Guidance for Evaluation of Brain-Computer Interface Systems

1. Introduction

Brain-computer interface (BCI), also known as brain-machine interface, refers to a technology that supplements, restores, or enhances certain bodily functions by enabling the exchange of information between the brain and a computer, allowing control of target devices and input of sensory information into the brain. BCI is considered useful for supporting the daily lives of patients who cannot express intent through limb movement or speech, including those with locked-in syndrome, and for promoting rehabilitation in patients with severe paralysis or with psychiatric disorders such as depression; accordingly, early practical application is anticipated. Research activity in this field has been increasing since the 1990s. More recently, clinical trials aiming for practical use have been progressing both domestically and internationally.

In Japan, the first guidance for evaluation of BCI as a medical device was "Guidance for Evaluation of Neurofunctional Modulation Devices - Detailed Discussion (6) Brain-Machine Interface," published in Attachment 2 of the notification entitled "Publication of guidance for medical devices with emerging technologies" (PFSB/ELD/OMDE Notification No. 1215-1, dated December 15, 2010, issued by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW). In the United States, the Food and Drug Administration (FDA) has issued guidance entitled "Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation - Non-clinical Testing and Clinical Considerations," issued in May 2021, addressing medical devices that utilize implanted BCI technology.

In light of these circumstances, this guidance has been formulated based on the "Guidance for Evaluation of Neurofunctional Modulation Devices," aiming to assess the effectiveness, safety, and quality of medical devices using BCI technology appropriately and promptly based on scientific evidence.

2. Scope of the guidance

This guidance applies to medical devices that use efferent BCI technology, include an implantable measurement unit, and are intended to supplement or restore bodily functions, such as movement and communication of intent. The design and development of such medical devices must consider both the benefits patients gain from restoring or supplementing lost bodily functions through BCI technology and the risks associated with the application of this technology. For instance, in patients with amyotrophic lateral sclerosis who are in a locked-in state, enabling communication is regarded as a significant benefit, and even when considering the risks of device implantation, it may be possible to justify the risk-benefit balance.

Efferent BCI refers to technology that measures brain activity, decodes the measured brain signals to infer intentions and similar information, and generates control signals based on that decoding to operate a target device. Accordingly, a medical device utilizing BCI technology can be considered a system consisting of four units: the measurement unit, decoding unit, control unit, and controlled unit (i.e., the device or component being controlled) (BCI system; Figure 1).

The measurement unit is categorized into implantable and non-implantable types depending on the method used to measure brain activity. An implantable type indicates that at least part of the measurement unit is implanted within the body. Implantable types are further classified into intracortical electrode types, subdural electrode types, epidural electrode types, intravascular electrode types, and others. A non-implantable type may involve partial contact with the body, yet all components remain outside the body.

The decoding unit extracts features from brain signals and decodes them using either machine learning or other similar methods to read neural information such as motor intentions. The control unit outputs signals required to operate the controlled unit based on the decoding results from the decoding unit. The controlled unit is the device that ultimately provides the intended effect for the patient within the BCI system, and it is assumed to include not only medical devices but also general-purpose devices classified as nonmedical equipment.

If the determination of whether each unit qualifies as a medical device (including medical device software) proves difficult, consultation with the relevant prefectural pharmaceutical affairs department (the Compliance and

Narcotics Division, Pharmaceutical Safety Bureau, MHLW, for program medical devices) is recommended, as needed. Furthermore, if uncertainty arises regarding whether each unit falls within the scope of this guidance, consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) is recommended when necessary.

However, the application of this guidance is not precluded for evaluations of neurostimulation therapeutic devices intended for disease treatment, such as deep-brain stimulation and the responsive neurostimulation system, as well as non-implantable BCI and afferent BCI that inputs information to the brain, which are not included in the scope of this guidance. Although BCI is a technology that supplements, restores, or enhances certain bodily functions, technologies intended for the enhancement of bodily functions, including military applications, involve ethical concerns and are therefore excluded; accordingly, the scope of use is limited to technologies that supplement or restore standard functions for patients.

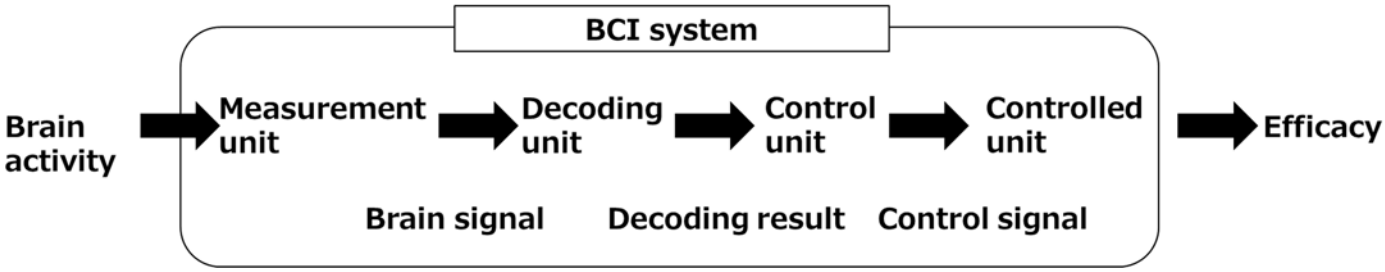

Figure 1. Architecture of the brain-computer interface (BCI) system

3. Role of this guidance

This guidance is intended for medical devices utilizing efferent BCI systems that incorporate an implantable measurement unit, a field in which technological innovation has advanced rapidly in recent years, and presents points currently considered necessary when evaluating such devices for marketing approval applications. Accordingly, it may need to be revised in the future in light of further technological innovation and the accumulation of knowledge, and it does not have binding force over the contents of marketing approval applications for individual medical devices.

Evaluation of medical devices using BCI systems should be approached flexibly

with scientific rationality after sufficiently understanding the characteristics of each individual product. In addition to this guidance, existing relevant domestic and international guidance documents and guidelines should be referred to. For the evaluation of medical devices intended for home use or those utilizing artificial intelligence technology, the following may also serve as references: FDA guidance entitled "Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation - Non-clinical Testing and Clinical Considerations," issued in May 2021; "Guidance for evaluation of home-use medical devices," published in Appendix 1 of the notification entitled "Publication of guidance for medical devices with emerging technologies" (PSEHB/MDED Notification No. 0925-1, dated September 25, 2020, issued by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW); and "Guidance for evaluation of artificial intelligence-assisted medical imaging systems for clinical diagnosis," published in Appendix 4 of the notification entitled "Publication of guidance for medical devices with emerging technologies" (PSEHB/MDED Notification No. 0523-2, dated May 23, 2019, issued by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

4. Points to consider in evaluation

(1) Basic matters

The development history and clinical positioning of the BCI system, specifications of the device under development, use status of the device under development and similar products in Japan and overseas, device design and principles of the BCI system (including algorithms), and standard methods of use should be clearly presented.

In the evaluation of the effectiveness and safety of the BCI system, it is necessary to demonstrate that information obtained by the measurement unit is properly processed by the decoding and control units, resulting in outputs from the controlled unit that have clinically meaningful effectiveness. It is also necessary to demonstrate the safety of the entire BCI system as well as all its constituent units. However, when making product improvements after obtaining marketing approval for a BCI system as a medical device, for example,

when there is no change in input information from the measurement unit to the control unit, evaluation of the effectiveness and safety of the control unit and controlled unit may be sufficient to explain the effectiveness and safety of the entire BCI system. Therefore, when developing and evaluating individual units using an already approved BCI system as a medical device, or when there are concerns regarding the selection of evaluation items or evaluation methods required for individual products, use of the PMDA consultation system is recommended as needed.

It is recommended that the description of the BCI system include the following items. Herein, a component refers to a part that constitutes a unit and possesses a certain function.

1) Overview of the BCI system

The positioning of each unit within the entire BCI system should be described. If there are multiple system configurations, an overview for each configuration should be provided.

2) Overview of units constituting the BCI system

Examples of units forming the BCI system are shown below. These are only examples, and descriptions should cover all the units composing the BCI system.

① Measurement unit

This device measures brain signals and consists of various components, such as leads, electrodes, amplifiers, wireless communication modules, and a wireless power supply. The main parts are implanted inside the body.

② Decoding unit

This device performs signal processing and includes software and associated hardware to decode intentions from brain signals measured by the measurement unit.

③ Control unit

This device generates signals to control the controlled unit based on results decoded by the decoding unit.

④ Controlled unit

This refers to devices or similar components that receive signals from the control unit and ultimately provide the intended efficacy and effects of the BCI system.

3) Overview of main components of units

Information such as functions, model numbers, materials, placement or attachment positions, and sizes should be provided for the main components constituting each unit. If an already approved or certified medical device is partially modified and used, its approval or certification numbers should be indicated, and differences from the approved or certified device should be explained. In addition, for certain main components, it is recommended that an overview be provided in consideration of the following points. The following are examples and may vary depending on the form, structure, and principles of the BCI system under development.

① Measurement unit

a) Lead wires and connection cables placed inside the body

b) Electrodes

c) Main body of the measurement unit

d) Wireless communication (if applicable)

e) A wireless power supply (if applicable)

f) Battery

g) Preprocessing, such as calculating the power in each electroencephalography (EEG) frequency band from EEG signals (if applicable)

② Decoding unit

a) Specifications of decoding units for physicians and for patients

b) User interface, including display screens and operation methods for patients or caregivers during actual use

c) Display screens and operation methods for physicians during adjustment

d) Decoding algorithm clearly outlined, e.g., using a flowchart

e) Hardware and software, including the operating system and algorithms

As machine learning may be used in BCI systems to decode EEG signals for each patient and optimize the decoding process, methods for obtaining training data should be described in these cases. For machine learning, refer to domestic and international guidelines.

In particular, detailed descriptions should be provided for the following:

- Details of training data
- Method for creating correct labels used during training and evaluation (in cases of supervised learning)
- Validation methods for constructed models
- Appropriateness of performance criteria that the constructed model must satisfy

③ Control unit

a) Signals from the decoding unit and control algorithms

b) Output control signals to the controlled unit

c) When sensor functions or autonomous control functions are included to support operation by the BCI system, the measurement and control algorithms should be clearly outlined, for example, using flowcharts

④ Controlled unit

The devices to be controlled vary, but examples include the following:

a) Switch control of communication devices

b) Flick operations of smart devices and similar equipment

c) Cursor control on computers

d) Operation of assistive robots or virtual avatars

e) Control of body movement through electrical stimulation of nerves or muscles, known as functional electrical stimulation

⑤ Other common matters (if applicable)

Methods of communication and connection with other units should be described, such as wired or wireless configurations, as well as lead wires and connectors. Details on the power supply and other settings should be included. Information on alert notifications and similar features should be provided.

4) Overall flow of the BCI system

A comprehensive view should be presented, including diagrams or flowcharts, illustrating the bidirectional flow of information and interactions among all BCI system components, physicians, caregivers, and patients.

5) Exploded assembly diagrams

For BCI systems that require assembly or adjustment before use, exploded assembly diagrams of each component should be provided, clearly indicating the names of all components.

6) Output stimulation characteristics

If there are components that apply electrical current to muscles or peripheral nerves, the output stimulation characteristics should be presented.

7) Accessories

Information on all the components expected to be used with the BCI system should be presented, such as specialized tools for implantation procedures like craniotomy templates and screws for fixing implanted components, and it should be specified whether these are included as part of the BCI system or supplied by other companies.

8) Noise and vibration for large equipment

9) Maintenance inspection and details thereof

10) Necessity of training plans and their contents

Training for subjects or patients is required to ensure safe use in a home environment.

Reference: “Guidance for evaluation of home-use medical devices,” published in Appendix 1 of the notification entitled “Publication of guidance for medical devices with emerging technologies” (PSEHB/MDED Notification No. 0925-1, dated September 25, 2020, issued by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

11) Documentation (such as operation manuals) for users and its contents

12) Software lifecycle processes

Given that units comprising the BCI system mainly function as information processing devices, it is necessary to consider change management and maintenance for all units, including updates and bug fixes, throughout the software lifecycle of medical devices.

Reference: JIS T 2304.

13) Cybersecurity

Cybersecurity measures should be implemented while considering the risk that third parties could intervene in or manipulate patient behavior or decision-making.

Reference: “Application of Article 12, Paragraph 3 of Essential Principles for Medical Devices” (PSEHB/MDED Notification No. 0331-8, dated March 31, 2023, issued by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW), etc.

14) Risk management

It is necessary to consider responses assuming worst-case scenarios, including not only device-related risks but also incidents occurring in clinical settings.

Reference: JIS T 14971.

15) Equivalence between final product and test device

When conducting nonclinical or clinical tests using a test device different from the final product, its equivalence with the final product should be evaluated.

16) Performance limits and responsibility

As there is a risk of malfunction when decoding patient intent and outputting it in the form of expressions of intent or bodily functions, it is necessary to explain the product principles, performance limits, and types of output

information to patients in advance and obtain their consent. In BCI systems, determining whether inappropriate expressions of intent or actions arise from patient intent or device malfunction is difficult. It is therefore desirable to clearly define disclaimers and similar matters in consultation with legal departments. As part of risk management, fail-safe measures, such as multiple confirmations, should be considered for important expressions of intent or actions involving physical risk to prevent malfunctions from leading to serious outcomes. Additionally, consideration may be given to providing mechanisms allowing patients to physically shut down the system in case of malfunction. The effectiveness of these risk management measures needs to be confirmed through clinical trials.

17) Usability engineering process

Usability should be considered in accordance with the International Electrotechnical Commission standard (IEC) 62366-1 or Japanese Industrial Standard (JIS) T 62366-1. Additionally, regarding usability engineering, refer to the notice entitled “Handling of Revision of Japanese Industrial Standards Concerning Requirements for Usability Engineering of Medical Devices” (PSEHB/MDED Notification No. 0930-1 and PSEHB/CND Notification No. 0930-1, dated September 30, 2022, issued jointly by the Director of the Medical Device Evaluation Division and the Director of the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

18) Patient preference information

This can serve as an important factor in BCI system design and risk-benefit evaluation. If the BCI system is highly convenient and reliable and the controlled unit is easy to attach and detach and is aesthetically acceptable, recommending the use of this system to patients becomes feasible.

Conversely, factors such as daily calibration, fatigue from use, and unstable performance may influence decisions regarding treatment options. It is desirable to examine patient preference information early when it may affect treatment choices. Patient preference information may also be evaluated separately from clinical trials.

(2) Matters related to nonclinical testing

The purpose of nonclinical testing is to obtain ethically and scientifically valid grounds for deciding whether to conduct clinical trials and to rule out unacceptable risks. Based on the following items, the effectiveness and safety of the entire BCI system and all constituent units should be evaluated appropriately through nonclinical bench testing and animal studies in accordance with relevant guidelines and certification standards, as needed. Maintenance of the performance and safety of the BCI system under expected usage environments and conditions should be verified.

Additionally, as described subsequently, considering the characteristics of BCI systems, some aspects may be limited in performance evaluations conducted through nonclinical testing; therefore, a comprehensive assessment incorporating findings from the existing literature and the experiences of other companies may be considered when determining whether to proceed with clinical trials.

From the perspective of explaining the validity of conducting clinical trials and supporting future clinical results, it is, in principle, required to use a BCI system identical or equivalent to the final product in nonclinical testing. However, when explaining the validity of early feasibility studies, the use of nonclinical test results obtained with a test device that is not the final product may be permitted if appropriate justification is provided.

When preparing marketing approval applications for medical devices, it is desirable to describe information on nonclinical testing in accordance with the notice "Partial Revision of 'Points to Consider in Preparing Summary Technical Documentation (STED) for Medical Devices'" (PSEHB/MDED Notification No. 0228-7, dated February 28, 2018, issued by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

1) In vitro evaluation

① Evaluation related to safety

a) Electrical safety and electromagnetic compatibility

References: International Organization for Standardization (ISO) 14708-1, ISO 14117, IEC 60601-1, IEC 60601-1-2, JIS T 0601-1, and JIS T 0601-1-2.

* If a stimulation function is present, the ISO 14708-3 standard should be referred to.

b) Mechanical safety

Reference: ISO 10218-1.

c) Quality management and risk management

References: ISO 13485, ISO 14971, JIS Q 13485, and JIS T 14971.

d) Types, structures, and validity of safety mechanisms

· Alarms, including types and displays; references: IEC 60601-1-8 and JIS T 60601-1-8.

· Emergency stop measures; references: ISO 10218-1, ISO 13850, IEC 60204, and IEC 80601-2-78.

· Emergency stop devices and their structures

· Conditions for emergency stop, such as malfunctions contrary to the intention of physicians or others, or activation of safety mechanisms

· Ensuring safety for patients and physicians or others during stoppage, including device posture retention

· Ease of restarting the device after an emergency stop

· Measures to prevent malfunction, including the user interface

e) Biocompatibility

ISO 10993-1 should be followed. For the approach used for evaluation and testing, the following references should be consulted: “Complete Revision of ‘Revision of Basic Principles of Biological Safety Evaluation Required for Application for Marketing Approval of Medical Devices’” (PSB/MDED Notification No. 0311-1, dated March 11, 2025, issued by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, MHLW), “Q&A on Basic Principles of Biological Safety Evaluation Required for Application for Marketing Approval of Medical Devices” (Administrative Notice dated March 11, 2025, issued by the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, MHLW), and “Review Points of Biological Safety Evaluation for Market Approval of Medical Devices” provided by PMDA. Because the contact site with the body differs among components of a BCI system, evaluation items should be considered for each component.

f) Stability

g) Durability

h) Sterility

Reference: “Establishment of Sterilization Validation Standards” (PSEHB/CND Notification No. 1017-1, dated October 17, 2022, issued by the Director of the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW), etc.

i) Pyrogenicity and endotoxin testing

As necessary, the ISO 10993-11 and 11737-3 standards should be referred to for evaluation according to the applicable site.

j) Shelf life and packaging

The ISO 11607-1 and ISO 11607-2 standards and the American Society for Testing and Materials standard F1980 should be referred to.

k) Wireless communications (if applicable)

If wireless functions are incorporated, the Association for the Advancement of Medical Instrumentation TIR69 standard, entitled “Technical Information Report-Risk Management of Radio-frequency Wireless Coexistence for Medical Devices and Systems,” may serve as a reference.

l) Wireless power supply (if applicable)

To demonstrate appropriate protection from heating during energy transmission and from ionizing radiation, it is desirable to refer to the general requirements for safety, labeling, and information supplied by the manufacturer described in the ISO 14708-1 standard.

In addition, the publication “Evaluation Guidelines for Contactless Power Supply Systems for Implantable Medical Devices” in the notice “Publication of Test Methods Established Based on the Results of the Project for Promoting Practical Application of Innovative Pharmaceuticals, Medical Devices, and Regenerative Medical Products” (PSEHB/MDED Notification No. 0809-7, dated August 9, 2017, issued by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW) may serve as a reference for the evaluation guidelines required for contactless power supply systems for implantable medical devices.

m) Magnetic resonance (MR) compatibility

The notices under “Measures for MR Safety in Implantable Medical Devices, etc.” (PSEHB/MDED Notification No. 0801-1 and PSEHB/PSD Notification No. 0801-4, dated August 1, 2019, issued jointly by the Director of the Medical Device

Evaluation Division and the Director of the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW) may serve as references for evaluating the safety and compatibility of BCI systems in the MR environment.

② Performance evaluation of the measurement unit

a) Electrodes

· Dimensional confirmation and visual inspection

· Impedance

· Accelerated aging testing

b) Leads and connectors (if applicable)

· Dimensional confirmation and visual inspection

· Leakage current

· Fatigue testing of the lead body and connector (if applicable)

· Tensile strength of leads

· Connector insertion and removal force (if applicable)

· Risks of particulate matter

Reference: ISO 14708-1.

· Corrosion resistance

· Percutaneous lead wires or other cables (if applicable)

Reference: JIS T 0601-1.

c) Casing, feedthroughs, and internal electronic circuits

· Hermeticity test

· Environmental testing

Evaluation of effects from temperature changes, including temperature cycling, atmospheric pressure changes, and mechanical forces.

Reference: ISO 14708-1.

· Header connection testing (if applicable)

· Adhesion and continuity testing between leads and feedthroughs (if applicable)

· Battery (if applicable)

Reference: IEC 62133-2.

d) Wireless power supply (if applicable)

The ISO 14708-1, ISO 14117, IEC 60601-1, IEC 60601-1-2, JIS T 0601-1, and

JIS T 0601-1-2 standards may serve as references.

e) Data communication, wired or wireless

Testing should include the information outlined for the decoding and control units. Testing of wireless transmitters and receivers needs to consider testing recommendations concerning wireless technology. It is desirable to evaluate data communications with reference to the following:

· Mechanical testing

· Electrical testing, such as leakage currents

· Transmission distance and orientation between an external radiating antenna and an antenna inside the receiver for wireless communications

③ Performance evaluation of the decoding unit

The BCI system should be verified to operate according to its specifications. Using the following as reference information, it can be demonstrated that the system can communicate with the measurement unit and process brain signals appropriately.

· Limitations of evaluation using simulated signals

Accuracy, sensitivity, specificity, processing stability, processing time, noise interference, log output, and similar items should be evaluated, and their limitations should be indicated.

· Validation testing for products utilizing artificial intelligence technology

When machine learning or similar methods are used after marketing, appropriate usage methods need to be specified, including methods for acquiring training data, learning procedures, and validation testing conducted after learning, as well as achievement criteria for this type of testing.

· Note that confirming the proof of concept (POC) may be difficult based on nonclinical testing alone.

④ Performance evaluation of the control/controlled units

For the control unit, its communication with the decoding unit and appropriate control of the controlled unit based on the decoding unit results should be demonstrated. Endpoints should be set according to the intended purpose, such

as the operation of a communication device or robotic arm, and testing should be conducted. Through operation confirmation testing using simulated signals that cover test cases, the intended response accuracy, reaction time, repeatability, output strength, long-term stability, fail-safe functions, and other matters should be evaluated.

⑤ Performance evaluation of the overall BCI system

Operation of all units and components of the BCI system according to the specifications of the BCI system should be evaluated. Testing should be conducted for electrical safety, electromagnetic compatibility, wireless coexistence, and similar matters while considering actual use conditions. Furthermore, specific criteria showing compatibility among units should be identified, along with providing scientific or clinical justification for these criteria.

For endpoints where overall performance evaluation cannot be performed, the grounds for excluding the overall performance evaluation and the risk mitigation methods should be explained. For malfunctions and similar events during BCI system operation, the causal units and components should be identified, along with methods for resolving them and the basis for risk mitigation.

When multiple decoding, control, or controlled units or combinations of these are assigned to one measurement unit, compatibility assurance is required. If compatibility is absent, damage to the BCI system or other clinical adverse events may occur. Therefore, in the test protocol and in instructions provided to operators or clinical trial investigators, it is desirable to explain the information necessary to ensure compatibility among all the components included in the BCI system.

2) In vivo evaluation

Animal testing of BCI systems should address factors that cannot be evaluated in bench testing, such as long-term safety and durability. Test design and endpoints should be based on the mechanism of action of the BCI system and risk mitigation.

Risk evaluation is required for the characteristics, properties, mechanism

of action, anatomical targets, device implantation procedures, and other aspects of the BCI system. Examples include the electrode type (e.g., penetrating or nonpenetrating), biological and mechanical stress on electrodes due to electrode placement, robustness of the device mechanism of action, and the expected device lifetime. The use of existing scientific information with an appropriate basis (e.g., evaluation results of BCI systems, units, and components in clinical studies, prior animal studies and bench performance test results using BCI systems or BCI system prototypes, and published studies directly related to the characteristics and properties of the BCI system) may enable the reduction of the burden associated with animal testing, such as reducing the number of animals or shortening the experimental period, and provide a reasonable explanation for why additional animal testing is unnecessary.

Animal test evaluation should desirably include gross and microscopic findings on tissue effects, along with evaluation of explanted units and/or components. The general matters to be considered for animal testing protocols are listed below:

· Study purpose

· Animal species, strain if applicable, number of animals, study duration, and study design, including the rationale

· Details of the test device, including the rationale for differences between the test device and the control device, recording site, electrode surface area, and materials

· If stimulation functions targeting muscles, peripheral nerves, or similar tissues are present, details on the stimulation site, stimulation intensity, stimulation type, voltage or current, amplitude, pulse mode (monophasic or biphasic), duration, frequency, charge density, charge per phase, electrode surface area, and materials should be included.

· Evoked response testing, if applicable

Using somatosensory evoked potentials, auditory evoked potentials, visual evoked potentials, and similar measures, brain activity evoked by sensory stimulation can be used and evaluated as data for brain signal decoding.

· Evaluation of decoding accuracy, sensitivity, specificity, processing stability, processing time, noise interference, and other matters using actual

signals, as well as evaluation of biological variability (e.g., individual differences, temporal changes, environment, alertness, and fatigue level)
· Recording of signal quality at both acute and chronic time points (if applicable)
· Histopathological examination of surrounding tissue
· Controls
Depending on the test, unstimulated contralateral tissue (e.g., muscle or peripheral nerve) may serve as the control.
· Safety evaluation
· Reliability testing of product performance
· Stimulation testing, such as when electrically stimulating muscles or peripheral nerves
Effects at both acute and chronic time points should be evaluated.
· Surgical approach

In performance evaluation, evidence obtainable from animal testing may, in some cases, be limited compared with that from clinical trials when considering the large differences between human and animal brains in size and cognitive function. For example, as animal brains are small, the size and other characteristics of electrodes that can be placed in the brain and the information that can be obtained are limited. Moreover, note that evaluation of communication is difficult during animal testing.

(3) Matters related to clinical trials

1) Human factors and usability

For BCI systems, attention must be paid to hazards caused not by device malfunction or failure but by the patient's inability to use the device correctly (i.e., use-related hazards). Therefore, in the clinical development of BCI systems, it is important to acquire knowledge on human factors, such as the difficulty in understanding device-use procedures or insufficient training before device use, from the earliest stage possible, and to optimize the user interface.

In clinical trials, it is desirable to include a plan for collecting usability

information in the clinical trial protocol and related documents. Usability information obtained during clinical development may also be used, as necessary, to improve BCI system use procedures or the device itself. To reduce use-related hazards in the final BCI system, it is desirable to conduct usability evaluations, such as simulated-use testing and satisfaction surveys, iteratively, from the early design stage of the applicable system through the development and evaluation process of the system.

2) Summary of prior studies when explaining the validity of conducting clinical trials

Owing to the characteristics of BCI systems, there are limits pertaining to the explanation of the validity of conducting clinical trials using only nonclinical tests, such as those using simulated signals. Accordingly, when conducting clinical trials, systematically organizing information from prior clinical research, clinical trials, and similar sources on related or similar BCI systems is also important for explaining the likelihood of human application of the device under development. This information is also important as a basis for the POC of the device under development and for considering safety measures.

3) Clinical trials

When preparing a clinical trial plan, general clinical trial guidance and similar materials should be referred to, and the following points should be noted. Additionally, personal information should be handled separately and appropriately in accordance with the Act on the Protection of Personal Information and other related laws, regulations, and guidelines.

① Trial design

When planning a clinical trial that enrolls multiple patient populations, such as patients with intractable neurological diseases, spinal cord injury, stroke, or other conditions, a reasonable explanation must be provided for why different patient populations can be evaluated together. The International Council for Harmonisation E9 Statistical Principles for Clinical Trials may serve as a reference for details on methods for effectively incorporating and analyzing multiple subject populations in one trial.

② Trial period and follow-up schedule

Clinical trials should obtain data that allow appropriate effectiveness and sufficient safety evaluations. To identify long-term safety signals, a long-term follow-up period sufficient for evaluation is recommended with reference to FDA guidance and other relevant sources. Long-term clinical durability and reliability are also important factors for long-term effectiveness. For example, implanted electrodes may lose their signal detection capability over time. Although animal testing can provide some information on electrode durability and reliability, animal testing may not accurately predict long-term clinical performance in humans. After marketing approval, conducting postmarketing surveillance for an additional appropriate period is recommended.

③ Inclusion criteria and exclusion criteria

The inclusion criteria for clinical trials of BCI systems differ depending on the population and disease type targeted by the proposed treatment. Inclusion criteria are set from the standpoints of clinical positioning and appropriateness of performance evaluation for the device under development, and they do not necessarily limit the postmarketing target population. When explaining effectiveness and safety in the postmarketing target population based on clinical trial results, the generalizability (external validity) of the clinical trial results should be explained based on the inclusion and exclusion criteria, along with postmarketing risk management.

<Inclusion criteria>

The following general inclusion criteria should be considered.

- Patient age
- Type of clinical condition (diagnosis name) and site and degree of impairment (e.g., C2-C7 or L2-S1 for spinal cord injuries)
- Clinical conditions for patient enrollment (e.g., preoperative functional and preoperative neurological scores)
- The patient's own ability to understand, provide informed consent, and agree to participate in the clinical trial, although the signature on the consent form itself may be written by a proxy

· Some method of communication, such as speech, a transparent letter board, or computer input
· Other criteria that can be reasonably explained

<Exclusion criteria>
Consider excluding the following patients and others according to the purpose of the clinical trial.
· Patients with severe cognitive or memory impairment
· Patients with severe psychosis or chronic psychiatric disease
· Patients with medical contraindications to general anesthesia or craniotomy
· Patients with serious structural cerebral disease observed by MR imaging or similar diagnostic methods
· Patients with serious functional abnormalities in the cerebrum observed by EEG or magnetoencephalography
· Patients using cardiac defibrillators, pacemakers, vagus nerve stimulation devices, spinal cord stimulation devices, or other active implantable devices
· Patients with severe impairment of vision, hearing, or somatosensation
· Patients with serious impairments of cardiac, pulmonary, hepatic, renal, gastrointestinal, hematologic, metabolic, psychiatric, or other functions
· Patients with bleeding tendencies or patients taking anticoagulants who have difficulty discontinuing them
· Other patients considered by the clinical trial investigator (or others) to be inappropriate for participation in this trial

When proposing other criteria, it is desirable to demonstrate their validity.

④ Treatment parameters/protocol, including the postoperative regimen
Sufficient information must be included regarding implantation procedures, postoperative recovery period and regimen, treatment period, removal of devices, and other anticipated surgical procedures.

⑤ Primary endpoints and secondary endpoints for effectiveness (if applicable)
When setting primary and secondary endpoints for effectiveness, at minimum,

items capable of evaluating the overall clinical effectiveness of the BCI system should be set. The primary effectiveness endpoint should be set in light of the positioning and purpose of the clinical trial, and the rationale should be explained for each effectiveness endpoint, appropriateness of the evaluation timing, and its clinical significance for the target patient population. As necessary, items capable of evaluating the effectiveness of each unit should also be set.

For example, when evaluating the effectiveness of the communication function of a BCI system, the accuracy of communication, communication speed, and other similar measures can be set as endpoints. Endpoints for each unit should be set as needed. For example, when conducting an individual evaluation of the measurement unit, items reflecting the measurement performance of brain signals may serve as effectiveness endpoints. In evaluating effectiveness, it is also important to assess patient quality of life (QOL) as a secondary measure.

⑥ Primary endpoints and secondary endpoints for safety (if applicable)

The primary and secondary endpoints should be set based on adverse events and the severity considered important for assessing the risk-benefit balance of the device under development. As safety endpoints, adverse events and malfunctions related to the entire BCI system should be collected and evaluated for all subjects. Adverse events may include, but are not limited to, those related to implantation surgical procedures and the BCI system. In addition to identifying safety endpoints, it is desirable to include in the clinical trial protocol and related documents a response plan for adverse events, methods for explanting the implantable components of the BCI system, and safety criteria for deciding discontinuation of the trial for individual subjects.

Furthermore, safety endpoints should be set for each unit, and identification of the unit that causes adverse events and malfunctions should be facilitated.

⑦ Patient opinions, and patient and public involvement

The opinions of patients, caregivers, and others on clinical trial design are important for evaluating BCI systems. Therefore, patient and public involvement should be considered. Considering patient opinions is expected to reduce the burden associated with conducting clinical trials, improve

efficiency, and contribute to the improvement of the usefulness of trial results.

⑧ Patient-reported outcome measurement

A patient-reported outcome measure (PROM) is important from various perspectives, such as QOL evaluation, and its appropriate use in clinical trials is desirable.

In particular, when outcomes are best evaluated from the patient's perspective or depending on the intended use, outcomes based on PROM, such as pain reduction, may be set as primary endpoints. In these cases, early consultation with the PMDA at the clinical trial planning stage is important. These scales are often used together with other clinical outcome assessments. When setting outcomes quantified by PROM as primary endpoints in international joint trials, it is desirable that the validity for evaluating the same pathology or condition across cultures and languages be confirmed, and at minimum, linguistic validation must have been completed.

The following guidelines/documents are useful when setting PROMs.

References:

· Guidance collection on patient-reported outcomes (PRO) use (Ministry of Health, Labour and Welfare scientific research project "Preparation of PRO Guidelines in Collaboration with Efforts by Related Academic Societies," published June 13, 2023)

· Pharmaceuticals and Medical Devices Agency Patient Engagement Guidance (Pharmaceuticals and Medical Devices Agency, Patient Engagement Working Group, September 7, 2021)

⑨ Home use

<Precautions due to differences among facilities>

For BCI systems used in a home environment, medical facilities conducting clinical trials may not be able to evaluate risks and benefits appropriately when the BCI system is used in a home environment. Therefore, it is important within clinical trials to conduct evaluations in an environment simulating the home environment where the BCI system will be used or to perform evaluations in the home environment itself.

<Precautions for caregivers>

For BCI systems used in a home environment, caregivers may need the willingness and ability to perform important BCI system-related tasks listed below:

- Initial setup and regular maintenance of the BCI system
- Follow-up observation of the patient
- Contacting physicians as necessary

To ensure the safety of the BCI system in the home environment, it is desirable to specify in detail in the clinical trial protocol and related documents a training program on the use of the BCI system for subjects and caregivers. It is also desirable to describe how the effectiveness of the training program for subjects and caregivers will be evaluated. Training in an environment simulating the home environment or in the home environment is also important.