Provisional Translation (as of August 2023)*

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March 30, 2023

To: Director, Prefectural Health Departments (Bureaus)

Director, Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
Director, Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Points to Consider for Informed Consent Using Electromagnetic Means in Clinical Trials and Post-marketing Clinical Trials

In conducting clinical trials and post-marketing clinical trials of drugs, medical devices, and regenerative medical products (referred to as "drugs, etc." in the Annex), when a prospective subject participates in a clinical trial, an appropriate explanation should be given in writing and written consent should be obtained in advance based on the Ministerial Ordinance on Good Clinical Practice for Drugs (Ministry of Health and Welfare Ordinance No. 28 in 1997), the Ministerial Ordinance on Good Clinical Practice for Medical Devices (MHLW[1] Ordinance No. 36 in 2005), and the Ministerial Ordinance on Good Clinical Practice for Regenerative Medical Products (MHLW Ordinance No. 89 in 2014) (referred to as "GCP Ordinance" in the Annex) in order for the subject to understand the contents of the clinical trial and other matters related to the clinical trial.

In consideration of the recent progress of information and communication technology and subsequent decentralization and improved efficiency of clinical trials by utilizing this technology, we provide the points to consider for conducting informed consent procedures using documents displayed and presented by electromagnetic means, video calls, etc. in the Annex. Please fully inform these points to the related business operators under your administration, medical institutions, etc.

The copy of this notification will be also released to the related organizations listed separately.

[1] The term “MHLW” refers to the “Ministry of Health, Labour and Welfare.”

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

(Annex)

Points to be Consider for Informed Consent Using Electromagnetic Means in Clinical Trials and Post-marketing Clinical Trials

*In this document, "sponsor" shall be read as "sponsor-investigator" in investigator-initiated clinical trials, and "clinical trial" shall be read as "post-marketing clinical trial" in post-marketing clinical studies.

1. Positioning of this guidance

When the trial-related information such as the content of the clinical trial is explained to subjects with documents, paper documents have been used for face-to-face explanations. In addition to this conventional method, remote explanation methods are actually being used such as documents displayed and presented in electromagnetic means including showing written information on the screen of a PC, tablet, etc. through a telecommunication line, videos, etc. played on a computer, and real-time video calls, etc. Also, when consent is obtained with documents, it is assumed that the consent will be confirmed and recorded using electromagnetic means instead of paper documents.

This guidance summarizes the points to consider when these processes are conducted. This guidance shows the idea at the present moment, and it may need to be reviewed based on technological progress, etc.

In conducting clinical trials, this guidance as well as related notifications, guidelines, etc. should be referred to as appropriate. If there is any question about the handling of individual cases, the Pharmaceuticals and Medical Devices Agency should be consulted as needed.

2. Definitions of terms used in this guidance

Electronic signatures

Electronic signatures defined in the "Act on Electronic Signatures and Certification Business" (Act No. 102 of 2000)

Digital signatures

Handwritten signatures by a signer on a screen of a tablet, etc. in electronic means

Electronic signatures, etc.

Electronic signatures and digital signatures

Explanation/obtainment of informed consent using electromagnetic means

A process of explaining the contents of the clinical trial and other matters related to the clinical trial remotely, by using documents displayed and presented by electromagnetic means, such as displaying the written information on the screen of a PC, tablet, etc.

through a telecommunication line, by using videos, etc. on a computer, and/or by using real-time video calls, etc. but not those of voice-only telecommunication means (hereinafter referred to as "video calls, etc."), and obtaining informed consent by electronic signatures, etc. It includes cases in which one or more of these elements are used in combination with an explanation/obtainment of informed consent by the conventional method.

Videos, etc.
Dynamic content such as videos, audio, animations, pop-ups, etc.

Information and communication system
A system used to explain/obtain informed consent by electromagnetic means.

General services
Widely used services, not limited for an explanation/obtainment of informed consent, by electromagnetic means including online meeting services that use a system of information and communication devices with vision and hearing.

Service provider
A business operator that supplies an information and communication system used for an explanation/obtainment of informed consent by electromagnetic means.

Identification
A process of confirming the names, etc. of users who use the electromagnetic means for an explanation/obtainment of informed consent.
This confirmation process is generally conducted by, for example, requesting the presentation of documents proving the information regarding the name, address, date of birth, and sex.

Authentication
A process in which an “executor” of an act is verified to be identical to the person with “identification information” and the credibility is established that the “executor” is the one who is linked to the identification information in advance. It is roughly classified into the following two types depending on the confirmation method of authentication information.
(1) Single-factor authentication
An authentication method to confirm the identity of the user with a single authentication information.
*For example, either one of a password, which is information memorized only by the person, property, or biological information, such as a fingerprint or iris, is used to link to the ID.
(2) Multiple-factor authentication

An authentication method to confirm the identity of the user by combining multiple authentication information among the elements such as memory, property, and biological information.

*For example, a password, which is information only memorized by the person, can be combined with a one-time password (confirming that the person has a smartphone that can issue a one-time password).

3. Basic principles

(1) On the premise that an explanation, questions, and answers, etc. related to the clinical trial are provided at the same level as a conventional face-to-face setting under the responsibility of the investigator and sub-investigator (hereinafter referred to as the "investigator, etc."), it is possible to explain/obtain consent using electromagnetic means.

Specifically, as is the case with the informed consent processes by the conventional method, subjects and their legally acceptable representatives (hereinafter referred to as "subjects, etc.") should be adequately given an explanation from all perspectives related to the subjects' participation in clinical trials or decision making of continuation of participation in clinical trials, and then, subjects, etc. should understand them and voluntarily agree to participate or continue participation in the clinical trials, and this needs to be confirmed in the document. The use of electromagnetic means should not affect the free decision of subjects, etc.

It is acceptable to combine the conventional method with electromagnetic means (e.g., obtaining written consent after giving an explanation by electromagnetic means) in the informed consent process.

As is the case with that by the conventional method, the investigators, etc. need to explain/obtain informed consent in compliance with the provisions for informed consent of subjects, etc. in the GCP Ordinance (Articles 50 to 55 in the case of the GCP Ordinance for drugs). Appropriateness of explaining/obtaining informed consent using electromagnetic means should be evaluated while considering the contents of the clinical trial and expected subjects, etc. Then, it should undergo the review by the institutional review board (hereinafter referred to as "IRB") after specifying the procedure for explaining/obtaining informed consent. In accordance with its result and after all these processes, explanation/obtainment of informed consent using electromagnetic means should be conducted. If the IRB or regulatory authorities ask questions about the details of the procedures for an explanation/obtainment of informed consent using electromagnetic means, the explanation should be made appropriately.

(2) An explanation/obtainment of informed consent using electromagnetic means should be conducted after establishing a necessary information and communication system, operating procedures, etc. based on the following points.

(a) Actions should be taken considering persons who are not familiar with information and communication devices or digital technologies. The level of understanding and familiarity with the operation of information and communication devices such as PCs and tablets and communication using them is expected to greatly vary among individuals. Therefore, a prior explanation/training on the operation of devices and the response to communication troubles, etc. should be considered and the procedures should be specified as necessary so that both the investigator, etc. (and the clinical research coordinator when he/she provides a supplementary explanation) and subjects, etc. can operate the devices appropriately.

(b) If subjects, etc. with impaired vision or motor function, etc. are expected to be enrolled, the measures to be taken should be examined and the procedure should be specified as needed after confirming that there is no problem with explaining/obtaining informed consent using electromagnetic means, including how an impartial witness (hereinafter referred to as "witness"), legally acceptable representatives, or a person who writes on b behalf of subjects, etc. is involved.

(c) If it is difficult to explain/obtain informed consent using electromagnetic means due to the circumstances of individual subjects, etc. or system trouble, etc., or if they do not desire the electromagnetic means, other alternative methods such as the use of paper documents or a face-to-face explanation should be available.

4. Points to consider, etc.

When explaining/obtaining informed consent using electromagnetic means, the investigator, etc. should establish procedures in advance considering at least the points below and implement the procedures in compliance with them. When the sponsor provides an information and communication system for an explanation/obtainment of informed consent using electromagnetic means, the sponsor should similarly consider the points below and, as necessary, assist the medical institution in preparing for an explanation/obtainment of informed consent using electromagnetic means.

The same applies to the case where information that may affect the intention of a subject, etc. to continue to participate in the clinical trial is obtained and the investigator, etc. confirm whether the subject, etc. continue to participate in the clinical trial (Article 54, Paragraph 1 in the case of the GCP Ordinance for drugs).

(1) Method of identification (identification, authentication)

(a) It is necessary to establish a procedure with which it can be surely confirmed that the person to whom the explanation/obtainment of informed consent is conducted is the subject, etc. himself/herself and to conduct it appropriately. In particular, when the investigator, etc. has never seen the subject, etc., it is necessary to handle the case very carefully.

(b) As the method of confirmation that the person is the subject, etc. himself/herself (identification) in the event of explaining/obtaining informed consent remotely using electromagnetic means, for example, presentation of an identification document (My Number Card, driver's license, passport, health insurance card, etc.) may be considered. In principle, the investigator, etc. (and the clinical research coordinator when he/she provides a supplementary explanation) and the subject, etc. (and the witness and/or the person who writes on behalf of the subject, if necessary. The same should apply to (c) below) need to confirm the identification of each other using identification documents. As identification documents of the investigator, etc. and clinical research coordinator, an employee card, etc. issued by the medical institution to which they belong may be considered. "Guidelines for the Appropriate Implementation of Online Clinical Practice" (March 2018 [partially revised in January 2022], MHLW) (hereinafter referred to as "Online Clinical Practice Guidelines") should be referred to, where necessary.

(c) As the method of identification of the subject, etc. (authentication) in the event of making an electronic signature, etc. using an information and communication system, utilizing single-factor authentication such as with a password by linking to the user ID, telephone number, or e-mail address, etc. or multi-factor authentication combining multiple factors such as a password only owned by the subject, etc., "knowledge" of secret questions, etc., "possession" of a smartphone, etc., and "living body" such as face and fingerprint may be considered. Currently, in the "Guidelines on Safety Management of Medical Information Systems, Ver. 5.2" (March 2022, MHLW) (hereinafter referred to as "Medical Information System Guidelines"), two-factor authentication is required. Based on that, it is desirable to obtain informed consent by conducting multiple-factor authentication.

It is acceptable to confirm that the signer is the subject, etc. himself/herself by signing a digital signature in a series of flow of identification in an explanation/obtainment of informed consent using electromagnetic means. Even in that case, it is desirable that a system for authentication of the person who gives digital signature is established in the information and communication system as much as possible.

(2) Places and conditions for explaining/obtaining informed consent

(a) If informed consent is remotely explained/obtained using electromagnetic means, both the investigator, etc. (and the clinical research coordinator when he/she provides a supplementary explanation) and the subject, etc. (and the witness or the person who writes on behalf of the subject, etc., if necessary) should participate at a place and by a method in which the privacy of a subject, etc. and the confidentiality related to the conduct of the clinical trial can be appropriately protected.

Specifically, the investigator, etc. should participate from the space in which confidentiality is protected, show a subject, etc. that there are no persons who are not involved in the clinical trial or medical care in the space where the investigator, etc. participate, and confirm that the subject, etc. participate from the space where their privacy is protected. The investigator, etc. should make sure that no audio recording, video recording, or photography will be conducted by the investigator, etc. or subjects, etc. without the consent.

(b) It is not necessary for the investigator, etc., clinical research coordinator, subject, legally acceptable representative, witness, or a person who writes on behalf of the subject to be present at the same place when informed consent is remotely explained/obtained using electromagnetic means. However, even in different places, it is necessary that the witness can adequately confirm that necessary information in the written information/informed consent form is appropriately provided to the subject, etc. who cannot read the written information/informed consent form.

(3) Procedures for explaining/obtaining informed consent

(a) Explanation may be given face-to-face or remotely using video call, etc. with a part or all of the written information/informed consent form and its supplementary explanation, etc. being displayed/presented in the form of documents and/or videos, etc. on the screen of a PC, tablet, etc. It is acceptable to include a video, etc. and/or slides to be seen in the explanation. But there is a concern that mere provision of self-learning/e-learning to subjects, etc. may increase differences in the level of understanding among subjects, etc. and/or the subjects, etc. make a decision without fully understanding the contents. Therefore, in addition to using them, the explanation should be basically made according to the level of understanding of subjects, etc. by combining with face-to-face explanation or by using video calls, etc.

(b) At the time of the explanation, subjects, etc. should be given an opportunity to ask questions about the contents of the explanation, and the questions should be appropriately answered. Responses may be provided by e-mail or chat as a supplement in addition to face-to-face setting or video calls, etc. with the investigator, etc.

For the case in which the subject, etc. have additional questions at a later time he/she should be informed of the method of making inquiries to the person in charge at the medical institution so that the investigator, etc. can adequately answer them.

(c) If the investigator, etc. who provide an explanation have never seen a subject, etc. when explaining/obtaining informed consent remotely using electromagnetic means, it is assumed that there will be more matters to be considered/noted such as establishing a relationship in which subjects, etc. can adequately ask questions about the clinical trial to the investigator, etc.

Necessary consideration should be given so that explanation/obtainment of informed consent can be conducted appropriately.

(4) Requirements for electronic signatures, etc.

(a) When electronic signatures, etc. are used as electromagnetic means instead of signatures in paper documents, the requirements, precautions, etc. described in an Annex to the "Use of Electromagnetic Records and Electronic Signatures in Submission for Application for Marketing Approval or Licensing of drugs, etc." (PFSB Notification No. 0401022 dated April 1, 2005 issued by the Director of Pharmaceutical and Food Safety Bureau, MHLW) (hereinafter referred to as the "ER/ES Guideline"), "Partial revision of 'Basic Concept of the Use of Electromagnetic Records in Clinical Trial-related Documents'" (Administrative Notice of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW dated July 1, 2014) (hereinafter referred to as “Basic Concept of the Use of Electromagnetic Record”) should be referred to.

(b) If it is difficult for subjects, etc. to address electronic signatures, etc., written information/informed consent form should be printed and mailed, and the action should be taken to make it possible for the subjects, etc. to return the form after signing. It should also be confirmed that the signer is the subject, etc. himself/herself.

(5) Provision of written information/informed consent form and related matters

(a) Copies of the written information/informed consent form may be provided by hand or postal mail after outputting electromagnetic records of the written information/informed consent form. Also, they can be provided by e-mail, DVD-R, etc. or by allowing the subjects, etc. to download the electromagnetic records of the written information/informed consent form through Cloud systems under the agreement of the subjects, etc. If videos, etc. are included in the written information, the videos, etc. should be provided in a form that can be viewed or in documents that enable the subjects, etc. to understand its contents (screenshots, script, etc. hereinafter referred to as “screenshots, etc.”) . For specific considerations in the event of providing electromagnetic records, the "Basic Concept of the Use of Electromagnetic Record" should be referred to.

If it is confirmed that the documents have actually been downloaded, they are regarded to have been provided. However, it should be noted that the provision is not deemed to have been completed simply by uploading the electromagnetic records of the written information/informed consent form to Cloud systems.

Also, if the output of the electromagnetic records of the written information/informed consent form is sent by postal mail or if the subject, etc.

download the electromagnetic records of the written information/informed consent form, the explanation/obtainment of informed consent and provision of the copy of the written information/informed consent form may not occur on the same day. In such a case, it is acceptable to start the clinical trial procedures promptly after explaining/obtaining informed consent, but a copy of the written information/informed consent form should be promptly provided and the receipt by the subject, etc. should be confirmed.

(b) Even if signature and date exist separately in electromagnetic records, the document should be provided to the subject, etc. in a manner in which both the signature and date are linked.

(c) If it is requested by a subject, etc., a copy of the written information/informed consent form should be provided in a paper document in which the signatures and date are linked.

(6) Handling of documents

(a) It should be clarified in advance whether documents, videos, etc. to be used for the explanation to subjects, etc. including those displayed and presented by electromagnetic means are included in the written information specified in the GCP Ordinance. If the written information to be presented by electromagnetic means contains videos, etc., it should be noted that they (or documents in which their contents can be understood such as screenshots, etc.) are considered to be a part of the written information/informed consent form and should be stored, delivered, and subject to the deliberation at the IRB.

Videos, etc. that are displayed together with the written information presented by electromagnetic means may be handled as not included in the written information if they can be regarded as reference materials for the written information to improve the understanding of subjects, etc. In this case, it should be confirmed that the items to be included in the written information specified in the GCP Ordinance are satisfied even if videos, etc. are excluded.

(b) For written information/informed consent forms displayed by electromagnetic means, prior approval of the IRB should be obtained after making clear how the videos, etc. are handled, such as whether videos, etc. are included in the written information or not included thus regarded as reference materials. If videos, etc. are included in the written information, the contents of a copy of the written information/informed consent form to be provided to the subjects (documents with which the contents of videos, etc. or screenshots, etc. can be understood) should also be approved by the IRB.

In addition, if requested by the IRB or the regulatory authorities, electromagnetic records such as documents, videos, etc. that are displayed/presented by electromagnetic means and used for the explanation to subjects, etc. (including each version and those positioned as reference materials if the written information/informed consent form are revised, etc.)

should be prepared for presentation.

(c) When submitting a clinical trial notification and change in a clinical trial notification (if applicable), the written information/informed consent form should be included in the submitted data. If the written information contains videos, etc., the documents with which the contents can be grasped, such as screenshots, etc., should be attached in PDF format. The submission of electronic media in an accessible format/file type may be requested as necessary. It is not necessary to attach videos, etc. if they can be regarded as reference materials for the written information.

(d) In consideration of GCP on-site inspection, the following points should be considered when storing documents, etc. at the medical institution.

(1) As in the case of obtaining informed consent using paper documents and face-to-face setting, even if informed consent is explained/obtained using electromagnetic means, necessary measures should be taken so that the signed informed consent form and the written information used (if the written information/informed consent form were revised, each version and its reference data should be included) are accessible at the time of the inspection of the medical institution regardless the timing of inspection, i.e, during the clinical trial or after the completion of the clinical trial.

(2) If Cloud systems are used for access/storage of the written information/consent form, etc., there should be no period in which the medical institution cannot the relevant electromagnetic records. If Cloud systems are scheduled to be closed, transfer of electromagnetic records to the system such as another Cloud system and storage in recording media, etc. shall be done in a way where the written information/consent form are linked with each person's signature and date. The storage of software for access to such electromagnetic records should also be considered.

(e) As for electromagnetic records related to the explanation/obtainment of informed consent using electromagnetic means, the authenticity, accessibility, and preservability should be secured with reference to the "ER/ES Guideline," "Basic Concept of the Use of Electromagnetic Records," and "Guidelines for Safety Management of Medical Information System." Also, the confidentiality of personal information, etc. of subjects should be protected by taking necessary security measures such as encryption and restriction of persons who access it, and safety management measures, etc. to appropriately store them. When the saved electromagnetic records are transferred to other electromagnetic recording media or format, the authenticity, accessibility, and preservability should be secured for the electromagnetic records after the transfer, and the electromagnetic records for which electronic signatures, etc. have been made should be transferred in a way where the signatures and dates are linked to the electromagnetic records.

(7) Use of information and communication systems and general services and training

(a) When explaining/obtaining informed consent using electromagnetic means, it should be implemented in accordance with the "ER/ES Guideline." Thus, it is important to take measures based on the risks associated with the systems to be used, etc. in order to appropriately select and use the information and communication systems and general services then explain/obtain informed consent.

(b) For appropriate use of information and communication systems and general services, the investigator, etc. should take necessary security risk measures, etc. with reference to V.2. (5). 1) of the "Online Clinical Practice Guidelines."

Also, the investigator, etc. should explain to subjects, etc. how to use the system, etc. and how to handle it safely in terms of security and obtain agreement on these from the subjects, etc. before using the system, etc. Also, the following points should be explained to and confirmed with subjects, etc.

(1) Information and communication devices, etc. used by subjects, etc. should meet necessary specifications and requirements, and the versions of OS and software should be appropriate.

(2) Subjects, etc. should not disclose the log-in information issued for them to any third party.

(c) When providing an information and communication system or general services to be used to medical institutions (including the case of using an information and communication system developed by an external service provider), the sponsor should take necessary security measures, etc. for risks with reference to V.2. (5). 2) of the "Online Clinical Practice Guidelines."

The information and communication system must be the one that has undergone the computerized system validation (CSV) and its function is guaranteed.

(d) When providing an information and communication system or general services to be used to medical institutions (including the case of using an information and communication system developed by an external service provider), the sponsor should provide necessary information (e.g, information materials) to medical institutions regarding the method of use of the information and communication system so that the investigator, etc. can properly explain/obtain informed consent using the information and communication system.

The investigator, etc. should make an effort to acquire knowledge necessary for appropriate the explanation/obtainment of informed consent using the information and communication system by receiving training, etc.

(e) If the medical institution uses an information and communication system prepared by themselves (including the case of using an information and communication system developed by an external service provider), security risk measures, etc. should be taken under the responsibility of the medical institution as in the cases of (c) and (d), and a necessary training environment

should be prepared.

Note

Federation of Pharmaceutical Manufacturers' Associations of JAPAN
Japan Pharmaceutical Manufacturers Association (JPMA)
Japan-Based Executive Committee of Pharmaceutical Research and Manufacturers of America
European Federation of Pharmaceutical Industries and Associations
Japan Medical Association
Japan Dental Association
Japanese Society of Hospital Pharmacists
Japanese Nursing Association
Japan CRO Association
Japan Association of Site Management Organizations
The Japan Federation of Medical Devices Associations
Forum for Innovative Regenerative Medicine
American Medical Devices and Diagnostics manufacturers' Association
European Business Council IVD Committee
Association of Registered Certification Bodies under the Pharmaceuticals and Medical Devices Act
Japan Municipal Hospital Association
Japan Hospital Association
All Japan Hospital Association
Japanese Association of Medicalcare Corporations
Japan Psychiatric Hospitals Association
Welfare Division, Local Public Service Personnel Department, Local Administration Bureau, Ministry of Internal Affairs and Communications
Medical Education Division, Higher Education Bureau, Ministry of Education, Culture, Sports, Science and Technology
Health & Medical Division, Bureau of Personnel & Education, Ministry of Defense
Hospital Management Department, Business Division, Japan Post Holdings Co., Ltd.
National Federation of Health Insurance Societies
Federation of National Public Service Personnel Mutual Aid Associations
SEMPOS
Japan National health insurance Clinics and hospitals Association
JA Zenkouren
Japanese Red Cross Society
Japan Organization of Occupational Health and Safety
National Hospital Organization
Japan Community Health care Organization
Pharmaceuticals and Medical Devices Agency
Regional Bureau of Health and Welfare