Testing the Effectiveness of an Evening Blue-depleted Light Environment in an Acute Psychiatric Ward

Statistical Analysis Plan

Version 1.0

STATISTICAL ANALYSIS PLAN for BAB-study

Administrative information

Sponsor name	St Olavs Hospital
Sponsor address	St. Olavs Hospital, Department Østmarka Trondheim, Norway, 7040
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SAP revision history

The SAP was developed based on the published protocol.

SAP version	Date changed	Comments
0.1	17.06.21	Stian Lydersen drafted analysis plan for primary outcome
0.2	01.07.21	Melanie Rae Simpson drafted SAP based on published protocol and analysis plan for primary outcome
0.3	27.08.21	Draft revised to include details about planned analyses for secondary and safety outcomes variables.
1.0	29.09.21	Minor revisions after discussions between study team and statisticians, including: clarification of recruitment and randomisation procedure (§2.2) and additional analysis for secondary outcomes (§5.2.4)

Signatures

	Name	Title	Signature	Date
Written by:	Melanie Rae Simpson	Statistician	M. SIMPSON	5th Oct 2021
Reviewed by:	Stian Lydersen	Trial statistician	S Lydersen	6th Oct 2021
Approved by:	Håvard Kallestad	Principle investigator		7th Oct, 2021

Abbreviations

AE	Adverse Event
BVC	Brøset Violence Checklist
CGI	Clinical Global Impression Scale
CGI-S	Clinical Global Impression Scale, Severity subscale
CONSORT	Consolidation Standards of Reporting Trials
CRF	Case Report Form
HES	Headache and Eye Strain Scale
ICD10	International Classification of Disease 10
iCGI-I	Improved Clinical Global Impression Scale, Improvement subscale
IMP	Investigational Medical Product
ITT	Intention-to-treat
LED	Light-emitting diode
NTNU	Norwegian University of Science and Technology
NW	Nocturnal awakenings
PP	Per protocol
PSG	Polysomnography
RCT	Randomised controlled trial
REK	Regional Etisk Komite (Regional Ethical Committee)
SAP	Statistical Analysis Plan
SE%	Sleep efficiency (percentage of time in bed spent asleep)
SOAS-R	The Staff Observation Agression Scale-Revised
SOL	Sleep onset latency
SPIRIT	Standard Protocol Items for Randomised Trials
TST	Total sleep time
WASO	Wake after sleep onset
AE	Adverse Event
BVC	Brøset Violence Checklist
CGI	Clinical Global Impression Scale
CGI-S	Clinical Global Impression Scale, Severity subscale
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Table of contents

1. Introduction

This Statistical Analysis Plan (SAP) should be read in conjunction with the published trial protocol [1] (Available at: https://doi.org/10.1186/s13063-019-3582-2). The information available here provides a more detailed description of the "Statistical analysis" section.

1.1 Purpose and scope of the statistical analysis plan

This document details the proposed analysis of the main paper(s) reporting results from the trial Testing the Effectiveness of an Evening Blue-depleted Light Environment in the Acute Psychiatric Ward. These main paper(s) will follow the strategy set out here. Any deviations from the analyses outlined in this SAP will be described and justified in the final report of the trial, including the inclusion of any analyses suggested by journal editors and referees. Modifications will be carefully considered and, as far as possible, will follow the broad principles set out here.

First and foremost, this SAP describes the analysis of the primary and secondary outcomes. Subsequent exploratory analyses are also expected to follow the broad principles of this SAP but are not described in detail here. Additionally, there is a parallel study being conducted investigating the experience of staff employed on the wards and the analyses planned for this study are not covered here.

The details presented here shall not prohibit accepted practices, such as data transformation prior to analysis. When possible, such data management and modelling decisions will be undertaken prior to revealing the treatment allocation.

The final analysis strategy will be available on request when the principal papers are submitted.

1.2 Background and rationale for the trial

There is increasing recognition of the need to stabilize sleep-wake cycles in individuals with major mental disorders. As such, clinicians and researchers advocate for the use of interventions targeted at sleep and circadian dysrhythmias as an adjunct to the standard treatments offered for acute illness episodes of a broad range of diagnoses. This project explored the benefits of admitting individuals with major mental disorders to an acute psychiatric inpatient unit where changes in light exposure are integrated into the therapeutic environment of a new psychiatric unit.

1.3 Objectives

1.3.1 Primary objective

The trial will test whether the environment with programmable lighting conditions offers any additional benefits beyond those associated with standard treatment in an acute psychiatric inpatient unit. Specifically, participants will be allocated to a ward with a lighting system that produces an environment with blue-depleted evening light or to a ward with the same layout and facilities but lacking the new lighting technology. The main objective is to examine if there is any difference between groups in the mean duration of hospitalization.

1.3.2 Secondary and exploratory objectives

The secondary objectives of this trial are to explore whether the blue-depleted evening light conditions influences are particularly beneficial in certain diagnostic subgroups, as well as the effect on the level of symptoms, functioning, episodes of suicidality or aggressive behaviour, medication usage, and self-reported side effects differ between groups and whether a shorter duration of admission is associated with greater stability of sleep-wake cycles and circadian rhythms.

2. Study design

2.1 Study design

This is a single-centre, unblinded, two-arm, parallel-group, pragmatic effectiveness randomised controlled trial (RCT).

2.2 Randomization and treatment assignment

A detailed description of the randomisation procedure can be found in the published protocol. Briefly, there will be a 1:1 block randomisation with varying block sizes, using the webCRF program (developed and managed at the Clinical Research Unit Central Norway). Patients who may need admission to the acute psychiatric hospital unit will initially be assessed by other health professionals (general practitioners, out-of-hours emergency services, and other somatic and psychiatric hospital departments). If hospitalisation is deemed necessary, patients will be directed to the acute admissions facility. For the purposes of the trial, patients will be randomised prior to arrival at the unit (i.e. prior to any psychiatric assessment at the acute unit). Clinical considerations may mitigate against following the random allocation procedure, in which cases some participants may be withdrawn immediately from the trial (see section §3.2.2).

2.3 Determination of sample size

The sample size calculation is described in detail in the published protocol[1].

2.4 Framework

This trial is designed to establish the superiority of blue-depleted evening lighting environment compared to normal lighting on the duration of admission to acute psychiatric wards:

- The primary null hypothesis is that the duration of admission does not differ between the lighting environment group
- The primary alternative hypothesis is that the duration of admission differs based on the lighting environment.

There is only one primary outcome in this trial. The other efficacy analyses will be regarded as secondary or exploratory.

2.5 Statistical interim analyses

No interim analyses were planned or performed.

2.6 Timing of final analysis

Data was collected until 14 days after the last participant was randomised. Participants who were still admitted at this time were considered as discharged with their length of stay ending on this date.

2.7 Data sources and timing of endpoint assessments

The primary outcome is duration of admission which is assessed upon discharge. Other secondary and exploratory outcomes are assessed either daily or upon discharge (See Table 1 in the published protocol[1]). Data will be obtained from two main sources: Electronic patient records and Xethru radar sensors as described in the published protocol.

The Xethru radar sensors will be used to obtain data on each patient's sleep-wake cycle. As described in the published protocol, developed algorithms will be used to estimate the total sleep time (TST), sleep onset latency (SOL), number of nocturnal awakenings (NW), wake after sleep onset (WASO), and sleep efficiency (SE%)[2].

3. Statistical principles

3.1 Confidence intervals and p-values

All efficacy and safety estimates will be presented with two-sided 95 % confidence intervals. Accompanying two-sided p-values will be calculated and compared to a 5 % significance level. No adjustments for multiplicity will be made since there is only one primary null hypothesis in this trial. This is in line with "Guideline on multiplicity issues in clinical trials EMA/CHMP/44762/2017".

3.2 Adherence, protocol deviations and protocol violations

Randomised individuals may withdraw or be withdrawn from the allocated treatment group for various reasons as outlined in the published protocol, or they may not be adherent to the light conditions. The published protocol did not distinguish between withdrawals from the intention-to-treat and per protocol analyses, which are clarified in the following sections.

3.2.1 Adherence

For individuals allocated to the blue-depleted light conditions, adherence with the intervention is assessed using an item checklist to record any exposure to normal lighting (duration and reasons), whether blue-blocking glasses were worn as appropriate (e.g., when exiting the unit) and whether blue-blocking filters were employed on media devices.

3.2.2 Withdrawn from study

Randomisation occurs at the point of admission which means that all withdrawals are post-randomisation. Participants withdrawn from the study for the following reasons will be removed from further analyses:

Immediately post randomisation:

- Lack of availability of rooms for the allocated light-condition
- Clinical imperative: A senior clinician decides that admission to the allocated room is inappropriate, e.g. due to case mix within the ward, staff-to-patient ratios

Any time during admission:

- Unwilling to give written informed consent at any time during admission
- Unable to give informed consent for the duration of the stay
- Consent procedure was incomplete
- Declines participation at any stage during the study

3.2.3 Protocol deviations

During the admission withdrawal may occur because:

- The participant is absent for >24 hours from the ward to which they were randomised, for example due to transfer to another hospital for medical/somatic reasons. Any participant who is absent from the ward voluntarily is considered to have been discharged and if they were to return they would be re-randomised and recorded as another admission.
- Clinical concerns regarding an individuals' participation

These scenarios will be considered protocol deviations, and the participants will be removed from any per-protocol analyses (see also §3.3.2).

3.3 Analysis populations

3.3.1 Intention-to-treat population

The intention-to-treat (ITT) population will include all participants who were randomised and provided informed written consent and excluding those withdrawn for reasons outlined in §3.2.2.

3.3.2 Per-Protocol Analysis Set

The per protocol analysis set will include all participants in the ITT population who were hospitalised for at least two consecutive evenings, and who had no protocol deviations (§3.2.3).

3.3.3 Subgroup definitions

A number of baseline characteristics have been identified *a priori* as both predictive of the length of stay and possible sources of treatment effect heterogeneity. These include the variables specified in §5.1

3.4 Allocation concealment and blinding

3.4.1 Allocation concealment

As described, all admitted patients will be randomised prior to arrival at the unit.

3.4.2 Blinded statistician

The analyses will be performed by the trial statistician who will be masked to the lighting conditions experienced by each group for the primary analysis and as far as practically possible for subsequent analyses. This document details the analyses planned *a priori* along with the anticipated assumption checks of the chosen analysis models. These model assumption checks and decisions about the final model will be performed prior to unblinding of the statistician and, if necessary, detailed in an amendment to the SAP that will be published with together with the trial results.

4. Presentation of study population

4.1 Screening data, eligibility, recruitment and withdrawal

All participants admitted during the trial period will be randomised. A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be used to summarise the number of participants as shown in the published protocol. Reasons for withdrawal post-randomisation will be summarised per treatment arm.

4.2 Baseline patient characteristics

As described in the protocol, the following participant demographics and baseline characteristics to be summarised include:

- Demographics: Age, sex, ethnicity, marital status, living situation, years of education, employment status
- Current diagnosis or diagnoses, according to International Classification of Disease 10 (ICD 10) at discharge
- Type of admission (voluntary or involuntary)
- Previous admission history: number of admissions, total number of inpatients bed-days in the 2 years prior
- Details of current presentation based on health records: sleep problems during previous month, level of functioning, alcohol and substance misuse, risk of or actual harm to self or others, current physical health
- Past psychiatric and forensic history, and history of comorbid illnesses

These demographics and baseline characteristics will be tabulated for each treatment arm and overall using descriptive statistics:

- Continuous variables: N, mean and standard deviation, and median and 25^{th} and 75^{th} percentiles as appropriate
- Categorical variables: counts and percentages for categorical variables.

No formal statistical comparisons of baseline characteristics will be conducted.

5. Analysis

5.1 Analysis of primary outcome

The primary outcome is duration of admission in days in the ITT population. Some patients will be re-admitted and re-randomized during the study period. As such, we plan to use a two-level linear mixed-model with duration of stay as dependent variable, with admissions within patient as level 1, and patient as level 2. The primary covariate is group (blue-depleted evening lighting versus normal lighting condition). We will adjust the analyses for a set of pre-specified baseline variables which can be strong predictors of the outcome, as generally recommended by Kahan et al[3] and Vittinghoff et al[4].

These covariates are:

- Age
- Sex
- Diagnosis (categorized as psychotic episodes/disorders, manic episode, severe depressive episode, or none of these)
- Comorbidities (categorized as alcohol/substance use disorders, borderline or other personality disorders, or none of these two)
- Involuntary versus voluntary status at admission
- Number of admissions in the previous 2 years
- Number bed-days in the previous 2 years.

If the model fails to converge using a two-level model we will consider at single-level model.

As this primary outcome is heavily skewed and not normally distributed, we anticipate the use of bootstrapping with the bias-corrected and accelerated (BC_a) method and B=5000 bootstrap samples. If this results in unpractical long computing time, we will use a lower number of bootstrap samples, such as B=1000.

5.1.1 Missing data

The primary outcome is based on hospital records of date of admission and date of discharge and will have no missing data. Similarly, the baseline variables included in the adjusted model should not have any missing data, perhaps with the exception of the number of admission and numbers of bed-days in the previous 2 years if the patient has recently moved to the Trondheim region. If this occurs, we anticipate that very few participants will have missing information for these variables. The need to employ missing data strategies, such as multiple imputations, will be considered depending on the proportion of missing information.

5.1.2 Subgroup analyses and treatment effect heterogeneity

To assess for treatment effect heterogeneity, subgroup analyses will be performed based on the covariates listed above (§5.1). For continuous covariates (age, number of previous admissions and duration of previous admissions), we will assess the appropriateness of including these in the mixed linear regression model with an interaction term for investigating treatment effect heterogeneity.

5.1.3 Additional analyses

The primary analysis and subgroup analyses will also be performed on the per protocol population.

5.2 Analysis of secondary outcomes

Table 1: Overview of secondary outcomes and their planned analyses

Secondary outcomes	Time(s) recorded	Timepoint / timeframe for analysis	Planned analysis	Brief description of recorded data
Clinical assessments and treatment during admission				
Sleep wake cycle parameters	Daily	During admission	Linear	Algorithm estimated variables (from Xenthru radar sensors)
Clinical Global Impression Scale – Improvement (iCGI-I) - During admission (day-to-day change) - Change from admission	 Daily Discharge	 During admission At discharge	 Linear Linear	Range: -6 (maximum deterioration) to 6 (ideal improvement)
Clinical Global Impression – Severity sub scale (CGI-S)	Baseline and discharge	At discharge	Linear	Likert scale with range: 1 (Normal, not at all ill) to 7 (Among the most extremely ill patients)
Suicide risk	Daily	During admission	Logistic	One item clinical assessment
Need for continuous observation (due to suicide risk)	Daily	During admission	Logistic	One item clinical assessment
Risk of harm to others (Brøset Violence Checklist)	8-hrly	During admission	Linear	6 item scale assessing 6 observable behaviours scored on binary scale. Risk of violence based on total scores: low = 0; moderate = 1-2, higher >2
Staff Observation Agression Scale-Revised (SOAS-R)	Daily	During admission	Linear	Context and severity of aggressive incidents recorded on scale with range 0 to 100 (0 = not severe, 100 = very severe)
Medication use	Daily	During admission	Logistic/Linear[a]	Daily doses and classes of medication recorded
Change in admission status	Daily	During admission	Logistic[b]	Changes from involuntary to voluntary and *vice versa* will be recorded
Patient-related experiences and other outcomes				
Adherence (item checklist)	Daily	During admission	Logistic	Duration and reason for exposure to normal lighting; use of blue-blocking glasses on exiting unit and filters on media devices
Satisfaction and benefits	Discharge	At discharge	Linear	10 items scored on 5-point Likert scale (1 = low satisfaction)

[a]We will first consider use of anxiolytic and hypnotic medication in addition to the frequency of extra medication that is taken as required (pro re nata). The dosage, frequency and changes in the use of different medication classes will be considered in exploratory analyses later; [b]Change in admission status will be investigated both as the proportion of involuntarily admitted patients who change to voluntary admission, and the number of days of involuntary admission.

5.2.1 Analysis of continuous secondary outcomes

For continuous variables measured only at discharge (iCGI-I and measure of satisfaction), between group comparisons will be conducted using linear regression adjusting for the same covariates as the in the primary analysis.

The remaining continuous variables are measured two or more times per admission, and these will be analysed using a mixed linear regression model. Where possible, we will use a three-level linear mixed-model with respective secondary outcome as the dependent variable, timepoint (or day of admission) as level 1, admissions within patient as level 2, and patient as level 3. The covariates will include treatment allocation, the prespecified baseline variables and an interaction term between treatment and day of admission. If the model fails to converge, we will consider removing the interaction term and or reduce the number of levels.

5.2.2 Analysis of binary secondary outcomes

Binary secondary outcomes recorded on a daily basis will be analysed using a three-level mixed logistic regression model with the same levels and covariates as described in the mixed linear models above (§5.2.1). Depending on the convergence of the model and frequency of the outcomes, these variables may be simplified into a single binary variable across the entire admission (for example, a binary variables representing suicide risk any time during the admission).

5.2.3 Missing data

We anticipate a high level of missing data for some secondary outcome variables. Under the assumption that they are "missing at random", the estimates produced by the mixed regression analyses should provide unbiased estimates of the effect of the lighting conditions on these secondary outcomes. For secondary outcomes that cannot be analysed using mixed regression modelling (i.e. those with only one measurement or those simplified to a single summary measure), we will use multiple imputations to handle missing data as appropriate.

5.2.4 Additional analyses

Subgroup analyses based on psychiatric diagnostic groups are planned for each of the secondary outcomes. Other exploratory subgroup analyses for on the covariates listed in §5.1 will also be considered, particularly if they are found to be important sources of treatment effect heterogeneity for the primary outcomes. These subgroup analyses may be presented in subsequent manuscripts after publication of the primary trial results.

5.3 Analysis of safety outcomes

As specified in the published protocol, the frequency of any side effects or adverse events will be recorded during the trial period. The eight-item Headache and Eye Strain (HES) Scale will be specifically used at discharge to measure adverse effects due to lighting conditions[5], along with another eight-item scale reflecting side effects of acute psychiatric treatments. The average value of these scores will be compared between groups using a t-test. Other reported adverse events will be summarised as binary variables and analysed using Chi-squared test. This will include an analysis of the proportion of patients which were transferred from their allocated ward after clinical opinion. For any adverse events occurring multiple times per participant per admission we will consider alternative statistical analyses such as Poisson regression.

5.4 Analysis of exploratory outcomes

Planned exploratory analyses to assessed in subsequent papers include:

- Causal mediation analyses to determine if improvement in sleep variables and intra-individual variability in sleep variables mediate the effect of the blue-depleted lighting conditions on duration of admission and risk of harm to self or others
- The dosage, frequency and changes in the use of different medication classes will be considered in exploratory analyses later

6. Reference

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