Sleep, Wake and Light therapy for depression

Informed Consent Form

1st July 2017

1. PROTOCOL FULL TITLE

Triple Chronotherapy compared to treatment as usual for the rapid treatment of depression: a feasibility study for a randomised controlled trial

Protocol Short Title

Sleep, Wake and Light therapy for depression

Trial Identifiers

ISRCTN:	Not yet registered		
REC Number:	Application not yet made		
UKCRN Number:	Application not yet made		
Protocol Version Number:	1.0	Date:	1st July 2017

(Co) Sponsor(s)

This is usually the substantive employer of the CI. If this is KCL then co-sponsorship with the participating NHS Trust may be required.

Name:	South London and Maudsley NHS Foundation Trust
Address:	c/o Jennifer Liebscher, The Institute of Psychiatry, Psychology and Neurosciences, London SE5 8Af
Telephone:	020 7848 0251
Email:	Jennifer.liebscher@kcl.ac.uk

Chief Investigator

Name:	Professor David Veale
Address:	CADAT, The Maudsley Hospital, 99 Denmark Hill, London SE5 8AZ
Telephone:	020 3228 2101
Email:	David.Veale@kcl.ac.uk

Name and address of Co-Investigator(s), Statistician, Therapy Service, Laboratories etc

Name:	Professor Allan Young
Position/ Role:	Co-investigator, Professor in Psychiatry
Address:	Institute of Psychiatry, Psychology and Neuroscience, King's College London

Telephone:	020 7848 0002 x0088
Email:	allan.young@kcl.ac.uk

Name:	Dr Marc Serfaty
Position/ Role:	Co-investigator, Reader in Psychiatry
Address:	University College London
Telephone:	020 7679 9712
Email:	m.serfaty@ucl.ac.uk

Name:	Dr Sarah Markham
Position/ Role:	Co-investigator, Visiting researcher & user perspective
Address:	Department of Biostatistics, King's College London
Telephone:	020 7848 0002
Email:	sarah.markham@kcl.ac.uk

2. Study Synopsis

3. Revision History

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

4. Protocol Contents

5. Background & Rationale

Depressive disorders are common mental conditions with a prevalence of about 17% in urban UK (Ayuso-Mateos, 2001). The impact of depression on social, occupational and physical health and mortality is substantial. Depression causes a greater impairment in health state than the major chronic physical illnesses such as angina, arthritis, asthma, and diabetes. Although evidence based treatments for depression exist in the form of anti-depressant medication and cognitive behaviour therapy (CBT), there is much room for improvement. Remission rates are 43% for antidepressants and 29% for placebo (Gibbons et al, 2012). Even fewer patients will sustain response in the long–term. Response rates using CBT are generally equivalent to antidepressant medication (Amick et al, 2015). Efficacy of CBT in a meta-analysis was a modest d=0.42 after the effect of publication bias was removed (Cuijpers, 2010). There is little enthusiasm amongst pharmaceutical companies to develop new anti-depressant medications that would then compete with cheaper generic drugs. Psychological therapies have reached a plateau and newer developments focus on more efficient ways of delivering therapy (e.g. computerised CBT). A significant additional problem is that the response for any established treatment of depression may not occur for 6 weeks or more. There is some research in evaluating newer compounds such as intravenous ketamine. However, this requires a hospital setting, may have significant adverse effects and would be unacceptable to many patients.

One of the most rapid anti-depressants known is a night of total sleep deprivation (or “wake therapy”) (Beneditti & Colombo, 2011); up to 60% of patients respond by the next day with a 50% reduction on the Hamilton Rating Scale for depression and a final score of <9 (Gillin et al 2001). However, there is a very high rate of relapse amongst responders. Several combination strategies have been used in pilot studies to augment and maintain the rapid response after wake therapy. These have included adding daily bright “light therapy” in the morning and advancing the sleep phase for 3 days after sleep deprivation (“wake therapy”) (the combination is called “triple chronotherapy”) which has resulted in long-term maintenance of response in 3 RCTs. For example, Wu et al (2009) randomly assigned 49 bipolar inpatients with depression to triple chronotherapy, as an adjunct to medication, or to a medication-only group. Significant decreases in depression were found on day 2 in the triple chronotherapy group compared to treatment as usual. This was maintained over 7 weeks. Martiny et al (2012, 2013, 2015) randomly allocated 75 inpatients with non-seasonal unipolar depression on an anti-depressant (duloxetine) to either triple chronotherapy or to daily exercise for 5 days. (Sleep deprivation in this study consisted of a variation of three alternate nights of being awake). The triple chronotherapy was superior to exercise at Day 2-7 with a large effect size of 1.45. This is a larger effect size than medication or CBT and acted within 5

days. It was maintained at 6 month follow up, when the remission rate was 61.9% in the triple chronotherapy group compared to 37.9% in the exercise group. Lastly, Neumeister et al (1995) recruited 20 non-seasonal depressed in-patients on medication. They all received Partial Sleep Deprivation (sleep from 9:30 to 1am) and were then randomly allocated to either Bright Light or Dim Light. Patients receiving Bright Light did significantly better than those on Dim Light from Day 2 to 7. All three RCTs have small numbers and therefore the effect size may be exaggerated. There are also several open label case series of triple chronotherapy in both unipolar depression (for example Sahlem, 2014; Moscovici & Kotler, 2009) and bipolar disorder (Bendetti et al, 2005). Triple chronotherapy has so far been conducted in in-patients although one group has demonstrated the feasibility in a case series of 27 non-medicated out-patients with major depression in the Netherlands (Dallaspezia, 2016). These patients were supported during the night to stay awake. The Beck Depression Inventory score reduced from a mean of 25.8 (SD 7.7)(moderate range) to 13.7 (SD 7.7) (mild range) at one week and to 11.8 (SD 10.2) (mild range) at 3 months.

In the UK, the large majority of patients with depression in the NHS are treated in the community and are only admitted to hospital if there is a severe risk of suicide or self-neglect that cannot be managed in the community. Psychological treatment as usual usually consist of behavioural activation delivered by Psychological Well-Being Practitioners (PWPs) in the Improving Access to Psychological Therapies service and/or anti-depressant medication. Thus, one of the major objectives of the study one is to determine if triple chronotherapy is a practical treatment in the community. We will also focus on patients with unipolar depression, as this is far more common than bipolar. Our study will therefore be a randomised controlled trial that is designed as a feasibility study to answer the question whether Triple Chronotherapy enhances standard treatment of care for depression after 1 week and whether this is maintained at follow up.

Rationale: There are no major breakthroughs on the horizon in the field of pharmacotherapy or psychotherapy for the rapid treatment of depression (within one week) without any significant side effects, so this is a novel approach. Triple chronotherapy is a term used to describe a combination of total sleep deprivation, followed by advance of sleep cycle and bright light therapy. Three small RCTs suggest that this is a promising treatment for the rapid treatment of depression. In addition, depression is a heterogeneous condition and this study has the potential in a larger trial to be part of a paradigm shift to determine subtypes of depression that may determine the type of treatment offered.

Trial Objectives and Design

Our objective is to determine the feasibility of conducting a larger randomized controlled trial (RCT) of triple chronotherapy in a community sample of patients with depression, and enable us to determine

1) agreement to be randomised.

2) whether clinicians can recruit participants.

3) estimates of participant flow.

4) the feasibility of delivering the intervention in the community.

5) adherence to the protocol.

Aims: To conduct a double blind RCT comparing adding triple chronotherapy to standard treatment of care. Both groups will receive standard treatment as usual (TAU).

We hypothesise that:

1) Triple chronotherapy (Total Sleep Deprivation, Phase Advance and Bright Light Therapy) with standard care will be more effective than the control treatment with standard care on the Hamilton Depression Rating Scale (6 item) at 1 week.

2) The superiority of Triple Chronotherapy over the control treatment will be maintained at follow up at 2, 4, 8 weeks and at 6 months.

3.1.1 Primary endpoints

Our outcome measures are

1) agreement to be randomised.

2) whether clinicians can recruit participants.

3) estimates of participant flow.

4) the feasibility of delivering the intervention in the community.

5) adherence to the protocol.

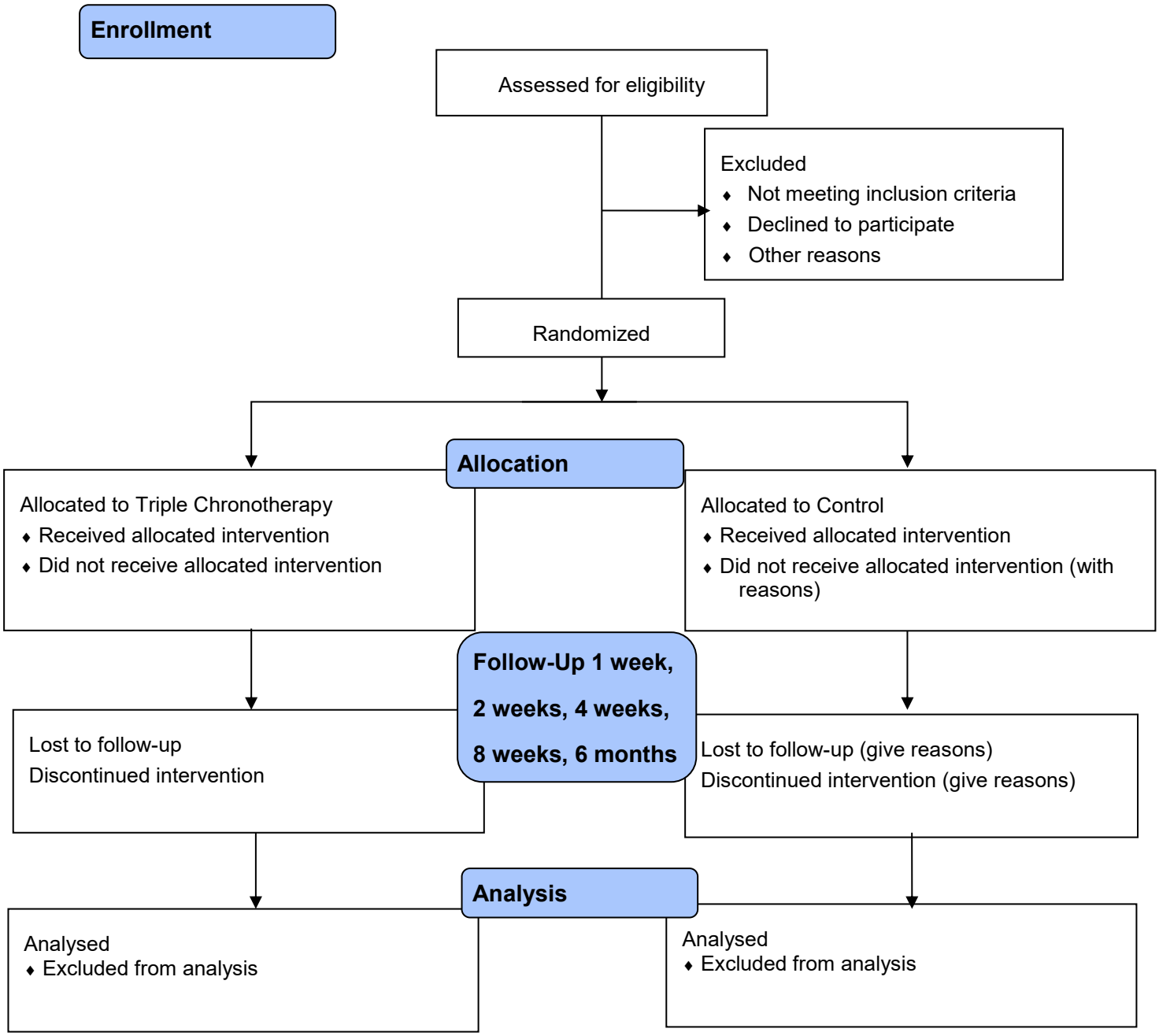
3.1.2 Secondary endpoints

We will explore the means and SDs of the 6 item Hamilton Depression Rating Scale (Bech, 1981; O'Sullivan, 1997) outcomes to help inform the power analysis for a larger RCT.

Trial Design

This is a randomised parallel group single blind design. We will evaluate adding either Triple Chronotherapy or a control treatment to standard care. This design aims to show that we are able to recruit participants and that participants are able to adhere to the interventions. We will explore whether Triple Chronotherapy plus treatment as usual is more effective than treatment as usual on the HDRS (6 item).

Trial Flowchart



	Screen Visit	Visit 2 re-baseline before intervention	Visit 3 (1 week follow up)	Visit 4 (2 weeks follow up)	Visit 5 (4 weeks follow up)	Visit 6 (8 weeks follow up)	Visit 7 (6 month follow up)
Patient information and informed consent	X						
Intervention		X					
Outcome measures (observer rated rating scale)	X	X	X	X	X	X	X
Self-report outcome measures	X	X	X	X	X	X	X
Actigraphy and sleep diary	X		X				

4. Trial Intervention

Intervention Details

All participants who provide informed consent to participate will t be randomised to receive either Triple Chronotherapy or a Control Treatment. Both groups will receive treatment as usual.

1) Triple Chronotherapy

   This consists of (a) *Total Sleep Deprivation* with group support on days one and two; (b) *Phase Advance of Sleep* over 5 days and daily Light Therapy. On Day 1 (e.g. Monday), patients are supported in a group to stay up all night. We will arrange various activities to help patients stay awake accompanied by a Health Care Assistant (HCA) at the Hospital (e.g. watch a film; exercise; receive information on sleep hygiene; listen to music; short walk) and have access to coffee/ tea and snacks.

   The next step is to *advance the phase of sleep*. Patients are helped to stay awake on Day 2 (Tuesday) at the hospital. They will either be collected by a relative or sent home by a taxi to go to bed at about 5pm. They should not drive or operate machinery. They wake by about 1am and will be invited to come to the hospital with support by a HCA in a group to stay awake. They will leave to go home by about 8am. They will then go to bed on Day 3 (Wednesday) at about 7.30pm. They will be asked to sleep until 3am. No further support is provided by the Hospital to stay awake at night. They then go to bed on Day 4 (Thursday) from 9.30pm to 5am and on Day 5 (Friday) at 11pm to resume a normal sleep routine waking by 6.30 to 7am. They will be given an information leaflet on sleep hygiene and given the opportunity to ask questions.

(c) Bright Light Therapy is given on Day 2 onwards daily. This is provided by a Carex Day Classic Light. The time of the therapy is optimised in the morning according to the patient's pattern of sleep. A patient sits about one foot away from a bright light box, that emits 10,000 Lux. It is positioned slightly above the head and pointing downwards at 45 degrees. Patients are free to have breakfast, read or use a computer while facing towards the light. Treatment normally last 30 minutes or more and will continue for 6 months. Possible side effects in the triple chronotherapy group include tiredness after sleep deprivation. A few people may experience nausea or headache after beginning light therapy. (In healthy individuals bright light therapy was not associated with any significant difference in side effects compared to dim light therapy (Botanov, 2013). However, patients with any significant side effects may be asked to reduce the exposure time by 10 minutes. Active treatment may theoretically trigger a manic episode, but patients with bipolar disorder are excluded and so this should be rare. We will however warn the patient and carer of this rare possibility. Patients may also receive standard care.

2) Control treatment

Participants will be given information on sleep hygiene and getting a good night's sleep in a written leaflet and given the opportunity to ask questions. They are then given SomniLight Amber Light daily for 1 week. Like the Bright Light Therapy, the timing is optimised in the morning according to the patient's pattern of sleep. A patient sits about one foot away from a light box, which is positioned slightly at 45 degrees above the head and pointing downwards. Patients are free to have breakfast, read or use a computer while facing towards the light. Treatment normally last 30 minutes.

The frequency of any side effect from either group will be monitored and clinicians would continue with treatment as usual. Participants with any significant side effects will be withdrawn, but included in the analysis.

Frequency and duration of intervention

The duration of the intervention is 1 week.

Intervention records

Therapy sessions (e.g wake therapy or sleep hygiene information) will be recorded in ePJS hospital records.

Subject Compliance.

Compliance to the intervention will be monitored and documented by the Health Care Assistant**.**

Study adherence

Participants will be encouraged to stay up during sleep deprivation as described above.

5.5 Concomitant Medication

A patient may be taking anti-depressant medication so long as the dose has been stable for 6 weeks and there are no plans to increase the dose or to alter the medication.
A wash out time for a patient deciding to stop anti-depressant medication and recruitment is 6 weeks.
Surgery/radiotherapy is allowed after the first week of the intervention.

5. Research environment

This is a single centre trial at the South London and Maudsley NHS Foundation Trust. There are no specific site requirements. Recruitment will be from local GPs on the Clinical Research Network; Improving Access to Psychological Therapies (IAPT); clinicians on the Home Treatment Teams (secondary care) in Southwark, Lewisham, Lambeth and Croydon; through Consent for Contact on CRIS and on a dedicated website. For all settings, the intervention will be conducted at a hospital where support will be provided by a health care assistant for two nights and for one day to help patients stay awake (e.g. watch a film; exercise; short walk) and have access to coffee/ tea and snacks.

6. Selection and Withdrawal of Subjects

Inclusion Criteria

1) Diagnosis of Depressive Episode (ICD10 F32) or Recurrent Depressive Disorder (F33).
2) Minimum score of 8 or more on the Hamilton Depression Rating Scale (6 item) (Range 0-22) (Bech,1981). This represents at least moderate depression.
3) Age 18-65
4) Able to give informed consent
5) Women of child bearing age may be included and no methods of contraception is required to enable inclusion into the trial.

Exclusion Criteria

1) Current diagnosis of Seasonal Affective Disorder
2) Current diagnosis of anorexia nervosa or bulimia.
3) Current diagnosis of an obsessive compulsive or related disorder
4) Current diagnosis of post-traumatic stress disorder
5) History of schizophrenia, schizoaffective disorder or bipolar disorder
6) Severe cognitive impairment, dementia, intellectual disability or organic brain disorder.
7) History of stimulant or hallucinogenic misuse, alcohol or substance misuse or dependence in past 3 months.
8) Borderline Personality Disorder or other personality disorder considered to be the main problem.
9) Duration of depression more than 2 years.
10) Significant risk of suicide that requires hospitalisation.

11) Severe eye disease or cataracts or traumatic injury or visual impairment affecting both eyes.
12) History of epilepsy, uncontrolled severe headaches, or stroke as this may lower seizure threshold through sleep deprivation.
13) Unstable medical condition that would make wake therapy intolerable
14) Untreated sleep disorder such as obstructive sleep apnoea or narcolepsy
15) Use of photo-sensitizing drugs.
16) Current night-shift work.
17) Non-English speaker.

If a patient meets the inclusion criteria but has withdrawal symptoms from alcohol or other substances, the patient will be re-assessed for eligibility when the patient has been abstinent for 3 months.

A patient may be taking anti-depressant medication so long as the dose has been stable for 6 weeks and there are no plans to increase the dose or to alter the medication.

Selection of Participants

Anonymised information on participants who are not randomised will be reported on according to CONSORT guidelines and will include age, gender, ethnicity, whether the patient is recruited or not recruited, the reason not eligible for trial participation, or if they are eligible but declined.

Participant identification

Participants will be identified by

a) A member of the patient's existing clinical care team will be asked to review the identifiable personal information of patients and check whether they meet the inclusion criteria or make the initial approach to patients. This may occur at the point of their initial assessment in Improving Access to Psychological Therapies (IAPT) or on Home Treatment Teams (secondary care) in Southwark, Lewisham, Croydon and Lambeth. Within IAPT settings, this is likely to be following their initial telephone screening (if appropriate), or at their high intensity assessment appointment, where depression is indicated as the client's primary problem. GPs will be encouraged to refer direct to the study.

b) Participants may be contacted directly under the Consent for Contact (C4C). This the Trust's patient research participation register. Patients are routinely asked for consent for contact and participation in research. This creates a registry for patients who are willing for researchers to contact them about research conducted in the Trust. Consent is recorded on the electronic notes. Researchers using C4C are required to notify the

patient's care team prior to contacting a patient, so the responsible clinician is aware their patient is being invited to take part in a research study. Researchers are also required to document any contact made with patients on the notes under 'Approaches and participation' on the consent form.

c) Participants may also refer themselves (for example on the registry of Clinical trials or by an advertisement on the web).

Randomisation Procedure / Code Break

The method of randomisation will consist of simple randomisation based constant allocation ratio of 1:1. It will be stratified according to the season. The King's Clinical Trials Unit will provide a secure web-based randomisation service. The unit is fully registered by the UKCRC and receives support funding from NIHR. A new patient alert will be sent by email (a) to the CI (b) to a research worker (non-blinded), who will inform the patient registration by telephone and arrange the intervention.

Withdrawal of Subjects

A patient would be withdrawn from the intervention if they were to become acutely manic, psychotic or suicidal or no longer wishes to continue. The reasons for withdrawal would be recorded. Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAE's, SUSAR's, protocol violations, cure, administrative reasons or other reasons. 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 intervention efforts will be made to continue to obtain all follow-up data as per protocol, with the permission of the patient.

Expected Duration of Trial.

The trial will last 6 months from randomisation to last follow up.

7. Trial Procedures

By Visit

Describe the sequence of procedures to be performed at each visit as detailed in the time/event flowchart in section.2.3.

Laboratory Tests

None required

8. Assessment of Efficacy

Parameter	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Efficacy Parameter To compare the rate of recruitment and adherence to the treatments in both groups	Number of participants recruited per month Adherence to the protocol This includes the number of length of naps in the active intervention.	At Week 1 At Week 1
Secondary Efficacy Parameter To compare the effects of the following measures in both groups		
1) Hamilton Depression Rating Scale	An observer rated measure of depression	Baseline, rebaseline and at 1, 2, 4, 8 weeks and 6-month post-randomisation.
2) Clinical Global Impression and Improvement Scale (Guy, 1976)	An observer rated measure of global severity	Baseline, rebaseline and at 1, 2, 4, 8 weeks and 6-month post-randomisation.
3) Quick Inventory of Depressive Symptomatology – SR version (Triveni et al, 2004).	A subjective measure of depression	Baseline, rebaseline and at 1, 2, 4, 8 weeks and 6-month post-randomisation.
4) Brief Ruminative Response Scale (Topper et al, 2014).	A measure of ruminative style	Baseline, and at 1, 2, 4, 8 weeks and 6-month post-randomisation.
5) Pittsburgh Sleep Index (Bysse et al, 1999)	A measure of sleep disturbance	Baseline, and at 1, 2, 4, 8 weeks and 6-month post-randomisation.
6) Euroquol 5D (EQ5-D) (1990).	A measure of quality of life	Baseline, and at 1, 2, 4, 8 weeks and 6-month post-randomisation.
7) Wrist actigraph from GeneActiv daily for 3 days pre-randomisation and 7 days post-randomisation.	A measure of the sleep/wake activity, which correlates with the gold standard of sleep physiology (polysomnography).	Baseline, and at 1 week post-randomisation. Baseline, and at 1 week post-randomisation
8) Sleep diary daily for 3 days pre-randomisation and 7 days post-randomisation.	A subjective measure of total sleep time	
9) The credibility of the intervention and expectation of whether their mood will improve rapidly (Devilly, 2000).	A measure of the credibility of the intervention	Baseline
10) Amount of anti-depressant drugs (in mg of anti-depressant equivalents) (Hayasaka et al, 2015) or	Any additional treatment received	Baseline, and at 1, 2, 4, 8 weeks and 6-month post-randomisation

benzodiazepine drugs (in mg of diazepam equivalents 11) The amount of Cognitive Behaviour Therapy or any other counselling or psychotherapy (number of hours) 12) Reported side effects at 1 week.	Any additional treatment received Any reported side effects	Baseline, and at 1, 2, 4, 8 weeks and 6-month post-randomisation At 1, 2, 4, 8 weeks and 6-month post

Procedures for Assessing Efficacy Parameters

The procedures are questionnaire based apart from the Actigraphy. This consist of a band worn around the wrist.

9. Assessment of Safety

Specification, Timing and Recording of Safety Parameters.

Sleep Deprivation has no reported side effects apart from tiredness. For light therapy, a few people may experience nausea or headache after beginning treatment. (In healthy individuals bright light therapy was not associated with any significant difference in side effects compared to dim light therapy (Botanov, 2013). However, patients with any significant side effects may be asked to reduce the exposure time by 10 minutes. Triple Chronotherapy may theoretically trigger a manic episode, but patients with bipolar disorder are excluded and so this should be rare. We will however warn the patient and carer of this rare possibility.

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.

Reporting Responsibilities

All SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator to the REC and Sponsor.

9.1.1 Adverse events that do not require reporting

Symptoms such as tiredness, nausea, headache as described above do not require reporting. An episode of mania may be regarded as Adverse Reaction.

Stopping Rules

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

10. Statistics

Sample Size

N=30 equally randomized to each group is usually adequate for a feasibility study exploring the rates of recruitment and attrition (Browne,1995). We will explore the data for an estimate of effect size to determine consistency with previous studies.

Randomisation

The method of randomisation will consist of simple randomisation based on a constant allocation ratio of 1:1. It will be stratified according to the season.

Analysis

We will explore the means and SDs of outcomes to help inform the power analysis for a larger RCT of clinical and cost effectiveness of adding triple chronotherapy in depression. Follow-up will be maximised to prevent missing data by reminding participants at each visit of the importance of collecting data. Participants will be telephoned when they do not provide follow up data. The reasons for missing data will be recorded. Missing data for the primary outcome will be handled by multiple imputation to estimate missing outcome data. The self-report depressive symptom measures will be used in the imputation process.

11. Trial Steering Committee

There is no trial Steering Committee as this is a feasibility study with no significant risks.

12. Data Monitoring Committee

There is no Data Monitoring Committee as this is a feasibility study with no significant risks.

13. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits and REC review by providing the Sponsor(s), and REC direct access to source data and other documents (eg patients' case sheets, blood test reports, X-ray reports, histology reports etc).

14. Ethics & Regulatory Approvals

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

This protocol and related documents will be submitted for review to XXXXXX Research Ethics Committee (REC)

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

15. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed by the study team. Reports will be made on progress of the trial and any violations by the research worker to the Chief Investigator and Trial Management Committee.

16. Data Handling

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

Patient data will be anonymised.

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

17. Data Management

An anonymised paper and electronic CRF will be used, which will be based on the outcome measures and demographic data. Participants are asked to consent to their data being shared anonymously with other researchers. They are also asked to consent to their General Practitioner being informed of participation in the study including any necessary exchange of information between their GP and the research team.

18. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

19. Insurance / Indemnity

Insurance an indemnity is arranged by the South London and Maudsley NHS Foundation Trust

20. Financial Aspects

Funding to conduct the trial is provided by King's Health Partners.

21. Signatures

_____

Chief Investigator 1/7/2017

David Veale

N/A

_____ _____

Statistician (if applicable) Date

Print name

22. References

Al-Karawi, D, Jubair, L. Bright light therapy for nonseasonal depression: Meta-analysis of clinical trials. J Affect Disord. 2016 Jul 1;198:64-71. doi: 10.1016/j.jad.2016.03.016

Amick, H. R., Gartlehner, G., Gaynes, B. N., Forneris, C., Asher, G. N., Morgan, L. C., . . . Gaylord, S. (2015). Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: systematic review and meta-analysis. *BMJ, 351*, h6019.

Ayuso-Mateos, J. L., Vázquez-Barquero, J. L., Dowrick, C., Lehtinen, V., Dalgard, O. S., Casey, P., . . . Dunn, G. (2001). Depressive disorders in Europe: prevalence figures from the ODIN study. *The British Journal of Psychiatry, 179*(4), 308-316.

Bech, P., Allerup, P., Gram, L., Reisby, N., Rosenberg, R., Jacobsen, O., & Nagy, A. (1981). The Hamilton depression scale. *Acta psychiatrica scandinavica, 63*(3), 290-299.

Benedetti, F., Barbini, B., Fulgosi, M. C., Colombo, C., Dallaspezia, S., Pontiggia, A., & Smeraldi, E. (2005). Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. *J Clin Psychiatry, 66*(12), 1535-1540.

Benedetti, F., & Colombo, C. (2011). Sleep deprivation in mood disorders. *Neuropsychobiology, 64*(3), 141-151.

Botanov, Y, Ilardi, SS (2013). The Acute Side Effects of Bright Light Therapy: A Placebo-Controlled Investigation. PLOS One. ttps://doi.org/10.1371/journal.pone.0075893

Browne, R. H. (1995). On the use of a pilot sample for sample size determination. *Statistics in Medicine, 14*(17), 1933-1940.

Bysse D, Reynolds III C, Monk T (1989). The Pittsburgh Sleep Quality Index (PSQI): a new instrument for psychiatric research and practice. *Psychiatry Res.* 28:193-213.

Cuijpers, P., Donker, T., van Straten, A., Li, J., & Andersson, G. (2010). Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. *Psychol Med, 40*(12), 1943-1957. doi:doi:10.1017/S0033291710000772

Dallaspezia, S., van Jaarsveld, A. (2016). Anti-depresant chronotherapeutics in a drug free out-patients. Psychiatry Research, 241, 118-121

Devilly, G. J., & Borkovec, T. D. (2000). Psychometric properties of the credibility/expectancy questionnaire. *Journal of Behavior Therapy and Experimental Psychiatry, 31*, 73-86.

Gibbons, R. D., Hur, K., Brown, C. H., Davis, J. M., & Mann, J. J. (2012). Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. *Archives of general psychiatry, 69*(6), 572-579.

Gillin, J. C., Buchsbaum, M., Wu, J., Clark, C., & Bunney, W. (2001). Sleep deprivation as a model experimental antidepressant treatment: findings from functional brain imaging. *Depression and anxiety, 14*(1), 37-49.

Guy, W. (1976). Clinical global impression scale. *The ECDEU Assessment Manual for Psychopharmacology- Revised* (pp. 612). Washington DC: U.S. Department of Health, Education, and Welfare.

Hayasaka, Y., et al., *Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials.* Journal of affective disorders, 2015. **180**: p. 179-184.

Hoflich, G., Kasper, S., Moller, H.J., 1992. Successful treatment of seasonal compulsive syndrome with phototherapy. Ner- venartz 63, 701–704.

Hooper, C. L., & Bakish, D. (2000). An examination of the sensitivity of the six-item Hamilton Rating Scale for Depression in a sample of patients suffering from major depressive disorder. *Journal of Psychiatry and Neuroscience, 25*(2), 178.

Horne, J. A., & Ostberg, O. (1975). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International journal of chronobiology, 4*(2), 97-110.

Lam, R. W., Levitt, A. J., Levitan, R. D., Michalak, E. E., Cheung, A. H., Morehouse, R., . . . Tam, E. M. (2016). Efficacy of bright light treatment, fluoxetine, and the combination in patients

with nonseasonal major depressive disorder: a randomized clinical trial. *JAMA Psychiatry, 73*(1), 56-63.

Martiny, K., Refsgaard, E., Lund, V., Lunde, M., Sørensen, L., Thougaard, B., . . . Bech, P. (2012). A 9-week randomized trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depressive disorder patients treated with duloxetine. *J Clin Psychiatry, 73*(9), 1234-1242.

Martiny, K., Refsgaard, E., Lund, V., Lunde, M., Sørensen, L., Thougaard, B., . . . Bech, P. (2013). The day-to-day acute effect of wake therapy in patients with major depression using the HAM-D 6 as primary outcome measure: Results from a randomised controlled trial. *PloS one, 8*(6), e67264.

Martiny, K., Refsgaard, E., Lund, V., Lunde, M., Thougaard, B., Lindberg, L., & Bech, P. (2015). Maintained superiority of chronotherapeutics vs. exercise in a 20-week randomized follow-up trial in major depression. *Acta psychiatrica scandinavica, 131*(6), 446-457.

Martiny, K, Lunde M, Undén M, Dam H, Bech P. The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression. Psychol Med. 2006 Sep;36(9):1247-52

Moscovici, L., & Kotler, M. (2009). A multistage chronobiologic intervention for the treatment of depression: a pilot study. *Journal of affective disorders, 116*(3), 201-207.

Neumeister, A., Goessler, R., Lucht, M., Kapitany, T., Bamas, C., & Kasper, S. (1996). Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. *Biological Psychiatry, 39*(1), 16-21.

O'Sullivan, R. L., Fava, M., Agustin, C., Baer, L., & Rosenbaum, J. (1997). Sensitivity of the six-item hamilton depression rating scale. *Acta psychiatrica scandinavica, 95*(5), 379-384.

Phillips KA, Hollander E, Rasmussen SA, Aronowitz BR, DeCaria C, Goodman WK. A severity rating scale for body dysmorphic disorder: development, reliability, and validity of a modified version of the Yale-Brown Obsessive Compulsive Scale. Psychopharmacol Bull. 1997;33(1):17-22.

Revah-Levy, A, Birmaher, B, Gasquet, I, Falissard, B (2007). The Adolescent Deperssion Rating Scale: a validation study. BMC Psychiatry, 7:2, DOI: 10.1186/1471-244X-7-2

Sahlem, G. L., Kalivas, B., Fox, J. B., Lamb, K., Roper, A., Williams, E. N., . . . El Sabbagh, S. (2014). Adjunctive triple chronotherapy (combined total sleep deprivation, sleep phase advance, and bright light therapy) rapidly improves mood and suicidality in suicidal depressed inpatients: an open label pilot study. *Journal of Psychiatric Research, 59*, 101-107.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. J Clin Psychiatry. 1998;59 Suppl 20:22-33

Topper M, Emmelkamp PM, Watkins E, Ehring T (2014). Development and assessment of brief versions of the Penn State Worry Questionnaire and the Ruminative Response Scale. Br J Clin Psychol. 53(4):402-21. doi: 10.1111/bjc.12052.

Trivedi, MH, Rush, J et al (2004) The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med. 2004 Jan;34(1):73-82 and http://www.ids-qids.org

Wu, J. C., Kelsoe, J. R., Schachat, C., Bunney, B. G., DeModena, A., Golshan, S., . . . Bunney, W. E. (2009). Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biological Psychiatry, 66*(3), 298-301.

23. Appendixes

This section should contain all pertinent documents associated with the management of the study. The following lists a few examples of potential attachments:

- Patient Information Sheet
- Consent Form