CLEVER

Cognitive Level Enhancement through Vision Exams and Refraction

A randomized controlled trial (RCT) to assess the impact of near and distance spectacles on reducing rates of cognitive decline with aging in community-dwelling older people in India

STUDY AIM

The aim is to determine whether free near and distance glasses provided to older adults living in or near Hyderabad, India, aged ≥ 60 years, with under- or un-corrected refractive error and normal baseline hearing and cognition (HMSE > 18), can reduce rates of cognitive decline, measured by a global cognitive score from the LASI-DAD cognitive testing battery over 36 months.

OBJECTIVES

- To assess the impact of glasses for distance and near on the cognitive decline among the community-dwelling elderly in India
- To assess the impact and cost-effectiveness of glasses for distance and near on the quality of life, falls, depression, social interaction, and physical activity in the among the community-dwelling elderly in India

The objectives of qualitative component:

- Co-developing a Theory of Change that shows what stakeholders think is needed for a successful trial
- Understanding prevalent views on normal or expected changes accompanying aging
- Analysing perceptions of the value of good vision for older adults
- Exploring current and changing patterns of elder care, including policy changes, in India and Telangana state/Hyderabad
- Exploring how the COVID pandemic has affected elder care
- Verifying the incentives planned for optimal recruitment and retention of trial participants
- Conducting a process evaluation of the trial.

This is a mixed-methods study, with the RCT being the main component and qualitative research being done to a) provide contextual information during the pilot testing stage of the trial and b) complete a process evaluation of the trial.

MAIN STUDY QUESTION

Will provision of near and distance spectacles significantly slow cognitive decline in older adults with under- or un-corrected refractive errors and normal baseline cognition and hearing?

SETTING

Peri-urban/rural areas of the city Hyderabad, in the state of Telangana in India. Participants will be recruited from the community.

PARTICIPANTS

Inclusion criteria:

≥ 60 years age, impaired distance (< 6/12) and/or near (< N8 at 40 cm) presenting vision in the better-seeing eye due to un- or under-corrected refractive error.

Exclusion criteria:

Impaired baseline cognition (HMSE score ≤ 18); Non-refractive cause(s) of vision impairment; Severely impaired mobility (immobile/bedridden/in a wheelchair/using walker); Severe medical illness; Self-reported hearing impairment and/or inability to hear and repeat short Telugu phrases.

Eligible participants will be transported to the clinic set in Gullapalli Pratibha Rao Campus, L V Prasad Eye Institute, Hyderabad.

SAMPLE SIZE

Imputing three-year un-intervened decline in the outcome variable (LASI-DAD global score from cross-sectional, age-stratified data, at 29% effect size, from the ACHIEVE study), 502 participants give 90% power at $p = 0.05$ (two-tailed). With annual follow-up loss=13% (based on estimation from previous studies done in India), 759 (rounded to 760) total participants are needed across the two study groups. With a 60% prevalence of uncorrected distance and/or near refractive error, the total number of people needing to be screened is estimated at 1,266 (rounded to 1300).

RANDOMIZATION

The randomization sequence will be generated by the study statistician at the Clinical Trials Unit at LVPEI using an online random number generator

(www.randomization.com) and concealed until a participant is determined eligible and agrees to participate.

MASKING

- **Intervention:** All participants randomized to the intervention group will be provided with free near and/or distance spectacles based on the results of refraction. Replacement glasses will be provided in case of broken or lost spectacles. Participants will undergo annual eye exams and refraction, and a change of glasses will be prescribed as needed.

- **Controls:** All participants randomized to the control group will receive a prescription for spectacles and will be given free near and/or distance glasses as needed at study closeout.

MASKING

CLEVER is an open-label trial where all participants are aware of the intervention. The trial participants are non-masked to the intervention as it is considered unethical to provide Plano spectacles to the control groups. Controls will receive a prescription, and the intervention group will receive the spectacles to correct their refractive error. All participants in the control group will receive a free pair of eyeglasses after the study to optimally correct the near and distance refractive errors unless they have obtained such glasses on their own during the study

MAIN STUDY OUTCOME

Three-year change in cognition measured by LASI-DAD global cognitive score

SECONDARY OUTCOMES

The CLEVER trial aims to determine whether free near and distance glasses for the elderly can improve quality of life, reduce falls, reduce depression, improve social interaction and physical activity in a cost-effective manner over 36 months.

TECHNIQUE FOR MEASUREMENT OF MAIN OUTCOME AND SECONDARY OUTCOMES

The primary analysis will be conducted on all outcome data obtained from all enrolled participants as randomised, i.e., intention-to-treat analysis. Per-protocol analysis will also be conducted as secondary analysis, analysing participants according to treatment they actually received. A detailed Statistical Analysis Plan will be completed and approved before data collection is final.

- Primary Outcomes
  (i)   Name of the outcome: Change in cognition

  (ii) The metric or method of measurement to be used: LASI-DAD global cognitive score

  (iii) Timepoint(s) of primary interest: 36 months

- Key Secondary Outcomes
  (i) Name of the outcome: Quality of life, Falls, depression, glasses compliance, cost effectiveness, social interaction/isolation, self-reported physical activity.

  (ii) The metric or method of measurement to be used:
    º Domain-specific cognitive function
    º Quality of life: WHOQOL BREF
    º Falls: Quick screen
    º Depression: PHQ9
    º Cost effectiveness
    º Eyeglasses adherence: Self report and observation by study personnel
    º Social interaction/isolation: Social Networking Index
    º Self-reported physical activity: Global Physical Activity Questionnaire (GPAQ)

(iii) Time point(s) of primary interest: 36 months, with primary and secondary outcomes collected every 12 months – ie at 12, 24 and 36 months

CAPACITY BUILDING PARTNERSHIPS

ALZHEIMER'S AND RELATED DISORDERS SOCIETY OF INDIA

CLEARLY INITIATIVES

GEORGE INSTITUTE FOR GLOBAL HEALTH

JOHNS HOPKINS UNIVERSITY

L V PRASAD EYE INSTITUTE

L V PRASAD EYE INSTITUTE CLINICAL TRIALS UNIT

NATIONAL INSTITUTE OF MENTAL HEALTH AND NEURO SCIENCES

NORTHERN IRELAND CLINICAL TRIALS UNIT

THE CHEN YET-SEN FAMILY FOUNDATION

UNIVERSITY OF MICHIGAN

QUEENS UNIVERSITY BELFAST

BASELINE DATA (POTENTIAL PREDICTORS OF OUTCOME)

Age, gender, education, visual acuity, refractive error in both eyes, ocular examination to rule out other ocular abnormalities, medical disorders, hearing impairment, cognitive tests, mobility, falls, quality of life, depression, social interaction and physical activity.

DESCRIPTION OF ANY QUALITATIVE WORK

The qualitative portion of the CLEVER study aims to provide information on the context and culture in which the CLEVER trial will be conducted. This information can help with the delivery, evaluation and possible scale-up of the trial account. The qualitative study uses a mixed-methods design, collecting data with several qualitative methods. These include document review, in-depth interviews, and facilitated workshops with stakeholders plus the interpretive phenomenological approach.

OUTLINE OF MAIN ANALYSIS

The primary analysis will use a significance level of <0.05 and will compare the change in LASI-DAD global cognitive score (primary outcome, with sensitivity analysis including and excluding vision-dependent tests) between groups using a 2-sample t-test. Both the raw comparison, and the comparison adjusting for potential determinants of change in cognitive status, such as baseline cognitive score, age, sex and education (further covariates will be detailed in the SAP) using general linear models. Similar methods will be used for other time-points and secondary outcomes that are continuous data.

A health and social care perspective will be adopted for the main analysis and a societal perspective in a sensitivity analysis. Planned sub-group analyses will include literacy levels, need for near vs distance glasses, age, gender and baseline cognitive status.

Exploratory subgroup analyses will be reported using 99% CI. General Linear models will be used with interaction terms (treatment group by subgroup) for the subgroups Stratified on domain-specific cognitive scores ,Compare those receiving distance correction (and also myopia vs hyperopia, if power permits) vs presbyopia glasses vs mixed correction, Gender-disaggregated analysis. Full details of the analyses will be given in the Statistical Analysis Plan.

PILOT STUDY

Prior to main study, a pilot study would be conducted on 20 participants to standardize the protocols and flow of participants.

TRIAL MANAGEMENT AND OVERSIGHT

An independent Data Monitoring and Ethics Committee (DMEC) will been established, whose remit will be to review the trial's progress. The DMEC is independent of the trial organisers. Interim analyses will be supplied, in strict confidence, to the DMEC, as frequently as the Trial Steering Committee (TSC) Chair requests. The DMEC Charter and Operating Procedures will be agreed before their first meeting. Meetings of the committee will be arranged periodically, as considered appropriate by the TSC Chair. In the light of interim data on the trial's outcomes, adverse event data, accumulating evidence from other trials and any other relevant evidence, the DMEC will inform the TSC if in their view there is evidence beyond reasonable doubt that the data indicate that any part of the protocol under investigation is either clearly indicated or contra-indicated, either for all participants, or for a particular subgroup of trial participants. Unless modification or cessation of the trial is recommended by the DMEC, the TSC, investigators, collaborators and administrative staff will remain ignorant of the results of the interim analysis. The accumulating trial data by step and interim analyses will be confidential and will only be viewed by the TSC upon the recommendation of the DMEC. The TSC will not be routinely privy to these interim reports. The DMEC will make recommendations to the TSC based on the interim data. Collaborators and all others

associated with the study may write to the DMEC to draw attention to any concern they may have about the possibility of harm arising from the treatment under study. The TSC Charter and its relationship to the DMEC will be discussed and agreed prior to the start of recruitment.

TIMELINE

- Protocol development and approvals: 12 months June, 2021-June, 2022
- Recruitment: 3 months
- June, 2022 to August, 2022
- Experiment: 35 months
- September, 2022 to July, 2025
- Analysis and report writing (not including peer review and approval): 17 months Aug, 2025 to Dec, 2026

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