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Special Feature Article

Practice and Research Ethics of Multicenter Collaboration Research in the Field of Psychiatry

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Abstract

Because research is a search for truth, if it goes too far, it may overstep the bounds of "ethics", which is "the path that should be followed as a human being". Therefore, ethical considerations must be taken into account when conducting medical research, and the research plan must undergo ethical review and approval. The definition of ethics is strongly influenced by culture and climate, making it difficult to standardize. In the case of multicenter research, the research protocol is reviewed by the ethics committees of each research institution and is affected by the differences among these ethics committees. The Cognitive Genetics Collaborative Research Organization (COCORO) is a 39-institution organization that conducts research on the biology of psychiatric disorders using intermediate phenotypic data and biological samples. COCORO project has obtained ethical approval as genetic research, in collaboration with genetic studies and other studies that have already begun at other research institutions, allowing the sharing of information and samples among the collaborating institutions. The Effectiveness of Guidelines for Dissemination and Education in Psychiatric Treatment (EGUIDE) involves 240 medical institutions from 44 universities and is examining changes in prescribing behavior in medical institutions after a course on the guidelines was taken by psychiatrists across the country. EGUIDE uses the

procedure of a central ethics review, and electromagnetic informed consent has also been introduced. We are expected to understand and comply with the essence of research ethics.

Keywords: COCORO, EGUIDE, multicenter collaboration research, central ethical review, research ethics

Introduction

Because research is the search for truth, if it goes too far, it may overstep the bounds of "ethics," which is "the path that should be followed as a human being." Therefore, ethical considerations must be taken into account when conducting medical research, and the research plan must undergo ethical review and receive approval. Ethics, by definition, is strongly influenced by culture and climate, and although there are general guidelines, the application of these guidelines tends to be individualized, making standardization difficult. In the case of multicenter research, the research protocol is reviewed by the ethics committees of each research institution and is affected by the differences among these ethics committees. The "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (hereinafter referred to as the "new guidelines"), which came into effect in 2021, allow centralized ethical review of multicenter

collaborative research due to standardization and economies of scale.

In this paper, we will focus on "COCORO (Cognitive Genetics Collaborative Research Organization)," which was started before the new guidelines came into effect, and the "EGUIDE Project (Effectiveness of GUIDeline for Dissemination and Education in Psychiatric Treatment)," which was started before the new guidelines but many centers switched to central review after the guidelines came into effect. COCORO is a biological study of psychiatric disorders involving 39 research institutes using intermediate phenotypic data and biological samples. It is positioned as a genomic study, and is being conducted with ethical approval in the form of collaborative genomic research with a study already started at another research institute, allowing the exchange of information and samples between the collaborating institutes. EGUIDE, on the other hand, involves 44 universities and 240 medical institutes,

and examines changes in prescribing behavior at medical institutes after psychiatrists across Japan take a course on the guidelines, and about half or more of the institutes are ready for central ethical review.

I. Research Ethics and Practice in COCORO

COCORO is a multicenter cooperative research system for research into the etiology and pathophysiology of mental disorders and elucidation of the molecular mechanisms of brain function.³⁾ COCORO was launched in 2013 with 24 research institutes, and 52 research institutes were participating as of May 2024. COCORO brings together researchers from various research fields (neuroscience, molecular biology, genomics, psychiatry, brain imaging, cognitive science, neurophysiology, psychology, etc.), mainly in the field of brain science, to develop and promote new research fields through interaction. The conference also promotes understanding and exchange of translational understanding between basic and clinical research by breaking down the barriers between researchers in Japan and having honest discussions with not only clinical researchers but also basic researchers from a wide range of fields. One of the features of this project is that it is a multi-center

collaborative study using more than 10,000 intermediate phenotype data (such as brain imaging, cognitive function, and neurophysiology) and more than 20,000 biological samples (such as genome, plasma, serum, lymphoblasts, and iPSC cells). In order to conduct this multicenter collaborative research, there are several issues that need to be addressed, including the "establishment of an ethical framework for collaborative research that allows sharing of samples and information," "compatibility of independence and complementarity between research institutes," "establishment of a common measurement system," and "collaboration with basic researchers"; however, the basic premise for this is that it is essential to build a relationship of trust. In order to conduct joint research, it is important to respect and respond to each other in good faith, based on the premise that both parties have differences in common sense, environment, and standpoints regarding research. Since the theme of this article is research ethics, we omit other details and describe the development of a collaborative research ethics system that enables the sharing of samples and information (Fig. 1).

In the previous collaborative research system, when COCORO and Research Institute A, and COCORO and Research Institute B obtained approval as

collaborative research institutes, it was possible to share samples and information between COCORO and Research Institute A and between COCORO and Research Institution B, respectively, but the relationship between Research Institute A and Research Institute B was not positioned as multicenter collaborative research, so samples and information could not be shared between them. Therefore, if all 30 research institutes were to share samples and information, 29 ethics procedures would be required per research institute to apply for changes, and if all 30 institutes were to do the same, 870 ethics procedures would be required in total. It would be almost impossible to do this in practice. Therefore, in the collaborative research system of COCORO based on the former ethical guidelines, the research plan was to share samples and information with each other among the collaborative research institutes belonging to COCORO. On newly adding Institute C to Institutes A and B, COCORO and Institute C will modify the research plan to add Institute C as a research institute belonging to COCORO, and both institutes will receive approval at the ethical review, enabling the sharing of samples and information among research institutes A, B, and C as COCORO's collaborative institutes. In this way, if there were 30 research

institutes, the number of ethics procedures for change application would be 58 times, and although COCORO itself requires ethics review each time and 29 ethics procedures for change application are necessary, each research institute would only have to go through the procedures once, which would significantly reduce the overall effort.

Once the sharing of samples and information has become possible in this way, it becomes necessary to reach a consensus on their utilization. Although this is related to the independence and complementarity of each research institute, if the research that requires the shared samples and information overlaps, once the samples and information are used in one study, it may not be possible to use them in another study. For this reason, the database committee has established a system for utilization. Specifically, in principle, utilization is positioned as collaborative research in COCORO, and collaborative research proposals must be presented by the proposers at the COCORO meeting and approved by all COCORO members. Since COCORO meetings are held only twice a year, proposals are also made in the form of research proposals that can be handled at any time. The utilization of samples and information is permitted only when the consent of the researcher who is providing them is obtained, and the

system allows individual laboratories to make decisions on the provision of samples and information according to their own circumstances.

COCORO produced nine papers in 2020, one of which is introduced below.⁵⁾ Although schizophrenia is known to be associated with cognitive dysfunction, there have been few studies on its associated brain pathology. Therefore, we examined brain structural features using brain MRI data from 633 healthy COCORO subjects, 111 schizophrenic patients with cognitive dysfunction, and 54 schizophrenic patients with preserved cognitive function. As a result, we found that brain structural abnormalities commonly observed in schizophrenia, regardless of the presence or absence of cognitive dysfunction, were characterized by the small volume of the left and right hippocampi and large size of the right putamen and left globus pallidus. However, the gray matter volume of the whole brain was smaller and left and right cerebral cortices were thinned as brain structural features specific to cognitive dysfunction. Therefore, we examined differences in functional connectivity of the brain between cognitively retained and cognitively impaired groups among schizophrenia patients. The results showed that the level of functional connectivity of the nucleus accumbens and frontal lobes

was higher in schizophrenia patients with preserved cognitive function (Figure 2). These results suggest that the mesencephalo-cortico-limbic circuit, which is a reward system, may play a role in the preservation of cognitive function.

II. Research Ethics and Practices in the EGUIDE Project

The EGUIDE project involves multicenter collaborative research that began in 2016 with 22 medical institutes, with a gradual increase in the number of participating institutes, and as of May 2024, it consisted of 47 universities and 302 medical institutes. In this project, we are conducting research to verify the effectiveness of the guidelines by providing psychiatrists nationwide with training on "Guidelines for Pharmacological Therapy of Schizophrenia" and "Guidelines for Treatment of Depression" (about 20 times a year; approximately 3,700 trainees in total). To examine the effectiveness of the guideline training for psychiatrists, QI (Quality Indicator), which quantitatively measures the quality of patient care, is being developed as an outcome of the research. QI refers to the percentage of patients receiving ideal treatment. For example, in the case of schizophrenia, the numerator is the percentage of schizophrenic patients

receiving monotherapy with antipsychotic drugs at discharge, and the denominator is the percentage of schizophrenic patients discharged from the hospital. The higher the percentage, the better, but it does not have to be 100%, because in practice, not all patients are in ideal situations. The information necessary to calculate this QI is collected by providing patients with the opportunity to refuse by disclosing information in their medical records in general practice (opt-out procedure). A survey of the current status necessary to verify the effectiveness of the training revealed that QI of standard treatment for schizophrenia and depression, antipsychotic monotherapy and antidepressant monotherapy rates, respectively, varied widely among facilities, ranging from 0 to 100%, indicating that equalization is necessary¹⁾²⁾ (Figure 3). We have been operating in cooperation with the Japanese Society of Neuropsychopharmacology, Japanese Society of Mood Disorders, and Japanese Society of Clinical Neuropsychopharmacology, which have developed guidelines, and from FY2021, the training also included the contents of the "Clinical Guide for Women with Mental Health Problems during the Perinatal Period" and "Prevention Guide for Obesity and Diabetes in

Patients with Schizophrenia", both of which were developed by the Japanese Society of Psychiatry and Neurology. The project is a collaborative effort among the four societies. In the training course, many psychiatrists have misconceptions about the guidelines themselves, so we make sure to inform them that the guidelines are "designed to support patients and medical professionals, and can be used as a decision-making tool in clinical practice." After that, the lecture on the specific contents of the guidelines is followed by case group discussions in small groups to learn about the actual use of the guidelines and clinical concepts for which there is no evidence. It is expected that this project will contribute to the dissemination of standard treatment in psychiatry, since psychiatrists' understanding of the guidelines will be markedly improved by attending this one-day course on treatment guidelines for schizophrenia and depression, respectively.⁴⁾ When the participants were surveyed not only about their understanding of the guidelines but also about their implementation, they showed improvement in all categories one year after the course, and this improvement was maintained two years later. The rates of monotherapy with antipsychotics for schizophrenia and monotherapy with antidepressants for

depression were higher in patients whose primary physicians attended the course than in patients whose primary physicians did not attend it (no grouping of primary physicians was conducted; data were collected retrospectively), and these rates improved over time. In this way, the EGUIDE project aims to ultimately improve patients' quality of life through the development of guidelines, guideline training, improved understanding of guidelines, improved implementation of guidelines, and improved prescribing behavior (Figure 4).

The EGUIDE project introduces centralized batch review of multicenter collaborative research at those institutes that are able to do so in order to comply with the new guidelines, and as of November 2021, 57 of the 60 collaborating institutes were undergoing batch review. In addition, based on COVID-19 measures, electromagnetic informed consent was also made possible. As the number of participating institutes gradually increased, the research protocol had to be revised several times a year, and each time revisions were made, the collaborative research institutes had to submit the revised contents to the respective ethics committees, which placed a heavy burden on each researcher. The new batch review

system has greatly reduced the burden on the research institutes.

Conclusion

This paper outlined the practice and research ethics of multicenter collaborative research in the field of psychiatry, using COCORO and EGUIDE as examples. In most cases, research that has been approved by the ethics review committee of the lead institute is approved as is, but in some instances this is not the case. In cases of such large multicenter research, it is necessary to respond to various inquiries from collaborating institutes, and differences among the ethics review committees can be marked. Research approved by one ethics review board may not be approved by another. Why does this happen? The EGUIDE project is being promoted because of the need to reduce the variation in treatment among psychiatric hospitals, but to what extent is such variation acceptable to ethics review committees? Have there been any attempts to standardize the quality of ethics review committees so that they can be quantitatively evaluated, compared, and improved, as in the case with the EGUIDE project? Under the new system in which centralized review is the principle, it may be necessary to evaluate the ethics of ethics review committees in the future.

Editor's note: This special issue is based on the symposium held at the 117th Annual Meeting of the Japanese Society of Psychiatry and Neurology, with Chieko Kurihara (National Institutes for Quantum Science and Technology) as a representative.

There are no conflicts of interest to disclose in connection with this article.

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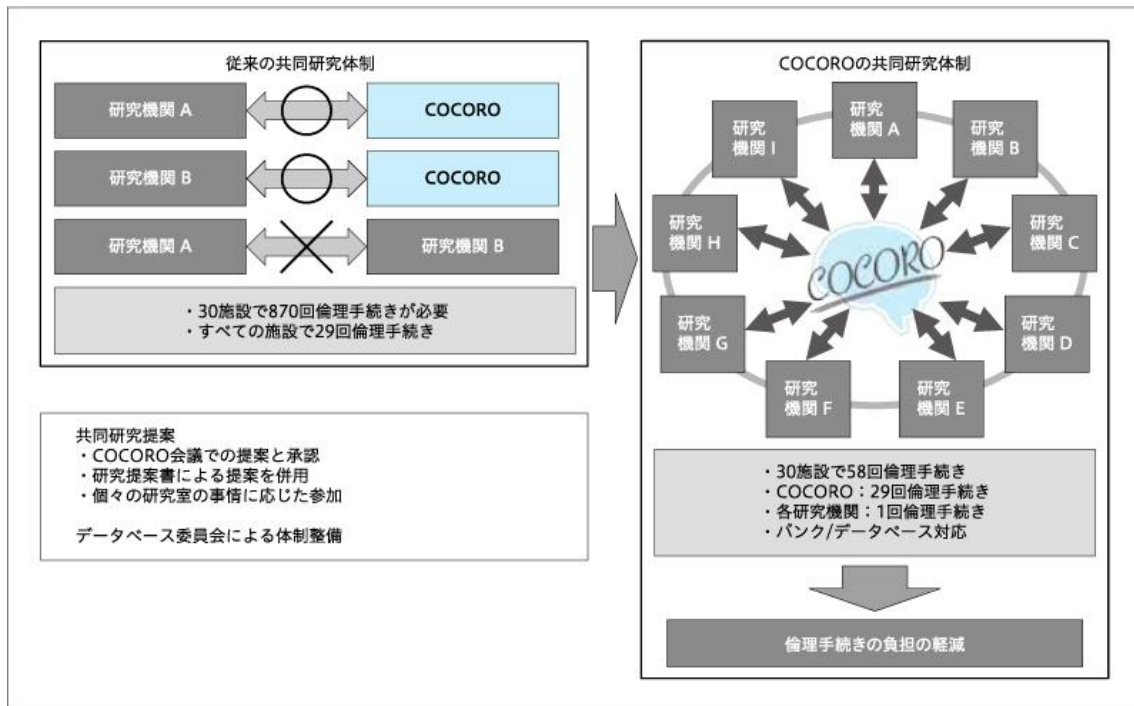


図1 共同研究体制の枠組み（データの共有と利活用）

Figure 1: Framework of Collaborative Research System (Data Sharing and Utilization)

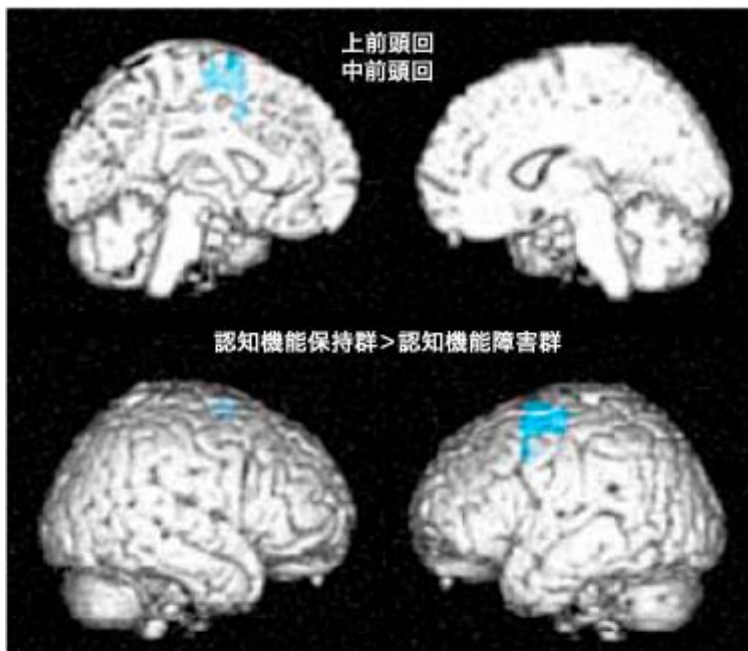


図 2 統合失調症の認知機能障害の脳病態基盤
シードを側坐核にして，統合失調症の認知機能保持群と認知機能障害群の機能結合性の比較を行い，上前頭回と中前頭回との機能結合性が，認知機能保持群にて高いことを示した。
(文献 5 より引用)

Figure 2: Brain Pathological Basis of Cognitive Dysfunction in Schizophrenia

The results of a comparison of functional connectivity between cognitively intact and impaired groups of schizophrenics using the nucleus accumbens as a seed, revealing that the level of functional connectivity between the superior frontal gyrus and middle frontal gyrus was higher in the cognitively intact group. (Adapted from Reference 5)

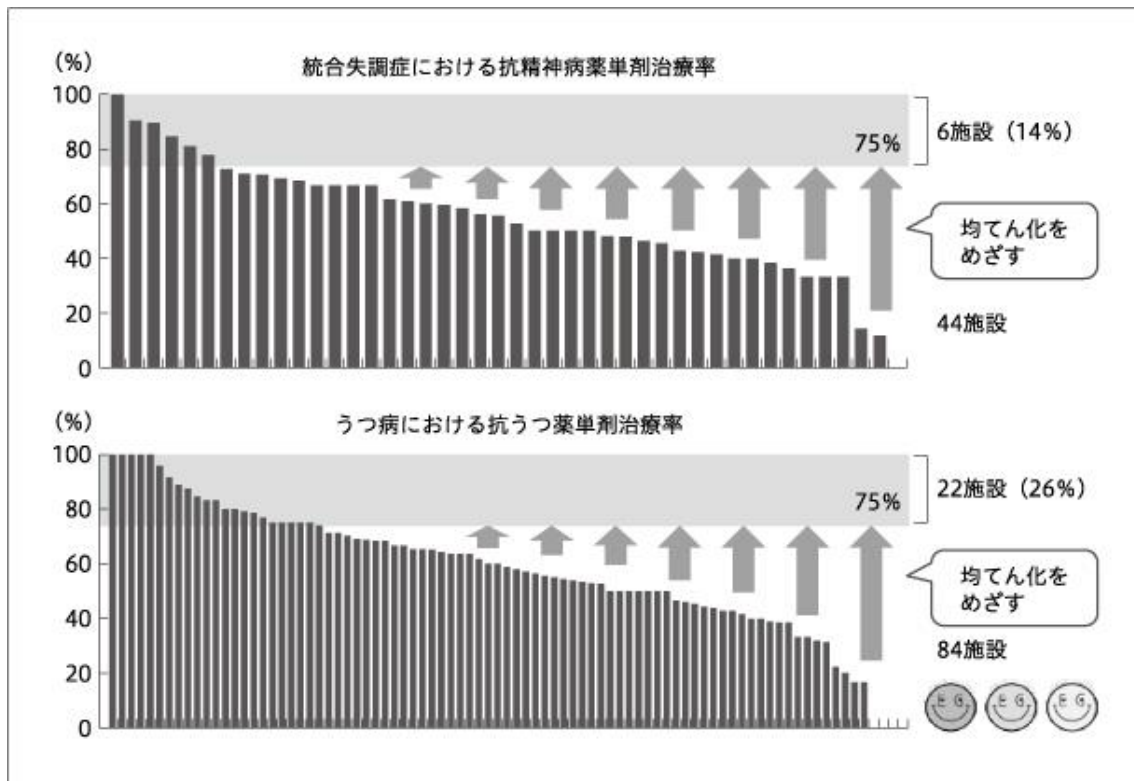


図3 精神科臨床のエビデンス・プラクティスギャップ
縦軸は、それぞれの単剤治療率、1つ1つのバーは各施設を示す。
(上段は著者作成、下段は文献2より改変して引用)

Figure 3: Evidence-practice Gap in Clinical Psychiatry

Vertical axis shows the percentage of patients treated with each monotherapy, with each bar representing a different center. (Upper panel prepared by the author; lower panel adapted from Reference 2)

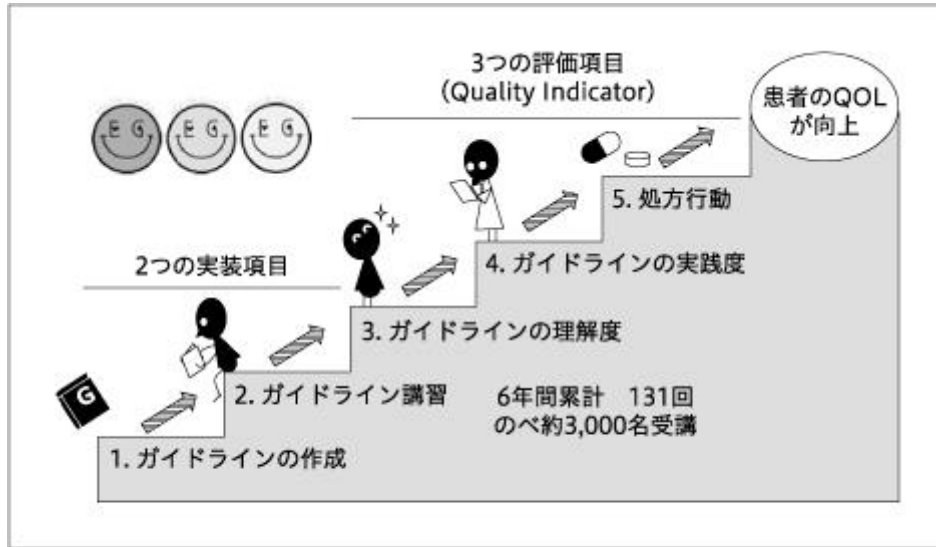


図4 EGUIDE プロジェクトの戦略

EGUIDE プロジェクトには社会実装する項目が2つあり、実装効果を検討する評価項目 (Quality Indicator) が3つある。

Figure 4: Strategy of the EGUIDE Project

The EGUIDE project has two items for social implementation and three evaluation items (Quality Indicators) to examine the effectiveness of implementation.