HGPI Health and Global Policy Institute

Health and Global Policy Institute (HGPI) Dementia Policy Project

Online Meeting: Global Round Table Session
"Building a Better Clinical Trial Environment for Dementia Through Multi-Stakeholder Collaboration"
Report

March 2022

March 8, 2022 Global Round Table Session

"Building a Better Clinical Trial Environment for Dementia Through Multi-Stakeholder Collaboration"

Event Overview

Summary of Issues:

Despite many clinical trials for drugs to prevent or treat Alzheimer's disease (AD) failing so far, aggressive and ongoing clinical trials are still needed in the future. At the same time, in the case of dementia, it is technically difficult to secure a sufficient number of trial participants. This remains a challenge in the advancement of research and development worldwide.

Under these circumstances, clinical trial implementation systems have been developed in Europe and the United States in recent years such as the European Prevention of Alzheimer's Dementia Consortium (EPAD). The EPAD system consists of three strategies: (1) enrolling a large number of people who have not yet developed dementia in a registry, (2) monitoring them over a long period of time, and (3) selecting eligible trial participants from among them. This process continues to produce some positive outcomes, such as the collection of high-quality patient data and the ability to conduct clinical trials more efficiently and effectively.

In Japan, a similarly structured drug trial-ready cohort, Japanese Trial Ready Cohort for preclinical and prodromal AD (J-TRC), has been established. It recently became operational in October 2019. For this system to operate sustainably and autonomously, it is essential that the significance of developing such a system in Japan is widely understood by the public and that many people participate in the process.

In that context, an international round table session was held in collaboration with the Unit for Early and Exploratory Clinical Department of the University of Tokyo Hospital, the implementing body of the J-TRC, to discuss future measures for the improvement and sustainable development of the clinical trial implementation system.

Although there were a wide range of issues discussed, there were some major takeaways. (1) In terms of measures to ensure sustainable funding, it is important to (i) create a transparent and fair system to facilitate the flow of private funding and (ii) have more people recognize the significance of dementia policy by having those directly affected and their caregivers actively talk about the fact that dementia is an issue for society as a whole.

Regarding (2) strategies for publicity and awareness-raising related to clinical trials, many experts commented that (1) it is important to educate the public on broader concepts such as "Brain Health" to avoid negative impressions of dementia. It was also pointed out that (2) it is desirable to identify biomarkers as early as possible and create an environment in which risk factors can be easily measured in health checkups so that everyone becomes more familiar with the disease.

Event Overview:

■ Date & Time: March 8, 2022, 15:30-17:45 JST (Local time in the U.K.: 06:30-08:45)
■ Format: Zoom Webinar
■ Hosted by: Health and Global Policy Institute (HGPI)
Unit for Early and Exploratory Clinical Development, The University of Tokyo Hospital
■ Languages: Japanese and English with simultaneous interpretation

■ Program (titles omitted / no particular order)
15:30-15:35 Welcoming Remarks and Explanatory Introduction
Ryoji Noritake (CEO, Board Member, HGPI)
15:35-15:40 Keynote lecture 1 "Current J-TRC Status and the Future"
Takeshi Iwatsubo (Professor, Graduate School of Medicine, The University of Tokyo)
15:40-15:50 Keynote lecture 2 "Forming Clinical Trial Environment for Dementia in Japan"
Toshihisa Tanaka (Special Officer for Dementia Policy and Assistant Section Chief, Division of Dementia Policy and Community-Based Long-Term Care Promotion, Health and Welfare Bureau for the Elderly, Ministry of Health, Labour and Welfare)
15:55-16:10 Keynote lecture 3 "Global Trends of Public-Private-Partnership for Drug-discovery in Brain Health"
Craig Ritchie (Director, Centre for Dementia Prevention, The University of Edinburgh)
16:15-17:00 Round table Discussion 1 "Global Trends and Japan's Challenges: Achieving Sustainability for Clinical Environment for Dementia"
17:00-17:35 Round table Discussion 2 "Earning Public Engagement and Awareness for Clinical Environment for Dementia"

Round table Panelists (no particular order):

- Takeshi Iwatsubo (Professor, Graduate School of Medicine, The University of Tokyo)
- Yoshiki Niimi (Special Appointed Lecturer, The University of Tokyo Hospital)
- Motoharu Kawai (Director, Alzheimer's Association Japan, AAJ; Director, the Yamaguchi Branch of AAJ; Vice Director, Neuromuscular Center Yoshimizu Hospital)
- Naomi Sakurai (President, Cancer Solutions Co., Ltd.)
- Ryoko Ihara (Chief Physician, Department of Neurology, Tokyo Metropolitan Geriatric Medical Center Hospital)
- Takeshi Ikeuchi (Professor, Brain Research Institute, Niigata University)
- Sayuri Watanabe (Japan Compound Development Team Leader, R&D Janssen Pharmaceuticals of Johnson & Johnson)
- Craig Ritchie (Director, Centre for Dementia Prevention, The University of Edinburgh)
- Lenny Shallcross (Executive Director, World Dementia Council)

17:35-17:45 Closing Remarks
Kiyoshi Kurokawa (Chairman, HGPI)

Notable Points from the Discussion:

Welcoming Remarks & Explanatory Introduction
Ryoji Noritake (CEO & Board Member, Health and Global Policy Institute)

Health and Global Policy Institute (HGPI) is an independent non-profit, non-partisan think tank established in 2004. Since its establishment, HGPI has been making policy recommendations as a neutral think tank, working with industry, government, academia, and global stakeholders to realize citizen-centered healthcare policy.

The institute's Chairman, Kiyoshi Kurokawa, serves as a member and vice-chair of the World Dementia Council (WDC), and has long been involved with dementia initiatives, recognizing the seriousness of the issue and making policy recommendations. Specifically, HGPI has made proposals from the perspective of (1) creating a society in which people living with dementia can live comfortably and (2) promoting multi-stakeholder collaboration across industry, government, academia, and civil society in the field of clinical research and development.

The European Prevention of Alzheimer's Dementia Consortium (EPAD) and other organizations in Europe have been working on the development of clinical trial implementation systems, the subject of this report. The Japanese Trial Ready Cohort for Preclinical and Prodromal AD (J-TRC), a drug trial-ready cohort, began operations in October 2019 and has been attracting attention.

Today, we would like to also invite leaders in cancer policy to join us in discussing the steps that need to be taken in the future for J-TRC to continue its efforts.

Keynote lecture 1 "Current J-TRC Status and the Future"
Takeshi Iwatsubo (Professor, Graduate School of Medicine, The University of Tokyo)

First, looking back at the status of development of drugs for the treatment and prevention of Alzheimer's disease (AD), only four "symptom-improving drugs" have been launched so far, including Aricept. As for "disease-modifying drugs" that target the mechanisms behind the onset of dementia, 146 clinical trials have failed so far, but some amyloid beta-directed monoclonal antibody drugs, such as Aducanumab, have finally been submitted for approval. However, the efficacy of Aducanumab and other drugs in the treatment of mild cognitive impairment (MCI) has been limited to slowing the worsening of symptoms by about 20–30%. The development of effective drugs remains a major challenge.

In this context, the target of therapeutic drug development for AD is shifting from the MCI phase (prodromal phase) to the preclinical phase during which there is no cognitive dysfunction. However, the eligibility rate for clinical trials (the probability that a candidate for a clinical trial will be eligible for a drug) is only 20% at best, and in the preclinical stage, it is difficult to invite participants for clinical trials, not to mention the challenges of making a diagnosis at the preclinical stage.

On the other hand, as far as academic research is concerned, longitudinal observational studies (J-ADNI: Japanese Alzheimer's Disease Neuroimaging) in which healthy subjects are observed over a long period of time without medication, are being conducted. Although these studies are very important in establishing new evaluation methods and clinical trial systems, there is inevitably an overlap of eligible patients between these observational studies and the clinical trials described above. This has led to a competition for participants worldwide.

In Europe and the United States, a "Trial Ready Cohort (TRC)" system has been established as a strategy to appropriately recruit participants for AD research (Europe: EPAD, United States: Trial-Ready Cohort for the Prevention of Alzheimer's Dementia (TRC-PAD)), which has been used to balance the recruitment of participants for observational studies with the recruitment of eligible participants for clinical trials.

In Japan, the J-TRC has just been launched as a mechanism similar to those found in Europe and the United States. J-TRC combines two stages in gathering participants for AD research and narrowing down the list of those eligible for clinical trials: a web study, in which participants can participate via the Internet, and an on-site study, in which participants are evaluated in person.

Specifically, the first step is to (1) recruit a large number of volunteers from the general public (approximately 20,000 people) via the Internet and have them take simple cognitive function tests on an ongoing basis. Second, (2) some of these people (about 1,000) will undergo in-person cognitive function tests, blood sampling, positron emission tomography (PET), and other tests to assess the risk of future cognitive decline (amyloid risk assessment). Based on the patient's wishes and approval, they are then referred to a clinical trial or for continue observation without medication (natural history follow-up).

J-TRC is also working with a consortium of pharmaceutical companies from Japan and abroad to utilize the clinical trial data obtained through the above mechanisms for the development of effective preventive and therapeutic drugs.

Keynote lecture 2 "Forming Clinical Trial Environment for Dementia in Japan"
Toshihisa Tanaka (Special Officer for Dementia Policy and Assistant Section Chief, Division of Dementia Policy and Community-Based Long-Term Care Promotion, Health and Welfare Bureau for the Elderly, Ministry of Health, Labour and Welfare)

The government's policy response to dementia came in the form of the "Outline for Dementia Policy Promotion" in June 2019, following the Orange Plan and the New Orange Plan. The outline aims to delay the onset of dementia and create a society in which people can live with hope even if they develop dementia, with "symbiosis" and "prevention" as the two pillars of the policy. The concept is based on the basic understanding that anyone can develop dementia and aims to create a society in which people can live their lives with as much dignity as possible. Specific measures include (1) public awareness and support for transmitting information, (2) prevention, (3) medical treatment and care and support for caregivers, (4) barrier-free access and support for social participation, and (5) research and development.

Looking at the basic ideas of the general outline on research and development, which is the subject of the event's discussion, first, it covers a wide range of areas, including (1) elucidation of the mechanisms behind the onset and progression of dementia; prevention, diagnosis, and treatment methods; rehabilitation; and research and development relating nursing care models. It also states that (2) the establishment of a registration system for research and clinical trials will be promoted, leading to early detection and the development of therapeutic and preventive drugs.

An overview of the respective roles of industry, government, and academia in R&D shows that (1) academia contributes research and development relating to new drug candidates, (2) industry leads to actual drug development through clinical trials, and (3) government agencies provide financial support for research and development. Looking at the roles of related ministries and agencies, (1) MEXT is responsible purely for academic-related matters, (2) MHLW for cohort research support, clinical research, and clinical trial support, (3) METI for industry promotion, and (4) the Japan Agency for Medical Research and Development (AMED) provides technical and research support as a relay point between the various actors.

In general, the key to accelerating innovation is to create an ecosystem that successfully facilitates the coordination of human resources, technology, and funds. In Japan, METI is taking the lead in managing this task when it comes to the development of new drugs.

On the other hand, the MHLW has stated that the Dementia Research and Development Project will promote (1) a cohort registry, which will serve as the center of dementia research, (2) biomarker research that will contribute to diagnosis, and (3) research aimed at clarifying pathophysiology such as genome research. Regarding the cohort portion of the project, the Key Performance Indicator (KPI) includes this event's theme of establishing a cohort that can immediately support drug trials.

There are four cohort-related research systems in place at present. In addition to (1) the J-TRC, which has already been introduced today, there is also (2) the prospective cohort study, which targets a large number of healthy elderly people (about 12,000), and utilizes multifaceted information including diagnostic imaging data and genome information in addition to conventional health information. Moreover, as part of (3) a retrospective cohort study, we plan to conduct research using genome samples that clearly indicate the presence of dementia disease. This will lead to the development of diagnostic markers, which, when combined with the prospective cohort, will hopefully lead to recommendations for effective risk-based prevention methods, etc.

In the (4) Dementia stage-specific cohort study, four stages of dementia are identified (healthy stage, preclinical stage, MCI stage, and post-onset AD), and research targeted toward each stage is promoted. The system also allows for research that looks at the stages from a bird's-eye view. In addition, research is being conducted to standardize the diagnostic techniques and treatment policies required throughout each stage.

We have been developing blood biomarkers for AD in collaboration with the private sector, although they need to be simple and easy to use. Developments over last few years have resulted in achievements such as mass spectroscopy (a blood biomarker for amyloid beta) and an instrument for measuring phosphorylated tau in blood using a digital Enzyme-Linked Immuno Sorbent Assay (ELISA).

Keynote lecture 3 "Global Trends of Public-Private-Partnership for Drug-discovery in Brain Health" Craig Ritchie (Director, Centre for Dementia Prevention, The University of Edinburgh)

Until now, the focus on neurodegenerative brain disease tended to be limited to the narrow area of "dementia," at which point serious cognitive symptoms eventually emerge. However, in the future, basic research and clinical practice will focus more on the preliminary stages of neurodegenerative brain disease and how to target people for early detection, prevention, and treatment.

Risk factors for dementia have been identified, for example, in a survey report in the medical journal The Lancet. The challenge, however, is how to apply this information to (1) prevention of the onset of the disease for those affected, (2) public awareness, and (3) research on the mechanism of onset that could lead to a cure. We present an early detection and prediction model ("Four Factor Model") for early Alzheimer's disease. Specifically, the model combines four factors: (1) comprehensive analysis of risk factors, (2) examination of neurodegenerative brain disease by biomarkers and (3) symptoms, and (4) measurement of changes over time. We are trying to utilize this information in the creation of multi-layered treatment plans.

[Overview of the European Prevention of Alzheimer's Dementia (AD) Consortium (EPAD)]

EPAD is an organization that aims to develop a platform that efficiently enables the undertaking of adaptive Proof of Concept (POC) studies. EPAD has invested a large amount of budget and human capital to promote research into the causes of AD, biomarker development, and the development of clinical trial systems. Various organizations, including academic societies, major pharmaceutical companies, patient groups, and small and medium-sized companies, are participating in the project as partners.

More specifically, (1) a registry of several hundred thousand people was established in Europe and (2) the cohort participants' risk factors and symptoms were closely examined over several years, and (3) a clinical trial is now underway. In terms of clinical trials, by standardizing the target group of placebo administration in many clinical trials, the efficacy of therapeutic agents can be measured and evaluated very efficiently and accurately.

Looking back on EPAD's achievements over the past several years, we have accumulated an enormous amount of data, and we have received requests from many large companies and start-ups to share our data. As the COVID-19 pandemic slowly comes to an end, we would like to further cooperate with them.

Efforts in Scotland

In Scotland, Brain Health Scotland (BHS), with financial support from local governments, has created an ecosystem for dementia prevention.

Specifically, BHS is applying the EPAD framework to (1) enroll a large number of people, (2) monitor them at local Brain Health clinics (instead of cohorts), and (3) link them to a clinical trial platform to promote AD prevention research projects in a community-wide clinical setting.

In addition, the BHS takes a broadly localized, individualized approach to each risk by, for example, promoting awareness-raising activities in schools, while offering prevention measures, advice, or individualized interventions for higher-risk populations.

As high-quality data is accumulated, a prediction pattern (algorithm) of progression with respect to the stages of dementia will be created. In clinical settings, this can be used to provide more precise advice, treatment, and intervention, including the ability to create individualized intervention plans that take

advantage of the identification of risk factors and early detection. In addition, by establishing a consistent treatment policy to be applied throughout the region, we have been able to collect uniform, high-quality treatment data, which has helped in selecting participants for clinical trials and in furthering research.

In addition to EPAD, BHS also works with the Davos Alzheimer's Collaborative (DAC) (an industry-government-academia coalition that connects research organizations and clinical entities related to Alzheimer's disease) and with global research projects, companies, and organizations. Scotland is the only country/region to collaborate with the DAC on all three tiers ("Triple Stack") of the DAC's scope: (1) cohorts, (2) clinical trials, and (3) clinical sites.

Although Scotland is only a small region, we hope that BHS's efforts will trigger a domino effect and lead to the further development of research and clinical practice in Alzheimer's disease.

Round table Discussion 1 "Global Trends and Japan's Challenges: Achieving Sustainability for Clinical Environment for Dementia" Key Takeaways

Continued public funding is vital

- In order to develop a sustainable dementia clinical trial platform, it is very important not to be biased toward either public or private funding, but to incorporate both in a balanced manner.
- In other countries, public funds are continuously invested in the management and development of dementia clinical trial platforms.
- Public funds will undoubtedly play an important role in this context. Although J-TRC has obtained public funds for the first five years since its establishment, considering that it takes about three years at the fastest for a project to get off the ground, public funds will continue to be greatly needed, and it is important to obtain them on an ongoing basis.

A transparent and fair system must be created to make it easier to attract private funding

- In order to attract private funding, it is important to create a system that facilitates transparent and appropriate clinical trials and enables the private sector to pay for the use of the cohort. At the same time, private and public funds must be held separately from one another.
- It is important to ensure transparency around how research funds are used in order to enable private companies easily proceed with internal approval procedures when contributing funds.
- Rather than responding to the requests of companies individually, it would be beneficial to create a consortium, an environment that private companies use in a fair manner.

Dementia is an issue for society as a whole, and those affected should actively communicate this fact

- Based on the experience in the field of oncology, it is important that people with dementia and their caregivers actively talk about the fact that dementia is an issue for society as a whole. Greater awareness among the general public may lead to individual donations in addition to funds from the public and private sectors.
- Public funds and other resources can be allocated only when society becomes more aware of dementia. The more people are diagnosed as "at risk for dementia" at an early stage and the more people are involved, the less prejudice and stigma there will be against dementia in society, the more people will see a doctor early and proactively, and the more research will be conducted, thus creating a virtuous cycle.

The perspectives of those affected must be incorporated from the research design phase

- The design and operation of biomarker-related research tend to be conducted with priority given to the convenience of the researcher and the research purpose. However, considering the high possibility that a large number of people will be diagnosed using such biomarkers in the future, it is important to make more use of the voices of the people concerned from the design stage.

Round table Discussion 2 "Earning Public Engagement and Awareness for Clinical Environment for Dementia" Key Takeaways

It is important to raise awareness of broader concepts such as "Brain Health"

- Developments in screening technology will increase the number of people who recognize they are at risk of developing dementia before they are symptomatic. There must be greater awareness surrounding the results of such diagnoses so that they can be understood within the wider context of "Brain Health". It is important to increase the general public's health literacy so that they are composed and positive after being diagnosed.
- How dementia is perceived in society is very much influenced by the way it is covered by the media. The media should promote reporting and awareness-raising from the perspective of how to maintain "a healthy state (of the brain organ)," not just one-off episodes related to dementia.
- There tends to be an image of dementia being a strictly terminal stage disease which leads to stigma. As with cancer, there is a lot of social support and various ongoing studies, and it is important to highlight that people with dementia lead diverse lives.

Clinical trial sites should work with local and regional communities to educate the public

- It is recommended that clinical trial sites actively promote dialogue with local residents in order to deepen two-way communication with participants and to promote understanding of dementia at the local level.

Biomarkers should be used to measure risk in a convenient manner

- In the near future, blood biomarkers and digital biomarkers should be made easily available for diagnosis by family doctors and for medical checkups and physical examinations. This will have a synergistic effect of increasing public awareness of dementia, accelerating the diagnosis of the disease type and definitive diagnosis, and advancing research.
- To avoid spreading the misconception of "early detection and early despair," it is necessary to provide careful feedback upon diagnosis and after clinical trial results have been released.

Closing Remarks

Kiyoshi Kurokawa (Chairman, Health and Global Policy Institute)

Digital technology is developing faster than research in the field of biochemistry, so we are paying a great deal of attention to this area. We hope that the data obtained from the clinical trial implementation system introduced today will also provide information that will be useful for research and development.

Looking back on the history of science, whether it is antihypertensive drugs or anti-cholesterol medications, there have been cases in which clinical and basic research rapidly progressed and led to the development of therapeutic drugs as specific substances were found to be associated with specific pathological conditions. In the same way, as the pathology of dementia is elucidated and markers that can be objectively evaluated to predict the onset of the disease are developed, it is anticipated that better preventive and therapeutic measures will be developed.

On the other hand, there are cases where a new efficacy is discovered by chance, such as when minoxidil, originally developed as a treatment for high blood pressure, is later found to be effective in treating alopecia and becomes a major hit as a hair-growth agent. In the case of dementia, serendipity may lead to the discovery of a breakthrough drug in an unexpected field.

Thus, it is important to challenge ourselves in new areas of biochemistry, while at the same time learning from history, looking at a wide range of research fields, and taking a hard look at existing ones.

HGPI Guidelines on Grants and Contributions

As an independent, non-profit, non-partisan, private think tank, Health and Global Policy Institute (HGPI) complies with the following guidelines relating to the receipt of grants and contributions.

Approval of Mission

The mission of HGPI is to improve the civic mind and individuals' well-being, and to foster a sustainable healthy community by shaping ideas and values, reaching out to global needs, and catalyzing society for impact. The activities of the Institute are supported by organizations and individuals who are in agreement with this mission.

Political Neutrality

HGPI is a private, non-profit corporation independent of the government. Moreover, we receive no support from any political party or other organization whose primary purpose is political activity of any nature.

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HGPI makes independent decisions on the course and content of its projects after gathering the opinions of a broad diversity of interested parties. The opinions of benefactors are solicited, but the Institute exercises independent judgment in determining whether any such opinions are reflected in its activities.

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In order to secure its independence and neutrality, HGPI will seek to procure the funding necessary for its operation from a broad diversity of foundations, corporations, individuals, and other such sources. Moreover, as a general rule, funding for specific divisions and activities of the Institute will also be sought from multiple sources.

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HGPI will not partake in any activity of which the primary objective is to promote or raise the image or awareness of the products, services or other such like of its benefactors.

Supporting organizations are asked to submit written agreement with HGPI's compliance with the above guidelines.

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