PROTOCOL TITLE

A multicentre randomised controlled trial to examine whether the addition of a patient and carer skill sharing intervention improves long-term patient wellbeing following hospital treatment for anorexia nervosa.

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CONTENTS

Study Synopsis

Title of clinical trial	A multicentre randomised controlled trial to examine whether the addition of a patient and carer skills-sharing intervention improves long-term patient wellbeing following hospital treatment for anorexia nervosa.
Protocol Short Title/Acronym	Transition care in AN: Through guidance online from peer and carer experts TRIANGLE
Study Phase if not mentioned in title	Phase III
Sponsor name	King's College London (KCL), Address: Strand, London, WC2R 2LS, Telephone: 02078365454 South London and Maudsley NHS Foundation Trust, Address: Maudsley Hospital, Denmark Hill, London, SE5 8AZ, Telephone: 02032286000
Chief Investigator	Prof Janet Treasure
REC number	IRAS 197114
Medical condition or disease under investigation	Anorexia Nervosa
Purpose of clinical trial	To demonstrate a beneficial effect of the ECHOMANTRA intervention for patients with Anorexia Nervosa admitted for intensive treatment (inpatient or daycare).
Primary objective	To demonstrate a beneficial effect of the ECHOMANTRA intervention in terms of patient's psychological well-being (depression, anxiety and stress) at 12 months after randomisation.
Secondary objective (s)	To demonstrate a beneficial effect of the ECHOMANTRA intervention in terms of further patient and carer outcomes at 12 and 18
Trial Design	A multicentre (UK sites) randomised parallel group-controlled trial to evaluate the clinical effectiveness and

	cost-effectiveness of the ECHOMANTRA intervention as an addition to Treatment As Usual (TAU) for patients with anorexia nervosa admitted for intensive treatment.
Endpoints	To evaluate the primary and secondary objectives, the following variables will be measured at 12 and/or 18 months post- randomisation. Patient outcomes: • Weight (12, 18 months) • Depression, Anxiety and Stress (12 and 18 months) • Eating disorder psychopathology (12 and 18 months) • Quality of life (12 months) • Social functioning (as reported by carers, at 12 months) • Importance and confidence to change (12, 18 months) • Work and social adjustment (12, 18 months) • Intervention cost-effectiveness (12 months) • Service use/ readmission rates (Hospital Episode Statistics, 12 and 18 months) Carer outcomes: - Psychological wellbeing (12 and 18 months) - Skills to cope with eating disorder behaviours (12 and 18 months).
Sample Size	380 patient-carer dyads
Summary of eligibility criteria	Patients aged 16 years or over admitted for intensive treatment and a: - Diagnosis of anorexia nervosa according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) - Carer willing to participate
Version and date of protocol at start of recruitment	Version 3, 07/07/2017
Version and date of amendments including protocol changes	❖ Substantial Amendment 1 (Protocol 2, 09/02/17) - Change to intervention delivery: 1:1 guidance sessions replaced with 8 online moderated. - Change to measures: DERS, PyAN and AESED removed. - Changes to inclusion criteria: a) Patients should be admitted for inpatient care or

	should be attending day care for a minimum of 4 days/week at the time of consenting b) patients with subclinical/atypical anorexia nervosa can be included c) participants must be able to access an electronic device d) informed consent should be provided within 2 months from admission. ❖ Substantial Amendment 2 (Protocol 3, 07/07/17) - Change to measures: Monthly surveys to clinicians now include information about SAE's. - Change to consenting process: Consent forms from non-NHS sites need to be password protected and send attached in an email to the research team. - Change to participant reimbursement: Patients now reimbursed by cheque every 6 months - Change to measures: Social Identity Map assessment added. ❖ Substantial Amendment 3 (Protocol 4, 28/09/17) - Change to data collection: RAs now provide telephone guidance to participants in completing CSRI and Social Identity Map assessment. - Change to measures: a) Questions regarding perceived treatment credibility and acceptability added to monthly questionnaire b) Sites will send medical records via encrypted email at baseline and discharge. ❖ Substantial Amendment 4 (Protocol 5, 08/11/17) - Change to measures: Other eating disorder related measures for patients willing to provide additional data were added. ❖ Substantial Amendment 5 (Protocol 6, 01/02/18) - Change to measures: Additional questions added to participant's feedback forms receiving ECHOMANTRA following skype sessions. - Change to protocol: a) Serious adverse events defined b) Procedure to address protocol violations added c) RAs now visit participating sites to assist with recruitment and consent of participants d) BMI inclusion criteria now applies when patient is approached (not at consent) e) exclusion criteria (i.e. patients admitted for inpatient care or attending day care min 4 days/week) now applies at the beginning of

	the study (not at consent). ❖ Non-substantial Amendment 5 (Protocol 7, 25/07/18) - Change to protocol: Clarification regarding reimbursement added (i.e. total reimbursement £60 for patients and £60 for carers). ❖ Substantial Amendment 6 (Protocol 8, 19/09/18) - Changes to inclusion criteria: a) Informed consent now signed at any time whilst patient is admitted into hospital (up to 4 weeks after discharge) b) Age extended to 16 years old c) patient now need to be admitted into hospital or attending daycare for a min of 3 days/week when consented in the study (instead of 4 days/week) d) study team now involved in all recruitment stages. - Changes to consenting process: Carers can now provide consent electronically via study website. - Changes to measures: a) Clinical teams no longer be asked to provide monthly updates from patients. Basic clinical information now collected at baseline only b) Brief monthly update questionnaire added to patient's measures c) Addition of 9 questions about involvement of family members and carers to be asked to the participating sites (at present and 18 months) and 6 questions about research perceptions (at present only). - Changes to intervention delivery: Content of joint sessions now delivered via study website through an online group format (instead of skype). - Changes to study advertisement: The study now advertised on social media. ❖ Non-substantial Amendment 7 (Protocol 9, 17/01/2019) - Addition of new site Addition of Cambridgeshire and Peterborough NHS Foundation Trust as a participating site ❖ Non-substantial Amendment 8 – In progress (Protocol 10, 19/03/2019) - BMI will be collected from clinical teams at the major time points until patient is discharged from their unit. - Principal Investigator change at Tees, Esk and Wear Valley's NHS Trust – from Katie Bell to Helen McLay.

	- Extension of recruitment end-date from 31st March 2019 to 31st March 2020 - Typo in the protocol rectified – the minimum age criteria specified specified in protocol 9, 7/01/2019 remained 17 years, after this was lowered to 16 years in substantial amendment 6. The age has now been changed in the protocol to read 16 years. - Addition of gift vouchers to the reimbursement of participants. Non-substantial amendment 9 - Principal Investigator change at Tees, Esk and Wear Valley's NHS Trust – from Helen McLay to Nicholas Wolstenholme. - Principal Investigator change at NHS Grampian from Jane Morris to Louise Johnston. Non-substantial amendment 10 - Extension to recruitment end date from 31st March 2020 to 31st May 2020. - Change to statisticians listed in the protocol ❖ Substantial amendment 7 - To obtain participant feedback on their participation in the TRIANGLE trial and to gather further information regarding patients' views on transition from intensive treatment, we will: - Invite a selected subgroup of patients and carers (up to n=22 patients and n=22 carers, selected based on pre-specified criteria) who were randomised to the ECHOMANTRA + TAU intervention group to participate in an interview about their experience of the TRIANGLE trial and intervention. The maximum number of participants is based on the high likelihood of reaching data saturation on the topic investigated, among the study population, with less than 22 participants. - Invite a selected subgroup of patients and carers (up to n=22 patients and n=22 carers, selected based on pre-specified criteria) who were

	randomised to the TAU only group to participate in an interview about their experience of transitioning from the intensive treatment (inpatient or day care) they were receiving when initially recruited to the trial back to the community. The maximum number of participants is based on the high likelihood of reaching data saturation on the topic investigated, among the study population, with less than 22 participants. - Participants will be recruited who are between the 6 months and 12 months timepoints in their study participation so that they have had enough time to offer a well formed opinion of what it meant to them to have participated in the study and to have transitioned from intensive treatment. To explore a range of opinions participants will be recruited purposively across study sites according to recruitment site location, gender, age, patient's eating disorder severity (>7 years of illness or below 3 years of illness) and carer's relationship to the patient. Sites will not be involved in the selection of participants. A King's College London researcher, one of the project's Co-Investigators will contact the participants to see if they are willing to take part in the additional interview. Interviews via Skype voice call or by telephone. The interview will last for up to 1 hour and will consist in a pre-specified list of questions. Data will be typed up, allocated an ID number for confidentiality purposes and then analysed. - An additional 3 process questions added to the participant feedback form, to be asked to participants in the intervention group at 6 and 12 months in the study. Substantial amendment 8 During the COVID-19 period, TRIANGLE sites remaining open to recruitment will become Patient Identification Centres (PICs). Local research staff will no longer be required to screen patients. Any staff who identify patients interested in triangle, or if patients hear about the study through flyers on the wards, patients can directly contact the TRIANGLE research assistants who will screen and consent patients into the trial remotely using telephone/encrypted email.

1. Background & Rationale

Anorexia nervosa and the ECHOMANTRA intervention

Anorexia nervosa can develop into a severe, enduring psychiatric disorder that is associated with increased mortality rates (Arcelus et al., 2011), substantial physical (Mitchell and Crow, 2006) and psychological comorbidities and adverse social consequences (Hjern et al., 2006). Hospital treatment is increasingly used in the management of this stage of illness (Holland et al., 2016). There is uncertainty about many of the parameters that might contribute to a good outcome during and following hospital care. NHS statistics in the UK indicate that the duration of admissions for anorexia nervosa are longer and the mortality rates post-admission are higher than for most other psychiatric disorders (Hoang et al., 2014; Thompson et al., 2004). Therefore, interventions that may optimise the outcome following hospital treatment are needed. Day hospital treatment is often used as an alternative to inpatient care or as a second phase of treatment in order to shorten admissions (Madden et al., 2015). A review of treatment settings for people in the early stage of illness found, as expected, that costs for day care or for shorter admissions were less that for full inpatient care, but the benefits appeared to be comparable (Madden et al., 2015).

The NICE guidelines suggest that after inpatient discharge, patients should have access to treatment focusing on eating psychopathology, but otherwise the form of treatment is left unspecified. Several systematic reviews have collated the data relating to inpatient treatment. A review of interventions added to usual inpatient care for anorexia nervosa concluded that there was little added short-term benefit (Suarez-Pinilla et al., 2015). However, various forms of aftercare have also been studied and these data suggest that education and skills sharing interventions such as cognitive behavioural therapy (CBT) have benefits (Fichter et al., 2008; Fichter et al., 2012; Pike et al., 2003). In addition, we found that a self-directed aftercare intervention (iMANTRA), showed promising results (Schmidt et al., 2015). Longer term benefits of after -care interventions have been found if the social networks are included. For example, family therapy improves the outcome of adolescent patients (Eisler et al., 1997; Godart et al., 2012; Russell et al., 1987) and carer skill interventions improve the outcome for adults (Hibbs et al., 2015; Magill et al., 2015). Based on the cognitive interpersonal model (Treasure & Schmidt, 2013; Schmidt and Treasure, 2006), a synergistic effect might be expected from combining approaches directed towards carers and patients.

Through a process of co-production with carers and patients, we have developed a range of skills-sharing materials for both carers and patients with anorexia nervosa. These have been built to fulfil the carers' needs for more information and help with their role (Haigh et al., 2003) and the patients' needs to have a balance of control within the therapeutic alliance (Westwood et al., 2012). The carers' module of the ECHOMANTRA intervention aims to improve interpersonal functioning and decrease isolation. It includes

three basic components (Treasure et al., 2015). First, it gives carers information in order to strengthen coping with the caregiving role. Second, it teaches carers how to reduce emotionally driven caregiving behaviours, such as high expressed emotion, accommodating and enabling, as well as disagreement and division within the family. Thirdly, it teaches skills of positive communication and behaviour change in order to increase social connection and support recovery. The carers' module of the ECHOMANTRA intervention also includes a set of videos and a workbook discussing adaptive and less adaptive support strategies. The topics of the workbook are also discussed during moderated and facilitated weekly online group forums. Carers will be invited to attend at least 4 group forums during patient admission and 4 groups forums after discharge.

Meanwhile, the patients' module of the ECHOMANTRA intervention is based on the Maudsley Model of Treatment for Adults with anorexia nervosa and targets intrapersonal risk factors such as difficulties in emotional regulation, sensitivity to social comparison, obsessive compulsive traits, and nutritional difficulties. The patients' manual has been adapted through a process of co-production as a form of self-management both for inpatient aftercare (Schmidt et al., in press) and as a supplement to outpatient treatment (Cardi et al., 2015). The manual uses specific behavioural change strategies, such as psychoeducation, prompts for instruction and practice, and explicit tools for encouragement in order to reduce and replace eating disorder habits. The patients' module encourages relatedness by including a library of short videos documenting the advice and experiences of individuals who have recovered from eating disorders. The short videos highlight behaviour change tips which are linked within the accompanying workbook. The patients' module of the ECHOMANTRA intervention also includes participation in moderated and facilitated online group forums. Patients will be invited to attend at least 4 online forum groups during their admission and at least 4 more after discharge.

The modules delivered to patients and carers separately will be complemented by a minimum of 6 joint online sessions ("joint sessions") to facilitate the synergistic effect of the other intervention materials.

Potential risks and their management

The risk for patient and carer involved in this project is unlikely to be greater than that of Treatment As Usual (TAU; Type A risk = No higher than the risk of standard medical care). However, it is possible that some carers may find being involved in providing support burdensome. It is also possible that some carers may find being open and honest about the impact of the eating disorder difficult.

We manage this risk by discussing with carers how it is good practice to include carers in mental health services. We also track with feedback carers' confidence and connection at monthly intervals in the study.

Another possible risk is that some patients may not engage with after care plans. We manage this risk by providing access to information about the value of this type of intervention. We provide regular monitoring and feedback via the study's web platform which in our pilot studies increases engagement.

Potential benefits
It is expected that both patients and carers will benefit from the ECHOMANTRA intervention. In particular, we expect improvements in psychological (e.g. lower levels of depression, anxiety and stress in patients and carers), physical (i.e. higher body mass index in patients) and socio-emotional (e.g. more social connection, greater interpersonal skills and better carer-patient relationship) wellbeing. Participants will be reimbursed by cheque or by gift voucher every 6 months. The total reimbursement (i.e. £120) will be divided between the patient and the carer (i.e. £60 patient and £60 carer).

Regulatory bodies
The trial will be conducted in compliance with the principles of the Declaration of Helsinki and the principles of GCP. The protocol is to be submitted for approval by an NHS Research Ethics Committee (REC).

2 Trial Objectives, Design and Statistics

2.1. Trial Objectives

The aim of the TRIANGLE trial is to examine whether adding a novel aftercare skills-sharing intervention – ECHOMANTRA – to TAU improves patient wellbeing, as well as increases carers skills and reduces care-giving burden in the 12 and 18 months post randomisation.

Primary objective:
To examine whether there is Improved **Tr**ansition care **i**n **AN**: Through **g**uidance on**l**ine from peer and carer **e**xperts (TRIANGLE) in terms of patient's psychological wellbeing (anxiety, depression, stress symptoms) at 12 months post randomisation.

Secondary objectives:

a) To assess the following regarding the hypothesised impact of TRIANGLE:
    i. Improved Body Mass Index (BMI), motivation to change and work and social adjustment for **patients** 12 and 18 months post randomisation.
    ii. Increased quality of life for **patients** 12 months post randomisation.
    iii. Improved social functioning for patients, as reported by carers, 12 months post-randomisation.
    iv. Improved psychological wellbeing (anxiety, depression, stress symptoms) for patients in the 18 months post-randomisation.
    v. Reduced eating disorder symptoms in patients 12 and 18 months post-randomisation.
    vi. Reduced number of days that patients spent in hospital up to 3 years post admission.
    vii. Intervention cost-effectiveness for patients at 12 months.
    viii. Reduced number of positive aspects of AN at 12 months.
    ix. Increased number of negative aspects of AN at 12 months

x. Reduced psychological distress, time spent caring, and improved skills in dealing with eating disorder symptoms in **carers** at 12 and 18 months after randomisation.

b) To have available a set of theoretically-grounded, empirically-supported tools (ECHOMANTRA) including highly-teachable health behaviour change techniques for patients, carers, and professionals that can be readily disseminated.

c) To evaluate the processes involved in facilitating changes in patients and caregivers.

i. To determine the impact of (ECHOMANTRA) on variables targeted by the various component parts of the intervention (potential mediators of any treatment effect; e.g. accommodation, expressed emotion, interpersonal functioning).

ii. To assess the fidelity of the intervention using (1) rating scales, (2) thematic analysis of guidance sessions (3) feedback (qualitative and quantitative) from patients and caregivers.

iii. To conduct exploratory analyses of whether baseline variables including BMI, level of psychopathology, motivation to change, social functioning, duration of illness, type and duration of admission (voluntary/involuntary), type of service used predict outcome overall or modify the effect of aftercare given (act as intervention effect moderators).

2.2 Trial Design

TRIANGLE is a multicentre, randomised, controlled, parallel group superiority trial. Clinicians treating anorexia nervosa, assessors and statisticians will be blind to the aftercare treatment allocated to the patient and their primary carer.
Anorexia nervosa patients admitted for hospital care or intensive day patient care (at least 3 days/week) and their carers are randomised as a dyad at a ratio of 1:1 (stratified by site and severity) to receive either (i) access to the ECHOMANTRA intervention package in addition to TAU or (ii) TAU alone. Those randomised to the ECHOMANTRA plus TAU arm will have access to the intervention materials. For carers, these materials include a workbook, a set of educational videos/podcasts and facilitated and moderated group discussion forum (8 sessions). For patients, these materials include a workbook, a set of video-podcasts (“vodcasts”) and an online, moderated and facilitated group discussion forum (8 sessions). Additionally, patients will receive online joint sessions with their carer/and or other patients and carers. The sessions will be facilitated by a mentor using a live chat format via the study platform. All participants will be followed up with short monthly tracking /feedback (to facilitate engagement) and deeper progress assessment measures 3, 6, 9, 12 and 18 months following randomisation.

2.2.1 Study interventions

After provision of the consent form, the study team will help the participant to create their account and log in to become familiarised with the study online platform (created and managed by Mindwave, http://mindwaveventures.com). Participants will be asked to complete the baseline questionnaires and on completion of the questionnaires they will be randomised to the TAU + ECHOMANTRA intervention group or to the TAU only group. Participants will receive a minimal level of feedback in both conditions after they complete the monthly assessment surveys. There will be no interaction with the mentor and no access to the intervention materials in the control group.

TAU inpatient or day clinic care
There are quality standards describing inpatient care or intensive day clinic care which usually involves a multidisciplinary team approach (dietician, psychologist, OT, physician, family therapist, social worker, nurse) ("Standards for Adult Inpatient Eating Disorder Services – 1st edition, The Royal College of Psychiatry, 2013). We have found in our previous study that there is a large amount of variation in length of stay of inpatient care although admission and discharge weights are similar.

TAU aftercare
There is very little information about TAU for aftercare of anorexia nervosa. In our pilot study (CASIS) we found that less than 50% of patients had outpatient support for the year after discharge (as recommended by the NICE guidelines). Often there is a split between services because inpatient care is paid for by NHS England and outpatient care is provided by clinical commissioning groups. The teams involved therefore can often differ. For example, many inpatient beds (>300) are in independent hospitals, but paid for by NHS England. We will ask the inpatient clinical sites to inform us about the responsible clinical team after discharge. We will inform the aftercare clinical team about what participation in TRIANGLE involves and suggest that they can continue with usual care.
TAU for aftercare of anorexia nervosa typically includes monitoring of physical risks, dietetic assessment and advice and some form of individual outpatient therapy (commonly CBT, interpersonal psychotherapy or focal psychodynamic therapy) or a transition to day-care. In our pilot study, we found that aftercare usually included two weekly visits to primary care and eating disorders outpatient clinics (and readmission) with very little involvement of social/family support.
Given the variability in aftercare, we will solicit precise information about the treatment received by patients in our trial through questionnaires.

TAU-only comparison condition
Similar to the ECHOMANTRA intervention group, the group allocated to the TAU-only comparison condition will be asked to complete trial assessments on the online platform.

Active treatment: TAU plus patient and carer skills-sharing intervention (ECHOMANTRA)
Patients allocated to the active trial arm will receive TAU as described above and will complete the assessment measures on the study online platform. This group will also be

able to access the patient skills sharing materials via the same platform. The aim of the skills sharing materials is to transfer the learning and progress gained from the intensive in/day-patient experience into the home-context via tools, which can be accessed where, when, and as often as needed. The behaviour change strategies we teach are the standard approaches recommended by the NICE guidelines (50). The actual ECHOMANTRA intervention materials will be accessed by the patient from randomisation and discussed during moderated and facilitated online forums.
Participants will be invited to take part in at least 4 online discussion group forums before discharge and in at least 4 online group forums after discharge. The online forums will be followed by 6 joint online sessions with patients and carers, moderated by a mentor.

ECHOMANTRA content
The materials include workbooks and short video podcasts based on our cognitive interpersonal model (Treasure & Schmidt, 2013). The workbooks aim to promote reflection, planning and new learning to modify the eating disorder habits and optimise socio-emotional functioning and interpersonal relationships. Patients are encouraged to ask the primary carer they have nominated (e.g., a family member or friend) to support their work and to use the carers' materials as a guide.

Patient Videos. The patients' "vodcasts" (brief video podcasts) map onto the patient workbook and relate to recovery experiences, anxiety management techniques, strategies to manage meal anxiety, and skills to develop acceptance and self-compassion and social functioning. The learning points are emphasised by the overlaid images and introductory and summary statements (which include prompts for behaviour change and reflection). The vodcasts illustrate the following behaviour change principles: goal setting, self-monitoring, utilizing social support, and implementation intentions. Patients will be invited to participate to moderated and facilitated group discussion forums to explore and reflect on these materials (8 sessions). Additionally, patients and carers will have up to 6 joint online sessions with a mentor ("participant-carer mentor") to discuss support. During the joint online sessions. patients and carers will have the opportunity to explore and reflect the materials with other patients and carers via the study platform. A summary of the protocol for patient's support is provided in Table 1.

Patient Forums. Participants will be invited to attend at least 4 group discussion forums during admission and 4 group discussion forums after discharge. Each session will last a maximum of 90 minutes and will be themed (denoted by session A – session H), following the structure of the patient workbook (see Table 1). We will have a bank of staff including some with experience from the UK charity "Beat Eating Disorders" (BEAT) and some research assistants (3-10 grade 5 individuals) who will facilitate and moderate the forums. The moderators and facilitators will receive weekly supervision (approximately 30 min/week) by our study team (i.e. Dr Cardi, Professor Treasure, Ms Todd). The facilitator will encourage discussion around the information and exercises proposed in the workbook. The group sessions will be open, and patients will be allocated on a rotational basis depending on caseload and will be able to take part in as many

groups as desired. Two group sessions per week will be offered to patients (e.g. Week 1: forums A, A; Week 2: forums A, B; Week 3: forums B, C; Week 4: forums C, D; Week 5: forums D, E, etc…). The text of the forums will be recorded, saved and used for team supervision.

Table 1: ECHOMANTRA intervention: Protocol for patients with anorexia nervosa

POST RANDOMISATION	Aim of this phase: to prepare for discharge with identification of goals and implementation of goal setting strategies. Materials: workbook, vodcasts and 4 online group discussion forums.
Forum A	Introduction and assessment of motivation. Discussion around the impact of the eating disorder on the brain and the body. Discussion of behaviour change strategies.
Forum B	Discussion around the impact of the eating disorder on social relationships. Discussion of behaviour change strategies.
Forum C	Identification and set-up of behavioural goals, with a particular focus on eating- and food-related goals.
Forum D	Discussion and implementation of goals setting strategies.
DISCHARGE	Aim: Target goal hierarchy and support motivation to change and behaviour change. Materials: 4 online group discussion forums. Up to 6 joint online sessions with a mentor.
Forum E - H	Revise goal setting and behaviour change strategies. Discuss strategies to support motivation to change and behaviour change. Re-visit implementation of some of the earlier concepts from the workbook.
Patients-Carers joint online sessions	Identification of behavioural goals that will allow patients and carers to use the knowledge and to practice the skills acquired during the online forums.

Carers' protocol

After providing informed consent, all carers will be introduced by the study team at the participating site to the carer online platform and baseline assessments. Those allocated to the ECHOMANTRA intervention group, will receive a workbook and will gain access

to a library of podcasts and DVDs (www.succeedfoundation.org/) produced by K Bertoud, a recovered patient, and the research team. The workbook and the DVDs offer a skills training programme including: training in stress management, communication (motivational interviewing) and strategies to reduce accommodation and expressed emotion and to increase extinction training and new habits at home via effective social support. Carers will be also invited to attend at least 8 online group forums (4 during patient admission and 4 after patient discharge) to discuss the information and exercises proposed in the workbook. The structure and timing of the forums will be the same as those illustrated in the patient section above.

Patients-carers Joint Sessions Protocol. Up to 6 joint online sessions will be timetabled between carers (parent, sibling, and friend) and patients with the aim of enlisting social support and generate perspective taking to attain behavioural goals.

Three band 6 health professionals will be appointed. Cases will be allocated on a random basis subject to availability. The mentors will be trained and supervised in the new Maudsley Model of family work including motivational interviewing and behaviour change strategies [29]. The training will involve a 3-day face-to-face workshop followed by two x 3-day booster sessions led by a professional who has worked in the field of eating disorders for 25 years and is trained in Motivational Interviewing. The training involves audio-visual materials and interactive role-plays. Audiotapes will be used for weekly clinical supervision by experienced clinicians (GT, JA). Supervision and mentor support will also be provided by email and telephone. Trainers will be available telephone to discuss any challenging situations that may arise which will be discussed with JT and US. JT will also be kept informed of any potentially challenging situations.
Mentors will also be asked to report their own adherence, acceptability and satisfaction with delivery. They will only be assigned study patients/caregivers once they have obtained a minimal level of competence with training samples (i.e. Individuals not within the proposed study). Adherence and fidelity to the model will be monitored by assessing the electronic records of the online sessions.

2.3 Flow chart

Screening phase
Participants in the study will be recruited from specialist eating disorder centres with inpatient and/or day patient care and/or the community via the advertisement of the study on social media (e.g. Facebook, twitter). During the COVID-19 period, the TRIANGLE sites will act as Patient Identification Centres (PICs)

Patient recruitment
The medical team from the trust/independent hospital will screen the records to find potentially eligible participants (patients). They will either start the process of recruitment and consenting patients themselves and/or they will inform the CSO who will approach potentially eligible participants, or the medical team will introduce the patient to the

TRIANGLE research workers who will visit participating centres regularly to provide more information about the study. During the COVID-19 period, the TRIANGLE research assistants will screen and consent patients remotely using telephone and encrypted email. Informed consent will be obtained either from medical trust staff, the CSO or the research assistants to participate in the trial. For the participants recruited from the community, the medical team from the trust/independent hospital will be contacted to confirm that the patient is receiving inpatient or attending daycare for a minimum of 3 days/week or within 4 weeks after discharge. Patients will be re-consented where applicable in order to access their Hospital Episode Statistics data for the 30-month period (starting from one year prior to their involvement in the trial and for the 18 months post-randomisation). The research team at King's College London will obtain consent from participants to access Hospital Episode Statistics data on the frequency with which they have used hospital services within a 30-month period (from the year before they joined the study and for 18 months post-randomisation). In order to do so, King's College London will need to provide NHS Digital with some information provided by participants that could identify them (i.e. Study ID, name, gender, date of birth, address, postcode, GP address and NHS number). The legal basis for the data being sent to (or reused by) NHS Digital is Consent (Reasonable Expectation). This means that we cannot lawfully request this data without participant consent. The purpose of collecting information about participants' use of hospital services over this period is to examine the clinical and cost-effectiveness of adding the triangle transition intervention to treatment as usual. In line with the guidelines from the Medical Research Council Regulatory Support Centre: Retention framework for research data and records, we will store the data for 10 years and then it will be destroyed. However, in accordance with General Data Protection Regulation (GDPR), the personally identifiable data may only be kept in a form that permits your identification for as long as it is necessary for the purposes for which it was processed.

Carer recruitment

The names and contact details of carers will be obtained from the patient participants and/or from the medical team from the trust/independent hospital/ or the CSO. TRIANGLE research workers will conduct the process of recruitment and consenting of carers (this may take place in their homes) to participate in the trial. The carers can provide consent electronically via the study website. If so, they will be asked to send a physical or electronic copy of the consent form. Once they receive the patient consent form they will contact the carer via phone or email to introduce them to the study and provide them with the information sheet and consent form.

Figure 1 shows a flowchart describing the phases and timings of the study.

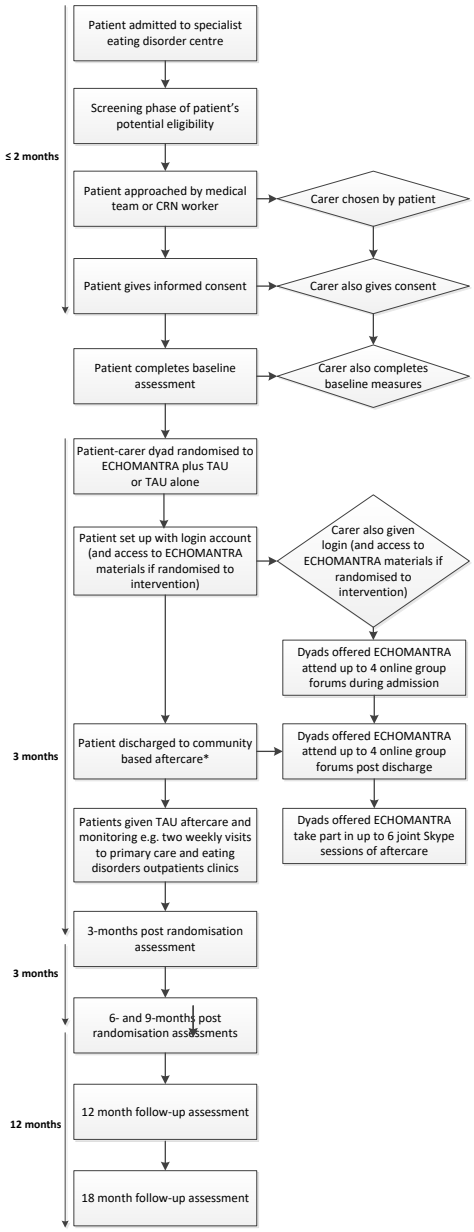


Figure 1: Trial flow chart

Figure 2 illustrates the progress through the phases of the trial of the ECHOMANTRA + TAU and TAU only groups (that is, enrolment, intervention allocation, assessments).

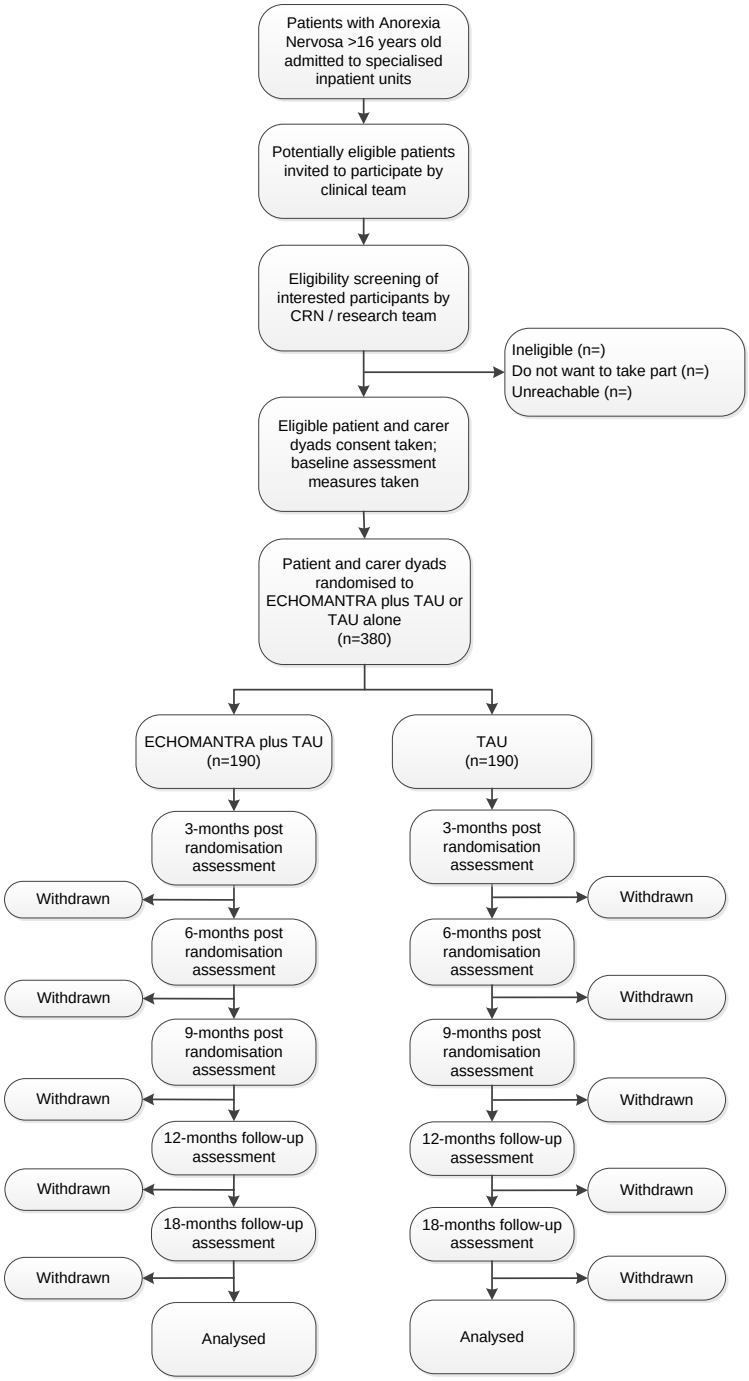


Figure 2: Consort diagram illustrating the progress through the study of the ECHOMANTRA + TAU and TAU only groups.

2.4 Trial Statistics

Findings will be reported following relevant CONSORT guidelines (www.mrc.ac.uk/complexinterventionsguidance). Figure 2 shows a consort diagram for the TRIANGLE trial.

2.4.1 Sample Size

A sample size of *n*=380 dyads will be sufficient to determine clinically significant improvements under ECHOMANTRA plus TAU compared to TAU alone and recruitment is feasible in two years. This calculation is based on wishing to detect an effect size of Cohen's *d* = 0.40 for patient distress (depression, anxiety, and stress; DASS-21) at 12 months with 90% power using a two-tailed *t*-test at a significance level of 5%, and allowing for attrition rates observed in previous studies (i.e., 30% at 12 months).
Our estimation of effect size is based on our previous research (Hibbs et al., 2015; Magill et al., 2015) along with our assessment of clinically significant change. The iMANTRA trial, which only targeted the patient, achieved an effect size of *d* = 0.64 on patient DASS-21 at 12 months; (Schmidt et al., 2015). The CASIS trial, which only tested the parent/partner component of the intervention, found an effect on patient DASS-21 of *d* = 0.17 at 12 months (Hibbs et al., 2015) and *d* = 0.25 at 24 months (Magill et al., 2015); thus *d* = 0.40 is a conservative estimate of the effect size we are hoping to achieve with this combined intervention. The DASS-21 profile sheet quotes the following reference ranges to interpret level of distress from the total score: moderate 43-59 points, severe 62-79 points, extremely severe 82+ points. Based on the CASIS study (mean=62, SD = 31 in TAU arm at 12 months, *n*=57), we expect our target population to be in the lower end of the severe range of distress at 12 months under standard treatment. An improvement of *d*=0.4 amounts to a reduction by 11 points (based on a SD= 28 from Hibbs et al., 2015) would shift the distress into the middle of the moderate range and would, therefore, be considered clinically significant.

2.4.2 Randomisation and Masking

A patient-primary carer identification number (dyad identification number or DIN) will be allocated by registering the patient on the MACRO eCRF system, after consent has been signed. The system will generate a unique identifier to be used throughout the study. The DIN will be a five-digit number; the initial two digits indicate the centre (e.g. SLAM = 01; St Georges = 02; Vincent Square = 03; St Annes = 04, Maidstone = 05, Cambridge = 06, Cotswold 07, Bristol 08, Dorset 09, Leicester 10, Newcastle 11, …) and then a three-digit number indicating the number within the centre.
Patients will be allocated to ECHOMANTRA or TAU by sites via an online randomisation system hosted by the King's Clinical Trials Unit (King's CTU) based at the Institute of Psychiatry, Psychology and Neuroscience. The randomisation website will be accessible at www.ctu.co.uk Allocation will be at the level of the patient/carer using block randomisation by minimisation and minimising on centre and illness severity (BMI <15 yes/no). This is performed with an 80 % probability of allocating to the arm which reduces the imbalance; the allocation sequence will be generated dynamically so the next allocation will only become known upon auctioning a request from the study site staff.

Only site staff authorised to request randomisation will receive passwords for the randomisation system. Requests for passwords are via the trial manager to the King's CTU.
Clinicians treating anorexia nervosa, assessors and statisticians will be blind to the aftercare treatment allocated to the patient and their primary carer. We will do this by having research assistants each allocated to a sub-cohort of patients. One researcher will not be blind and will be responsible for management of this cohort. Another researcher will serve as assessment facilitator for this group and will be blind to group. It is possible that clinicians can elicit by deep questioning of the patient the exact content of the platform and hence what group the patient is in. In the information given to clinicians we will explain that the project requires them to be blind to treatment unless there are reasons why. We will ask clinicians to speculate as to which group the patient belongs at the end of treatment. Statisticians will be kept blind as long as possible; analyses requiring unblinding (e.g. those involving process variables such as the number of sessions attended) will be carried last.

2.4.3 Analysis

All formal analyses for the evaluation of clinical effectiveness will be carried out following the intention-to-treat principle by the trial statistician who will be kept blind to treatment allocation as long as possible. Modelling will be carried out to estimate differences between trial arms at the post randomisation assessment time points of interest. For the primary outcome (DASS) linear mixed models assuming normal distributions will be used to simultaneously model continuous outcome variables at various post-randomisation time points. The models will be parameterised, such that a separate group effect is estimated at each time point. Models will always include baseline values of the variable under investigation as a covariate to increase power. They will further include effects of time (3, 6, 9, 12- and 18-months post randomisation), trial arm (ECHOMANTRA plus TAU or TAU only) and group x time interaction terms. Models also condition on variables that may be found empirically to predict attrition, and on randomisation stratifiers (site and BMI). To detect baseline predictors of missingness, a forward logistic selection procedure will be used. Finally, the linear mixed models will fit an unstructured covariance model to account for the correlations between the repeated measures and a further random intercept that varies at the level of the mentor to account for mentor effects if necessary. The modelling is valid (i.e. provides unbiased estimates of trial arm differences) provided the missing data generating process is missing at random (MAR, here meaning that trial arm, time, baseline values and the identified predictors of missingness can drive loss-to-follow up.) Furthermore, regarding missing values (MVs): missing values in baseline variables can be imputed [30]. We will investigate whether non-adherence with ECHOMANTRA is predictive of later drop-out from the trial. Should this be the case, then we will employ multiple imputations to provide an analyses approach that can accommodate such an MV generating process. Analysis of continuous secondary outcomes will follow the same approach; with distributional assumptions checked and transformations applied as required. Analyses of

non-continuous secondary variables will be based on more appropriate distributional assumptions. For example, re-admission rates will be analysed using a Poisson model. A full statistical analysis plan will be developed in collaboration with the trial statistician.

Economic evaluation
Service use, lost employment/education and costs will be described and compared between the two groups. Public sector costs will be estimated by combining patients' service use data with unit costs to derive costs by provider agency and total costs per person. Lost employment costs will be estimated based on days missed from work due to AN, and average wage rates. Cost data are likely to be skewed, so we will use bootstrapping methods to estimate 95% confidence intervals around the mean total cost differences. We will assess relative cost-effectiveness of the intervention and TAU using public sector costs and DASS at the 18-month follow-up. We will also undertake a cost-utility analysis using public sector costs and health related quality of life gains estimated from the EQ-5D (quality adjusted life years or QALY). If costs are higher for one group and outcomes are also greater, we will construct incremental cost-effectiveness ratios (ICER) to show the cost per extra unit for outcome gained (DASS point or additional QALY) with the uncertainty plotted on cost-effectiveness planes. From these data, we will generate cost-effectiveness acceptability curves (CEAC), using the net-benefit approach, to indicate the probability that one option is more cost-effective for different values placed on a one-point outcome gain. The range of values used will be within £0 to £100,000, which includes the QALY threshold used by NICE.

3 Selection and Withdrawal of Subjects

Participants in the study will be recruited from specialist eating disorder centres with inpatient and/or day patient care. The following UK centres have agreed to participate:

- Cheshire and Wirral Partnership NHS Foundation Trust (inpatient unit and daycare)
- South Staffordshire and Shropshire Healthcare NHS Trust
- Oxford Health NHS Foundation Trust
- Avon and Wiltshire Mental Health Partnership NHS Trust
- Dorset HealthCare University NHS Foundation Trust
- 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
- Barnet, Enfield and Haringey Mental Health NHS Trust
- Leicestershire Partnership NHS Trust
- Northumberland, Tyne and Wear NHS Foundation Trust
- South East Scotland Regional Eating Disorders Unit, Edinburgh
- NHS Grampian - Royal Cornhill Hospital. Eden Unit, Aberdeen
- North Essex NHS Foundation Trust.
- Cardiff and Vale University Health Board (NHS).

- 2GETHER NHS Foundation Trust- Berkshire
- Ellern Mede, Service for Eating Disorders
- The Priory Group (multisites: Cheadle, Altrincham, Bristol, Roehampton, Southampton, Hayes).
- Berkshire Healthcare NHS Foundation Trust
- Surrey and Borders Partnership NHS Foundation Trust
- Ellern Mede, Barnet (non-NHS site)
- Hayes Priory (non-NHS site)
- Newmarket House Health Care Ltd (non-NHS site)
- Cygnet Hospital Ealing, Cygnet Health Care (non-NHS site)
- Cardinal Clinic (non-NHS site)
- Cambridgeshire and Peterborough NHS Foundation Trust

3.1 Inclusion Criteria

The inclusion criteria for participants are as follows:

(a) Aged 16 or over;

(b) DSM-5 diagnosis of Anorexia Nervosa or subclinical/atypical Anorexia Nervosa, with a body mass index (BMI) of $\leq$ 18.5 kg/m$^{2.}$
N.B. Patients can be consented at a BMI of over 18.5 kg/m^2 if they were $\leq$ 18.5 kg/m^2 when first admitted into hospital or when first attending daycare 3 days/week or at any time within 4 weeks after discharge from hospital.

(c) With a carer willing to participate. We will use a broad definition of "carer" to include family and/or friends willing and able to provide some aftercare support;

(d) Informed consent signed whilst patient is admitted into hospital up to 4 weeks after discharge.

(e) Participants able to access an electronic device (e.g. mobile phone, computer, laptop, tablet) and the internet in order to use the study's website).

3.2 Exclusion Criteria

Participants are excluded from participation in this trial if:

(a) The patient is not admitted to hospital or attending daycare for a minimum of 3 days/week when they are consented in the study.

(b) The patient has an insufficient knowledge of English.

(c) The patient has severe mental or chronic physical illness needing treatment in its own right (e.g. psychosis, diabetes mellitus, cystic fibrosis etc.).

(d) The patient is pregnant.

(e) The patient-carer dyad has previously received treatments involving the ECHOMANTRA materials [e.g. as part of iMANTRA trial or CASIS study].

3.3 Withdrawal of Subjects

It is unlikely that there will be a need for patients to be withdrawn from this trial because of medical reasons. If patients need to be readmitted to hospital they will continue with

the skill sharing intervention. It is unlikely that carers will be withdrawn from the study for clinical reasons.

4 Assessment of Efficacy

4.1 Efficacy Parameters

4.1.1 Primary Efficacy Parameters

The primary efficacy parameter is patient's wellbeing (anxiety, depression and stress symptoms) measured by DASS at 12 months after randomisation.

4.1.2 Secondary Efficacy Parameters

Secondary efficacy parameters include:

- Patients' BMI, eating disorder symptoms, work and social adjustment, social functioning as reported by carers, motivation to change and quality of life in the 12 months post-randomisation.
- Patients' BMI, eating disorder symptoms, depression, stress and anxiety, work and social adjustment and motivation to change in the 18 months post-randomisation.
- Patients' number of days in hospital in the 18 months following admission and intervention's cost-effectiveness compared to treatment as usual in terms of distress and quality-adjusted life years gained at 12 months following randomisation.
- Carers' wellbeing (anxiety, depression, stress symptoms) and skills in dealing with eating disorder symptoms at 12- and 18-months post-randomisation. These will be measured at regular intervals post-randomisation.

4.2 Procedures for Assessing Efficacy Parameters

Efficacy measures will be collected using participants' self-reports completed on the study online platform and later transcribed into the trial database. Patients' BMI will also be measured at the participating site by the clinical team, reported to the research team and entered into the trial database. Short monthly tracking assessments will be used to maintain engagement and a selected number of core assessments will be measured at regular intervals (3, 6, 9, 12, 18 months after randomisation) on the study online platform. Participants will receive automatic email reminders from the researchers to complete the online assessments. The research team will track the completion of the assessments weekly and will follow-up with additional phone prompts, if necessary. A summary of the timeline and assessment measures for patients and carers is provided in Table 2.

4.2.1 Assessment measures

Assessments will be made for patients, their carers, the joint-session mentors and clinicians.

The following baseline and outcome measures are obtained for **patients:**

- Demographic questionnaire to identify demographic features.
- Depression, Anxiety and Stress Scales (DASS-21; Lovibond et al., 1993): To assess psychological wellbeing. This is the primary patient outcome.
- Weight, height and BMI will be obtained from clinical measurement at each centre and from participants, monthly, up to 18 months post-randomisation.
- Autism-Spectrum Quotient (AQ; Allison et al., 2012): To screen for autistic symptoms (as a marker of social functioning).
- Obsessive-Compulsive Inventory (OCI; Foa et al., 2002): To screen for obsessive-compulsive symptoms.
- Eating Disorder Examination-Questionnaire (EDE-Q; Faiburn and Beglin, 1994): To assess eating disorder symptoms.
- Work and Social Adjustment Scale (WSAS; Mundt et al., 2002): To assess work and social functioning.
- Motivational ruler: to measure confidence and importance to change eating disorder symptoms.
- EQ-5D (Herdman et al., 2011): A 5-level health status measure developed by a European consortium for use in health economics.
- Social Identity Mapping (SIM): An online social identity mapping exercise where participants complete a visual map of their social network.
- Client Service Receipt Inventory (Beecham, 2001): A well-established method of data collection, linked to cost analysis, including each person's use of specialist and generic health services, and education or employment.
- Hospital episode Statistics to assess days in hospital.
- Feedback form: It includes an area for free expression about how the intervention was helpful and how it could be improved. For those in the treatment arm, it also includes Likert scales to measure participant's use and feedback of the intervention materials and guidance. Patients in the intervention group will be asked 3 additional process questions related to the online group at 6 and 12 months. We will invite a selected subgroup of patients (up to n=22 patients, selected based on pre-specified criteria) who were randomised to the ECHOMANTRA + TAU intervention group to participate in an interview about their experience of the TRIANGLE trial and intervention. We will invite a selected subgroup of patients (up to n=22 patients, selected based on pre-specified criteria) who were randomised to the TAU only group to participate in an interview about their experience of transitioning from the intensive treatment (inpatient or day care) they were receiving when initially recruited to the trial back to the community. Participants will be recruited who are between the 6 months and 12 months timepoints in their study participation so that they have had enough time to offer a well formed opinion of what it meant to them to have participated in the study and to have transitioned from intensive treatment. To

explore a range of opinions participants will be recruited purposively across study sites according to recruitment site location, gender, age, patient's eating disorder severity (>7 years of illness or below 3 years of illness) and carer's relationship to the patient. Sites will not be involved in the selection of participants. A King's College London researcher, one of the project's Co-Investigators will contact the participants to see if they are willing to take part in the additional interview. Interviews via Skype voice call or by telephone. The interview will last for up to 1 hour and will consist in a pre-specified list of questions. Data will be typed up, allocated an ID number for confidentiality purposes and then analysed.Post joint sessions survey: Visual analogue scales and open-ended questions to measure participant's feedback after each joint online session.

- Patient's brief monthly update questionnaire: Brief update questionnaire including questions about their admission/discharge date/day care or inpatient care, if they are under Mental Health Act, if they have been transferred from another service or community treatment, home leave, weight, treatment received and medication.
- Coronavirus survey (general impact qualitative questions and impact on sleep). These questions will be administered to patients enrolled in the TRIANGLE study during the Coronavirus outbreak at any time point during their participation.

The following baseline and outcome measures are obtained for **carers**:

- Demographics questionnaire
- Depression, Anxiety and Stress Scale (DASS-21): As described above.
- The Caregiver Skills (CASK) scale (Hibbs et al., 2014): To assess skills helpful in managing eating disorder behaviours.
- Feedback form: As described above. Carers in the intervention group will be asked 3 additional process questions related to the online group at 6 and 12 months. We will invite a selected subgroup of carers (up to n=22 carers, selected based on pre-specified criteria) who were randomised to the ECHOMANTRA + TAU intervention group to participate in an interview about their experience of the TRIANGLE trial and intervention. We will invite a selected subgroup of carers (up to n=22 carers, selected based on pre-specified criteria) who were randomised to the TAU only group to participate in an interview about their experience of supporting their loved one during the transition from the intensive treatment (inpatient or day care) they were receiving when initially recruited to the trial back to the community. Participants will be recruited who are between the 6 months and 12 months timepoints in their study participation so that they have had enough time to offer a well formed opinion of what it meant to them to have participated in the study and to have transitioned from intensive treatment. To explore a range of opinions participants will be recruited purposively across study sites according to recruitment site location, gender, age, patient's eating disorder severity (>7 years of illness or below 3 years of illness) and carer's relationship to the patient. Sites will not be involved in the selection of participants. A King's College London researcher, one of the project's Co-Investigators will contact the participants to see if they are willing to take part in

the additional interview. Interviews via Skype voice call or by telephone. The interview will last for up to 1 hour and will consist in a pre-specified list of questions. Data will be typed up, allocated an ID number for confidentiality purposes and then analysed.Strengths and Difficulties Questionnaire (SDQ, Goodman, 2001): To assess patients' broad social functioning (peer problems, pro-social difficulties, hyperactivity, emotional problems, and conduct problems), completed by informants, in this case the primary carer.

- Post joint sessions survey: Visual analogue scales and open-ended questions to measure participant's feedback after each joint online session
- Coronavirus survey (general impact qualitative questions, impact on sleep, and impact on caregiving). These questions will be administered to carers enrolled in the TRIANGLE study during the Coronavirus outbreak, at any time point during their participation.

Measures obtained from **mentors of the joint sessions**:

- Post joint sessions survey: Visual analogue scales and open-ended questions to measure mentor's feedback after each joint online session
- Mentor's feedback form: Ares of free expression and visual analogue scales to measure mentor's fidelity and satisfaction with delivering the intervention.

Measures obtained from the clinical team

A member of the clinical team will be asked to provide patient's BMI measurement at baseline and every 3 months up to discharge. They will be asked also to inform the study team the date of admission and to notify the study team when the patient has been discharged. Patient-reported BMI will be used for analysis, but clinician-reported BMI will be collected and used to fill in gaps from missing data. If BMI measurement for a specific time point has not been collected, BMI measurements collected within a 1-month window can be used instead. Additional biomarker information (i.e. patient blood pressure, pulse, temperature, oxygen saturation, blood results) will also be asked if possible, for the clinical team to provide these details

The compliance of the clinical team to provide this information is not an essential condition to include the participant in the study. The study team would greatly appreciate if this information could be sent, but also understand that in some cases the clinical team will not be able to accommodate this request. A brief questionnaire about carer/family involvement will also be asked to the participating sites (e.g. carers involvement in transition planning, resources and supports available for carers and families). This brief questionnaire will be completed twice (i.e. at present and at 18-months). Six additional questions regarding research perceptions will also be assessed at baseline.

4.2.2 Assessment schedule

Table 3 provides the assessment schedule.

Table 3: Assessment schedule

Participant	Recruitment (within a month from admission)	Baseline	Randomisation	Post-randomisation					
				Monthly- up to 18 months	3 Months	6 months	9 months	12 months	18 months
Patient	Information sheet and consent form Eligibility criteria	Demographics BMI DASS-21 EDE-Q Motivation Ruler WSAS AQ-10 OCI EQ-5D CSRI HES		BMI Likert scales on social connection Patient's brief monthly update questionnaire Carer Demographics	DASS-21 EDE-Q BMI Motivation Ruler Carer Demographics	DASS-21 EDE-Q BMI WSAS Motivation Ruler Process question for intervention group Telephone interviews (≤ 22 intervention group participants and ≤22 TAU group) Carer Demographics	DASS-21 EDE-Q BMI Carer Demographics	DASS-21 EDE-Q BMI WSAS Motivation Ruler EQ-5D CSRI Process question for intervention group Carer Demographics	DASS-21 EDE-Q BMI WSAS Motivation Ruler HES Feedback form Carer Demographics
Carer	Information sheet and consent form	Demographics DASS-21 CASK SDQ		Likert scales on social connection	DASS-21	DASS-21 CASK Process question for intervention group Telephone interviews (≤ 22 intervention group participants and ≤22 TAU group)	DASS-21	DASS-21 CASK SDQ Process question for intervention group	DASS-21 CASK Feedback form
Mentor									Feedback form
Clinician		BMI at baseline and every							Carer/family involvement brief

		3 months up to patient's discharge, admission and discharge date and additional biomarker information Carer/family involvement brief questionnaire Research perceptions questions							questionnaires

5 Assessment of Safety

5.1 Specification, Timing and Recording of Safety Parameters

A serious adverse event (SAE) in this context would be a suicidal act or death. We will also record readmission for management of eating disorder symptoms. We will register the participants in the study with the NHS register after obtaining informed consent to link our records with mortality and Hospital Episodes Statistics data.

In line with the HRA guidance on what constitutes a Serious Adverse Event for non-CTIMP studies, a serious adverse event (SAE) will be defined as an untoward occurrence that:
(a) results in death;
(b) is life-threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation;
(d) results in persistent or significant disability or incapacity;
(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator.

5.2 Procedures for Recording and Reporting Adverse Events

Recording and reporting of SAEs will start from consent. All **SAEs*** occurring from the time of **written informed consent** until 18 months following the assessment will be recorded on the SAE Form

.

In compliance with the HRA guidance on expected reporting and timelines, only reports of Serious Adverse Events (SAEs) that are 1) **related** to the study (i.e. they resulted from

administration of any of the research procedures) and/or 2) **unexpected** (i.e. not listed in the protocol as an expected occurrence) will be submitted to the REC using the 'Non-CTIMP safety report to REC form'. These will be sent within 15 days of the Chief Investigator becoming aware of the event.

To decide whether an event is related or unrelated to the intervention the research assistants report any adverse or serious adverse events to the trial manager and chief investigator for their review on a weekly basis.

	Expected	Unexpected
Related	Mild distress in relation to questionnaires or any tasks associated with the TRIANGLE study (i.e. completing the workbook exercises, online groups, watching videos, taking part in the joint online sessions)	Severe psychological distress due to completion of questionnaires or any tasks associated with the TRIANGLE study in the opinion of the Chief Investigator, that are also considered serious, defined as events which: (a) results in death; (b) is life-threatening; (c) requires hospitalisation or prolongation of existing hospitalisation; (d) results in persistent or significant disability or incapacity
Unrelated	Any event (e.g. weight deterioration, development of severe comorbid mental or chronic physical illness, medical complications associated with anorexia nervosa, drug overdose, expressions of suicidal thoughts, suicide attempt, or death of a participant) that is not due to the intervention in the opinion of the Chief Investigator	Significant psychological distress, self-harm, expressions of suicidal thoughts, suicide attempt, or death that, in the opinion of the Chief Investigator, is not related to participation in the intervention

For each **SAEs*** the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator
- Whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

The responsibility for reporting and reviewing safety information arising from the trial will include the PI, the trial coordinator, the Sponsor, Trial Steering Committee (TSC) and Data Monitoring Committee (DMC).

Individual SAEs and trends in SAEs will be independently reviewed as follows:

- Clinical review of all life threatening or SAEs resulting in death within 1 week of their occurrence (for lower risk trial).
- Clinical review of a line listing of all other SAEs on a monthly basis (for lower risk trial).
- Cumulative review of all safety information by the DMC on a 3 or 6 monthly basis by sending total numbers of SAEs per month sent to the DMC Chair – in order to expedite a safety review if more SAEs are being seen than would be expected.
- JA of the Trial Management Group (TMG) should also be identified to prepare the written sections of the Development Safety Update Report (DSUR).

6. Trial Steering Committee

The Trial Steering Committee (TSC) will provide overall trial supervision supported by the Data Monitoring and Ethics Committee (DMEC). Professor Paul Robinson has accepted the lead role of chairperson for the TSC. The main ethical consideration is to ensure that the risk of harm to participants is minimized and that they are fully informed of any risks. We will take into account literacy and cultural sensitivities in obtaining informed consent. Other ethical considerations are ensuring that recruitment and informed consent are handled in such a way that potential participants are not put under pressure to take part and that confidentiality is preserved. The members of the TSC will meet regularly (2/year) and will send reports to the sponsor.

Members: Prof. Paul Robinson (chair), Dr S McClusky (consultant psychiatrist), Jenny Langley (carer), Rosemary Marston (recovered patient), Lynn/Brian McDonogh (carer).

Data Monitoring Committee

The members of the Data Monitoring Committee are: Dr John Morgan (chair;

psychiatrist), Victoria Cornelius (statistician) and Dr Eric Sabine (Psychiatrist).

7. Direct Access to Source Data and Documents

The investigator and the institutions (King's College London and South London and Maudsley NHS Foundation Trusts) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing direct access to source data and other documents.

8. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki and the principles of GCP. The protocol is to be submitted for approval by an NHS Research Ethics Committee (REC). Any subsequent protocol amendments will be submitted to the REC. The research team will provide the REC with progress reports and a copy of the Final Study Report.

9. Quality Assurance, Data Handling, Publication Policy and Finance

Electronic Case Report Forms (eCRFs) will be created using the InferMed Macro system. This system is regulatory compliant (GCP, 21CRF11, EC Clinical Trial Directive). The eCRF will be created in collaboration with the trial statisticians and the investigators and maintained by the King's Clinical Trials Unit. It will be hosted on a dedicated secure server within KCL. Source data will be entered by authorised staff onto the eCRF with a full audit trail. The trial database will accessible at www.ctu.co.uk.
Database access will be strictly restricted through passwords to the authorised research team. The trial manager will request usernames and passwords from the KCTU administrator. It is a legal requirement that passwords to the eCRF 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 personalised username and password should be requested via the Trial Manager.
We will obtain the data from the self-report assessments from the study online website, where participants will be completing the assessment measures, with the exception of the Client Service Receipt Inventory which will be completed via telephone with one of the research assistants. Similarly, the Social Identity Mapping task will be completed on the TRIANGLE website but will be supported by a research assistant over the telephone. The text of the forums and the audio content of the joint online sessions will also be recorded. Only the researchers involved in the study will have access to the data stored on the website. The trial manager will obtain the access details to the website for the research staff from the website's IT team (Mindwave's). The research staff will then be able to set up their personal accounts to log in onto the platform. If new staff members join the study, a personalised username and password will be requested via the Trial Manager.
All original signed informed consent forms and copies of any paper copies of data produced through interviews will be kept at the research site with the CRF pages for the participants. For non-nhs sites, the consent forms themselves (the actual document) will

be password protected and attached in a normal email to the research team. The research team will be able to access the informed consent forms received by non-nhs sites by entering a password that has been agreed with the site in a separate email.

Data handling and record keeping

Data handling: Personal data will be anonymised using the DIN.

The consent forms from patient participants will be scanned and transferred by post and by NHS email to the central research hub. The original copies will be kept at the IoPPN. The consent forms from carers will be transferred by post and email to the research hub. Data from self-reported assessments of participants will be captured by the study online platform. The research co-ordinator and research assistants at the research hub IoPPN will access this data from the study online platform and will enter it into the MACRO database.

Therapy compliance and withdrawal: The progress of therapy and supervision of the mentors will be managed from the research hub at the IoPPN. The number of the online forums and of the joint sessions attended by patients and carers will be recorded.

Data monitoring and quality control of data: The research co-ordinator and research assistants at the research hub IoPPN will be responsible for data monitoring and quality control of data.

The procedures for data handling, record keeping and monitoring include:

- MACRO: software for data entry. Data will be copied from the study online platform (where participants will complete the assessment measures) to the MACRO database by the authorised researchers involved in the study. The researchers will be provided with a password to access the MACRO database by the KCTU and with a password to access the study's website by the website's IT team (Mindwave's), via the Trial coordinator. The security of the data during transfer will be ensured in accordance with the UK Data Protection Act 1998.
- Data will be stored on the KCL site and password protected.
- Data will be stored on the study online platform and password protected.
- The PI (JT) and the project co-ordinator (VC) will hold the responsibility for data entry and quality. The trial statistician (ER) will check that the eCRFs are consistent with the protocol and enable meeting the trial's objectives. ER will also serve the DMC and provide high level monitoring reports to aid data quality assurance by VC.
- Prof S Landau is responsible for data analysis.
- Prof J Beecham is responsible for Health Economic Assessment.

Data monitoring

The data is gathered on the study online platform. Reports will produced by exploring the trial dataset by the research assistants every week for the purposes of monitoring participant enrolment, consent, eligibility, and allocation to trial groups; completion of the assessments, policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. The weekly monitoring reports will be shared with the PI (JT) and project coordinator (VC) to discuss any issues relating to project implementation.

Access to Data
Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Archiving

- Archiving will be authorised by the Sponsor following submission of the end of study report.
- The sponsor will be responsible for archiving the MACRO trial database and other trial documents
- All essential documents will be archived for a minimum of 5 years after completion of trial and destruction of essential documents will require authorisation from the Sponsor.

Conduct and management of the trial
The sites (NHS and non NHS) will be responsible for identifying suitable participants and helped by CRN staff who will approach potentially eligible participants and obtain consent from both themselves and carers. The CRN staff (and in some sites medical staff) will be responsible for introducing participants to the study online platform (i.e. helping to set up participants accounts). The CRN and staff from the research hub may also be involved in introducing carers to platforms.
Staff engaged at the research hub of the IoPPN will be involved in delivering and quality control and data monitoring for the on line support. Staff engaged at the research hub of the IoPPN will be involved in obtaining assessment data from participants (patient and carers) from the online platform and weight and hospital day usage from sites and entering it into the MACRO data base.

Protocol violations

A protocol violation will be any procedures undertaken contrary to the study protocol. Protocol violations are recorded with justifications. These are discussed during regular meetings with the statistician and based on those discussions the study team consider whether an update to the protocol will be necessary.

Publication policy
The aim will be to generate publications in high quality peer reviewed journals. The data arising from the trial will be owned by the trial management group. On completion of the trial, the data will be analysed and tabulated and a Final Study Report prepared. A full study report will be prepared for the HTA. All investigators will have rights to publish any of the trial data and will have access to the full dataset if a formal request describing their plans is submitted and the final paper is approved by the steering group.
Baseline data analysis might be possible after cleaning and locking baseline data. Any secondary outcome analyses can only ever be done after the end of the trial.

The funding body will be acknowledged within the publications but they will not have rights to review and publish data from the trial. The expert review committee of the HTA (funders) made suggestions about the study design. However, data analysis and interpretation, manuscript writing, and dissemination of results will be conducted independently from the funder. This will be acknowledged by the following statement attached to all articles. "The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health". Participants will be informed about the outcome of the trial, either by provision of the publication, or via a specifically designed newsletter. The trial protocol, full study report, anonymised participant level dataset, and statistical code for generating the results will be made publicly available 3 years after the publication of the primary outcomes paper. The trial management group will be offered authorship on the outcomes of the trial if they meet the International Committee of Medical Journal Editors criteria for authorship of a manuscript.

Indemnity arrangements

The co-sponsors will at all times maintain adequate insurance in relation to the study. King's College London provides its own professional indemnity (Clinical Trials) and no fault compensation and NHS having duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient.

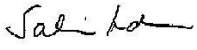
Finance

This trial is funded by the NIHR Health Technology Assessment (HTA) Programme, for 5 years (start date: 01/11/2016).

10. Signatures

To be signed by Chief Investigator minimum and statistician if applicable.

PROF. JANET TREASURE
Chief Investigator Date 09/02/2017



SABINE LANDAU
Statistician Date 09/02/2017

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11. Acknowledgement

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