**[Recommended Form No. 38] STUDY PROTOCOL (For Human Subjects Research) ver4.0**

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| ***Public Institutional Review Board Designated by the Ministry of Health and Welfare*** |

**STUDY PROTOCOL**

**(For Human Subjects Research)**

ver1.1

Study Title: Patient Registry Study of Cognitive Impairment Patients Receiving Korean Medicine Treatment, Including Acupotomy, in Primary Clinic Settings

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**1. Background**

□ South Korea on route to becoming a super-aged society by 2025, with older adults making up 43.9% of the country’s population by 2060

○ According to the report of Statistics Korea, after seven years from the country having entered the 'aged society' in 2018, 43.9% of the country’s population will be made up of older adults by 2060.

○ Due to the decline in the working-age population (15-64 years old), the old-age dependency ratio, which refers to the number of individuals aged 65 years or older per 100 people of working age, was 21.7 in 2020, but it is expected to rise to 51.0 in 2036 and reach 91.4 in 2060.

- To provide financial aid for those aged 75 years or older, the amount of governmental support, including the Basic Pension, which refers to a non-contributory pension for aged Koreans, more than doubled from KRW 12.834 trillion in 2010 to KRW 28.96 trillion in 2016.

텍스트, 스크린샷, 그래프, 폰트이(가) 표시된 사진

자동 생성된 설명

□ Medical expenses for the elderly population accounted for more than 40% of total national medical expenses in 2018, and by 2025, as high as KRW 60 trillion will be spent as medical costs for older adults aged 65 years or older

□ As we face the reality of a super-aged society, there is a clear need for research on aging, aimed at promoting health aging of the population and improving the quality of life of the elderly population

○ There have been few effective therapies for treatment of age-related diseases, resulting in a growing emphasis on ‘healthy aging’\* where physical and mental health is preserved as we age through proactive measures of prevention and management.

\*WHO published the 'Decade of Healthy Ageing 2021–2030: Plan of Action'. Healthy aging is a continuous process of optimizing opportunities to maintain and improve cognitive and physical functional ability with low morbidity rate, enabling active engagement as a member of society. The concept is opposite to ‘general aging,’ where individuals experience various age-related diseases in their normal process of aging.

○ As aging has become a global phenomenon, research on aging has emerged as a new growth industry

- The global anti-aging market was valued at $62.5 billion in 2017, increasing to $88.6 billion (KRW 109 trillion) in 2022 with an average annual growth rate of 6.5%.

□ According to a report in 2019, 788,000 Korean senior adults aged 65 and over had dementia, pointing to the need for proactive management from the stage of mild cognitive impairment

○ According to the National Institute of Dementia of the Ministry of Health and Welfare (MOHW), as of 2019, the number of people with dementia aged 65 and over was 788,000, showing a clear trend of growth. In line with the increase in the dementia population, the cost of dementia management is expected to double every 10 years, and the social cost of dementia is expected to reach about KRW 78 trillion by 2050. In response, the Korean government announced the 'State Responsibility System for Dementia,' a national system for prevention and efficient treatment of and coping with dementia in 2017.

○ In addition, in recent years, as global pharmaceutical companies have gradually pulled out of their research efforts on development of new drugs for Alzheimer’s disease, there has been a growing interest in the treatment of cognitive impairment, which is the pre-dementia stage. Although there are variations in the published figures, it has been reported that 10-41% of the patients diagnosed with mild cognitive impairment (MCI) progress to develop dementia within one year. This indicates the necessity for proactive management and treatment from MCI, the pre-dementia stage.

□ Korean medicine treatment has been shown to be effective in cognitive impairment, but not included governmental plans for its treatment

○ In the case of dementia and cognitive impairment, which are neurological diseases associated with aging, measures to prevent gradual deterioration of cognitive function, manage behavioral and psychological symptoms, provide emotional support, and treatment options other than medications are required,

○ For reducing symptoms of senile dementia and cognitive impairment through improvement in cognitive function, behavioral and psychological symptoms, and provision of patient support, and family care, Korean medicine treatment has demonstrated effectiveness in certain areas. Therefore, the treatment and management of dementia by Korean medicine doctors (KMDs) in clinical practice will ensure an access to a variety of treatment options for the public, and provide benefits to cognitive impairment patients and high-risk groups .

□ Active implementation of Korean medicine treatment is required for patients with cognitive impairment or dementia

○ In 2011, with the enactment of Dementia Management Act and pursuant to Article 11, Paragraph 1 of the act, MOHW implemented the Dementia Screening Program for early detection of dementia, and Korean medicine (KM) institutions were excluded from the eligible medical institutions for provision of medical services for patients diagnosed with dementia.

○ That is, although the KM institutions had rights to diagnose dementia, rights for treatment of dementia were not granted within the dementia health center program. After checkup at dementia health centers, the designated hospitals and clinics benefited from strong national health insurance (NHI) coverage, and it has been almost 10 years that KM clinics were excluded from the area of dementia treatment.

○ Lack of evidence-based institutional entry has become an issue. There is an urgent need to create evidence that reflects the clinical field in order to reimburse drugs and strengthen coverage so that Han's medical technology can easily access patients with cognitive impairment. The issue was the lack of evidence base for KM institutions’ entry to the system. There is a pressing need for building evidence reflecting clinical practice so that herbal medicine preparations can be entitled for NHI reimbursement and increase the NHI coverage to provide easier access to medical knowledge and skills of Korean medicine for patients with cognitive impairment.

○ In 2022, the types of medical institutions that the general public visited to use the health service of Korean medicine were KM clinics (94.4%) and KM hospitals (12.4%). In the current settings of clinical practice, KM treatment is mainly provided at KM clinics, whereas KM research is mainly conducted at KM hospitals. There are differences in terms of patient characteristics and severity of the condition between the patients with cognitive impairment visiting KM hospitals and those visiting KM clinics. Accordingly, it is difficult to apply the results of research conducted and implemented at KM hospitals to KM clinics (the primary care centers). Therefore, there is a clear need to establish a cognitive impairment registry system by examining the patterns and effectiveness of KM treatment provided at KM clinics (as primary care centers) so as to build evidence for effectiveness of KM treatment for treatment of cognitive impairment. In addition, the characteristics of the patients visiting KM clinics (as primary care centers) and severity of their conditions can be examined.

□ Korean medicine presents a wide range of preventive and management measures for healthy aging

○ In Korean medicine, medical care to control the aging process is provided by controlling fundamental flow of energy in the human body through treatment modalities such as acupuncture, moxibustion, and herbal medicine, and effectiveness of Korean medicine for prevention and treatment of age-related diseases have been reported.

- With age, changes occur in various dimensions of biological rhythms of an individual such as hormone secretion, sleep patterns, body temperature maintenance, and blood pressure. These changes may lead to age-related diseases and interfere with the process of healthy aging.  
- In <Donguibogam (Principles and Practice of Eastern Medicine)> Sinhyeongmun (External Body) (身形門), various methods for healthy aging by living in accordance with the flow of nature and one's own biorhythm were presented, such as ‘taking care of the body according to the four seasons (四時節宣)’, ‘training the navel (煉臍法)’, ‘secret method of fuming on the navel (熏臍秘方)’, ‘moxibustion method (灸臍法)’, and ‘fetal breathing (胎息)’.

□ Implementation of local health center-based Korean Medicine Dementia Program related to cognitive impairment led by local governments

○ In 2016, the Seoul Korean Medicine Association secured KRW 500 million from the Seoul Metropolitan City budget to conduct a pilot program, and a total of 146 KM clinics participated in the 4-week/8-week program. As a result, the satisfaction score was 9.02 out of 10. The result of this pilot program, along with the State Responsibility System for Dementia, is the first step to build evidence toward expanding the areas of KM treatment. In addition to the leading example of Seoul, other local governments such as Busan Metropolitan City and Gyeonggi-do Province, have actively participated in the local health center-based Korean Medicine Dementia Program.

○ Among the 5-year plans for administration of state affairs by Moon Jae-in Administration, policies in the field of mental health were included. In line with the policy direction, a strong connection was developed between the strategies for state affairs including establishment of mental health promotion system and State Responsibility System for Dementia and KM dementia treatment guidelines (Table 1).

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| Details of systematic implementation | **Description** |
| Establishment of mental health promotion system | - Restructuring of mental health-related service delivery system, recruitment of mental health professionals, and improvement of working conditions  - Suicide prevention and diffusion of a culture of respect for life (Increase in the rate of mental health service utilization from 15% to 20% ) |
| State Responsibility System for Dementia | - From 2017, to start establishment of 252 Dementia Care Centers nationwide and increase the number of dementia specialty hospitals  - From 2018, to reduce the copayment rate (patient’s share for the cost) for patients with severe dementia and provide NHI reimbursement for the costs of expensive diagnostic tests  - To expand the reduction of copayment amount for dementia patients who are recipients of long-term care services |

□ Overview of the current progress on research related to cognitive impairment among older adults

(1) Current progress on the national cohort project and hospital cohorts (Clinical Research Center for Dementia of South Korea: CREDOS) related to cognitive impairment including senile dementia in conventional (Western) medicine

○ Currently, follow-up of the cohort for the nationwide registry study for the patients with senile dementia (Alzheimer’s Disease in the case of this cohort) has been ongoing since 2006. According to the dementia prevalence data provided by the National Institute of Dementia, the number of dementia patients in Korea is estimated to be about 840,000, and this figure is estimated to increase to 1.27 million and 2.71 million by 2030 and 2050, respectively

○ According to Health Insurance Review and Assessment Service (HIRA)'s analysis on the current status of dementia treatment based on nationwide data of medical service utilization for a total of 11 years from 2009 to 2019, the number of patients who received treatment due to dementia and the number of medical service utilization increased by 3.6 times and 5.5 times, respectively, and the increase in medical expenses was 7.3 times, which is considerably greater than the rate of overall medical expense growth of 3.4 times over the same period.

○ In addition, among the type of dementia, Alzheimer's disease ranked first in the total amount of medical care benefits among all diseases in 2018, which is about 1.4 times the cost of treatment for cerebral infarction, the disease that ranked second. In addition, according to the Department of NHI Policy Research under the Health Insurance Research Institute of National Health Insurance Service (NHIS), the third project of the ongoing 'Long-Term Care Elderly Cohort Study' has begun with the aim of providing evidence for policy development for 'Healthy Aging in Place' in the community.

(2) Current progress on Korean medicine technology development and intellectual property rights related to cognitive impairment among older adults

○ In Korean medicine, clinical symptoms of memory impairment, cognitive impairment, emotional and behavioral problems, and personality changes that are manifested in neurocognitive disorders are examined under categories such as dementia (癡呆), mental disease (呆病), amnesia (健忘), psychosis (癲狂), and exhaustion syndrome (虛勞).

○ The Pattern Identifications Tool for Dementia has not been standardized with objective evidence as yet, making it difficult to utilize the tool as a standardized tool for diagnosis in clinical settings. Accordingly, Lee et al. designed a scale for evaluation of the clinical symptoms of cognitive impairment into four patterns: Qi-deficiency (氣虛), Yin-deficiency (陰虛), fire-heat (火熱), and phlegm-retained fluid (痰飮) based on literature review and a survey of expert panel opinions, and developed the Pattern Identifications Tool for Cognitive Disorders (PIT-C) Ver. 2.1 through a clinical study. Subsequently, Lee et al. verified the reliability and validity of the developed PIT-C Ver. 2.1 through another clinical study.

(3) Current progress on Korean medicine research related to cognitive impairment among older adults

○ In a study investigating the effect of acupuncture on MCI patients, changes in brain activity and also the changes in clinical and neuropsychological indicators for cognitive function were observed by functional magnetic resonance imaging (fMRI). As a result, changes in brain activity were measured in about 20 brain regions of the patients who received acupuncture treatment. In addition, the scores of Clinical Dementia Rating (CDR) scale and Mini-Mental State Examination (MMSE) showed significant improvement in older adults who received acupuncture treatment.

○ A meta-analysis of clinical studies on acupuncture for amnestic MCI reviewed five clinical studies with 578 participants in total, and the acupuncture group showed higher clinical efficacy than the group treated with nimodipine, a calcium channel blocker that works by increasing the blood flow to injured brain tissue.

○ Acupotomy is similar to acupuncture, but combines the benefits of acupuncture and minimally invasive procedure by using a needle added with a scalpel function, with the needle tip being slightly flatter and thicker than the standard needles used for acupuncture. Acupotomy is frequently applied for musculoskeletal disorders, but Koo et al. presented a case report in which acupotomy was applied to a patient with MCI and symptoms of MCI were improved.

○ Herbal medicine has been reported as one of the most effective options with minimal adverse events among the available options of pharmacological treatments for MCI.

○ A clinical study investigating the efficacy of Shenwu, a herbal capsule, on amnestic MCI patients showed that the herbal medicine had the equivalent level of the effect of preventing memory decline up to 48 weeks to that of the patients who received donepezil. Also, fewer adverse events of gastrointestinal and neuropsychiatric systems were reported in the group treated with herbal capsules than the donepezil group.

□ For reducing symptoms of cognitive impairment through improvement in cognitive function, behavioral and psychological symptoms, and provision of patient support, and family care, KM treatment has demonstrated effectiveness in certain areas. Therefore, the treatment and management of cognitive disorder at KM clinics (as primary care centers), which is the type of medical institution most commonly visited for KM treatment will ensure an access to a variety of treatment options for the citizens of South Korea, and provide benefits to cognitive impairment patients and high-risk groups. However, to date, there have been no previous studies in Korean medicine that collected and analyzed data from KM clinics (as primary care centers) for management of cognitive impairment among older adults.

**2. Objectives**

□ This study is a patient registry study, and aims to conduct an observational study by collecting real-world patient information and treatment process utilized in clinical practice. A patient registry study is an observational study typically conducted to evaluate the characteristics of diseases and treatments, clinical effectiveness of treatments, safety, quality of care, and improvements. It has the advantage of flexibility according to the purpose of the investigators without a standardized framework as in the case of randomized controlled trials. Thus, by collecting real-world data, the result obtained is expected to have general applicability, reduces the burden on the investigators and patients. A patient registry study is conducted for various purposes (product registry, health services registry, disease registry, etc.), and there may be a registry developed for a specific purpose or a single registry built with multiple purposes combined. A patient registry study is often utilized for building a disease registry with recruitment of patients with a specific disease or a medical device registry for post-market surveillance for the performance and safety of a medical device. Although this type of study is often conducted at a national level, there are also studies conducted by academic or professional societies for the purpose of improving the quality of care and public reporting. This study aims to recruit patients with a specific disease using health services of KM treatment, and aims to build a registry that combines the purposes of a health service registry and a disease registry. In this way, the status of treatment used, effects of the treatment used, and safety can be evaluated. Likewise, by building a registry, this study also aims to perform comprehensive evaluation on the status of health service, which is KM treatment used in practice, effectiveness of KM treatment used, and safety

Therefore, this study aims to build a patient registry for those with mild neurocognitive disorder or subjective cognitive decline receiving KM treatment including acupotomy with the Korean Medical Society of Acupotomology (<https://www.acupotomy.kr/>) as the sponsor.

To sum up, the objectives of this clinical study are to investigate the following:

**1) Process of Korean medicine treatment including acupotomy** performed for improvement of cognitive function

**2) Characteristics of patients with cognitive impairment** visiting primary care centers for Korean medicine treatment

**3)** Short-term **Korean medicine treatment response rate**

**4) Difference in the effect of treatment** according to the Korean medicine treatment

**5) Safety.**

○ Primary objective: To investigate the characteristics of the patients with mild neurocognitive disorder or subjective cognitive decline visiting primary care settings for KM treatment, to evaluate the quality of KM treatment process including acupotomy and develop the measures for improvement (exploring the optimal treatment process by considering treatment methods, number of visits and treatments, duration of treatment, etc.) and to examine and evaluate the effect of improvement in cognitive function after KM treatment.

○ Secondary objective: To investigate the difference in the treatment effects according to the KM treatment interventions used, and characteristics of treatment responders, and to perform safety assessment through examining any adverse events that occurred after treatment.

**3. Names and Positions of Principal investigators, Co-investigators, and Investigators**

□ Principal investigators

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| --- | --- | --- | --- | --- |
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□ Co-investigators

|  |  |  |  |  |
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**4. Name and Address of Study Institutions**

□ Study sites for data collection

○ Daemyung Korean Medicine Clinic (3rd floor, Wonwoo Building, 105 Yangpyeong-ro, Yeongdeungpo-gu, Seoul)

○ Seonyujae Korean Medicine Clinic (2nd floor, Songran Art Plaza, 95 Songok-ro, Suji-gu, Yongin-si, Gyeonggi-do)

○ Mapo Hongik Korean Medicine Clinic (1st floor, 16 Samgae-ro, Mapo-gu, Seoul)

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○ Unjeong Seum Korean Medicine Clinic (4th floor, World Tower 2, 53 Cheongam-ro 17beon-gil, Paju-si, Gyeonggi-do)

○ Bareun Kyung Hee Korean Medicine Clinic (No. 404, 70 Taebong-ro, Seocho-gu, Seoul (Umyeon-dong, Umyeon Plaza))

○ Bonecure Korean Medicine Clinic (3rd floor, 767 Samseong-ro, Gangnam-gu, Seoul)

○ Jaemin Korean Medicine Clinic (99 Beomil-ro, Dong-gu, Busan)

○ Daejeong Korean Medicine Clinic (12 Seojeong-yeok-ro, Pyeongtaek-si, Gyeonggi-do)

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□ Data analysis

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**5. Study Sponsor**

○ National Institute for Korean Medicine Development (94 Hwarang-ro, Gyeongsan-si, Gyeongsangbuk-do (Gapje-dong))

**6. Study Period**

○ Date of IRB approval-31 December, 2026

**7. Participants**

□ Number of patients to be recruited

○ A total of 500 participants, who will sign the informed consent form (ICF), undergo the screening process to determine the eligibility according to the inclusion/exclusion criteria, and be assigned with an enrollment number, will be recruited.

○ Participants must meet all items of the selection/exclusion criteria to be eligible for enrollment in the study

□ Eligibility Criteria

○ Inclusion Criteria

1) Men and women aged not less than 55 years and not more than 85 years;

2) Those diagnosed with mild neurocognitive disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5), or those who do not meet the criteria for mild neurocognitive disorder but complain of subjective cognitive decline;

Diagnosis of mild neurocognitive disorder requires evidence of mild decline from the individual’s previous level of neurocognitive functioning in one or more cognitive domains. This shall be based on concerns expressed by the patient, an informant who knows the patient, or a clinician about mild cognitive decline, and as for criteria of quantitative assessment, it shall be evidenced by the Montreal Cognitive Assessment-Korean (MoCA-K) score < 23. However, the cognitive decline shall be not severe enough to interfere with an individual’s ability to independently perform activities of daily living. Also, the impairment shall not occur in circumstances of delirium, or the symptoms shall not be better explained by another neurocognitive disorder;

3) Those who heard and fully understood the explanation about the study, voluntarily expressed his/her willingness to study participation, and signed the informed consent form;

4) Those who intend to receive KM treatment (acupuncture, pharmacopuncture, herbal medicine, etc.) including acupotomy for treatment of their cognitive decline.

○ Exclusion criteria

1) Those diagnosed with major neurocognitive disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition;

2) Those who have difficulties with taking tests during the study due to illiteracy, loss of vision, hearing loss, severe speech impairment, etc.;

3) Those who do not speak Korean;

4) Those who are deemed not suitable to participate in this study according to the clinical judgment of the investigators.

**8. Sample size estimation and grounds for calculation**

□ Recruitment of participants and target number of participants for enrollment

○ Eligible participants: Adult men and women between the ages of 55 and 85 who have been diagnosed with mild neurocognitive disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5), those complaining of subjective cognitive decline.

○ A total of 500 volunteers are recruited in a mode of competitive enrollment from 22 KM clinics for 6 months starting from the first date of recruitment of volunteers. For the target number of participants for enrollment for each study institution, please refer to an annex file describing the respective institutions and the investigators in charge.

□ Sampling method

○ Since this study is designed as a patient registry study to identify the characteristics of the patients visiting KM clinics (as primary care centers) for KM treatment of cognitive impairment and to improve the treatment process, there is no need to test a predetermined statistical hypothesis, indicating that there is no need for sample size estimation in advance. However, considering the research grant and the circumstances of the study, we aim to determine the sample size within the range that sampling is feasible in practice.

○ A total number of new patients who presented for treatment of cognitive impairment at 22 study institutions for 1 year is approximately 1670, and calculation shows that data of about 500 patients will be collected for 6 months based on the assumption that up to 60% of the new patients will give their consent to study participation. However, there may be loss in the patient registry due to violation of the inclusion criteria, cases corresponding to the exclusion criteria, or other reasons. Therefore, we aim to ensure that not less than 70% of the registry is retained despite various reasons for possible losses.

○ In addition to examining the characteristics of the patients visiting KM clinics (as primary care centers) for KM treatment of cognitive impairment and the treatment process, this study also aims to perform statistical analysis on the factors influencing treatment success. We plan to perform linear regression analysis of continuous variables for assessment scores of cognitive function, and selected 25 covariates as potential factors influencing treatment success as follows: gender, age, region, smoking history, history of alcohol consumption, physical activity, family history, education, past occupation, current occupation, marital status, depression (PHQ-2), type of health insurance, hypertension, diabetes, dyslipidemia, stroke, cardiovascular disease, depression, insomnia, treatment for cognitive impairment, MoCA-K score at baseline, K-ECog-12 score at baseline, cognitive decline NRS score at baseline, and ISI-K score at baseline. To perform linear regression, 20 samples are generally required for a single variable; thus, 25\*20=500 participants are required in total.

**9. Recruitment of volunteers**

□ Method of volunteer recruitment

○ Recruitment advertisements for this study will be posted on the bulletin board of the study institutions recruiting volunteers and also on the website of the institutions (For information on the study institutions recruiting volunteers and their website, please refer to the annex file describing the respective institutions and the investigators in charge). All recruitment of volunteers is coordinated by Jungtae Leem, a co-investigator.

○ This is a patient registry study, and the process of volunteer recruitment is a part of the general treatment process of patients visiting KM clinics. Therefore, patients with mild neurocognitive disorder or complaining of subjective cognitive decline visiting the study institutions recruiting volunteers are provided explanations on this study. During this process, patients who show their willingness to voluntarily participate in the study will be provided with a detailed description of the study along with the patient information leaflet (PIL). Finally, on the day when a patient expresses his/her intention to participate in the study, an investigator will receive the signed consent form from the patient.

□ Period of volunteer recruitment

○ Recruitment advertisements will be posted from the date of IRB approval, and the planned duration of recruitment will be 6 months from the date of IRB approval.

**10. Informed consent**

□ Overview of the informed consent process

○ Before obtaining consent for study participation, an investigator will provide full explanation on the ‘patient information leaflet (PIL) and informed consent form (ICF)’ approved by the Public Institutional Review Board to the participants who expressed their willingness to participate in the study. After obtaining the signed ICF from the participants, a copy of the ICF will be provided to the participants, and the original ICF will be kept in a place equipped with a locking device at the corresponding study institution to prevent access by anyone other than the relevant study personnel.

□ Method, procedure, venue, time and responsible personnel for informed consent process

○ Study institutions recruiting volunteers shall provide full explanations on this study including the following information to patients who visited the institution for KM treatment due to mild neurocognitive disorder or subjective cognitive decline: the purpose and procedure of the study, study methods including tests performed during the study, schedules and timelines, information on the confidentiality, the fact that the patient collected from the study institution may be transferred to other study institutions for the purpose of data analysis, and that a participant may withdraw his/her consent whenever he/she wishes to do so. An investigator shall provide answers to the questions of the participants. He/she should also inform the patient that the patient's study participation should be determined voluntarily, and not participating in the study will not affect the treatment of the patient.

○ On the day when the participant voluntarily expressed his/her intention to participate in the study, the investigator shall obtain the signed ICF from the patient and then proceed with the subsequent procedure of study participation. Signing of the ICT indicates giving his/her consent to participate during the entire study period. However, additional consent may be obtained for cases such as when the participant requests to complete or sign the ICF again.

- Procedures to minimize the patient risks regarding study participation: The capacity of the participant on making decisions about giving consent to study participation shall be checked repeatedly, and it shall be informed multiple times that the patient may decide on his/her continuation or discontinuation of study participation at any time, and that there will be no disadvantages because of discontinuing (withdrawing from) study participation.

- Plan for assessing the individual participants’ capacity related to giving consent: the following aspects shall be comprehensively considered and evaluated: 1) Whether the participant understands the information provided in relation to the study, 2) Whether the participant can logically handle the information about the study, 3) Whether the participant have the ability to clearly express his/her choice in relation to the study participation, etc.

- Plan for obtaining a participant’ consent in appropriate cases: If a participant is judged to have adequate capacity to make decisions and give consent based on the assessment of the capacity to consent as above, the consent will be obtained directly from the patient.

- Plan to include a consent from legal representative: If a participant is judged to have difficulties in making decisions and giving consent based on the assessment as above, the participant will sign the ICF and the consent from the legal representative will be obtained.

○ Provision of explanation on the study and obtaining the patient consent shall take place in an area with a stable and quiet environment within the study institution recruiting volunteers, ensuring smooth communication between the investigators and participants. The names of the participants will be accessible only to the investigators.

○ In accordance with Article 18 of the Bioethics and Safety Act, the collected study information may be provided to third parties or used for secondary research. Therefore, patient information leaflet (PIL) and informed consent form (ICF) on provision of the study information to third parties and use of the information for secondary research are distributed separately, and the information is used only when the patient gives additional consent to this PIL and ICF. If the patient reads the information provided in PIL thoroughly and gives consent accordingly, the study information may be linked and combined with the databases of governmental public institutions (Health Insurance Review and Assessment Service (HIRA), Statistics Korea, National Health Insurance Service, Korea Disease Control and Prevention Agency, National Cancer Center, etc.) and utilized for future research. Even if a patient does not give consent to the ‘ICF on provision of the study information to third parties and use of the information for secondary research,’ he/she can still participate in the patient registry study if the consent to the ‘PIL and ICF for participants’ is given. In this case, due to no consent on provision of the study information to third parties and use of the information for secondary research, the information of the patient will not be provided to the National Institute for Korean Medicine Development.

○ In order to participate in the patient registry study, ‘PIL and ICF for participants’ must be provided and the consent should be obtained, and the consent to ‘PIL and ICF for third-party provision and secondary research use’ shall be obtained separately. However, even if a patient does not give consent to the ‘ICF on provision of the study information to third parties and use of the information for secondary research,’ he/she can still participate in the patient registry study.

**11. Methods**

□ Study Design

○ A patient registry study is a method of observational study that uses an organized system to continuously collect uniform data to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, deriving meaningful results and serving a predetermined scientific, clinical, or policy purpose.

○ This study aims to build a registry for patients with mild neurocognitive disorder or subjective cognitive decline visiting KM clinics (as primary care centers), collect data on KM treatment process and patient characteristics, and explore treatment response rates and responders through clinical assessments.

○ Participants who voluntarily signed the ICF for the clinical study will be registered in the patient registry if they are determined to be suitable for the study upon reviewing the eligibility based on the inclusion and exclusion criteria. Competitive patient enrollment will be adopted across the 22 study institutions.

□ Standard of care

○ For patients with mild cognitive impairment, the following treatments and lifestyle modifications are typically used or practiced as a part of the usual care:

- Cholinesterase inhibitors

- Antioxidants

- N-methyl-D-aspartate receptor antagonists

- Periodic cognitive function tests to examine and determine progression to dementia

- Regular exercises

- Non-smoking

- Staying socially active

- Continuous brain activities (reading newspapers, magazines, books, learning, journaling, puzzle solving)

- Moderate drinking (1-2 glasses per day, no more than 3 times a week)

- Daily consumption of fruits and vegetables

○ Participants in this study have no restrictions on receiving the standard of care as listed above. In this study, once the intervention (KM treatment) has started, the patient condition will be monitored and assessed every 3 months, and as a part of the monitoring and assessment, “changes in medical and medication history” will be checked and recorded. Other than that, there will be no restrictions on the standard of care or changes in medications in this study. In addition, if a sudden aggravation in the patient’s cognitive functioning is detected in the cognitive function tests conducted every three months in this study, additional visits to a hospital will be recommended.

□ KM treatment protocol

○ For the patients with mild neurocognitive disorder or subjective cognitive decline visiting KM clinics for KM treatment, KM treatment is provided based on the following KM treatment protocol, and the overall treatment process, number of visits and treatments, duration of treatment, treatment effect, and adverse events are observed and recorded.

○ As in the process of real-world clinical practice, the patient will visit the study institution on a regular basis according to the treatment plan of the physician (KMD) in charge. The following assessments will be performed once every three months: cognitive functioning (MoCA-K, K-ECog-12, NRS), sleep patterns (insomnia; ISI-K). The KM treatment including acupotomy performed and the assessment scales used in this study constitute the cognitive impairment treatment protocol of the Korean Medical Society of Acupotomology, and they are identical to those administered and used in the real-world clinical practice of treatment in respective study institutions, which are the KM institutions where the KMDs who are members of the Korean Medical Society of Acupotomology work for.

○ Visit protocol

- Cognitive impairment is a condition in which it is practically difficult to completely resolve the problem and achieve full recovery with no symptoms, and treatment and follow-up observation will continue without

- The schedule of visits may vary depending on the individual study institutions conducting the KM treatment, but in general, the recommended frequency of the visits for treatment is not less than three times a week in the early stages of treatment and one or two times a week in the later stages of treatment.

○ KM treatment protocol

- The following illustrates the treatment process of acupuncture and acupotomy that is typically administered on patients with cognitive impairment. Other KM treatments, such as herbal medicine, Chun manual therapy, moxibustion (and frequency of these treatments etc.), will be prescribed and administered at the discretion of the physician (KMD) in charge.

- At each visit, either acupotomy or acupuncture will be administered on the same treatment sites once daily. However, since acupotomy involves applying stronger stimulation than acupuncture, it should only be performed no more than once a week

텍스트, 스크린샷, 디자인, 템플릿이(가) 표시된 사진

자동 생성된 설명

- Treatment sites

① 8 points in the occipital region (back of the head) (C2 transverse process, splenius capitis muscle, rectus capitis posterior minor muscle, rectus capitis posterior major muscle)

② C4 transverse process

③ Yifeng (TE17) acupoint

④ 3 points along the fascia of atlas (first cervical vertebra, C1) (Center of the atlas fascia, C1-3 facet)

⑤ C6-7 splenius capitis muscle attachment

⑥ T2-4 facet

⑦ Levator scapulae muscle (trapezius muscle) region

⑧ Emissary vein exit point

텍스트, 살, 사람이(가) 표시된 사진

자동 생성된 설명실내, 텍스트, 사람, 피부이(가) 표시된 사진

자동 생성된 설명

- Acupotomy

텍스트, 공구, 압정, 문구용품이(가) 표시된 사진

자동 생성된 설명

① With the patient in prone position, the treatment sites are marked with a medical marker pen.

② Povidone-iodine is applied onto the treatment sites, followed by disinfection with alcohol.

③ Acupotomy is performed by inserting and removing 0.40 mmx40 mm needle-knife on the treatment sites.

④ Cupping therapy is administered to all treatment sites, any signs of bleeding are checked, and the blood is removed.

(To check for bleeding at the sites where acupotomy was administered and drain the blood if there is bleeding)

⑤ Then, povidone-iodine is applied to the treatment sites where treatment has been completed, followed by disinfection with alcohol.

⑥ Circular bandages are attached to all treatment sites to prevent infection

* Acupuncture

① With the patient in prone position, perform transcutaneous heat therapy on neck muscles by applying heat with a hot pack (80℃) wrapped in a towel to the neck area for approximately 10 minutes.

② Among the treatment sites, acupuncture is performed by inserting 0.30 mm × 40 mm (filiform) needles on the three points along the fascia of atlas, facet of cervical and thoracic vertebrae, and C4 transverse process, and 0.25 mm×30 mm (filiform) needles are used for other transverse process sites.

③ One cup for cupping therapy is attached to each side of the C1-C3 facet area, and wet cupping therapy is performed for about 1 minute.

④ Electroacupuncture is performed by applying electrical stimulation to the needles inserted into the left and right atlantoaxial joints at 100 Hz for about 10-15 minutes.

⑤ After removing the needles, interferential current therapy (ICT) is performed, which applies stimulation with interferential current to the neck area for 15 minutes.

○ Progress monitoring and assessment during the intervention (KM treatment) period

- For progress monitoring and assessment of the patients, objective and subjective assessment on cognitive functioning, and assessment of sleep patterns (insomnia) are performed at 3-month intervals during the intervention (KM treatment) period.

○ Additional procedure required due to study participation other than the KM treatment protocol

- All participants will receive treatment according to the KM treatment protocol of individual study institutions, but, as with general clinical practice of KM clinics, the types and modalities of treatment, such as acupotomy, acupuncture, Chun manual therapy, pharmacopuncture, herbal medicine, moxibustion or cupping, are determined by the condition of individual patients and clinical judgment of the physician (KMD). Since this study aims to collect data on the KM treatment process performed for patients with cognitive improvement in KM clinics that use acupotomy as one of the treatment options, under real-world clinical practice settings, patients will receive no additional treatment because of their study participation but receive the same treatments as in the general practice of these KM clinics. The only differences that require additional procedures arising from study participation would be the process of informed consent for study participation and screening based on the inclusion/exclusion criteria. Other than the two aspects, the following items are performed as a routine practice in individual study institutions for evaluation of the treatment effects and monitoring of the patient condition and progress: collecting personal information, sociodemographic investigation, taking medication history, height/weight measured on site, measurement of vital signs, questionnaire for assessment of patient condition (MoCA-K, K-ECog-12, NRS, ISI-K), changes in medical and medication history, checking for adverse events.

□ Recruitment of volunteers and enrollment method

○ The number for each participant is assigned as follows according to the order of obtaining the consent. The number of each participant is recorded as per the method described below.

- Study Institution Code: Daemyung Korean Medicine Clinic (DMC), Seonyujae Korean Medicine Clinic (SYJ), Mapo Hongik Korean Medicine Clinic (MHC), Chamjoeun Korean Medicine Clinic (CJE), Jeongwoori Korean Medicine Clinic (JWR), Jayang Korean Medicine Hospital (JYH), Unjeong Seum Korean Medicine Clinic (YSC), Bareun Kyung Hee Korean Medicine Clinic (BKC), Bonecure Korean Medicine Clinic (BCR), Jaemin Korean Medicine Clinic (JMC), Daejeong Korean Medicine Clinic (DJC), Cheongidam Korean Medicine Clinic (CID), Daon Korean Medicine Clinic (DOC), Yesan Kyung Hee Korean Medicine Clinic (YKC), Korea-Su Medical Clinic (KRS), Haenamu Korean Medicine Clinic (HNM), 365 Okgil Korean Medicine Clinic (OKC), Kimhakdong Korean Medicine Clinic (KHD), Wolbaewolseong Branch of Ona Korean Medicine Clinic (OAW), Bonsuho Korean Medicine Hospital (BSH), Keumho Branch of Ona Korean Medicine Clinic (OAK), Seojaesecheon Branch of Ona Korean Medicine Clinic (OAS)

Study Institution Code-Year of study-Order of study enrollment

(e.g. DMC-2024-015: A patient who was enrolled as the 15th participants in a study conducted at Daemyung Korean Medicine Clinic in 2024)

○ The name of the participants shall be recorded in initials.

|  |  |
| --- | --- |
| **Participant’s ID code** | **Participant’s initial** |
| □□□**– 202\_ -**□□□ | |  |  |  | | --- | --- | --- | |  |  |  | |
| □ NA (Screening Fail) |

□ Methods and items of measurement

○ Study participation requires the patients to undergo the process according to the following schedule. The study period is one year, and participants are required to participate in not less than one KM treatment session, which takes about 30 minutes in general per session. Additionally, approximately 30 minutes of time is required for patient surveys conducted for the purpose of progress observation/monitoring once every 3 months. Due to the nature of mild neurocognitive disorder/subjective cognitive decline, patients are likely to repeatedly experience improvement and aggravation of their condition over time, which means that the timepoint for ending the treatment is different for each patient, and prediction is not possible. Therefore, rather than setting the timepoint to end the treatment, the study period was set to one year, and treatment can be terminated before one year depending on the patient's condition and the physician (KMD)'s clinical judgment. In addition, visiting the KM clinic is left to the voluntary decision of the patient, and although the study schedule is set as follows, participation in every process is not mandatory.

- Study schedule

① When a patient expresses his/her willingness to participate in the study, the patient will sign the ICF and undergo the following process: eligibility checking based on inclusion/exclusion criteria, assigning of the participant number (enrollment number), collection of personal information (name, date of birth, age, gender), sociodemographic investigation (Chief complaint for visiting the KM clinic (Korean Standard Classification of Disease (KCD) code and date of initial visit), Sociodemographic information (smoking, alcohol consumption, physical activity, family history, education level, past and present occupation, marital status, depression [PHQ-2], type of NHI benefit), medication history, height/weight measured on site, and measurement of vital signs.

② Patient surveys (MoCA-K, K-ECog-12, NRS, ISI-K) are conducted for assessment of patient condition at baseline.

③ Patients receive KM treatment by visiting the study institutions for 3 months

④ Patient surveys (MoCA-K, K-ECog-12, NRS, ISI-K) are conducted for assessment of patient condition as they receive KM treatment.

⑤ Steps ③ and ④ are repeated at 3-month intervals until the end of treatment for individual patients.

The above constitutes the usual schedule for the patient participating in this study. However, the treatment schedule is carried out according to the clinician's medical judgment regardless of the study participation status, and there is no need for visits to undergo extra treatment or assessment specifically due to participation in this study. Therefore, the same treatment process is carried out for those who do not participate in the study, but their data will not be collected as they have not given the consent for study participation.

○ The questionnaires for patient surveys, MoCA-K, K-ECog-12, NRS, and ISI-K, are scales commonly used for monitoring patient progress in real-world clinical practice at the study institutions. That is, patients are not required to visit KM clinics to undergo extra treatment or examination or any extra visits specifically because of their participation in this study. Therefore, the completed questionnaires will be collected on specific dates when a patient visits the KM clinic for his/her treatment, and this will take place once every three months in general.

○ Visits 1, 2, 3, 4... refer to the schedule of patient visits for treatment, and in this study, only measurements data from Measurement 1 to Measurement 5 are collected regardless of the number of visits. The number and interval of treatment visits may vary depending on the condition of individual patients and the clinician's medical judgment, and accordingly, Measurement 2 to Measurement 5 will take place at different numbers of treatment visits for each patient. Therefore, the schedule for treatment visits and the schedule for measurements/assessments are managed separately.

○ Study schedule (KM treatment protocol): A total of 5 times of clinical assessment

Baseline (Day 0, screening and enrollment, Measurement 1)

Measurement2 (3 months after treatment initiation)

Measurement3 (6 months after treatment initiation)

Measurement4 (9 months after treatment initiation)

Measurement5 (12 months after treatment initiation)

○ As for the case report form (CRF) data collection, myTrial program of National Institute for Korean Medicine Development is used, and eCRF is prepared using the same items of information collected in Moaform (Screening <https://moaform.com/q/73tMeA>; Measurement 1 <https://moaform.com/q/5YcoU5>; Measurement 2-5 <https://moaform.com/q/9Y5ASI>; Reporting adverse events <https://moaform.com/q/tCEwzn>; Reporting discontinuation of the clinical study <https://moaform.com/q/9Zxkgi>) and used for data collection.

|  |  |  |
| --- | --- | --- |
| Screening | Informed consent | \*Informed consent form received from the participants |
| Investigation at screening | \*Personal information  \*Sociodemographic investigation, investigation of medication history  \*Measurements of vital signs, height, and weight |
| **Measurement 1** | Baseline investigation | \*Assessment by patient surveys |
| **Measurement 2-5** | Follow-up investigation | \*Vital signs  \*Checking for changes in medical and medication history  \*Assessment by patient surveys  \*KM treatment  \*Adverse Events |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Measurement**1) | | **Screening**  **(Visit1)** | **1** | **2** | **3** | **4** | **5** |
| Months | | **0** | **0**  **(+14 days)** | **3**  **(±30 days)** | **6**  **(±30 days)** | **9**  **(±30 days)** | **12**  **(±30 days)** |
| Obtaining the signed informed consent form | | ○ |  |  |  |  |  |
| Inclusion/exclusion criteria | | ○ |  |  |  |  |  |
| Assigning the participant number (enrollment number) | | ○ |  |  |  |  |  |
| Personal information2) | | ○ |  |  |  |  |  |
| Sociodemographic investigation3) | | ○ |  |  |  |  |  |
| Investigation of medication history4) | | ○ |  |  |  |  |  |
| Height/weight measured on site | | ○ |  |  |  |  |  |
| Vital signs5) | | ○ |  | ● | ● | ● | ● |
| Patient condition | MoCA-K |  | ● | ● | ● | ● | ● |
| K-ECog-12 |  | ● | ● | ● | ● | ● |
| NRS6) |  | ● | ● | ● | ● | ● |
| ISI-K |  | ● | ● | ● | ● | ● |
| KM treatment7) | |  |  | ● | ● | ● | ● |
| Checking for changes in medical and medication history | |  |  | ● | ● | ● | ● |
| Adverse events | |  |  | ● | ● | ● | ● |

● Measurements are made only for those who were determined to be eligible based on the inclusion/exclusion criteria.

1) For eligible participants, Measurement 1 can be performed, and the subsequent measurements will be performed at 3-month intervals.

2) Personal information: name, date of birth, age, gender

3) Sociodemographic investigation: the following information is investigated-chief complaint for visiting the KM clinic (KCD code and date of initial visit), Sociodemographic information (smoking, alcohol consumption, physical activity, family history, education level, past and present occupation, marital status, depression [PHQ-2], type of NHI benefit).

4) Investigation of medication history: Medication history for the last three years is collected including the following items: medications for hypertension, diabetes mellitus, dyslipidemia, stroke, cardiac disease, depression, insomnia, and medicines taken for cognitive decline. Also, the status of current medications is checked.

5) Vital signs: Body temperature, blood pressure (systolic/diastolic) and pulse rate are measured.

6) NRS: The severity of cognitive decline symptoms subjectively experienced by the patient is collected.

7) KM treatment: Information on the KM treatment interventions administered during the three months between the previous Measurement and this Measurement, including the duration and number of treatments is collected.

□ Data collection method for measurement items

○ Questionnaire for assessment of patient condition

For collection of the study data, MoCA-K questionnaire is administered by an investigator of the study institution or by a person delegated by the investigator to administer the questionnaire according to the treatment process of the study institution, and for K-ECog-12, NRS, and ISI-K, questionnaires will be distributed to the patient and he/she shall complete the self-report questionnaires. MoCA-K is used for cognitive functioning assessment, K-ECog-12 and NRS are used for subjective assessment of his/her cognitive decline, and ISI-K is used for sleep pattern (insomnia) assessment. These data will be collected for one year from the start of KM treatment, starting from the baseline (Measurement 1), then every three months after the KM treatment initiation (Measurement 2-5).

Measurements shall take place in an area with a stable and quiet environment within the study institution, ensuring smooth communication between the investigators and participants. For one-time measurement using the questionnaires, a participants will answer a total of 31 questions and completing all the questionnaires will take about 30 minutes.

○ KM treatment information

In the same manner as the routine treatment process of KM clinics, after KM treatment is performed, treatment information is recorded in the electronic medical record (EMR) system of the KM clinic, and the information on KM treatment is recorded into Moaform (https://moaform.com/q/9Y5ASI) and eCRF at 3-month intervals (Measurement 2-5) from the start of KM treatment. At this time, the items reported into these forms include the types and frequency of KM treatment interventions performed on the patient for the last three months, herbal medicine prescriptions, and duration of taking herbal medicine. Provided, if additional checking of the information is deemed to be necessary according to the judgment of an investigator, the data recorded in the EMR system of the study institution will be viewed for checking.

○ Adverse events information

Each time a participant visits the study institution for treatment, adverse events (AEs) are checked through the patient reports and questions. If an investigator judges that the participant has symptoms or changes with clinical significance, or if a participant voluntarily reports any sign of AEs, the investigator shall record the details regarding the AEs including the occurrence, assessment, and actions (treatment) for the AEs in Moaform (https://moaform.com/q/tCEwzn) and eCRF using standardized medical terminology. If there are no AEs, the expression ‘no adverse effects since the last assessment’ shall be recorded in the EMR chart. If AEs occur after administration of acupotomy, they shall be reported using the developed ACUPOCHECK (ACUPOtomy-related adverse event CHECKlist).

In case of an AE occurrence, the investigator will review the data recorded in the EMR system in the study institution if checking of additional information is deemed to be necessary according to the judgment of the investigator.

**12. Observation Items**

The observation items collected in this study are as follows: sociodemographic information, medication history, measurement items (height, weight, vital signs, assessment of patient condition [MoCA-K, K-ECog-12, NRS, ISI-K]), KM treatment, and adverse events (AEs). The details of the observation items for each category are as follows.

Provided, in all questionnaires, ‘name’ of a participant is used after converting into a code for deidentification for analysis. Patient names are used only for identification of medical records, and investigators receive data in coded, anonymous forms to prevent any identification of personal information of the patients.

○ Personal information

- Name, date of birth, age, gender

- According to Korean laws in relation to personal information protection, the resident registration number cannot be used as a combination key, and the name, date of birth, and gender of the participants, which can be used as a combination key for combining secondary data in the future should be collected. This study is a part of the project led by the National Institute for Korean Medicine Development, and it is stated in the requirements, “the selected project must show active cooperation with the ‘Establishment and Operation of a System of Korean Medicine Clinical Study Data for Utilization in accordance with Public Interest’ conducted by the project group, and information regarding the third-party provision of the study data and its use for secondary research must be included in the PIL and ICF for participants.” In addition, because mild neurocognitive disorder and subjective cognitive decline are highly likely to progress to dementia, long-term follow-up observation is necessary. However, this study has a relatively short study period of 1 year, making long-term follow-up monitoring and evaluation not possible. To address this limitation, linkage and combination with database of governmental public institutions (e.g. Health Insurance Review and Assessment Service, Statistics Korea, National Health Insurance Service, Korea Disease Control and Prevention Agency, National Cancer Center) is planned. Therefore, name, date of birth, and gender should be collected as combination keys, and these are also the types of data that are always collected during the treatment process regardless of the patient's study participation status. Study data including personal information are accessible only to principal investigators and co-investigators, and related data/records are stored securely in a place where only authorized persons can have an access to and where access by non-authorized persons is prevented by a locking device (a cabinet with a locking device and a computer with password-restricted access in the investigators' office, and a computer with password-restricted access in the analysts' and assessors' offices).

○ Sociodemographic information

- Information on the primary diagnosis: The chief complaint for the visit and the date of the initial visit shall be recorded. If the chief complaint is a disease other than cognitive impairment, the KCD code for the disease and the date of the initial visit shall be recorded.

- Smoking, alcohol consumption, physical activity, family history, education level, past and present occupation, marital status, depression (PHQ-2), type of NHI benefit

○ Investigation of medication history

- Medication history: Information on the current medications and the medication history for the last three years is collected including the following items: medications for hypertension, diabetes mellitus, dyslipidemia, stroke, cardiac disease, depression, insomnia, medicines taken for cognitive decline, and others.

○ Measurement items

- Measurement of height, weight, vital signs (blood pressure, pulse rate, body temperature): taking 5 minutes in total.

- Assessment of patient condition: taking 30 minutes in total

|  |  |  |
| --- | --- | --- |
| Cognitive functioning assessment | Objective | MoCA-K |
| Subjective | K-ECog-12 |
| NRS |
| sleep pattern (insomnia) assessment | | ISI-K |

① Montreal Cognitive Assessment-Korean (MoCA-K) (See [Annex 1])

MoCA was developed for screening mild cognitive impairment (MCI) among the elderly with normal findings as a result of Mini-Mental State Examination (MMSE). The scale consists of the following seven areas: short term memory, visuospatial abilities, executive functions, attention, concentration and working memory, language, and orientation to time and place. The total possible score is 30 points. It takes about 10 minutes to administer the test; and professionals consider a score of 23 or above to be normal. MoCA-K is not recommended for those with a low level of literacy (poor or no reading or writing skills).

② Short form of Korean-Everyday Cognition (K-ECog-12) ( See [Annex 2])

ECog is a questionnaire for assessing cognitively-relevant everyday abilities, developed by Farias et al.. Song et al. developed a Korean version of the scale and verified the reliability and validity of the scale. Recently, a short form questionnaire consisting of 12 items was developed specifically for the older adults in South Korea. The scale enables assessment of everyday functioning by categorizing into domains of memory, language, visuospatial function and cognitive function, and executive function (planning, organization, divided attention), and the participants assess the changes in the level of functioning by responding with one of the five options as follows: 1) better or no change compared to 10 years earlier. 2) questionable/occasionally worse. 3) consistently a little worse. 4) consistently much worse. 5) I don’t know (or not applicable). The proposed cutoff values for mild neurocognitive disorder and dementia patients were 1.42 (sensitivity 72.4%, specificity 73.4%) and 1.71 (sensitivity 85.7%, specificity 86.9%), respectively.

③ Numeric Rating Scale (NRS) ( See [Annex 3])

The scale is used for assessment of the severity of the symptoms of cognitive decline subjectively felt by individual patients.

④ Korean version of Insomnia Severity Index (ISI-K) (See [Annex 4])

A significant correlation between sleep disorder and cognitive impairment has been reported. Accordingly, additional assessment is made on the sleep patterns of the patients complaining of subjective cognitive decline in this study, so as to analyze the association between sleep problems and cognitive impairment and evaluate the treatment responses.

The ISI-K scale, originally developed by Bastien and Morin, and translated into a Korean version and validated by Cho et al., is used for assessing the severity of each symptom of insomnia (difficulty falling asleep, difficulty staying asleep, problem waking up too early), satisfaction with the current sleep pattern, extent of interference with daily functioning due to insomnia, and level of worriedness/distress over the last two weeks. A total of seven items are assessed on a 4-point Likert scale (0 point = None - 4 points = Very much), with a total score range of 0-28 points. Higher score indicate more severe insomnia. The threshold score for insomnia is 8 points or above, and scores of 15 points or above are interpreted as clinical insomnia.

○ KM treatment

To identify the patterns of KM treatment administered for cognitive decline over the last three months, the following information is collected and used for assessment: the sizes of the needles mainly used for acupuncture or acupotomy, the number of acupuncture or acupotomy sessions administered per month, the name of the herbal medicine prescription used, the duration of use, and the use of moxibustion, cupping, Chun manual therapy, pharmacopuncture, and other KM interventions.

○ Adverse Events

- Adverse events checklist after administering acupotomy (ACUPOtomy-related adverse event CHECKlist, ACUPOCHECK) (See [Annex 5] )

If adverse events (AEs) occur after receiving acupotomy, the AEs are reported using ACUPOCHECK. ACUPOCHECK is a checklist developed by this research team through a Delphi method with experts in 2018. Then, the usability of the developed checklist was finally confirmed with 73 KMDs who are administering acupotomy in their clinical practice. The checklist has been submitted to the Journal of Integrative Medicine (SCIE), and is under review.

Using the checklist, the following information can be collected: the date and treatment sequence of AE occurrence, whether the AE falls under serious adverse events (SAEs), the types of local and systemic AEs that occurred, the time of onset, the outcome after AE occurrence, the severity of AEs, and the assessment of causal relationship with KM treatment. In a multicenter study as in this study, using the standardized checklist allows systematic collection of AEs that occurred after administration of acupotomy.

**13. Efficacy Assessment**

This is a patient registry study, and the primary objective is to explore the characteristics of patients with mild neurocognitive disorder/subjective cognitive decline who visit KM clinics, the optimal KM treatment process, and assess the efficacy of KM treatment for improvement in cognitive function. Based on the primary objective, the outcomes for efficacy assessment are presented as follows.

□ Primary outcome

○ This study is a single-arm observational study without a control group: the study aims to identify the patterns of KM treatment including acupotomy performed on cognitive impairment patients, and compare MoCA-K scores before and after KM treatment to explore the efficacy of the KM treatment for improving cognitive functioning.

- Changes in MoCA-K scores at the end of treatment (Measurement 5) compared against the baseline (Measurement 1)

Null hypothesis (H0): There is no change in the MoCA-K score at the end of treatment (Measurement 5) when compared against the score at baseline (Measurement 1).

Alternative hypothesis (HA): The MoCA-K score at baseline (Measurement 1) and the score at the end of treatment (Measurement 5) are not equal.

□ Secondary outcomes

○ Changes in MoCA-K scores at Measurement 2, Measurement 3, and Measurement 4 against the baseline (Measurement 1).

○ Changes in MoCA-K scores by domain (visuospatial/executive function, naming, attention, language, abstraction, delayed recall, orientation) at Measurement 2, Measurement 3, Measurement 4, and end of treatment (Measurement 5) against the baseline (Measurement 1).

○ Changes in K-ECog-12, NRS, and ISI-K scores at Measurement 2, Measurement 3, Measurement 4, and end of treatment (Measurement 5) against the baseline (Measurement 1).

○ Changes in K-ECog-12 scores by domain (memory, language, visuospatial function and cognitive function, executive function (planning, organization, divided attention) at Measurement 2, Measurement 3, Measurement 4, and end of treatment (Measurement 5) against the baseline (Measurement 1).

○ Comparison of mild neurocognitive disorder vs subjective cognitive decline patients for changes in MoCA-K, K-ECog-12, NRS, and ISI-K scores at Measurement 2, Measurement 3, Measurement 4, and end of treatment (Measurement 5) against the baseline (Measurement 1).

○ Comparison of acupotomy high-dose group high-dose group vs low-dose group for changes in MoCA-K, K-ECog-12, NRS, and ISI-K scores at the end of treatment (Measurement 5) against the baseline (Measurement 1).

- The definitions for the acupotomy high-dose group and low-dose group will be based on the median value of the number of acupotomy treatments, and the two groups will be classified accordingly.

○ Logistic regression analysis to identify the characteristics of the group showing discrepancy between subjective and objective assessments of cognitive decline

○ Ratio of treatment responder group

○ Regression analysis for factors influencing treatment effects

- Factors influencing KM treatment effects are explored through analysis methods of dichotomous (treatment responder group, treatment non-responder group) logistic regression or continuous linear regression

□ Criteria for efficacy assessment

○ As for the statistical analysis in this study, the degree of improvement of continuous variables will be presented through descriptive statistics. To determine the efficacy in terms of primary outcomes, paired t-test (or Wilcoxon signed-rank test) will be performed for differences in the changes in MoCA-K scores at the end of treatment (Measurement 5) compared against the score at baseline (Measurement 1).

○ The statistical analysis for secondary outcomes will be conducted as follows: paired t-test (or Wilcoxon signed-rank test) will be performed for differences in the changes in K-ECog-12, NRS, and ISI-K scores at Measurement 2, Measurement 3, Measurement 4, and end of treatment (Measurement 5) compared against the score at baseline (Measurement 1). In the case of MoCA-K, analysis will be performed for scores at Measurement 1 through Measurement 4. However, since this is a patient registry study without a control group, there are limitations in determining the efficacy for KM treatment.

○ Treatment responder group analysis: The group showing improvement in outcomes will be determined as the group showing treatment effect, and the ratio of this group will be presented. In addition, the minimum clinically important difference (MCID) for each assessment scale is used to define those showing improvement above the MCID as a treatment responder group. If there are specific subgroups, exploratory analysis will be performed to present the ratio of improvement for each subgroup.

○ Since this is an observational study based on the KM treatment protocol of routine clinical practice, for variables that may have an impact on cognitive functioning of the participants, data will be collected as follows, and these variables will be controlled through the process of statistical analysis.

- Information on the status of taking medications for treatment of cognitive impairment is collected.

- If a participant is taking medications for treatment of cognitive impairment, the participant shall be guided to notify the investigator for any changes in the dosage or regiment of the medications.

For these variables, logistic regression analysis with adjustment for the following factors will be performed: gender, age, smoking history, history of alcohol consumption, physical activity, family history of dementia, education level, occupation, marital status, depression (PHQ-2), status of taking medications for treatment of cognitive decline. These are the factors that may influence cognitive functioning of the participants among the sociodemographic information collected in this study.

**14. Expected AEs, precautions and actions to be taken**

□ Adverse events that occurred due to participation in this observation study

○ In this observation study, in the same manner as the standard treatment process of KM clinics, after KM treatment is performed and patient surveys are completed, information is recorded and reported into Moaform (screening <https://moaform.com/q/73tMeA>; Measurement 1 <https://moaform.com/q/5YcoU5>; Measurement 2-5 <https://moaform.com/q/9Y5ASI>; Reporting adverse events <https://moaform.com/q/tCEwzn>; Reporting discontinuation of the clinical study <https://moaform.com/q/9Zxkgi>) and eCRF. Therefore, apart from AEs that may occur during the process of standard KM treatment, almost no additional AEs are expected to occur because of the study participation, since this study requires no additional tests or intervention for research purposes.

□ AEs expected from study interventions (KM treatment including acupotomy) during the routine process of treatment

○ KM treatment performed in this study for treatment of cognitive impairment at KM clinics (as primary care centers as mentioned earlier in this study) is the same as those administered in the routine practice of KM treatment, such as acupuncture, acupotomy, pharmacopuncture, herbal medicine, Chun manual therapy, moxibustion, and cupping. Also, because KM treatment consists of minimally invasive procedures, the risk of AEs and resistance is low. The needle-knife used for acupotomy is thicker than (filiform) needles used for acupuncture, but the treatment process is the same apart from the fact that acupotomy requires no needle retention. The incidence and types of AEs for acupotomy are similar to those of general acupuncture, and the reported AEs are those observed in the routine practice of KM treatment. Possible types of AES that may occur after administration of acupuncture or acupotomy are: transient symptoms in the autonomic system or autonomic responses (dizziness, excessive sweating, tachycardia, palpitation) and local bleeding, bruising, pain, itching at the treatment sites. However, these risks are at the same level as the general risks experienced in the routine practice of KM treatment, and there are no AEs involved from measurements in the survey-based assessments in this study.

○ Apart from AEs of general KM treatment administered for treatment of cognitive impairment, it is expected that there will be no or minimal potential risks or AEs that occur additionally because of study participation

○ The participants in this study are patients with mild neurocognitive disorder or subjective cognitive decline receiving KM treatment regardless of whether they receive standard of care for cognitive impairment. Therefore, participants in this study have no restrictions on receiving the standard of care, but as a part of the monitoring and assessment in this study, “changes in medical and medication history” will be checked for assessment of treatment progress conducted every three months. In addition, if a sudden aggravation in the patient’s cognitive functioning is detected in the cognitive function tests, additional visits to a hospital will be recommended

□ Adverse events education

○ The principal investigators or co-investigators shall explain to the participants the possible AEs that may occur during study participation and explain that since there are no additional interventions or tests outside of the actual process genuinely required for treatment, it is expected that there will be almost no additional AEs that are expected to occur from study participation. However, participants shall be trained to contact investigators immediately when an AE occurs.

□ Collection and reporting of AEs

○ Participants shall be monitored for the occurrence of AEs through measurement of vital signs, tests and questionnaires for measurement/assessment of observation items, or monitoring at each visit to the study institution. If an investigator determines that participants have clinically significant symptoms or changes, or if a participant voluntarily report any signs of AE, the investigator shall record the occurrence, assessment (additional laboratory tests if necessary), and actions taken for the AE in the CRF using standardized medical terminology. If AEs occur after administering acupotomy, ACUPOCHECK shall be used for assessment of AEs and the AEs shall be recorded in the CRF.

○ If serious adverse events (SAEs) occur during study participation, they shall be promptly reported through the e-IRB system in accordance with Article 25 in Chapter 5 of the Standard Operating Guidelines of the Public Institutional Review Board. The definition of SAEs shall follow the definition in the Standard Operating Guidelines of the Public Institutional Review Board.

□ Treatment of AEs

○ In the event of a direct injury/damage that occurred in relation to the KM treatment in the course of routine treatment, appropriate medical treatment shall be provided by the medical staff based on the routine process of treatment

○ This study is a patient registry study for cognitive impairment patients who visit KM clinics (primary care centers) for KM treatment, and there is no intervention other than KM treatment, and there are no additional tests required because of participation in the study. Nonetheless, in the event of AEs, according to the general treatment protocol of the study institution, interventions with suspected causality should be discontinued, and progress observation and appropriate measures and treatment should be taken until the recovery of the patient.

○ Since the expected AEs are not those of severe ones, it is expected that this study will impose no significant burden on the patient's safety, and in principle, safety monitoring should be carried out, principal investigators and co-investigators should be notified of the occurrence of AEs, and appropriate medical treatments should be provided in the event of AEs until the patient is recovered from the AE.

□ Assessment of safety outcomes

○ Safety assessment is performed for all AEs that occurred during the study period. The incidence of AEs, the incidence of AEs that caused dropout of the patient, and the incidence of SAEs will be reported. As for the incidence of AEs, incidence of all AEs and that of AEs related to the KM treatment shall be presented.

○ AEs are collected through a patient's self-report of symptoms, the observation of the physician (KMD) in charge at each visit, and vital signs measured at the time of the visit, and statistical analysis may be performed as necessary only for items determined to be clinically significant by the physician (KMD).

**15. Data Analysis and Methods of Statistical Analysis**

Statistical analyses are planned as appropriate for additional needs, and all analyses in this study will be performed using R Version 4.3.3 (The R Foundation, www.r-project.org). All statistical testing not specifically defined will be conducted as a two-tailed test at a significance level of 5%

For data on efficacy assessment, Full Analysis Set (FAS) will be used for the primary analysis, and data on safety assessment will be assessed using the safety set. If there is a missing value for FAS in the process of efficacy assessment, the LOCF (Last Observation Carried Forward) method will be applied for statistical processing, and for other cases, statistical analysis will be performed based on the original data

Full Analysis Set (FAS): The intention-to-treat (ITT) principle is applied, and FAS refers to a group of participants with at least one measurement of the primary efficacy outcome following KM treatment.

Safety Set (SS): SS refers to a group of participants who have received at least one KM treatment and have undergone at least one safety-related follow-up observation.

□ Descriptive statistics for patient characteristics

○ Demographic information and baseline characteristics are represented using n (%) for categorical data, and mean ± SD for continuous data.

□ Efficacy and safety assessment

○ As for efficacy outcomes, for continuous variables, paired t-test or Wilcoxon signed rank test is performed depending on the status of meeting normality condition, and chi-square test or Fisher's exact test is performed for categorical variables

○ As for analysis of safety outcomes, AEs and SAEs are represented using n (%), and the difference in the incidence (%) between treatment interventions is tested using chi-square test or Fisher's exact test

○ As for subgroup analysis, the participants will be grouped according to the dose of acupotomy (high-dose group/low-dose group) or the severity of cognitive impairment (mild neurocognitive disorder/subjective cognitive decline patients) to examine the difference in efficacy. For comparison of percentage, chi-square test (or Fisher’s exact test) will be used, and for comparison of mean, independent t-test (or Wilcoxon signed-rank test) will be used.

- The definitions of the acupotomy high-dose group and low-dose group will be based on the median value of the number of acupotomy treatments.

□ Selection of covariates for analysis of treatment effects

○ To perform statistical analysis on covariates that potentially influence the treatment effect, for dichotomous dependent variables, logistic regression analysis will be used, and for continuous dependent variables, linear regression analysis will be used. Covariates influencing the treatment effect include the following variables: gender, age, height, weight, smoking, alcohol consumption, physical activity, family history, education level, past and present occupation, marital status, and depression (PHQ-2).

**16. Withdrawal and Dropout**

□ Dropout criteria

○ A participant may be dropped out from the study in the following cases.

- Withdrawal of consent during study participation

- In case of violation of the inclusion criteria or falling under the exclusion criteria.

- In the event of a serious AE occurring to a participant or when continuation of the study is deemed to be difficult due to an AE

- Other cases that are deemed not appropriate to continue the study according to the judgment of the responsible investigator.

○ If a participant drops out from the study, the study data collected before withdrawal will be used for the study. However, if the participant withdraws consent for the use of his/her study data when signing the ICF, during the study process or after dropout, the data of the participant will be excluded from use.

○ Participants who dropped out of this study will not be allowed to participate again later.

□ Criteria for study discontinuation

○ If serious AEs suspected with causal relationship with the treatment occur, the principal investigators shall report the SAE to the Public Institutional Review Board within 24 hours and the study will be discontinued.

○ This study may be subject to premature termination in the following case:

- When the study is deemed to cause risks to the safety and well-being of the participants.

□ Withdrawal of consent

○ Participants may withdraw their consent at any time during the study, even after they have given their voluntary consent to participate in the study, and will not be subject to any disadvantages due to such withdrawal of consent.

**17. Risk/Benefit Assessment**

□ Potential risks

○ Since this study is designed as a single-arm study without a control group, and reflects interventions and tests administered in routine clinical practice of KM treatment, there are no additional risks arising from the study participation itself. Since KM treatments in routine clinical practice are minimally invasive procedure, the risk of AEs or resistance is low, but there are potential risks of AE, although rare, such a local bleeding, bruising, pain, dizziness, and fatigue occurring after administration of acupuncture or acupotomy. However, these risks are at the same level as the general risks experienced in the routine practice of KM treatment, and throughout the process of this study, investigators will continuously monitor the participants to prevent situations of potential risks in advance

○ Since there are no additional interventions or tests related to this patient registry study, injuries directly resulting from study participation are not anticipated; however, if any, compensation may be received according to the provisions in the Study Indemnification Agreement.

□ Potential benefits

○ If a patient is enrolled as a participant and receive KM treatment, there are no direct benefits due to study participation because the process follows the general treatment protocol of the medical institution.

○ By participating in the study, through continuous management of cognitive decline by administering KM treatment, information on the improvement effect can be obtained, and the progress can be observed, which is expected to contribute to the development of KM treatment process for cognitive decline in the future.

□ Analysis of potential risks and benefits

○ Considering the risks, potential risks and benefits as above, the risk of AEs is low and no additional benefits can be expected in terms of the treatment; as a result of the above risk/benefit analysis, since there is no additional risk arising from participation in this study, the level of risk to the study participants is judged to be “less than minimal risk.”

**18. Compensation for Study Participation**

Since this study requires no additional tests or interventions during the treatment process, there is no compensation for the patients because of study participation.

**19. Confidentiality and Privacy Policy**

□ Information collected for routine process of treatment and patient management

○ In this study, personal information of the participants for treatment (information necessary to provide treatment such as name, gender, and date of birth), sociographic information (diagnosis code (KCD), smoking, alcohol consumption, physical activity, family history, education level, past and present occupation, marital status, depression (PHQ-2), type of NHI benefit), medication history, height, weight, vital signs, assessment of patient condition (MoCA-K, K-ECog-12, NRS, ISI-K) will be collected. These data are mainly the observation items for assessment of cognitive function collected in the general practice of providing KM treatment for improvement of cognitive functioning. All of this information does not exceed the scope of information collected in the routine process of KM treatment

○ This study is conducted as a part of a national research and development project commissioned by the National Institute for Korean Medicine Development, and therefore, the study information collected in accordance with the notice and PIL of this study will be recorded and stored through the eCRF (Mytrial) built by the National Institute for Korean Medicine Development and provided to the institution accordingly. A separate PIL and ICF for third-party provision of the study data and its use for secondary research will be distributed to the patients, and the study information will be provided to the third parties and used for secondary research only when the separate consent for this purpose is given.

□ Confidentiality

○ Records that may reveal the identity of the participants will be kept confidential, and the participants’ identities will remain confidential even when the results of the observational study are published. The details are as follows

○ All study data containing the patients’ personal information collected in the study process will be accessible only to the principal investigators and co-investigators.

○ Investigators should be aware that the study sponsor or auditor may review or copy the participants’ charts (EMRs) and CRFs in order to check or verify them once the contract for this observational study is executed.

□ Retention of study data/records

○ The study-related data/records shall be stored in a place where only authorized persons can access them and where access by non-related persons is prevented by attaching a locking device (a cabinet with a locking device and a computer with password-restricted access in the investigators' office, and a computer with password-restricted access in the analysts' and assessors' offices). Access is limited to principal investigators and co-investigators only.

□ Retention period

○ In accordance with Article 15 of the Enforcement Rule of the Bioethics and Safety Act, the study data (written notice of IRB approval, informed consent form, report on the collection/use/provision of personal information, end of study report) shall be stored for at least three years after the end of the study. Data passed on to the analysts and assessors shall also be stored for at least three years from the end of the study.

□ Destruction of study data/records

○ In accordance with Article 15 of the Enforcement Rule of the Bioethics and Safety Act, records related to the study, including electronic documents (written notice of IRB approval, study protocol, study report/end of study report, etc.), shall be permanently deleted and destroyed by shredding using a paper shredder after having been retained for at least three years from the end of the study

○ Data provided to analysts and assessors shall also be permanently deleted and destroyed by deleting for electronic files and by shredding in a document shredder for paper-based documents after having been for at least three years from the end of the study.

○ Information provided to the National Institute for Korean Medicine Development through myTrial shall be retained for 10 years after the end of the study.

**20. References**