**Study protocol registered at Umin CTR**

UMIN000014559, registered date: 2014/07/15

### Basic information

<table>
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<tr>
<th>Official scientific title of the study</th>
<th>A randomized controlled trial to determine the short-term influence of cataract surgery on circadian biological rhythm and related health outcomes</th>
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<tr>
<td>Title of the study</td>
<td>The CLOCK-IOL Study</td>
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<td>Cataract Surgery and Circadian Biological Rhythm among Japanese Older People with Cataract in Nara, Kansai Region: Influence of Intra Ocular Lens Implantation</td>
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### Condition

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<td>Classification by specialty</td>
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<td>Genomic information</td>
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### Objectives

<table>
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<th>Narrative objectives</th>
<th>To determine whether cataract surgery modifies the internal biological rhythm and improves its related health outcomes such as depression, sleep quality, body mass regulation and glucose/lipid metabolism at 3 months after surgery.</th>
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<tr>
<td>objectives2 Efficacy</td>
<td>Confirmatory</td>
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### Assessment

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<th>Primary outcomes</th>
<th>Depressive symptoms assessed using the short version of geriatric depression scale (GDS-15)</th>
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<tr>
<td>Secondary outcomes</td>
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<tr>
<td></td>
<td>1) Objective sleep quality (measured using actigraph)</td>
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<td></td>
<td>2) Subjective sleep quality (Pittsburgh Sleep Quality Index :PSQI)</td>
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This Statistical Analysis Plan (ASP) of the CLOCK-IOL study was previously published. (Trials 2014;15(1):514)

The CLOCK-IOL Study about the short-term influence of cataract surgery on circadian biological rhythm and related health outcomes: study protocol for a randomized controlled trial

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Background
Light information is the dominant stimulus synchronising the master clock internal biological clock at suprachiasmatic nuclei (SCN) with the external environment. The internal biological rhythm of humans is close to that of the earth’s rotation, according to a study of the rhythm of core body temperature independent of the external environment [1]. The misalignment of biological rhythm and external environment is associated with many health problems. Epidemiological studies among shift workers suggest that circadian misalignment is significantly associated with the increased risk of sleep disturbance [2], depression [3], obesity and metabolic syndrome [4, 5], diabetes [6, 7], ischaemic heart disease [8, 9] and stroke [10]. Light information modifies the timing of the internal biological rhythm according to the phase response curve to light [11]. Light exposure in the early morning (after core body temperature minimum) is responsible for the subsequent phase advance in melatonin secretion; in contrast, light in the evening (before core body temperature minimum) is responsible for the subsequent phase delay. Simultaneously, the amplitude of the internal biological rhythm is modified
by light information [12]. In contrast to visual light information received by rod and cone cells of the retina and transmitted via the optic nerve, non-visual light information is mainly perceived by recently discovered intrinsically photosensitive retinal ganglion cells (ipRGCs) which contains melanopsin, and is transmitted to SCN via the retinohypothalamic tract (RHT) [13]. The action spectrum for melatonin suppression among humans showed a peak at a shorter wavelength (464 nm) than that for visual information (approximately 555 nm) [14].

Cataracts are an important cause of visual impairment and a leading cause of blindness worldwide. The World Health Organisation reported that 33% of visual impairment (representing 95 million people) and 51% of blindness (representing 19.9 million people) are due to cataracts [15]. Among age-related cataract patients, the light transmission at the most sensitive spectrum for the photic entrainment of internal biological rhythms decreases from 82% at 10 years to 23% at 80 years [16]. Circadian misalignment because of the decreased input of light information caused by cataracts may explain the higher prevalence of depression among cataract patients [17], and the association of decreased light transmission by lens yellowing, with sleep disturbance [18].

The research hypothesis of the present study is that cataract surgery, which removes the clouded lens and implants an artificial intraocular lens (IOL), will increase the input of non-visual light information and improve circadian alignment and its related health outcomes, such as depression, sleep disturbances, body mass regulation and glucose/lipid metabolism [19]).

The hypothesis is supported by studies of bright light intervention and light exposure in real-life situations. A Cochrane systematic review showed a significant reduction of depressive symptoms (standardised mean difference −0.20, 95% CI, −0.38 to −0.01) from meta-analysis of 18 randomized controlled studies (RCTs) among 505 patients with non-seasonal depression [20], and another systematic review also revealed the significant effectiveness of bright light intervention and light exposure among seasonal affective disorders (8 RCTs, 132 patients) [21]. In addition, recent RCTs revealed the effectiveness of bright light therapy on depression, accompanied by improved sleep quality and internal biological rhythm. Bright light therapy (pale blue light 7500 lux for 1-h) significantly decreased depressive symptoms compared with the placebo control group (red dim light 50 lux) among 89 patients with non-seasonal depression, and was accompanied by an increase in salivary melatonin in the evening and better actigraphic sleep parameters [22, 23]. An intervention to increase light exposure by installing a ceiling light in the shared living room in group care facilities significantly decreased depressive symptoms, and increased total sleep time assessed by actigraph among elderly participants. In addition, a significant interaction of light intervention and melatonin administration on sleep efficiency was observed [24]. Higher day light exposure increase melatonin secretion at night according to an interventional study [25] and our population-based observational study [26].
Short-term and long-term influence of cataract surgery on depression and subjective sleep quality has been reported by some observational studies. Compared with depressive symptoms assessed before cataract surgery, significant decreases in depressive symptoms were reported at 2 months [27, 28], 3 months [29] and 1 year [30] after surgery. In addition, improved subjective sleep quality was reported at 1 month [31], 2 months [32, 33] and 9 months [34] after surgery. However, evidence from RCT on the effect of cataract surgery on depressive symptoms, sleep disturbance and internal biological rhythms is lacking.

In contrast to bright light therapy conducted during the daytime, cataract surgery may increase the input of light information not only in the daytime but also during the night-time. Increased input of light information during the night-time may be deleterious to health outcomes. Indeed, we found significant cross-sectional association of increased light at night with increased prevalence of obesity, dyslipidaemia [35], sleep disturbance [36] and depression [37] in real-life situations among elderly individuals. These associations are supported by previous experimental evidence [38-40].

Here, we will conduct a parallel-group, assessor-blinded, simple randomized controlled study comparing the intervention group with the control group at 3 months after surgery, to determine whether cataract surgery modifies the internal biological rhythm and improves its related health outcomes such as depression, sleep quality, body mass regulation and glucose/lipid metabolism.

Methods and design
All intervention associated with the present study is conducted at Nara medical University hospital. The protocol of this study has been registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; trial ID: UMIN000014559). The CLOCK-IOL (Cataract Surgery and Circadian Biological Rhythm among Japanese Older People with Cataract in Nara, Kansai Region: Influence of Intra Ocular Lens Implantation) study was approved by the Institutional Review Board of Nara Medical University (No.13-032). This research complies with the Declaration of Helsinki. Before enrolment to this study, we will obtain written informed consent from all participants.

Design
We continuously include participants through the year with similar speed, and inclusion of the present study will finish at the same date as the started year. After baseline measurements, all participants will be randomly allocated to intervention group and control group with 1:1 ratio without restriction such as blocking and stratification. The outcomes among intervention group will be measured at 3 months after surgery. Among control group, the outcomes will be measured at 3 months after baseline. Control group will receive delayed cataract surgery shortly after outcome measurement (Figure 1).
We will assess the eligibility of patients diagnosed as having cataracts in Nara Medical University Hospital for the present study according to the following inclusion and exclusion criteria.

**Inclusion criteria:**
- patients scheduled for the first cataract surgery
- age $\geq 60$ years
- cataract with grade $\geq 2$ nuclear opacification according to lens opacities classification system III [41]

**Exclusion criteria:**
- Major depression with current therapy
- severe mental illness and dementia
- severe corneal opacities with difficulty in assessment of lens opacity or fundal examination
- glaucoma with visual field deficit of at least Mean Deviation $> 14$dB (Humphrey Perimeter)
- vitreous haemorrhage
- proliferative diabetic retinopathy
- macular edema
- age-related macular degeneration
- patients needing immediate cataract surgery
- patients needing combined cataract and glaucoma surgery or combined cataract surgery and vitrectomy

**Intervention**
Before the cataract surgery, the axial length of the eye will be measured with the A-scan UD-6000 (Tomey, Nagoya, Japan). For cataract surgery, yellow aspherical IOL (SN60WF, Alcon, Fort Worth, TX, USA), yellow spherical IOL (SN60AT, Alcon, Fort Worth, TX, USA), and clear spherical IOL (SA60AT, Alcon, Fort Worth, TX, USA). The appropriate power of IOL will be estimated using the SRK/T formula for each IOL [42]. The kind of IOL used for cataract surgery was randomly allocated to yellow spherical IOL, yellow aspherical IOL, and clear spherical IOL with 1:1:2 ratios. After phacoemulsification with a small incision, IOL will be implanted.

**Patients of cataract surgery for both eyes**
We include participants with cataract surgery for single eye and participants for both eyes. The surgeries for both eyes among intervention group will be completed within the same time-scale in 1-2 weeks, and the same kind of IOLs will be used for both eyes. Outcomes will be measured at 3 months after the latest surgery.
Primary outcome
We will assess depressive symptoms as a primary outcome of the present study using the short version of geriatric depression scale (GDS-15). Prevalence of depression, median of GDS-15, and the mean value of difference between baseline and 3 months later will be compared between intervention group and control group.

Secondary outcomes
As secondary outcomes, we will measure subjective and actigraphic sleep quality, sleepiness, glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), body mass index (BMI), abdominal circumference, circadian rhythm of physical activity and wrist skin temperature, urinary melatonin metabolite, chronotype, post illumination pupil response (PIPR), visual acuity and subjective visual function.

Self-reported questionnaires
Depressive symptoms are measured using GDS-15 is a self-administered questionnaire consisting of 15 items [43]. The sensitivity and specificity of GDS-15 compared with diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 4th was 92.7% and 54.8% with cut-off point 4/5, and 84.8% and 67.7% with cut-off point 6/7, respectively [44]. According to meta-analysis about the validity of GDS-15, the mean sensitivity was 0.805 and the mean specificity was 0.750, respectively [45]. Higher score of GDS-15 was significantly associated with self-report and clinician-administered measures of suicidal ideation [46] and higher mortality of suicide [47]. Subjective sleep quality and daytime sleepiness are assessed using the Pittsburgh Sleep Quality Index (PSQI) [48] and the Epworth Sleepiness Scale (ESS) [49, 50], respectively. Chronotype and subjective visual function are determined by the “morningness–eveningness” questionnaire (MEQ) [51], the Munich Chronotype Questionnaire (MCTQ) [52] and the National Eye Institute visual function questionnaire (NEI VFQ25) [53, 54].

Analysis of venous blood sample
Overnight fasting venous blood samples will be analysed at a commercial laboratory (SRL Co. Inc., Tokyo, Japan) using standard clinical chemistry analysis to determine the concentrations of HbA1c, FPG, TG, LDL-C and HDL-C.

Morning spot urine
We will measure 6-sulfatoxymelatonin (aMT6-s) in a spot morning urine sample. Peak nocturnal plasma melatonin is significantly associated with aMT6-s in subsequent morning spot urine ($r = 0.69$) [55, 56]. Urinary 6-sulfatoxymelatonin concentration will be measured at a commercial laboratory.
Actigraph
Objective sleep will be measured by actigraph (ActiSleep-BT Monitor; ActiGraph Inc., FL, USA), worn on the non-dominant arm for 5 days, including weekdays and a weekend. Participants will be instructed to keep a standardised sleep diary logging bed time and rising time. Sleep parameters such as total sleep time, sleep efficiency, sleep onset latency and wake after sleep onset will be calculated with ActiLife 6 (ActiGraph Inc.). A validation study of this device showed moderate to high agreement with sleep parameters measured by polysomnograph [57].

Circadian rhythm of physical activity and wrist skin temperature
Invasively measured biomarkers usually used in laboratory settings, such as fluctuation of plasma cortisol, melatonin and rectal temperature, are difficult to conduct, because they disturb the normal life of participants. To assess the influence of cataract surgery on internal biological rhythms using non-invasive methods, we will measure the phase and amplitude of circadian activity rhythm and the wrist skin temperature.
According to large scale prospective cohort studies, decreased amplitude, later phase and decreased robustness of circadian activity rhythm showed a significantly higher hazard ratio for incidents of cognitive disorders, cancer mortality and all-cause mortality [58-60]. Wrist temperature reveals heat loss from arteriovenous anastomoses at the skin [61], and shows a mirror image of core body temperature [62] and blood pressure [63, 64]. The validity of using wrist skin temperature as an acceptable measure to assess circadian phase is indicated by the significant correlation of dim light melatonin onset and the increase of wrist skin temperature in the evening in real-life situations (r = 0.76) [65]. The wrist skin temperature at inside of the wrist, near the radial artery of the dominant arm will be measured using a temperature data logger (Thermochron iButton; Maxim/Dallas, Dallas, TX) at 3-min intervals [62].

Post-illumination pupil response (PIPR)
By pharmacological blockage of the rod and cone cells, the melanopsin-associated ganglion cell response is isolated as a slow, maintained depolarisation to light stimulation, which repolarises slowly after light-offset in vitro [66]. This PIPR is indicated as an index of the sensitivity of the melanopsin-containing ipRGC pathway [67]. In the present study, baseline and sustained pupil diameter after blue and red light stimulation will be measured. Baseline pupil diameter is the average pupil diameter in a 7-s period before light onset. Sustained pupil diameter is the average from 10 to 40 s after light offset. PIPR (mm), PIPR change (%), net PIPR (mm) and net PIPR change (%) will be calculated as follows: [68]
PIPR (mm) = Baseline pupil diameter (mm) − Sustained pupil diameter (mm)

PIPR change (%) = (PIPR/Baseline pupil diameter) × 100

Net PIPR (mm) = Blue PIPR − Red PIPR

Net PIPR change (%) = Blue PIPR change (%) − Red PIPR change (%)

Other variables
Using a standardised questionnaire, trained researchers will interview participants about basic characteristics, such as age, gender, smoking and drinking habits, past history of cardiovascular events, stroke, and cancer; medication; household income; years of education; and history of shift work. BMI will be calculated as weight (kg) per height (m2). Waist circumference will be measured at the level of the umbilicus in the standing position.

Sample size
According to the Heijo-kyo study a community-based cohort study among the elderly (mean age ± SD: 72 ± 7.1) in the same district as the present study, the prevalence of depression was 20.0% (101/506) [37]. To detect its 7% difference as significant at a two-sided α level of 5% with a power of 80%, it was calculated that 475 participants in each group would be required. Assuming a dropout of 5%, we estimated that a total of 1000 participants would be needed.

Randomization, masking
Allocation concealment will be maintained by central randomization using computer-generated random sequences, independent of care-providers. The results of allocation will be masked from the assessors of the outcomes, but will be available to both the care providers and the participants.

Statistical analysis
We will compare the outcomes between control group and cataract surgery group based on the intention-to-treat principle. For missing values due to loss to follow up after baseline measurement, we will impute baseline data using LOCF (Last-observation-Carried-Forward) method. For continuous variables with normal distributions, the mean and standard deviation will be reported. For variables not distributed normally, the median and interquartile range will be reported. Means, medians and proportions will be compared using the t test, the Mann–Whitney test and the χ2 test, respectively. We will use analysis of covariance to estimate adjusted mean values and 95% CIs. The prevalence of the two groups will be tested using multivariate logistic regression analysis. To assess the phase, amplitude and robustness of the circadian rhythm, we will use the cosinor model [69], the sigmoidally transformed cosine model [70] and the generalised additive model [71]. We will conduct subgroup analysis according to the severity of cataract and chronotype, at base line.
List of abbreviations
suprachiasmatic nuclei (SCN), intrinsically photosensitive retinal ganglion cells (ipRGCs), intraocular lens (IOL), randomized controlled studies (RCTs), the short version of geriatric depression scale (GDS-15), fasting plasma glucose (FPG), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), body mass index (BMI), post illumination pupil response (PIPR), 6-sulfatoxymelatonin (aMT6-s)

Reference
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**Study design**

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<th>Eligibility</th>
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<tbody>
<tr>
<td>Age-lower limit</td>
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<tr>
<td>Age-upper limit</td>
</tr>
<tr>
<td>Gender</td>
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| Inclusion criteria                | 1) severe mental illness and dementia  
|                                  | 2) severe corneal opacity  
|                                  | 3) glaucoma with visual field deficit of at least MD $> 14$dB (Humphrey Perimeter)  
|                                  | 4) vitreous haemorrhage  
|                                  | 5) proliferative diabetic retinopathy  
|                                  | 6) macular edema  
|                                  | 7) age-related macular degeneration  
|                                  | 8) patients needing emergent cataract surgery  
|                                  | 9) patients needing combined cataract and glaucoma surgery or combined cataract surgery and vitrectomy |

| Exclusion criteria                | Patients with disease as follows:  
|                                  | - Difficulty due to sever dementia or psychological disease to provide informed consent  
|                                  | - Severe cornea diseases  
|                                  | - Vitreous bleeding  
|                                  | - Glaucoma (Over moderate glaucoma which is graded with the Anderson classification)  
|                                  | - Retinal diseases  
|                                  | - proliferative DM retinopathy  
|                                  | - Macular edema  
|                                  | - Patients who need emergent cataract surgery. |

| Target sample size               | 1000 |