

HEALTH ECONOMIC ANALYSIS PLAN (HEAP)

DREAMS START

VERSION 1.0, 8TH DECEMBER, 2023

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Version 0.3 Comments from Penny Rapaport and Gill Livingston included.

Version 0.4 Comments from Julie Barber included.

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Version 1.0, 8th December 2023. Signed

Approved by:

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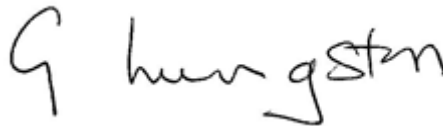
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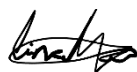
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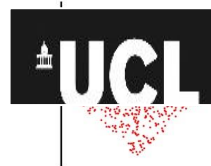


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1. AIM

1.1 Purpose and Scope of the Plan

This health economic analysis plan presents the proposed health economic analyses for the DREAMS START study.

The aim of this health economic analysis plan is to outline the methods that will be used for the economic evaluation of the trial intervention. This document intends to establish the rules and principles to guide the analysis and report of the economic analysis of the trial. It should be read in conjunction with the study protocol and statistical analysis plan.

1.2 Study Background

The Lancet Commission on dementia and our systematic review of evidence up to June 2017 found no conclusive evidence that any therapy to treat sleep disorders is effective. A Cochrane review of pharmacotherapies found no conclusive randomised controlled trial (RCT) evidence for people with dementia. Hypnotic drugs can have adverse effects, including increased daytime sedation, falls and mortality in older adults.

Pharmacological interventions, including melatonin, are not recommended as treatments and studies consistently indicate that patients and their doctors prefer non-drug approaches for sleep problems. Dementia is often characterised by circadian rhythm disruption that is at least partly due to progressive loss of SCN neurons. Strengthening circadian rhythmicity through bright light therapy is theoretically appealing, but light therapy delivered to everyone at a standard time, whether they require extra light or not may exacerbate sleep disruption and agitation. As sleep disturbances in people with dementia have mixed causes, it makes sense that promising interventions are multi-component.

The DREAMS START intervention is delivered to family carers, who implement strategies to reduce the person with dementia's sleep disturbances. It uses natural daylight (where feasible) and if necessary, timed phototherapy to strengthen and stabilise sleep-wake

timing. Additionally, it, alerts carers to consider pain, uses strategies to increase comfort, reduce anxiety, increase daytime activity and CBT for sleep management, which Cochrane reviews found effective for older adults and family carers of people with dementia.

Participants will include family carers and people with dementia of any type, severity or any or no medication will be included in the trial, except for those who currently excessively drink alcohol (see full inclusion and exclusion criteria in the study protocol for more information).

Researchers will aim to recruit 370 family carer-people with dementia dyads from memory services, older adult mental health services and primary care in NHS Trusts supported by local Clinical Research Networks (CRNs) and from JDR (Joint Dementia Research).

Participants will be randomly allocated to the intervention arm and the TAU arm, 185 participants in each arm. Those in the treatment arm will be given six sessions being delivered remotely weekly or fortnightly for 3 months, the sessions will cover understanding sleep and dementia, making a plan using actigraphy watches to generate information on activity patterns and timed phototherapy, using light boxes, daytime activity and routine, difficult night-time behaviours, taking care of your own (carer's sleep), and using strategies that work for the future.

The sessions will be delivered by trained facilitators, those are trained graduates in psychology belonging to NHS band 4 and 5 mainly.

Treatment as usual (TAU) varies according to where the person living with dementia is being treated and their individual needs but incorporates NICE guidelines for dementia and consists of assessment, diagnosis, symptomatic interventions, risk assessment and management, advice and information. Currently, there is not a consistent approach for the treatment of sleep difficulties for people with dementia.

In this way, the trial represents a comparison of DREAMS START + TAU vs. TAU. Patients will be followed up at 4 and 8 months. An extension with 24 months post-randomisation follow-up has also been agreed but does not form part of this HEAP.

The primary outcome is the Sleep Disturbances Inventory (SDI) (person with dementia) at 8 months. Details of the analysis of this outcome are given in the SAP version 2, 21st November 2023.

Secondary outcomes include quality of life: DEMQOL-Proxy (person with dementia); Health Status Questionnaire, HSQ-12 (Carer); daytime sleepiness: Epworth Sleepiness scale; ESS; Client Service Receipt Inventory (CSRI) and EQ-5D 5-level self-reported and proxy (EQ-5D-5L); neuropsychiatric symptoms –NPI; carer’s sleep: sleep condition indicator SCI; carer’s mood: Hospital Depression and Anxiety Scale HADS; carer’s burden: Zarit Burden interview ZBI. This HEAP only includes only the Client Service Receipt Inventory (CSRI) and EQ-5D 5-level proxy (EQ-5D-5L); Quality Adjusted Life Years (QALYs) from DEMQOL-Proxy and EQ-5D-5L.

1.3 Health Economic Objective

The aim of the health economics component of the DREAMS START intervention is to evaluate the cost-effectiveness of the intervention (DREAMS START + TAU) compared with TAU only.

The primary outcome of this analysis will be the incremental cost-effectiveness ratio (ICER) of DREAMS START+TAU compared with TAU using trial data at 8 months from a health and social care perspective, using the EQ-5D-5L proxy to calculate QALYs in line with NICE guidance.

Table 1. Objectives and outcomes measures addressed by Health Economics Analysis Plan

Objectives	Outcome measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
To quantify the intervention costs of DREAMS START	Any training, supervision and associated training costs and consumables for the trained facilitators to deliver the 6 sessions.	Trial record of intervention, training and supervision delivery

	Quantify participants' attendance and duration of DREAMS START sessions and associated facilitator's time.	
To compare the effect of DREAMS START + TAU vs. TAU on health care resource use in carers and people with dementia	Primary care, community health, hospital visits, social care or emergency services. Personal care and help at home, or accommodation changes, medications, and any other information collected using client services receipt inventory (CSRI).	4 and 8 months asking about previous 4 months with baseline adjustment
To compare the effect of DREAMS START + TAU vs. TAU on health-related quality of life in carers and people with dementia.	People with dementia: EQ-5D-5L proxy DEMQOL-Proxy Carers: EQ-5D-5L	Baseline, 4 and 8 months and area under the curve to calculate QALYs
To compare the effect of DREAMS START + TAU vs. TAU on wider societal costs	Work productivity and impairment (WPAI) questionnaire and the Valuation of Informal Care Questionnaire (iVICQ)	4 and 8 months asking about previous 4 months with baseline adjustment

	Out-of-pocket costs and the cost of help from unpaid carers.	
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This will be calculated using a within trial analysis (comparing intervention and TAU groups) to calculate the mean incremental cost per QALY over **8 months** using the EQ-5D-5L proxy to calculate QALYs. The primary analysis for this will be from the health and social care cost perspective. A secondary analysis from a wider societal cost perspective will also be conducted. Other secondary analyses will include a calculation of QALYs using the DEMQoL proxy and associated utility algorithm.

All analyses will follow the assumptions made in the statistical analysis plan version 2 regarding missing data and loss to follow-up.

Sensitivity analyses will be conducted accounting for loss to follow up and missing data as described below (Sensitivity analyses).

2. ANALYSIS PLAN

2.1 Perspective

The main analysis will take a healthcare and personal social services (PSS) perspective.

Secondary analysis will take a societal perspective, incorporating the results of the productivity and valuation of informal care questionnaire. The time horizon will be 8 months.

2.2 Demographics

Information about the family carer

1. Age, sex, marital status, employment, ethnicity, first language, education and living arrangements, type of accommodation.

2. Relationship to person with dementia

Information about the person with dementia

1. Diagnosis of dementia, type of dementia (DLB + Parkinson's+ Vascular / other types), and baseline HSQ physical health score
2. Age, sex, marital status, employment, ethnicity, first language, education, living arrangements, type of accommodation, if they are in receipt of home care services.

2.3 Economic measurements

Training and set up cost

The fixed cost of training will be determined by looking at study records of the quantity and grade of the trained facilitators attending the two-day online training sessions on dementia and sleep-wake regulation, as well as additional hours on supervision and the delivery of DREAMS START. These records will include time spent by both the trainer and the trainees, preparation time, attendance incentives (if any). On top of the above mentioned, we will include sign off role pay for facilitators before it was ensured they could deliver. Only people who went on to deliver the intervention will be included in the costs.

Cost of delivery of intervention

Study records of each participant's attendance and modality (face to face, remotely, or by phone) at DREAMS START will be gathered, on top of the actigraphy watches and light boxes, in order to calculate the cost of the delivery of the intervention.

Health and social care resource use

Individual patient's health care resource use will be collected at baseline and 4 and 8 months after randomization using the self-reported modified version of the client service receipt inventory (CSRI), capturing information on health care resource use involving

medications, primary care, secondary care including emergency care, inpatient and outpatient contacts and social care including publicly funded care homes and respite.

Wider resource use

The wider perspective analysis will include out of pocket costs, unpaid help from family/friends, carer time taken off work to care for their relative and any voluntary care services. The average time spent per month on unpaid help will be calculated from responses to the CSRI, and iVICQ on unpaid carer time for different activities.

The WPAI will be used to calculate employment and productivity related costs in relation to absenteeism and presenteeism.

The total cost for each participant with dementia will be estimated as the sum of the cost of resource use items consumed. All costs will be reported in 2022-2023 pounds sterling.

Costing of resource use

The Unit Costs of Health and Social Care (PSSRU, 2022) is a national standard for health and social care unit costs that will be used to cost staff time spent training and delivering the intervention.

Resource use will be costed using PSSRU and national reference costs (NHS Improvement, 2022). The British National Formulary (NICE, 2020) will be used to determine the costs of prescription drugs.

Carer's time absences from work due to sleep will be taken directly from the WPAI and iVICQ. Unpaid carers will be costed as the equivalent cost of social care providing assistance on the basis that if the help were not able to be provided by unpaid carers, social care staff or home care workers would need to provide the service.

The total productivity loss will be calculated as the sum of time both productivity effect and absence from work. Productivity costs will be estimated based on average hourly salaries by gender and age group from national statistics source (**Leaker, 2023**) combined with the total productivity loss.

For patients who die between follow-ups we will assess the suitability of entering 0 for costs, or if sufficient information is available to estimate costs from follow-up until death i.e., cause of death registered in the database and any care home costs.

Statistical Analysis

Resource use and mean cost per patient for DREAMS START +TAU versus TAU will be reported by type of service use at baseline and 4- and 8-months follow-up and (a) for patients that have completed the measures at each time point; (b) using multiple imputation for the ITT results for mean costs (see below).

The difference in costs at 8 months between DREAMS START +TAU and TAU will be calculated with linear mixed effects multiple regression model which allows for clustering by facilitator in the intervention arm. Intervention group, site and baseline costs will be included as fixed effects. 95% CIs will be calculated based on bootstrapped bias corrected results (Briggs et al 1997). Only the ITT difference will be reported.

Effects

Effectiveness will be estimated in QALYs, calculated as the area under the curve over the 8-month follow up.

EQ-5D-5L

EQ-5D-5 level (EQ-5D-5L) proxy is a generic measure of health-related quality of life. Carer proxy responses will be used to calculate QALYs and incremental cost per QALY gained. This is a five item, five level questionnaires, scored 1 (no problems) to 5 (extreme problems).

The EQ-5D-5L will also be used to assess the health-related quality of life of carers.

Value sets corresponding to the responses participants give to the items are available from EuroQol and the paper published by Devlin (2018).

Mean utility value and mean unadjusted QALYs for baseline, 4 and **8 months** will be reported for both groups.

QALYS will be calculated as the area under the curve. Participants who die between time-points will be entered as 0 at the date of death and any subsequent time points. The incremental difference in QALYs at 8-months between DREAMS START +TAU and TAU will be calculated with linear mixed effects multiple regression model which allows for clustering by facilitator in the intervention arm. Intervention group, site and baseline utilities (Hunter et al 2015) will be included as fixed effects. 95% CIs will be calculated based on bootstrapped bias corrected results (Briggs et al 1997). Only the ITT difference will be reported.

EQ-5D-5L responses are also collected for carers at baseline, 4 and 8 months and will be used to calculate QALYs in a secondary analysis.

DEMQOL Proxy

The overall DEMQOL score is computed by adding up items 1-28 and provides a score between 4 and 112, with higher scores indicating better quality of life.

QALYs will be calculated based on family carer responses to the DEMQOL proxy using the DEMQOL-U-proxy classification system (Mulhern et al., 2013). Means and QALYs will be reported as above for the EQ-5D-5L proxy.

2.4 Economic analysis

2.4.1 Cost-effectiveness analysis

All analysis will be conducted using intention-to-treat principles, comparing the two arms as randomized and including all patients in the analysis where practical.

Data cleaning and missing costs and outcomes

Data cleaning will include correction of obvious response errors to enable unit costing or utility calculation, and simple imputation of data missing minor details based on reasonable assumptions or reasonable interpretation. Any areas of uncertainty will be discussed and referred with the trial team and clinical experts. Data missing status will be explored and assessed by the percentage of data missing for cost and effectiveness items.

Multiple imputation statistical methods will be used to predict missing costs and outcomes.

The primary analysis will be ITT. For patients where insufficient information is available to calculate an ICER (they are missing data required for costs or QALY calculation at one or more timepoints) we will examine the data for predictors of missingness assuming that data are missing at random. If predictors of missingness can be identified these will be used to impute data using multiple imputation by chained equations (Van Buuren et al 1999). The primary ICER, CEAC and CEP will be reported based on imputed results, seemingly unrelated regression and the methodology set out in Leurant et al (2018).

2.4.2 Discounting

Given that the analysis is for an 8-month time horizon no discounting is required.

2.4.3 Incremental cost-effectiveness ratio (ICER)

We will report the mean incremental cost per QALY gained between the DREAMS START + TAU arm vs. TAU only at **8 months**.

The primary analysis will use a 2-step bootstrap with bias corrected and accelerated standard errors.

Costs and QALYs will be analysed within the 2-step bootstrap as specified above and will include the cost of health and social care resource use in both arms, the cost of the DREAMS START + TAU intervention will be included for the intervention arm only. These will be used to calculate the adjusted mean costs and QALYs for the intervention and control and 95% confidence intervals.

Cost-effectiveness acceptability curve (CEAC) and cost-effectiveness plane (CEP).

The bootstrapped coefficients will be used to calculate the probability that the DREAMS START + TAU intervention is cost-effective compared with TAU only for a range of cost-effectiveness thresholds for one QALY gained. A cost-effectiveness plane will show the bootstrapped results.

2.4.4 Secondary analyses

Cost-effectiveness from a wider societal perspective

We will report the ICER, CEP and CEAC for the DREAMS START + TAU intervention vs. TAU only at **8 months**, from a wider societal cost perspective (see section 2.3 wider resource use above) using the methods described in the primary analysis but including wider societal costs on top of health and social care resource use for both interventions.

QALYs calculated using the DEMQOL

We will run the same analysis as in section 2.4 calculating QALYs based on proxy responses to the DEMQOL and using the algorithm for the DEMQOL-U. This will be done from a health and social care as well as wider cost perspective.

Including carer QALYS

An analysis where carer QALYs are added to those of the participants' (based on proxy EQ-5D-5L) will be included, will be conducted from a societal perspective in line with the analysis set out in section 2.2.

2.4.5 Sensitivity analysis

A number of sensitivity analyses will be performed to test the impact of changing assumptions on the ICER.

We will vary the cost of the DREAMS START intervention such as:

- The frequency of supervision and number of researchers per supervision group
- Including people who received the training but didn't go onto to deliver the intervention in the costs of the intervention.
- The number of sessions delivered
- The NHS band from mentees and mentors.
- Difference proportions of participants receiving the intervention face-to-face, by phone and at home.

3. REFERENCES

Banerjee, S., et al., DEMQOL - Evaluation of a new system for measuring quality of life in people with dementia: Validity, reliability and use in regular practice. *Neurobiology of Aging*, 2004. 25: p. S321-S321.

Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Econ* 1997;**6**:327-40.

Mulhern, B., Rowen, D., Brazier, J., Smith, S., Romeo, R., Tait, R., Watchurst, C., Chua, K.C., Loftus, V., Young, T., Lamping, D., Knapp, M., Howard, R., & Banerjee, S. Development of DEMQOL-U and DEMQOL-PROXY-U: generation of preference-based indices from DEMQOL and DEMQOL-PROXY for use in economic evaluation. *Health Technol Assess*. 2013. 17(5):v-xv, 1-140.

The primary analysis will use a non-parametric 2-stage bootstrap (TSB) to account for the relationship between costs and outcomes (Gomes et al., 2012).

Debra Leaker, C.R. (2023) *Earnings and employment from pay as you earn Real time information, UK: September 2023, Earnings and employment from Pay As You Earn Real Time Information, UK - Office for National Statistics*. Available at: <https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworking/hours/bulletins/earningsandemploymentfrompayasyouearnrealtimeinformationuk/september2023>

Devlin, N. J., Shah, K. K., Feng, Y., Mulhern, B., & van Hout, B. (2018). Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health economics*, 27(1), 7–22. <https://doi.org/10.1002/hec.3564>

Herdman, M., Gudex, C., Lloyd, A. et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* **20**, 1727–1736 (2011). <https://doi.org/10.1007/s11136-011-9903-x>

Hunter, R. M., Baio, G., Butt, T., Morris, S., Round, J., & Freemantle, N. An Educational Review of the Statistical Issues in Analysing Utility Data for Cost-Utility Analysis. *PHARMACOECONOMICS*. 2015; 33 (4), 355-366.

Leurent B, Gomes M, Faria R, Morris S, Grieve R, Carpenter JR. Sensitivity Analysis for Not-at-Random Missing Data in Trial-Based Cost-Effectiveness Analysis: A Tutorial. *Pharmacoeconomics*. 2018;1–13. Available from: <http://link.springer.com/10.1007/s40273-018-0650-5>.

National Institute for Health and Care Excellence. (2022). *NICE health technology evaluations: the manual*. <https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation>

PSSRU. Unit Costs of Health and Social Care, 2022. Available at: [Unit Costs of Health and Social Care programme \(2022 – 2027\) | The new home for the Unit Costs of Health and Social Care report \(pssru.ac.uk\)](https://pssru.ac.uk/unit-costs-of-health-and-social-care-programme-2022-2027-the-new-home-for-the-unit-costs-of-health-and-social-care-report)

NICE, 2022. Introduction to health technology evaluation: Nice health technology evaluations: The manual: Guidance. [Online] Available at: <https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation>

NICE. British National Formulary, 2020. Available at: <https://bnfc.nice.org.uk/2020>

NHS improvement. Archived Reference Costs, 2020. Available at: <https://improvement.nhs.uk/resources/reference-costs/2020>

Van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med*. 1999;18(6):681-94.