1. PROTOCOL FULL TITLE

A Randomised Controlled Multi-Centre Open-Label Parallel Group Non-Inferiority Trial of the Clinical Effectiveness, Acceptability and Cost-Effectiveness of a 'Stepping into Day Treatment' Approach versus Inpatient Treatment as Usual for Anorexia Nervosa in Adult Specialist Eating Disorder Services

Protocol Short Title/ Acronym: DAISIES

Trial Identifiers

ISRCTN:			
REC Number:			
IRAS Number:	272903		
Protocol Version Number:	1	Date:	19.12.2019

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2. Study Synopsis

TITLE OF CLINICAL TRIAL:	A Randomised Controlled Multi-Centre Open-Label Parallel Group Non-Inferiority Trial of the Clinical Effectiveness, Acceptability and Cost-Effectiveness of a 'Stepping into Day Treatment' Approach versus Inpatient Treatment as Usual for Anorexia Nervosa in Adult Specialist Eating Disorder Services
Protocol Short Title/ Acronym:	DAISIES
Study Phase If Not Mentioned In Title:	N/A
Sponsor Name:	King's College London
Chief Investigator:	Professor Ulrike Schmidt
IRAS Number:	272903
REC Number:	
Medical Condition Or Disease Under Investigation:	Anorexia Nervosa (AN)
Purpose Of Clinical Trial:	To investigate the clinical effectiveness, acceptability and cost-effectiveness of a stepped care day patient treatment approach to inpatient treatment as usual (IP-TAU) for adults with severe AN.
Primary Objective:	To assess whether in adult patients with severe AN in need of intensive specialist treatment, a stepped care approach [with the option of brief inpatient treatment for medical stabilisation, the need for and duration of which is decided according to weekly assessments from baseline and clear decision rules around patients' suitability for stepping into multi-disciplinary specialist day patient treatment] is non-inferior to IP-TAU in relation to

	improving body mass index (BMI; primary outcome) at 12 months post-randomisation.
Secondary Objective(s):	To assess: (a) What are the differences between a stepped care day treatment approach and IP-TAU in remission rates, AN symptoms, psychosocial outcomes and acceptability at different time points? (b) Is the stepped care approach cost-effective compared to IP-TAU in terms of quality-adjusted-life-years (QALYs) and BMI at 12 months post-randomisation?
Trial Design:	A pragmatic 2-arm multi-centre open-label parallel group non-inferiority randomised controlled trial.
Endpoints:	The primary endpoint will be at 12 months, where we will compare BMI change in the two treatment conditions (primary outcome).
Sample Size:	386
Summary Of Eligibility Criteria:	People aged 17 years or above, with a diagnosis of severe anorexia nervosa (AN) or of Avoidant Restrictive Food Intake Disorder (ARFID) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5, a body mass index (BMI) of less than 16 kg/m^2 and who are in need of intensive treatment.
Intervention (Description, frequency, details of delivery)	This is a stepped care approach which combines intensive day patient treatment with the option of initial inpatient treatment for prior medical stabilisation and progression to day patient treatment at the earliest opportunity. An initial risk assessment will be performed when the patient is assessed for study eligibility and regular (weekly) risk assessments will start at randomisation with clear decision rules around patients' suitability for stepping into multi-disciplinary specialist day patient treatment. Day patient treatment will involve 4-5 days treatment a week with 2-3 meals per day, multi-disciplinary support, expert refeeding and high-quality evidence-based psychological interventions for patients and their carers.
Comparator Intervention:	IP-TAU is the current standard patient care pathway where patients are admitted to a specialist eating disorder inpatient unit. Patients admitted to IP-TAU are treated by a multidisciplinary team (including psychiatrists, psychologists, nurses, dieticians and others), and receive supervised meals and snacks and therapeutic programmes.
Maximum Duration Of Treatment Of A Subject:	Patients will remain in treatment until they reach a healthy weight and normalise their eating, or get as close to this point as possible. This will be evaluated on a case-by-case basis.
Version And Date Of Final Protocol:	

Version And Date Of Protocol Amendments:	

3. Revision History

Document ID - (Document Title) revision X.Y	Description of changes from previous revision	Effective Date

4. Glossary of terms

AN – anorexia nervosa

ARFID – avoidant restrictive food intake disorder

BMI – body mass index

CI – Chief Investigator

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders-5

ED – eating disorder

HES – Hospital Episode Statistics

IP-TAU – inpatient treatment as usual

KCTU – King's College London Clinical Trial's Unit

PPI – Patient and public involvement

QALYs – quality-adjusted-life-years

RCT – randomised controlled trial

REC - Research Ethics Committee

ISD – information Services Division

5. Protocol Contents

6. Background & Rationale

Brief description of proposed trial:

In adults with severe Anorexia Nervosa (AN) or Avoidant Restrictive Food Intake Disorder (ARFID), who are in need of intensive treatment, we will conduct a non-inferiority randomised controlled trial (RCT), with an internal pilot study, comparing a stepped care approach starting with in-patient treatment if necessary and stepping into day treatment versus inpatient treatment as usual (IP-TAU). Outcome assessments will take place at pre-randomisation, 6 and 12 months post-randomisation. The primary outcome is body mass index (BMI) at 12 months. Secondary outcomes include a range of other clinical variables, treatment acceptability and cost-effectiveness. This is a pragmatic two-arm multi-centre open-label parallel group non-inferiority RCT, rated 'very pragmatic' on the PRECIS-2 tool (PRECIS-2, 2016). A further follow-up study at 24 months post-randomisation is also planned, outside the funded trial. Data collection for this will start during the trial period as agreed with the funder.

Population to be studied:

AN is a serious mental disorder associated with high levels of mortality and disability, physical and psychological morbidity and impaired quality of life (Klump, Bulik, Kaye, Treasure, & Tyson, 2009). A related disorder is ARFID, where food restriction and weight loss occur in the absence of concerns about weight or shape. About 20-30% of patients with AN need intensive treatment (either day or inpatient treatment) to achieve improvements or recovery.

Trends in hospital admission rates from the Oxford Record Linkage Study (ORLS; 1968-2011) and similar data from England (1990-2011) (Holland, Hall, Yeates, & Goldacre, 2016) show that in recent years there has been a sharp rise in intensive treatments (day- and inpatient) in AN. Likewise, a study comparing hospital admission rates for mental disorders in England (1998-2012) found that whilst for most major mental disorders, such as schizophrenia, depression, bipolar disorder, and dementia, admission rates had been falling during this period, for eating disorders (EDs) they rose significantly (Green & Griffiths, 2014). Despite this increase in demand for intensive treatments for AN, the relative merits of day- and inpatient care for patients, families, the NHS and wider society are relatively unknown.

Summary of evidence:

We searched systematic and narrative reviews and individual studies, published since 2004, as following the publication of the 2004 NICE Guidelines for Eating Disorders (NICE, 2004) the treatment ethos in inpatient units has changed significantly. Specifically, we searched systematic reviews of published AN treatment trials (Brockmeyer, Friederich, & Schmidt, 2018; NICE, 2017), ongoing RCTs listed in widely used trial registries (Brockmeyer et al., 2018) and reviews of trials assessing different intensive treatment settings (Madden, Hay, & Touyz, 2015), day patient treatment programmes (Abbate-Daga et al., 2009; Friedman et al., 2016; Hepburn & Wilson, 2014; Zipfel et al., 2002) and inpatient treatment (Meads, Gold, & Burls, 2001; NICE, 2017). We identified two RCTs (Freeman, 1992; Herpertz-Dahlmann et al., 2014) and one case-control study (Zeeck, Hartmann, Wetzler-Burmeister, & Wirsching, 2006) that compared inpatient to day patient treatment in AN. In the case control-study (n=26), after inpatient treatment significantly more patients had a good outcome (on predefined criteria) (Zeeck et al., 2006). Effect sizes also pointed to a superiority of inpatient treatment. A small RCT in 32 adults with AN was never published and is therefore difficult to assess (Freeman, 1992; Meads et al., 2001). It found no difference in outcome between the two approaches. A large (n=172 participants) well-conducted trial showed that adolescents with a first episode of AN could safely be stepped down to day treatment after a 3-week inpatient period and that this stepped care approach was non-inferior to IP-TAU and less costly (Herpertz-Dahlmann et al., 2014). At 2-year follow-up, social outcomes were better in stepped care than in IP-TAU (Herpertz-Dahlmann, personal communication). Reviews of ongoing AN treatment trials listed in trial registries (Brockmeyer et al., 2018); search updated to June 2018) identified no ongoing trial comparing day patient with inpatient treatment in AN.

To gauge how inpatient and day treatments are used in AN, we reviewed admission BMIs, length of stay and predictors of length of stay in naturalistic studies (since 2004) of these treatments. For intensive (4-7 days) day treatment of adults with AN, based on a narrative review (Meads et al., 2001), and two further studies (Brown et al., 2018b; Guarda et al., 2017), we identified 11 uncontrolled studies

(n=1010 AN patients) from different countries (USA, Canada, Australia, Germany, Italy, Holland, UK). Across these studies, admission BMIs ranged from 15.7-18.7 kg/m^2. With the exception of one study (Guarda et al., 2017), all others had a mixture of patients who were stepped down from inpatient treatment or admitted from the community. Length of stay ranged from 32-182 days, with most programmes offering treatment for 10-16 weeks. In all programmes, patients showed significant improvements in BMI, ED symptoms, and mood at end of treatment. Five studies had follow-up data, showing that therapeutic gains were stable or increased further (Brown et al., 2018b). Three studies assessed predictors of outcome, one found no predictors, the others found that treatment motivation and 'group climate' predicted treatment attendance, completion and outcomes (Crino & Djokvucic, 2010; Fittig, Jacobi, Backmund, Gerlinghoff, & Wittchen, 2008; Jones, Bamford, Ford, & Schreiber-Kounine, 2007). In one study, lower BMI and longer illness duration were associated with poorer treatment outcomes (Jones et al., 2007). This evidence suggests that internationally, day treatment is typically used for patients that do not have severe AN (defined by BMI).

For inpatient treatment of adults with AN, we found 15 adult inpatient cohorts (n=2100) from different countries (USA/Canada: Guarda et al., 2017; Lund et al., 2009; Treat et al., 2005; Woodside, Carter, & Blackmore, 2004; Australia/New Zealand: Surgenor, Maguire, & Beumont, 2004; Germany: Kästner et al., 2018; Schlegl, Quadflieg, Löwe, Cuntz, & Voderholzer, 2014; Italy: Calugi, El Ghoch, & Dalle Grave, 2017; Dalle Grave, Calugi, Conti, Doll, & Fairburn, 2013; UK: Brown et al., 2018a; Collin, Power, Karatzias, Grierson, & Yellowlees, 2010; Goddard et al., 2013; Hibbs et al., 2015; Long, Fitzgerald, & Hollin, 2012; Lynch et al., 2013; Magill et al., 2016; Morris, Simpson, & Voy, 2015). Across studies, mean admission BMIs ranged from 13.9-16.3 kg/m^2. The mean length of stay ranged from 33-232 days. Patients in all studies showed significant improvements in BMI, ED symptoms and mood at the end of the admission. Key predictors of length of stay included admission BMI, purging type AN and illness duration (Kästner et al., 2018). Only 3 studies provided follow-up data (Calugi et al., 2017; Dalle Grave et al., 2013; Goddard et al., 2013; Hibbs et al., 2015; Magill et al., 2016). There usually was some weight loss post-discharge with a nadir at 6 months, with weight stabilising or increasing thereafter. In line with this, readmission rates were higher during the first year post-admission (~ 30%) compared to the second year (~20%) (Magill et al., 2016). These data suggest that internationally there is considerable variation in the severity and length of stay of inpatients with AN. Whilst inpatient treatment is effective in the short-term, there is potential for deterioration and relapse, particularly in the first few months post-discharge.

Clinical practice in the UK:

The 2017 NICE Guidelines for Eating Disorders (NICE, 2017) recommend that people whose physical health is severely compromised should be admitted to a specialist inpatient or day patient service for medical stabilisation and to initiate refeeding. When deciding whether day patient or inpatient care is most appropriate, the person's BMI or weight, and broader medical risk needs to be considered and where these can be safely managed. NICE Guidelines (NICE, 2017) also state that whether or not the person is medically stable, within 1 month of admission a review with them and relevant others (parents/carers, referring team) should be conducted to assess whether inpatient care should be continued or stepped down to a less intensive setting. A schedule for further (at least monthly) reviews should be made to take into account the risk that people with an ED can become institutionalised by a long admission, and that a lack of change in their condition could indicate that inpatient treatment is harmful. In the case of differing views between professionals about the benefit of continued inpatient care, a second opinion should be considered. However, relatively little is known about inpatient and day patient practice in the UK. With regards to inpatient treatment for adults with AN, out of 15 studies identified, six were from the UK (512 patients; Brown et al., 2018b; Collin et al., 2010; Goddard et al., 2013; Hibbs et al., 2015; Long et al., 2012; Lynch et al., 2013; Magill et al., 2016; Morris et al., 2015) with mean admission BMIs between 13.6-14.9 kg/m^2. The mean length of stay ranged from 102-232 days (i.e., 14.5-32.2 weeks). In addition, a UK-wide survey of specialist ED units estimated the mean IP-TAU length of stay as 127 days (i.e., 18.2 weeks) (Royal College of Psychiatrists', 2012). In relation to day patient treatment, the same survey found that 49% of specialist ED Units had day patient provision (Royal College of Psychiatrists', 2012). However, in our review of recent studies on day patient treatment, only two out of 11 studies identified were from the UK (Goddard et al., 2013; Jones et al., 2007). One of these included 30 AN patients with a mean BMI of 16.4 kg/m^2 and a standard length of stay of 12 weeks (Jones et al., 2007). The other study included 16 day patients with a mean admission

BMI of 17.3 kg/m^2 and a 17.8 week length of stay (Goddard et al., 2013). Finally, an unpublished series of 92 AN day patients from the Maudsley Hospital had a mean BMI of 16.7 kg/m^2 and a 26 week length of stay (Tchanturia, personal communication).

These studies suggest that whilst day patient practice in the UK is similar to that elsewhere (e.g., similar illness severity), inpatient treatment in the UK is reserved for the most severe patients, whereas elsewhere inpatient treatments cater for a wider range of severities.

Cost and cost-effectiveness of intensive treatments for AN

AN has one of the highest treatment costs of any psychiatric disorder (Mitchell et al., 2009; Striegel-Moore, Leslie, Petrill, Garvin, & Rosenheck, 2000; Stuhldreher et al., 2012). This is largely due to the high cost of inpatient treatment. In patients needing such treatment, costs are directly related to illness severity (i.e., BMI), as this affects length of stay (Stuhldreher et al., 2012). Most cost-effectiveness studies have focused on cost/day or cost per admission (Mitchell et al., 2009; Striegel-Moore et al., 2000; Stuhldreher et al., 2012). Given wide variability in both rates of weight gain and discharge BMIs among programmes, one US study used cost/pound (in weight) gained, rather than cost/day, as an indicator of treatment cost (Guarda et al., 2017). These authors found that whilst the average cost/day was $2295 for inpatient treatment and $1567 for day treatment, the average cost/pound gained was $4089 and $7050 respectively, suggesting that inpatient treatment may be a more efficient way of achieving weight recovery. However, this study only focused on short-term weight outcomes, and longer-term weight and psychological outcomes were not considered. In contrast, the large RCT by Herpertz-Dahlmann et al. (2014) found that short admission followed by day treatment of adolescents with AN was less costly and at least as effective as prolonged inpatient treatment, in terms of weight gain and psychosocial outcomes. In addition, a large Canadian series of patients receiving day treatment assessed the cost-effectiveness of a 4 vs a 5 day treatment regime (Olmsted, McFarlane, Trottier, & Rockert, 2013). Whilst for weight gain it did not matter which programme was used, for binge-purge cessation the 5-day programme was more cost-effective.

Risk and Benefits

Risks: The stepped care approach may be frightening for patients and carers, as there may be the perception that little has changed after a short inpatient stay. Patients who live alone may perceive that having to spend evenings and weekends at home is increasing their isolation, causing them distress. Families may feel that they are asked to carry an unacceptable burden by having their family member with AN at home during evening/night times and at weekends, whilst they are still significantly unwell.

These risks can be overcome by optimal preparation of patients and families on what to expect from stepped care treatment, involving them in the decision making, assessing that they have the necessary resources and skills to deal with the step-down to day treatment, and where these are lacking, helping patients/families to access/acquire these. For example, carers skills programmes and support groups are provided in all participating ED services, and help carers to optimally support the person with AN in different settings.

Benefits: In the stepped care approach patients either have short admissions and are stepped down into day patient treatment or receive immediate day patient treatment. As a result, they are less likely to become institutionalised, passive and disempowered. They are more likely to display adaptive behaviours in response to care, to retain links with their family and friends and to have better psychosocial outcomes. They may also realise the important and active role they play in their own recovery, and by doing so may become more resilient against relapse and more able to cope with any setbacks. Likewise, the stepped care approach may also contribute to helping carers feel more empowered to support the person at home.

Justification for choice of interventions and study design:

The study was conceived in response to an NIHR commissioned call for trials comparing specialist day treatment with inpatient treatment given the limited evidence on effectiveness, cost and cost-effectiveness of day treatment for severe adult AN. We considered three design options, all for a non-inferiority trial. Firstly, we considered comparing day patient treatment with inpatient treatment as usual (IP-TAU), as described in the commissioning brief. This would mean that only those patients could be included who at baseline could immediately safely be allocated to day patient treatment. This would

exclude large numbers of patients from the population of patients qualifying for intensive treatment and severely reduce generalisability of the trial. Secondly, we considered modelling our trial on the large well-conducted German trial in adolescents with a first episode of AN (Herpertz-Dahlmann et al., 2014). In this trial, all patients initially had a 3-week inpatient treatment for medical stabilisation and then were randomly allocated to either continue with inpatient treatment or to step down to day patient treatment. However, adults with AN are more heterogeneous than adolescents in terms of medical risk and thus a fixed-duration initial inpatient stay would 'overtreat' some patients and 'undertreat' others. Finally, we considered (and decided to use) the stepped care approach described here, as this allows delivery of personalised care, tailoring intervention according to patient risk and progress. An internal pilot study will be included within the trial, to assess recruitment.

Conclusion:

Relatively little is known about the comparative effectiveness, cost and cost-effectiveness of day treatment. If at least a proportion of patients needing intensive treatment could be treated as day patients or be stepped down from inpatients earlier, this could have significant cost savings for the NHS. Thus, the proposed trial is timely and highly relevant.

7. Trial Objectives and Design

7.1 Trial Objectives

Aim:

To assess the relative merits of a stepped care intensive day treatment approach in comparison to inpatient treatment as usual (IP-TAU) in adults with AN.

Objectives:

To evaluate the clinical effectiveness, acceptability and cost-effectiveness of these interventions in a multi-centre two-arm non-inferiority RCT of adults with severe AN, i.e., whose symptoms are worsening or unresponsive to outpatient treatment.

Research Questions:

In adult patients with severe AN in need of intensive specialist treatment, is a stepped care approach [with the option of brief inpatient treatment for medical stabilisation, the need for and duration of which is decided according to weekly assessments from baseline and clear decision rules around patients' suitability for stepping into multi-disciplinary specialist day patient treatment] non-inferior to IP-TAU in relation to improving BMI (primary endpoint) at 12 months post-randomisation?

What is the impact of these two approaches on remission rates, AN symptoms, psychosocial outcomes and acceptability at different time points?

Is the stepped care approach cost-effective compared to IP-TAU in terms of quality-adjusted-life-years (QALYs) and BMI at 12 months?

Although our primary clinical analysis is based on a non-inferiority hypothesis, for secondary endpoints we will simply evaluate the trial arm difference. A superiority hypothesis for the economic evaluation is appropriate given the lower cost of day treatment compared to inpatient treatment, as well as being preferred methodologically (Bosmans et al., 2008; Briggs & O'Brien, 2001).

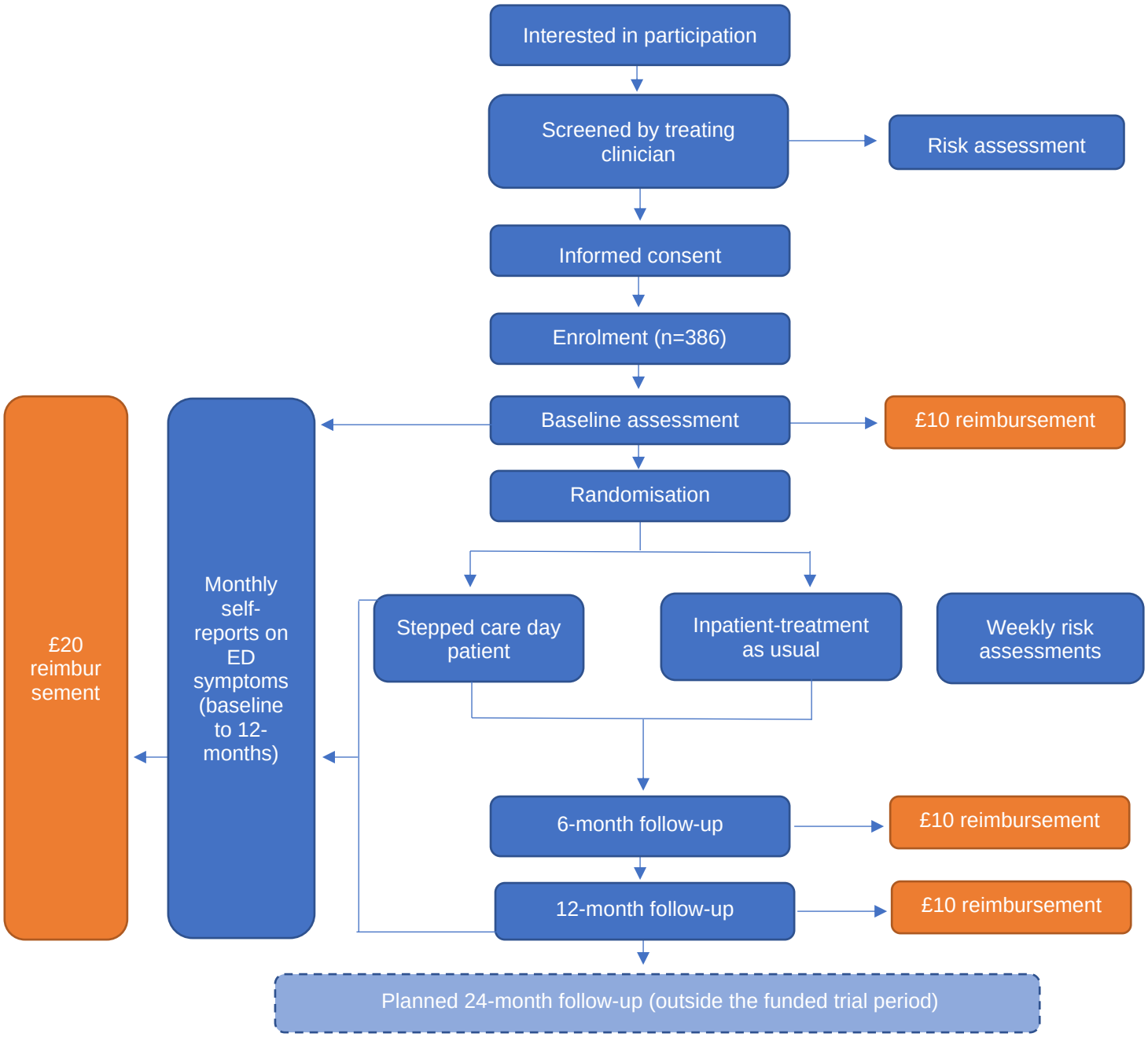
7.2 Trial Design

We will conduct a pragmatic two-arm multi-centre open-label parallel group non-inferiority RCT comparing the two intensive treatment approaches in routine NHS practice. To assess recruitment rates, an internal pilot trial (aiming to recruit 62 patients over 4 months) is included in the study design. If this is successful (recruitment of more than 50% of the desired sample), we will continue with the full study which will include 386 adults (including pilot participants) with severe AN, deemed to need intensive treatment.

Following MRC guidance (Moore et al., 2015), we will conduct a qualitative process evaluation to contextualise and understand the trial outcomes. The process evaluation will involve qualitative interviews with patients, carers, and clinicians in both arms to understand views on the treatment experience and how this produced change.

7.3 Trial Flowchart

Figure 1. Trial flowchart



8. Trial Intervention

8.1 Therapy/Intervention Details

Intervention to be tested: The stepped care intervention combines intensive specialist day patient treatment with the option of initial inpatient treatment for medical stabilisation and progression to day patient treatment at the earliest opportunity. An initial risk assessment will be performed when the patient is checked for study eligibility to inform the initial decision (prior to randomisation) on whether the patient ought to start the trial treatment in inpatients or day patients. Regular weekly risk assessments will start at randomisation, with clear decision rules around patients' suitability for stepping into multi-disciplinary specialist day patient treatment. Day patient treatment will involve a programme covering 4-5 days a week with 2-3 meals per day, multi-disciplinary support, expert refeeding and high-quality evidence-based psychological interventions for patients and their carers. Patients will return home for weekends and evenings. Those allocated to the stepped care intervention can either start day patient treatment immediately or be stepped down to day patient treatment after a period of inpatient treatment. The main aim of the day patient treatment will be to treat patients, until they reach a healthy weight and normalise their eating, or get as close to this point as possible.

Comparison intervention: This will be inpatient treatment-as-usual (IP-TAU). IP-TAU is the current standard patient care pathway. In this care pathway, patients admitted to a specialist ED inpatient unit are treated until they reach a healthy weight and normalise their eating, or get as close to this point as possible. Patients admitted to IP-TAU are treated by a multidisciplinary team (including psychiatrists, psychologists, dieticians, nurses and others), and receive supervised meals and snacks and therapeutic programmes. A proportion may also have day patient treatment at the end or be discharged to outpatient treatment, at the discretion of the treating team.

8.2 Frequency and duration of intervention

The duration of both IP-TAU and day patient treatment will depend on the individual progress of each patient, which will be regularly assessed by the treating clinical team. In UK studies the average length of stay in IP-TAU ranges from 14.5 to 32 weeks (Brown et al., 2018b; Collin et al., 2010; Goddard et al., 2013; Hibbs et al., 2015; Long et al., 2012; Lynch et al., 2013; Magill et al., 2016; Morris et al., 2015). The average length of day treatment in UK studies ranges from 12 to 26 weeks (Goddard et al., 2013; Jones et al., 2007).

Research assessments including BMI measurements, clinical interviews and a battery of questionnaires will be conducted pre-treatment (baseline), at 6-months follow-up and 12-months follow-up. In addition, patients will be asked to complete monthly brief online self-report questionnaires of ED symptoms to assess remission and relapse rates up to and including month 12. A further 24-month follow-up is planned outside the funded trial, as improvements in both nutrition and psychological functioning can continue over a number of years.

8.3 Intervention records

This is a trial assessing specialist treatment settings/care pathways consisting of multi-component and multi-disciplinary treatment programmes. We will obtain detailed information on the exact nature (i.e., timetables) of therapeutic programmes delivered in each participating site. We will also record the number of inpatient days and day-treatment days patients have received and any specialist outpatient treatments.

8.4 Subject Compliance

Treatment/intervention compliance will be defined as uptake of inpatient/day patient treatment as planned and remaining an inpatient until the mutually agreed discharge date, or attending day treatment as planned. Patient initiated self-discharge prior to the agreed date will be defined as non-compliance.

8.5 Study adherence

Researchers will monitor study adherence through regular communication with the clinical teams including planned site visits. Any deviations from the study protocol will be recorded immediately.

Compliance with assessments will be closely monitored by the research team. We have extensive experience of keeping people in studies, e.g., with follow-up rates of ~ 80% in previous AN trials. Strategies to ensure adherence to assessments and mitigate against study drop-out include informing patients that whatever they think of treatment or services received, we will be wanting to follow them up over 24 months. We will also ask patients for multiple contact details, including those of close family members to ensure that if they move or change their mobile number we still are able to contact them. We will reimburse participants for completing assessments. We will send patients reminders regarding their follow-up assessments. If necessary, we will give patients the option of completing only a limited set of essential outcome criteria. Additionally, we will buy, for example, pens, notebooks, data sticks with a study logo as small gifts to patients to increase study retention. We will also send patients' birthday and Christmas cards to remind them of being part of the study. We have previously used all of these strategies with good results.

8.6 Concomitant Medication

A range of medications are often prescribed during IP-TAU and day patient treatment, as part of the patients' treatment plan. There are no medications that will be proscribed. We will record medication prescriptions and any changes in medications at each of the assessment points.

9. Research environment

The study will take place in UK-based specialist ED units. Study assessments will take place online, by phone, or if appropriate, in-person. In-person assessments will take place at either the South London and Maudsley NHS Foundation Trust, Institute of Psychiatry, Psychology & Neuroscience at King's College London, at any of the recruiting sites or at the patients' home. A list of the recruiting sites can be found in section 10.3.

10. Selection and Withdrawal of Subjects

10.1 Inclusion Criteria

- Male and female adults
- Aged 17 years or above
- Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 diagnosis of anorexia nervosa (AN) or avoidant restrictive food intake disorder (ARFID)
- BMI of less than 16 kg/m²
- In need of intensive treatment either because of rapid weight loss, and/or evidence of system/organ failure/medical instability and/or unsuccessful outpatient treatment
- Have mental capacity to give informed consent to participate in the study

10.2 Exclusion Criteria

- Individuals with insufficient knowledge of English to complete study assessments or understand treatment
- Individuals with severe learning disabilities
- Individuals with a severe medical or psychiatric (co)morbidity (e.g., psychosis, substance dependence) requiring treatment in its own right
- Those living too far away from day patient treatment (and where no alternative arrangements for regular attendance at day patient treatment can be made)
- Those who are involved in current research or have recently been involved in any research prior to recruitment

10.3 Selection of Participants

Patients will be recruited from specialist ED services across the United Kingdom, including:

- South London and Maudsley NHS Foundation Trust
- Central and North West London NHS Foundation Trust
- South West London and St George's Mental Health NHS Trust
- Leicestershire Partnership NHS Trust and Nottinghamshire Healthcare NHS Foundation Trust
- Surrey and Borders NHS Mental Health Trust
- Dumfries and Galloway NHS Trust
- NHS Grampian
- Dorset Healthcare University NHS Foundation Trust
- 2gether NHS Foundation Trust, Gloucester
- We are currently also in discussion with additional centres such as Oxford, Cambridge, Southampton, Liverpool and Hayes Grove Priory.

Participants will be recruited from the pool of patients with a diagnosis of AN or ARFID who have a BMI below 16 kgs/ m^2 who are referred to or currently being treated in participating specialist ED services. Any such patients deemed by their assessing or treating ED clinician to be in need of intensive treatment (in- or day patient treatment) will be approached by their treating clinician, informed that the study is taking place, and given a brief description of it. Patients will be clearly informed that whether they decide to participate in the study or not will in no way influence their care or the timing of their treatment.

In each service there will be one or several designated clinicians with whom study researchers can liaise with on a regular basis to identify new patients who are/ or become eligible for study participation due to deterioration or non-response to outpatient treatment.

Patients who wish to receive further information about the study will be contacted by the research team through a mode of communication preferable to them (letter, email, text, telephone or in person if a suitable distance). A member of the research team will provide the patient with a detailed information sheet and a consent form and give them the opportunity to ask any questions. We are also planning to produce a video describing the pros and cons of the care pathways in the study. Patients will then be given the opportunity to decide whether or not to participate (up to a week). Those that wish to participate will complete an online or written (in-person or returned to researchers via mail) consent form. We will then inform the treating clinician and the patient's general practitioner of their participation.

10.4 Randomisation Procedure / Code Break

A web-based randomisation system will be designed, using the bespoke King's College London Clinical Trial's Unit (KCTU) randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the Chief Investigator (CI) and maintained by the KCTU for the duration of the project. It will be hosted on a dedicated server within King's College London.

The CI or delegate (e.g., Trial Manager) will request usernames and passwords from the KCTU. System access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the randomisation system are not shared, and that only those authorised 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.

Study research workers will request randomisation for each participant following completion of the baseline assessment. The trial manager or delegate will be informed about the trial arm allocation and inform the treating clinical team. Participant initials and date of birth will be entered on the randomisation system. NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the randomisation system. No data will be entered onto the randomisation system unless a participant has signed a consent form to participate in the trial. Randomisation will be undertaken centrally by the co-ordinating study team, by authorised staff onto the randomisation system by going to www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trial of

data entry will be automatically date and time stamped, alongside information about the user making the entry within the system.

Data cannot be amended in the randomisation system, however, the CI or delegate (e.g., Trial Manager) may request KCTU to add notes against individual subject entries to clarify data entry errors.

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.

10.5 Withdrawal of Subjects

Participants have the right to withdraw from the study at any time for any reason, without affecting the care they receive. The investigator also has the right to withdraw patients from the study in the event of an illness, adverse events or serious adverse events. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a patient withdraw from the study intervention only, efforts will be made to continue to obtain follow-up data, with the permission of the patient. Should a patient withdraw from the overall study, previously collected data will only be withdrawn if requested by the patient.

10.6 Expected Duration of Trial

Time from first patient recruited to the final patient completing their 12-month follow-up is expected to be 37 months. The last patient visit for the separate (but integrated) 24-month follow-up study will be after 49 months.

11. Trial Procedures

11.1 By Visit

11.1.1 Screening and Recruitment

Potential participants from ED services across the UK will be approached by their treating clinician, informed of the study taking place and provided with a brief description. If interested, the clinician will screen for eligibility using a brief assessor checklist, conduct a risk assessment and ask the patient for consent to be contacted by the research team.

A member of the research team will then get in contact with the patient, give a detailed description of the study (with an information sheet), and give the patient the opportunity to ask any questions. Patients will be given up to a week to decide on participation. Three copies of informed consent will be taken, either online, via mail or in-person. The participant and the clinical team will be provided with a copy, and one will be kept by the research team. The patient will also be asked for consent to contact their carer for participation. If this is given, the patient will be asked to provide contact details and their carer will be contacted by a member of the research team. Carers will be provided with an information sheet and given the opportunity to ask any questions. If interested in participation, consent will also be taken from the carer either online, via mail or in-person.

As part of their consent to the study, the patient will be asked to consent to the research team requesting Hospital Admission Statistics (HES) from NHS Digital (for participants from England) or Information Services Division (ISD; for participants from Scotland) (e.g., number of admissions one year prior to participating and two years post-randomisation). If patients are happy to consent to this, a member of the research team will ask the participant for some identifiable data to send to NHS Digital or ISD. Identifiable data will include NHS number, full name, date of birth, address and postcode.

Lastly, study consent forms will also ask patients to consent to a qualitative researcher contacting them after the 12-month follow up to discuss taking part in a one-off qualitative interview about their treatment experiences during their study.

The treating clinician will then be informed of their participation.

11.1.2 Baseline assessment

The baseline assessment will take place as soon after consent has been given as possible and will consist of three parts which together take a maximum of 2 hours 15 mins (weight and height measurement; approximately 90 minutes self-report questionnaires and an interview typically lasting no longer than 45 minutes). The self-report questionnaires will usually be completed in the patient's own time and do not have to be completed in a single session.

Where possible baseline assessments will be conducted face-to-face at the patient's treating ED service, or the Institute of Psychiatry, Psychology & Neuroscience at King's College London or at the patient's home. Alternatively, a scheduled phone/Skype call will be scheduled. In addition, we will train up Clinical Studies Officers (CSOs) to conduct baseline assessments, including the Eating Disorder Examination Interview (EDE) (Fairburn, 2008), so more interviews can take place face-to-face.

Participants will be able to complete the self-report questionnaires online (on a secure online platform for which they will be provided with a link). Alternatively, they will be able to complete paper versions of the self-report questionnaires. These will be made available in participating sites or can be mailed to the participant, along with a free postage stamp to return them to the study research team at King's College London once completed. All data will be manually inputted into the MACRO trial database. The following measures (along with the expected completion times) will be included in the baseline assessments:

Body Mass Index:

Where researchers are able to see patients face-to-face they will measure their weight and height. Alternatively, this information will be obtained from the patient's clinical team, via their GP or their hospital records. Every effort will be made to ensure that objective measurements are obtained. If this is not possible, the participant will be asked to self-report their weight.

Eating Disorder Symptoms:

- The Eating Disorder Examination Interview (EDE) (Fairburn, 2008) (~45 minutes). This is a semi-structured interview conducted by a trained individual to assess the psychopathology associated with the diagnosis of an ED. Depending on practicalities this will be carried out in person or by phone/ Skype call to the patient. This interview will be audio recorded (with the patients consent) for quality assurance purposes.
- Eating Disorders Examination - Questionnaire Short (EDE-QS) (Gideon et al., 2016) (5 minutes) - a 12-item measure of ED symptom severity over the previous 7 days.

Comorbid symptoms:

- Depression, Anxiety and Stress Scales-Version 21 (DASS-21) (Lovibond & Lovibond, 1995) (5 minutes) - a 21-item self-report questionnaire which aims to evaluate mood, anxiety and stress levels over the previous week.
- Obsessive Compulsive Inventory-Revised (OCI-R) (Foa et al., 2002) (5 minutes) - an 18-item self-report measure of Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV symptoms of obsessive compulsive disorder.

Psychosocial Adjustment:

- Clinical Impairment Assessment (CIA) (Bohn & Fairburn, 2008) (5 minutes) - a 16-item self-report measure of psychosocial impairment secondary to ED features over the past 28 days.
- Significant Others Scale (SOS) (Power, Champion, & Aris, 1988) (10 minutes) - measures an individuals significant relationships (e.g., closest friend, closest member of family, partner), and both their perceived and ideal levels of emotional and practical support.
- Work and Social Adjustment Scale (WASA) (Zahra et al., 2014) (2 minutes) - a 5-item self-report scale designed to measure patients' perceived functional impairments resulting from a given problem, in this case, AN.
- Revised UCLA Loneliness Scale (Russell, Peplau, & Cutrona, 1980) (5 minutes) - a 20-item self-report measure of social satisfaction and dissatisfaction.

Treatment Motivation, Expectations and Experience:

- Motivational rulers (willingness and readiness to change) (5 minutes) (Schmidt et al., 2015) - The Motivational rulers consist of a 10-point scale. Participants are asked to indicate the importance of the personal changes they desire and to evaluate their confidence about making those changes.
- Visual Analogue Scales (VAS) assessing treatment expectations and acceptability (Schmidt et al., 2015) (2 minutes) - These scales consist of a 10cm line. Participants are requested to indicate on this line (rated on a 0 to 10 scale) a degree or level of expectation or acceptability regarding treatment.
- Perceived Coercion Scale (PCS) – adapted (Guarda et al., 2017; Schreyer et al., 2016) (5 minutes) - a 16-item self-report measure asking participants how they felt they had influence, freedom, control, and choice regarding the decision making and admission process for intensive treatment.
- Therapeutic Environment Scale (TESS) (Veale, Miles, Naismith, Pieta, & Gilbert, 2016) (10 minutes) - measures the occurrence of various interpersonal processes in a therapeutic environment, on 9 different subscales of interpersonal behaviour.

Economic Measures:

- The 5-level version of the EuroQol (EQ-5D-5L) (Herdman et al., 2011) (5 minutes) - a measure of health-related quality of life which assesses the severity of problems across the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
- Adult Service Use Schedule (AD-SUS), designed for mental health populations (Perez et al., 2015; Richards et al., 2016) and modified for AN (15 minutes) - measures the number and length of contacts with various services and professionals relevant to the disease of interest. This will be modified for service use related to AN.
- We will obtain Hospital Episode Statistics (HES) data from NHS Digital (for participants from England) or Information Services Division (ISD; for participants from Scotland). Data requested will include the number of admission days to A&E, specialist ED units, and general psychiatric inpatient wards in the year prior to participation in the study and for 2-years post-randomisation.

Carer burden:

If consent has been given for carer participation, the following questionnaires will be sent to the carer for completion either online (on a secure online platform for which they will be provided with a link) or by post:

- Depression, Anxiety and Stress Scales-Version 21 (DASS-21) (Lovibond & Lovibond, 1995) (5 minutes), described above.
- Eating Disorder Symptom Impact Scale (EDSIS) (Sepulveda, Whitney, Hankins, & Treasure, 2008) (5 minutes) - a 24-item self-report measure rating carers' perceptions of ED-specific burden using a 5-point Likert scale.

Members of the research team will manually check that baseline assessments have been completed. After completion, participants will be randomised into either IP-TAU or a stepped care day patient treatment approach.

11.1.3 Treatment intervention

Those randomised to IP-TAU will be admitted into an inpatient ward at a specialised ED service and treated by a multidisciplinary team (including psychiatrists, psychologists, dieticians, nurses and others), receive supervised meals and snacks, expert refeeding and therapeutic programmes. Patients will be treated until they reach a healthy weight and normalise their eating, or get as close to this point as possible.

Those allocated to the stepped care day patient treatment approach will either start the multi-disciplinary specialist day patient treatment immediately, or if deemed high-risk, be admitted into inpatient care until they have been medically stabilised. This decision will be based on the risk assessment performed when the patient is checked for study eligibility. Regular risk assessments will then be conducted on a weekly basis from randomisation to monitor risk in order to step-up/ step-down treatment as appropriate.

Day patient treatment will involve 4-5 days of treatment a week with 2-3 meals per day, multi-disciplinary support, expert refeeding and high-quality evidence-based psychological interventions for patients and their carers. Patients will be treated until they reach a healthy weight and normalise their eating, or get as close to this point as possible.

11.1.4 Monitoring questionnaires

Participant's BMI and ED symptoms will be monitored on a monthly basis from randomisation to 12-months post-randomisation. The Eating Disorder Examination - Questionnaire Short (EDE-QS) (described above, Gideon et al., 2016) will be sent to the participant via an email link, and participants will be asked to fill it in on a monthly basis. This questionnaire will be phone-compatible and will be automatically sent back to researchers once it is completed. Participants will be sent weekly reminders about the questionnaire.

11.1.5 Follow-up assessments

Follow-up assessments for patients and carers will take place at 6-months and 12-months and will follow the same procedures as the baseline assessment. A separate 24-months follow-up study is also planned. The follow-up assessments will consist of the same measures and follow the same procedures as the baseline assessment.

11.1.6 Qualitative interviews

A nested purposive sample of patients (n~40; 20 per treatment arm) and family carers (n~40; 20 per treatment arm) will participate in a qualitative interview about their experience of treatment within the trial. Participants will be recruited purposively across study sites to explore a range of opinions, e.g., according to gender, age, baseline ED symptoms, treatment motivation, expectations and experience. Inpatient and day patient staff will be invited to participate in a one-off qualitative interview over the course of the trial to investigate expectations, concerns and experiences of managing patients within the context of the two treatment arms (~20 per group). Qualitative interviews will be conducted face-to-face at the patient's home, at the Institute of Psychiatry, Psychology & Neuroscience at King's College London or treating ED service, according to patient/carer preference. Alternatively, a phone/Skype call will be scheduled. Qualitative interviews with clinicians will be conducted face to face in the workplace wherever possible or scheduled over the phone/Skype. All interviews will be audio recorded with the patient's/family carer's/staff's consent.

11.2 Laboratory Tests

Laboratory tests are not part of the outcome assessment in this study.

12. Assessment of Efficacy

12.1 Primary Efficacy Parameters

Our primary outcome will be patients' BMI at 12-months post-randomisation. Most AN trials use BMI as their primary outcome as it is a proxy for physical health status and improvements in BMI correlate with improvements in quality of life (Bamford et al., 2015). The non-inferiority margin for BMI difference at 12-month post-randomisation will be based on that of Herpertz-Dahlmann et al. (2014) which was based on clinical experience. These authors decided that a difference in BMI as small as 0.75 kg/m² would not be clinically relevant. Thus, we consider stepped care to be non-inferior to IP-TAU as long as any reduction in BMI in stepped care compared to IP-TAU is less than 0.75 kg/m².

12.2 Secondary Efficacy Parameters

The secondary aim of this study is to investigate the differences between a stepped care day patient treatment approach and inpatient treatment as usual using the following efficacy parameters:

BMI:

- At time points other than 12 months, i.e., 6 months.

Eating disorder symptoms:

- Eating Disorders Examination-Interview (EDE) at 6- and 12-months.
- Short questionnaire version of the EDE-Q (short EDE-Q) (Gideon et al., 2016) monthly up to 12 months to assess remission and relapse rates according to standardised definitions (Khalsa et al., 2017).

Comorbid Symptoms (at 6- and 12-months):

- Obsessive Compulsive Inventory-Revised (OCI-R) (Foa et al., 2002)
- Depression Anxiety Stress Scale-21 (DASS-21) (Lovibond & Lovibond, 1995)

Psychosocial Adjustment (at 6- and 12-months):

- Clinical Impairment Assessment (CIA) (Bohn & Fairburn, 2008)
- Significant Others Scale (SOS), (Power et al., 1988)
- Work and Social Adjustment Scale (WASA) (Zahra et al., 2014)
- Revised UCLA Loneliness Scale (Power et al., 1988; Russell et al., 1980; Zahra et al., 2014)

Patients' treatment motivation, expectations and experiences (at 6- and 12-months):

- Motivational rulers (willingness and readiness to change) (Schmidt et al., 2015)
- Visual Analogue Scales assessing treatment acceptability (Schmidt et al., 2015)
- Perceived Coercion Scale – adapted (Guarda et al., 2007; Guarda et al., 2017; Schreyer et al., 2016)
- Therapeutic Environment Scale (Veale et al., 2016)
- Proportions of patients who self-discharge (at 6- and 12-months)

Economic measures (at 6- and 12-months):

- Health-related Quality of Life (EQ-5D-5L) (Herdman et al., 2011)

Additional measures:

Service Utilisation

- Adult Service Use Schedule (AD-SUS), designed for mental health populations and modified for AN (Herdman et al., 2011; Perez et al., 2015; Richards et al., 2016). at 6- and 12months
- Hospital Episode Statistics (HES) data from NHS Digital or ISD. Data requested will include the number of admission days to A&E, specialist ED units, and general psychiatric inpatient wards in the year prior to participation in the study, and for 2-years post-randomisation.

Carer Burden at 6- and 12- months:

- Depression Anxiety Stress Scale-21 (DASS-21) (Lovibond & Lovibond, 1995)
- Eating Disorder Symptom Impact Scale (EDSIS) (Sepulveda et al., 2008).

Process evaluation:

The qualitative process evaluation has three main components that are designed to investigate views on treatment and how it produced change from the perspective of patients, families and clinicians. Firstly, qualitative interviews with patients and family members will investigate positive and negative experiences of treatment, including its perceived short and long term effects. Secondly, interviews with inpatient and day patient staff about their experiences of managing patients and using the risk assessment tool within the context of the two treatment arms, staff training and views on providing treatment to this patient group beyond the trial context will provide additional information on the acceptability of the two approaches. Thirdly, Trial Management Group Meetings will be audio recorded to provide further data on the perceived contextual factors at the patient, provider or system level that may contribute to variation in outcomes.

24-month follow-up study:

Regulatory approvals will also be obtained to carry out a 24-month assessment. Measures obtained at 24 months will include BMI and ED symptom measures, as described above, except the EDE interview which will not be repeated. We will also obtain comorbid symptom measures and psychosocial

adjustment measures, economic measures and service utilisation data as described above. For a proportion (~ 60%) of participants, the 24-month assessment will take place during the period of the trial and will therefore be carried out by study researchers, as agree with the HTA. For the proportion of 24-month assessments that take place after the end of the study period, we will request a small amount of additional funding from the HTA in the future. We have successfully used this strategy in a previous NIHR-funded trial of outpatient treatment (Schmidt et al., 2015; Schmidt et al., 2016).

12.3 Procedures for Assessing Efficacy Parameters

Procedures for assessing efficacy parameters involve BMI measurements as well as the use of extensive questionnaires, and interviews outlined under point 11.

13. Assessment of Safety

13.1 Specification, Timing and Recording of Safety Parameters

Formal clinical risk assessments carried out by senior clinicians will be conducted when the patient is checked for study eligibility, and then on a weekly basis from randomisation. In the stepped care day treatment approach in particular, this will facilitate decision making as to the most appropriate setting of treatment for the patient at a given point of time; for example, (a) the initial decision (prior to randomisation) on whether the patient allocated to day treatment ought to start off the trial treatment in inpatients or day patients, (b) whether they can safely be stepped down into day treatment after initial hospitalisation, and (c) once people are day patients, if necessary, facilitate step-up into inpatients, in case of deterioration or relapse.

The risk assessment tool will be based on a modified version of the Maudsley Medical Risk Assessment tool which uses a traffic light system for quantifying medical risk. It comprehensively assesses medical risk, using objective indicators of nutritional status (e.g., BMI, weight change), cardiovascular function (blood pressure, pulse, postural drop), laboratory parameters and other physical risk indicators. In addition, we have added a psychiatric/psychosocial risk category (including suicidality, major self-harm, availability of support, safe-guarding concerns, patient/carer concerns). These risk indicators will be combined into a one page easy-to-use proforma.

Patients with any indicators in the red risk category will usually be admitted to or continue inpatient treatment. Patients whose risk indicators fall exclusively or predominantly into the green category (with isolated or borderline amber indicators only) will start or be stepped down into day patient treatment. Patients with several indicators in the amber category will usually be admitted to/stay in inpatients until there are clear signs of improvement. Staff training will be provided in using this tool.

A risk reference committee will be set up, involving a number of senior clinicians. Any uncertainty about a patients risk will be taken to the committee for discussion. If an in-patient has remained on amber for $\geq$ 4 weeks, their scores will be discussed with the risk reference committee, to ensure that there is consensus.

13.2 Procedures for Recording and Reporting Adverse Events

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a therapy has been administered including occurrences which are not necessarily caused by or related to that therapy.

Adverse Reaction (AR): Any untoward and unintended response in a subject to a therapy which is related to any duration of therapy administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information known about the therapy in question in the view of the investigator

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): 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.

13.2.1 Reporting Responsibilities

All AEs and SAEs occurring to a research participant should be reported to the Research and Development office where in the opinion of the CI the event was related and unexpected.

We do not expect any ARs, UARs, SARs or USARs. We will define a priori SAEs and AEs based on previously used criteria in AN trials (Zipfel et al., 2014) and record these as they occur.

SAEs will be recorded for 14 days after the intervention has finished. No follow-up care will be given as the intervention does not involve the use of drugs.

For each AE the following information will be collected:

- full details and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e., relatedness to the intervention), in the opinion of the investigator

13.3 Stopping Rules

The trial may be prematurely discontinued by the Sponsor or CI 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.

The trial may also be prematurely discontinued due to lack of recruitment within the internal pilot study (<50% of the desired sample size) or upon advice from the Trial Steering Committee, who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

14. Statistics

While the treating clinicians and patients will be aware of the type of care they are delivering/being offered, research assessors and the senior trial statistician will be blind to intervention allocation. We will assess blinding success of researchers at 12 months.

14.1 Sample Size

We aim to recruit 386 patients into the trial (including 64 pilot participants; 193 per trial arm). This sample size calculation is based on a one-sided non-inferiority test at 97.5% confidence. Previous studies suggested a standard deviation for within-group BMI at 12 months of 2.3 kg/m^2 (Herpertz-Dahlmann et al., 2014; Magill et al., 2016). Based on Herpertz-Dahlmann et al. (2014), we defined our non-inferiority threshold as a 0.75 kg/m^2 decrease in BMI for stepped care relative to IP-TAU. If there is truly no difference between stepped care and IP-TAU, then 198 participants per trial arm are needed to be 90% sure that the lower limit of a one-sided 97.5% confidence interval (or equivalent a 95% two-sided confidence interval) will be above the non-inferiority limit of -0.75. To account for the precision gain due to including baseline BMI in the modelling, we applied a deflation factor (0.78, based on a pre-post correlation of 0.47; (Magill et al., 2016) to the estimated sample size (Borm, Fransen, & Lemmens, 2007). We also inflated the requirement to account for 20% dropout at 12 months, based on our previous studies (Schmidt et al., 2016).

14.2 Randomisation

After baseline assessment eligible participants will be randomly allocated to stepped care or IP-TAU at a 1:1 ratio. Randomisation will be at the level of the individual and stratified for known prognostic variables of outcomes (previous inpatient treatment [yes/no], illness duration [< or > 3 years] and recruitment centre). Minimisation with a stochastic component will be used to balance these three prognostics variables across trial arms. Randomisation will be performed using an online system provided by KCTU (see section 10.4). While the treating clinicians and patients will be aware of the type of care they are delivering/being offered, research assessors and the senior trial statistician will be blind to intervention allocation. We will assess blinding success of researchers at 12 months.

Patients, carers and treating clinicians will be aware of treatment allocation. The trial statistician can become unblinded once an initial draft of the statistical analysis plan is agreed. The senior statisticians and the research assistants carrying out assessments will remain blind to treatment allocation throughout the trial.

14.3 Analysis

A statistical and health economic analysis plan will be developed by the trial statistians and trial health economists and agreed with the CI and Trial Steering Committee.

All formal effectiveness analyses will follow the intention-to-treat principle. For continuous clinical outcomes variables such as BMI, linear mixed models will be fitted to the outcome measures at 6 and 12-months to estimate the trial arm differences. The fixed part of these models will contain the explanatory variables of interest (trial arm, time and an interaction term) and also baseline values of outcome variables and randomisation stratifiers as these variables are known to explain variability in outcome. To account for correlation between repeated measures at 6 and 12 months a subject-varying random intercept will be included. Results are valid under a missing at random (MAR) missing data generating mechanism that allows earlier outcome values to predict missingness of later ones.

To judge non-inferiority of the stepped care approach in terms of the primary outcome (BMI at 12 months) a two-sided 95% confidence interval of the trial arm difference in the clinical measure will be generated and this interval compared with the non-inferiority threshold (0.75 kg/m² decrease on BMI). The threshold defines a region for the trial arm difference in BMI in which the stepped care would be considered non-inferior to the gold standard IP-TAU. To confirm the non-inferiority hypothesis the whole 95% confidence interval would need to lie within this region.

Economic evaluation: The economic evaluation will take the NHS/personal social services perspective preferred by NICE and shown in previous AN studies to constitute over 90% of total societal costs. Nationally applicable unit costs will be applied to all services, including the inpatient and day patient-based interventions (Curtis & Burns, 2016; Department of Health and Social Care, 2016). Cost-effectiveness will be explored at the 12-month follow-up point in terms of QALYs measured using the EQ-5D-5L, with a sensitivity analysis using the primary clinical measure of outcome (BMI), given the limited evidence available for the validity of the EQ-5D in ED populations. Further sensitivity analyses will explore cost-effectiveness at 24-months. For QALY calculations, appropriate utility weights will be attached to health states (Dolan & Gudex, 1995) and QALYs will be calculated using the total area under the curve approach with linear interpolation between assessment points (Manca, Hawkins, & Sculpher, 2005).

Mean differences in costs and 95% confidence intervals will be obtained by nonparametric bootstrap regressions to account for the non-normal distribution often found in economic data. Cost-effectiveness analyses will be undertaken irrespective of whether non-inferiority is demonstrated, since exploration of the joint distribution of costs and effects is recommended to represent uncertainty (Briggs & O'Brien, 2001) and to help interpret the economic results (Bosmans et al., 2008). Incremental cost-effectiveness ratios (ICERs) will be calculated if higher costs and better outcomes are found in either the intervention or control group. Uncertainty around cost-effectiveness estimates will be explored using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) based on the net-benefit approach (Fenwick & Byford, 2005). All economic analyses will be adjusted in line with the clinical approach (baseline values of the variables of interest and randomisation stratifiers) and will be valid under a missing at random assumption.

Qualitative analysis: Qualitative data will be analysed using the Framework Approach (Ritchie & Spencer, 2002) to facilitate analysis within and between individual cases and groups of participants. The thematic framework will draw on a priori issues around perceived mechanisms of impact, implementation and context, but be responsive to emergent and analytical themes. Once applied to individual transcripts, data will be charted to map and interpret the data set as a whole. Qualitative process data will be analysed prior to the outcome data, but any insights will not be communicated to the wider team until the RCT outcome is known.

15. Trial Steering Committee

A Trial Steering Committee will be formed to provide overall supervision on behalf of the Project Sponsor and Project Funder and ensure the study is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The external members of the committee will consist of at least 2 patient and public involvement (PPI) representatives, a statistician and a senior researcher with expertise in EDs. Trial steering committee meetings will be held twice in the first year, and then on a yearly basis thereafter.

16. Data Monitoring Committee

A Data Monitoring & Ethics Committee will be formed due to the risk associated with individuals with severe AN. This committee will monitor the data and report directly to the Trial Steering Committee. The Data Monitoring & Ethics Committee will consist of at least 3 members who are experts in the field, e.g., a clinician or senior researcher with experience in EDs, expert trial. They will meet twice in the first year, and then on a yearly basis thereafter.

17. Direct Access to Source Data and Documents

The Investigator will permit trial-related monitoring, audits and Research Ethics Committee (REC) review by providing the Sponsors, and REC direct access to source data and other documents.

18. Ethics & Regulatory Approvals

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

The trial is registered with the ISRCTN trial registry (ID: ISRCTN10166784) and this protocol and related documents will be submitted for review to the REC.

The Chief Investigator will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor.

19. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice (GCP) and scientific integrity will be managed by the study team through regular review of study procedures by the trial investigators.

20. Data Handling

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

- Patient data will be pseudonymised

- All anonymised data will be stored on a password protected computer.
- All trial data will be stored in line with the General Data Protection Regulation (GDPR) 2018 and Good Clinical Practice.
- Hardcopies of participant-related data will be kept in locked cabinets at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. Data will not be accessed by anyone other than members of the research team.
- All trial data archived in line with Sponsor requirements.

21. Data Management

Confidentiality and anonymity of all personal data will be maintained throughout the entire study. Identifying information will be removed from the data, stored separately and replaced with a numeric identification code. All participants will be allocated a numeric code, which will be used to identify their data. The master list of names which correspond to participants' numeric identification codes will be stored electronically and will be password protected. This information will only be accessible to the key researchers involved in the study.

Data will be stored in the following way:

1) Personal data in the paper form will be stored in securely locked filling cabinets at the Eating Disorders Unit, Institute of Psychiatry, Psychology & Neuroscience, King's College London.

2) Personal data in the electronic form data will be stored in password protected folders on university desktop computers.

3) Anonymised data in the paper form will be stored in securely locked filling cabinets at the Eating Disorders Unit, Institute of Psychiatry, Psychology & Neuroscience, King's College London.

4) Anonymised data in the electronic form will be stored on university desktop and laptop computers.

22. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences (preferably those that include patients and carers) and in peer-reviewed open-access scientific journals. We will also disseminate findings through relevant websites, and work with the King's College London press office to disseminate study findings via traditional and social media. Patient representatives will have a key role in our dissemination programme. Finally, we will work closely with NHS England to implement findings.

23. Insurance / Indemnity

Standard King's College London insurance and NHS indemnity arrangements apply.

24. Financial Aspects

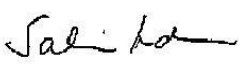
Funding to conduct the trial is provided by National Institute of Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre (NETSCC).

25. Signatures

Date: 10/11/2019

Chief Investigator

Ulrike Schmidt



Date: 08/11/2019

Statistician (if applicable)

Sabine Landau

26. References

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