability and Relations to Worry. Behav Cogn Psychother 2018;46:633-8.
59. Chorpita BF, Moffitt CE, Gray J. Psychometric properties of the Revised Child Anxiety and Depression Scale in a clinical sample. Behav Res Ther 2005;43:309-22.
60. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989;46:1006-11.
61. DeVeaugh-Geiss J, Katz R, Landau P, Goodman W, Rasmussen S. Clinical predictors of treatment response in obsessive compulsive disorder: exploratory analyses from multicenter trials of clomipramine. Psychopharmacol Bull 1990;26:54-9.
62. Costa DLC, Diniz JB, Requena G, Joaquim MA, Pittenger C, Bloch MH, Miguel EC, Shavitt RG. Randomized, Double-Blind, Placebo-Controlled Trial of N-Acetylcysteine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder. J Clin Psychiatry 2017;78:766-73.
63. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168:1266-77.
64. Wolfe KL, Nakonezny PA, Owen VJ, Rial KV, Moorehead AP, Kennard BD, Emslie GJ. Hopelessness as a Predictor of Suicide Ideation in Depressed Male and Female Adolescent Youth. Suicide Life Threat Behav 2019;49:253-63.
65. van Duijn E, Vrijmoeth EM, Giltay EJ, Bernhard Landwehrmeyer G; REGISTRY investigators of the European Huntington's Disease Network. Suicidal ideation and suicidal behavior according to the C-SSRS in a European cohort of Huntington's disease gene expansion carriers. J Affect Disord 2017;228:194-204.
66. Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). Br J Rheumatol 1997;36:551-9.
67. Batóg P, Rencz F, Péntek M, Gulácsi L, Filipiak KJ, Prevolnik Rupel V, Simon J, Brodszky V, Baji P, Závada J, Petrova G, Rotar A, Golicki D. EQ-5D studies in cardiovascular diseases in eight Central and Eastern European countries: a systematic review of the literature. Kardiol Pol 2018;76:860-70.

68. Byford S. The validity and responsiveness of the EQ-5D measure of health-related quality of life in an adolescent population with persistent major depression. J Ment Health 2013;22:101-10.
69. Kuyken W, Byford S, Taylor RS, Watkins E, Holden E, White K, Barrett B, Byng R, Evans A, Mullan E, Teasdale JD. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. J Consult Clin Psychol 2008;76:966–78.
70. Sepulveda AR, Whitney J, Hankins M, Treasure J. Development and validation of an Eating Disorders Symptom Impact Scale (EDSIS) for carers of people with eating disorders. Health Qual Life Outcomes 2008;6:28.
71. Hiemke C, Baumann P, Bergemann N, Conca A, Dietmaier O, Egberts K, Fric M, Gerlach M, Greiner C, Gründer G, Haen E, Havemann-Reinecke U, Jaquenoud Sirot E, Kirchherr H, Laux G, Lutz UC, Messer T, Müller MJ, Pfuhlmann B, Rambeck B, Riederer P, Schoppek B, Stingl J, Uhr M, Ulrich S, Waschgler R, Zernig G. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry 2011;44:195-235.
72. Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int 2015;2015:217047.
73. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Thibaut F, Möller HJ; WFSBP Task force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J Biol Psychiatry 2013;14:2-44.
74. Steffenhagen N, Rummel-Kluge C, Himmerich H. Metabolic disorders under antipsychotic treatment. Nervenarzt 2012;83:337-44.
75. Lingjærde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychatr Scand 1987;76 Suppl 334:1-100.
76. Olsen RB, Gydesen SU, Kristensen M, Eschen FT, Sørensen C, Hasle H, Lund S, Baastrup PC, Gylding-Sabroe J. Psychotropic medication in the elderly. A survey of prescribing and clinical outcome. Dan Med Bull 1990;37:455-9.
77. Zastrozhin MS, Grishina EA, Ryzhikova KA, Smirnov VV, Savchenko LM, Bryun EA, Sychev DA. The influence of CYP3A5 polymorphisms on haloperidol treatment in patients with alcohol addiction. Pharmgenomics Pers Med 2017;11:1-5.
78. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.
79. Richards A, Quaghebeur G, Clift S, Holland A, Dahlitz M, Parkes D. The upper airway and sleep apnoea in the Prader-Willi syndrome. Clin Otolaryngol Allied Sci 1994;19:193-7.
80. Tasbakan MS, Gunduz C, Pirildar S, Basoglu OK. Quality of life in obstructive sleep apnea is related to female gender and comorbid insomnia. Sleep Breath 2018;22:1013-20.
81. Lauer CJ, Krieg JC. Sleep in eating disorders. Sleep Med Rev 2004;8:109-18.
82. Della Marca G, Farina B, Mennuni GF, Mazza S, Di Giannantonio M, Spadini V, De Risio S, Ciocca A, Mazza M. Microstructure of sleep in eating disorders: preliminary results. Eat Weight Disord 2004;9:77-80.
83. Fang F, Sun H, Wang Z, Ren M, Calabrese JR, Gao K. Antipsychotic Drug-Induced Somnolence: Incidence, Mechanisms, and Management. CNS Drugs 2016;30:845-67.
84. Spettigue W, Buchholz A, Henderson K, Feder S, Moher D, Kourad K, Gaboury I, Norris M, Ledoux S. Evaluation of the efficacy and safety of olanzapine as an adjunctive treatment for anorexia nervosa in adolescent females: a randomized, double-blind, placebo-controlled trial. BMC Pediatr 2008;8:4.

85. Nazar BP, Gregor LK, Albano G, Marchica A, Coco GL, Cardi V, Treasure J. Early Response to treatment in Eating Disorders: A Systematic Review and a Diagnostic Test Accuracy Meta-Analysis. Eur Eat Disord Rev 2017;25:67-79.
86. Wilson MP, Chen N, Vilke GM, Castillo EM, MacDonald KS, Minassian A. Olanzapine in ED patients: differential effects on oxygenation in patients with alcohol intoxication. Am J Emerg Med 2012;30:1196-201.
87. Ritchie J, Spencer L. 1994. Qualitative data analysis for applied policy research. In: Bryman A, Burgess RG (EDs): Analyzing qualitative data, London: Routledge, 1994.
88. Cohen LG, Fatalo A, Thompson BT, Bergeron GDC, Flood JG, Poupolo PR. Olanzapine overdose with serum concentrations. Ann Emerg Med 1999;34:275-8.
89. Bosch RF, Baumbach A, Bitzer M, Erley CM. Intoxication with olanzapine. Am J Psychiatry 2000;157:304-5.
90. Powell G, Nelson L, Hoffman R. Overdose with olanzapine (Zyprexa), a new antipsychotic agent. J Toxicol Clin Toxicol 1997;35:550.
91. O'Malley GF, Sifert S, Heard K, Daly F, Dart RC. Olanzapine overdose mimicking opioid intoxication. Ann Emerg Med 1999; 34:279-81.
92. O'Malley GF, Sifert S, Heard K, Yip L. Pupillary effects of olanzapine overdose mimic opiate and alpha-2 agonists [abstract]. J Toxicol Clin Toxicol 1998;36:523.
93. Fogel J, Diaz JE. Olanzapine overdose. Ann Emerg Med 1998; 32:275-6.
94. Chambers RA, Caracansi AM, Weiss G. Olanzapine overdose cause of acute extrapyramidal symptoms. Am J Psychiatry 1998;155:1630-1.
95. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004;10:307-12.
96. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. J Clin Epidemiol 2012;65:301-8.
97. https://111.wales.nhs.uk/encyclopaedia/c/article/cholesterol
98. Aigner, M., Treasure, J., Kaye, W., Kasper, S., & WFSBP Task Force On Eating Disorders (2011). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry, 12(6), 400–443.

15. APPENDICES

Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	04/03/2022	Hubertus Himmerich	Detailed section on distress management, safeguarding and confidentiality management has been added as per REC recommendation, clarifications have been made to the inclusion and exclusion criteria to avoid confusion and improve consistency with the EDC.
2	1.2	11/08/2022	Hubertus Himmerich	Minor clarifications on measures used including explaining use of the EQ-5D-Y questionnaire, CAA-SUS, as well as correcting an erroneous deletion of UKU-SERS from the Schedule of Events. A clarification that carers will have an opportunity to voice their opinion at the Week 16 qualitative interview.
3	1.3	02/12/2022	Hubertus Himmerich	Minor clarifications of acceptable assessments of plasma glucose – both fasting plasma glucose and random plasma glucose are acceptable as well as glycated hemoglobin measurement.

List details of all protocol amendments here whenever a new version of the protocol is produced.