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[Brief Report]

Use of Electronic Consent Forms in an Observational Pilot Study of Coronavirus Disease in Japan

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ABSTRACT

Background　Face-to-face explanation and paper-based consent acquisition protocol commonly used for obtaining informed consent may increase the risk of infection spread between the participants and the investigators of coronavirus disease（COVID-19）-related studies. We examined the use of electronic informed consent（e-Consent）, obtained through REDCap, an electronic data capture（EDC）system developed by Vanderbilt University, as an alternative.

Methods　We utilized the REDCap e-Consent framework as an alternative to face-to-face method for obtaining informed consent in an observational pilot study. We collected requests, inquiries and issues from the pre-construction to production phase, determined if they are major or minor problems, and analyzed the solutions. We set to judge for the feasibility using EDC like Redcap, if there were no adverse major or minor problems and all participants can complete informed consent with the e-Consent.

Results　Between August and November 2020, a total of 26 participants completed the informed consent from the two centers using REDCap. Since no adverse problems were encountered during e-consent acquisition, participant enrollment, or data collection, the feasibility was confirmed.

Conclusions　Non-face-to-face informed consent can be obtained from study participants using an e-Consent like REDCap for a single site or a small multicenter study. In cases of a large multisite clinical study, either the site settings should be managed by an organization such as a data center or an alternate method should be used till the usage of e-Consent is upgraded due to system updates.

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KEY WORDS　COVID-19, observational study, informed consent, e-Consent, REDCap

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日本国内での新型コロナウイルス感染症のパイロット観察研究における電子同意書の使用

于　佳[*1]　今井康人[*1]　野村章洋[*1]　米田　隆[*2]　村山敏典[*1,*3]：[*1]金沢大学附属病院先端医療開発センター；[*2]金沢大学大学院医薬保健学総合研究科未来型健康増進医学；[*3]金沢大学附属病院臨床開発部

Introduction

The coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is not yet over. In Japan, as of April 2022, more than 7 million infections and 28,000 deaths attributable to COVID-19 have been confirmed.1) The incubation period for COVID-19 is 2-14 days.2) However, SARS-CoV-2 is highly infectious, and the infected people appear to be most infectious just before they develop symptoms (approximately 2 days before they develop symptoms) and early in their illness. The virus is transmitted mainly through the respiratory system via three major routes namely aerosol, droplet, and direct contact. Both symptomatic and asymptomatic individuals infected with SARS-CoV-2 are potential sources of infection.3)

Owing to the highly contagious nature of COVID-19, conducting face-to-face discussions to obtain informed consent on paper-based forms for clinical research may not be practical, as study participants and investigators are in close contact with each other for a substantial amount of time in the explanation room increasing the risk of transmission manifested by the 3C conditions (closed space, crowded place, and close contact). Moreover, grouping participants into clusters can further spread the infection.

REDCap, a data collection and management system developed at Vanderbilt University in the United States has been used successfully in a previous study4) for detection of SARS-CoV-2 (hereinafter referred to as the pilot study). It is the most widely used database for clinical research including observational studies and is used by more than 5,000 organizations in over 140 countries. Kanazawa University Hospital has a collaboration with Vanderbilt University and has already used REDCap as an electronic data capture (EDC) system to collect clinical data for more than 10 investigator-initiated clinical studies. The purpose of the previous pilot study was to acquire and measure biometric data using a wristwatch device called Fitbit® (**Figure 1**), and to explore parameters that predict the transition to deterioration by observing changes in biometric data during the natural course of disease among COVID-19-positive patients placed in home isolation.

Figure 1 Fitbit® Charge 3
https://www.fitbit.com/
Fitbit® is an activity meter manufactured by Fitbit, Inc. (San Francisco, CA, US). It is a device that can measure the number of steps walked, calories burned, sleep status, and estimated oxygen variation, using a built-in accelerometer.

For observational studies without invasiveness/intervention, the “Ethical Guidelines for Medical and Health Research Involving Human Subjects” state that informed consent is not mandatory; however, it is desirable to obtain “appropriate consent” according to the Act on the Protection of Personal Information, including receipt of electromagnetic documents (e.g., digital devices and online).5) Therefore, we focused on this new “non-face-to-face” method of obtaining consent, using e-Consent with REDCap. e-Consent, also called electronic informed consent, allows participants to give their consent to participate in clinical research via the Internet. The US Food and Drug Administration (FDA) defines e-Consent as “the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, and passive and interactive websites to convey information related to the study and to obtain and document informed consent”.6) The e-Consent in REDCap complies with 21CFR Part 11 regulations provided by the FDA regarding electronic signatures, electronic records, and handwritten signatures on electronic records, and is feasible for use in clinical research.7)

Although e-Consent has already been implemented in the United States and other countries, as the e-Consent Global Landscape Assessment Survey by Transcelerate,

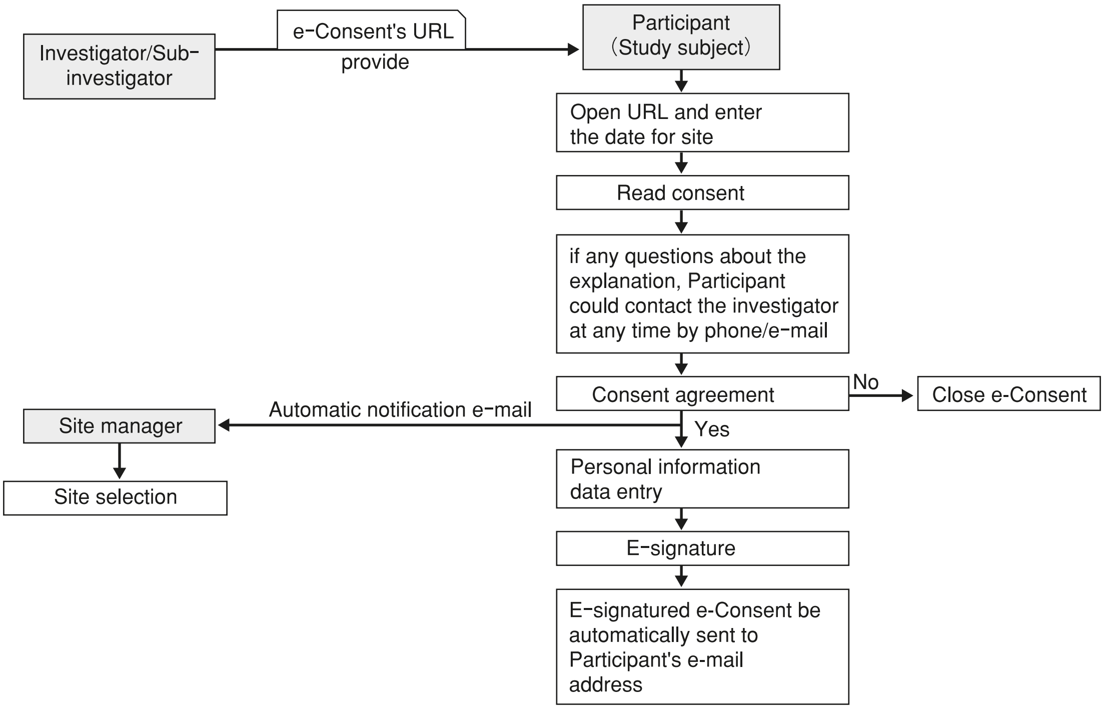


Figure 2　**e-Consent process for the observational pilot study**

from 2016 to 2019, 40 countries have had e-Consent submissions (to Hospital Authority (HA) s and/or Institutional Review Boards (IRB)/Independent Ethics Committees (IEC)), and 31 countries have actively collected consents from patients using e-Consent.[8] To our knowledge, no clinical research using e-Consent has been published in Japan at the time of submission of this paper. Therefore, this study is thought to be the first report in Japan wherein e-Consent was obtained via REDCap. The specific objective of this study was to verify whether informed consent using e-Consent through REDCap in the pilot study was sufficiently practical enough to replace the traditional face-to-face method of obtaining informed consent. Also, while operating e-Consent framework using REDCap, most of its limitations could be detected at the database set-up stage, which helped us to consider solutions to them.

Methods

Ethical Consideration

The pilot study (clinical trial registry number: UMIN000041421; institutional review board approval number: #2020-045 of the Medical Ethics Committee of Kanazawa University) was a two-site observational study conducted at Kanazawa University and its affiliated facility in compliance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects," and the Declaration of Helsinki. The implementation of e-Consent was also approved by the Institutional Review Boards of two sites by stating the usage of informed consent by e-Consent in the protocol and submitting the actual screenshot of e-Consent. e-Consent acquisition, participant enrollment, and data collection and management were all performed via REDCap.

Procedure of obtaining e-Consent using REDCap

To obtain e-Consent for the pilot study, we used REDCap's survey function, which does not allow a third party to view the participant's personal information and protects the privacy of participant data. In this survey, the participant does not need to register as REDCap users, and the investigator provides the participant with an e-Consent URL which is created using e-Consent function, that can be viewed on a PC or tablet. If the participant consents to the content of the pilot study and provide the Fitbit biometric data after browsing through the explanatory document displayed at the URL, they can sign electronically on their device. The e-Consent process is illustrated in **Figure 2**, and specifications and operations of e-Consent in

Table 1 e-Consent specifications and operations

No.	e-Consent specifications	Operations
1	e-Consent's URL address which was accessed by participants	The investigator/sub-investigator provided REDCap e-Consent's URL address to participants, and the URL address was set so that it could be opened freely anywhere without any restrictions on the place for informed consent.
2	The participating site on e-Consent page which was chosen by participants	We set the format such that the participants selected the participating site according to the instructions of the investigator/sub-investigator.
3	Content of e-Consent which was read by participants	We separated each item in the e-Consent form as a page, set up the option of "I understand" at the end of each page. The next page could be accessed only when the participants understood the content of e-Consent and clicked "I understand." If the participants did not understand the content of e-Consent, contact phone number/e-mail address was displayed so that the participants can contact the investigator by phone/e-mail at any time.
4	Consent agreement to participate in the research	We set up the options of "Read the above informed consent form and agree to participate in this study" and "Read the above informed consent form and will not participate in this study," so that it could move to the next page of "Consent to provide Fitbit biometric data" page, only when "Agree to participate in this study" was selected.
5	Consent agreement to provide Fitbit biometric data	We set up the options of "Yes" and "No" for the question "Do you agree to provide the biometric data from your wearable device (Fitbit) to our study?" so that it could move to the next "Items entered by the participants" page only when "Yes" was selected.
6	Personal information data entry and e-signature by participants	Data related to personal information were set as the "Identifier" by REDCap. The data set as the "Identifier" are a function that can be identified from the system and the identifier data can be hidden when output in the dataset.
7	Display and storage of the e-Consent forms automatically created which viewed and entered by participants	We set up the system so that the participant can download a PDF of the original consent form with e-signature, and at the same time the PDF of the e-Consent form with e-signature was automatically sent to the participant's e-mail address.

REDCap are summarized in the **Table 1**.

When designing the content of this e-Consent, we referred to the e-Consent made with REDCap by Stanford University's clinical research team, designed separately for study participation consent and Fitbit biometric data provision consent in accordance with Stanford University's "General Requirements and Elements for Informed Consent."9)

To verify the identity of the participant in the electronic signature, the investigator provided the e-Consent URL only to participants of the pilot study. When the participant accessed the e-Consent URL, the system verified the participants' identity and attributed the corresponding electronic signature to that participant. After the investigator confirmed the participant's consent, and the electronic signature in the REDCap database, the investigator promptly directed Fitbit®, the test device used in the pilot study, via email to the address provided by the participant.

Identifying issues related to e-Consent operations in REDCap

Since this pilot study was the first to use e-Consent in REDCap in Japan, we assumed that various unexpected problems would arise during its operation.

We collected data on the following three items for e-Consent and verified the equivalence with the face-to-face informed consent acquisition method.

1 issues which we noticed while building e-Consent in REDCap,
2 requests for e-Consent from investigators before and during construction,
3 inquiries from participants, investigators and other medical staffs during production use.

Specifically, while construction, we created demo versions of countermeasures for each request and obtained confirmation and feedback from investigators after their actually operation. Also, we collected the issues during the construction of e-Consent, considered solutions and created a demo version based on the solutions to operate it in real-time simultaneously with investigators and brought it to the production use. During production use, we collected inquiries from the participants via investigators and examined whether there were any issues that should be improved in the e-Consent.

As a verification method, we defined the major problems which can cause the participant's failure to participate in the study together with minor problems for all requests, suggestions and inquiries from data manager, participants, investigators and other medical staffs from pre-construction to the end of production use.

For the above data, from pre-construction to production use, if there were no major or minor problems that cannot be dealt with, and all participants can complete informed consent with the e-Consent in REDCap without any system glitches, feasibility of REDCap e-Consent was confirmed to be suitable to replace the conventional face-to-face method of acquiring informed consent. In case of any major/minor problem that cannot be dealt with, the e-Consent in REDCap was judged to be unable to replace the conventional consent acquisition method.

Results

Feasibility of e-Consent in REDCap in the pilot study

The tenure of the pilot study was from August to November 2020. A total of 26 participants were enrolled from the two centers using the e-Consent in REDCap. There were no problems that cannot be dealt with in e-Consent acquisition till the successful completion of this pilot in November 2020. Thus, using the e-Consent in REDCap allowed us to conduct the study without any direct contact with COVID-19 patients.

1　Issues which we noticed while building e-Consent in REDCap

As the definition of the major and minor problems in the method, one important and noteworthy major problem and two minor problems were identified while building the database and considering the solution as given below:

1）Major problem: Protection of personal information of participants

In this pilot study, the survey function of REDCap was used to create an e-Consent form in a similar format as a questionnaire, so that participants could access the e-Consent URL provided by the investigator without registering as a REDCap user and could browse the e-Consent form for study contents. If the participant understood and consented to the study, they entered personal information and study-related items on the e-Consent form and signed it electronically to participate in the pilot study. Since the participants did not need to create a user ID for themselves to use REDCap's survey function, the completed e-Consent form could be viewed by any investigator at any site in the system, rather than being distributed only to the site where the participant registered. For example, when a Kanazawa University participant received the e-Consent URL from a Kanazawa University investigator and completed the data entry and electronic signature on the e-Consent form, REDCap was unable to recognize the participant's data access group（DAG）. This was a serious problem because the personal information entered by the participant could be viewed not only by the investigator at Kanazawa University, but also by investigators at the affiliated site. This was because the REDCap system specifications allows only one e-Consent URL to be created in one project. In other words, as the system specification did not allow multiple e-Consent URLs to be issued to multiple sites in a single project, there was a risk of participant's personal information being viewed by investigators at all participating sites, rendering the need for multiple e-Consent forms in multicenter clinical research. However, since the pilot study had only two sites（centers）, we implemented the following method to overcome the situation.

For the pilot study, a new role of "Site Manager" was created in REDCap, and the coordinating investigator was delegated as the site manager. A notification e-mail was set up to be sent automatically to the site manager's mailbox when a participant began the e-Consent process. Whenever the site managers received this notification, they immediately logged into REDCap and temporarily blocked other site investigators from accessing the e-Consent with their user privileges. Each REDCap user was informed to not access the REDCap until notified by the site manager till such time that the DAG for new records of the added participant was established.

After the participant completed the e-Consent entry, the site manager promptly set up a DAG on the participant's record. Once the DAG was established, the restrictions on the REDCap participant's site was lifted, and users at the other site were notified that REDCap could be used again. The users at the other site were always prohibited from accessing the participants' data.

2）Minor problem 1: Modification of data entered by participants

In our pilot study, a part of items entered by the participants in REDCap's e-Consent was the baseline electronic case report form（eCRF）. We set the items（sex, date of birth, height, weight, smoking history, complications, subjective symptoms, COVID-19 confirmation）entered in the e-Consent was displayed on the patient background page and the investigator/sub-investigator could enter the EDC data based on it. However, the participants did not have any rights to access the information once they had entered and it was not possible to change or delete the data already entered on the e-Consent form by the participant. Therefore, to accommodate any corrections to the entered data, the following methods were employed:

- Background information, such as participant's date of birth, sex, height, and weight, was collected on the REDCap participant enrollment page where it could be corrected by re-entering the information rather than on the e-Consent form where making changes were not possible.
- If there was a data entry error on the date when the participant's consent was obtained, e-Consent data for that participant were not corrected. If the coordinating investigator determined that the data needed correction, the data manager（DM）was tasked to prepare a"Data Replacement Report"with the permission of the coordinating investigator. The DM replaced the data in the output dataset after all data collection was completed.

3）Minor problem 2: DM access rights to e-Consent data

To manage the personal information of the participants, the DM's access rights to e-Consent data were set as follows, in contrast to conventional observational studies:

- Viewing restrictions on DM of the e-Consent data（last name and first name of participant, zip code, address, telephone number, e-signature, e-mail address）. The DM was not granted access to view the data entered by the participant on the e-Consent form on REDCap.
- e-Consent data with no restrictions for viewing by DM（sex, date of birth, height, weight, smoking history, complications, subjective symptoms, date of COVID-19-positive confirmation）.

Because the DM did not have the right to view the e-Consent form, and in order to prevent the misidentification of participants, only e-Consent data with no restrictions for viewing by the DM were set to be displayed on the patient background page of EDC, so that the DM could manually check these data. Therefore, the DM performed the data checking（with data that did not identify the participant mentioned above）on the participant's enrollment page based on these non-restricted data and these e-Consent data were displayed on the patient background page of EDC.

2　Requests for e-Consent from investigators before and during construction

We received 4 requests from investigators before and during construction. We considered these requests as minor problems and the solutions for each was as given below. There were no major problems in these requests:

1）Minor problem 1:

＜Request＞

"There should be an'I understand'field on each page of e-Consent form so that if the participant does not understand the content, they will not be able to proceed to the consent or e-signature field, and the e-Consent form is closed at that point."

＜Solution＞

We added an'I understand'field to each page. It is now impossible to proceed to the next page unless a participant clicks'I understand'（**Figure 3**）. We also set it up such that if the participant clicks'No'in the'Consent agreement'field, the entire e-Consent form closes immediately（**Figure 4**）.

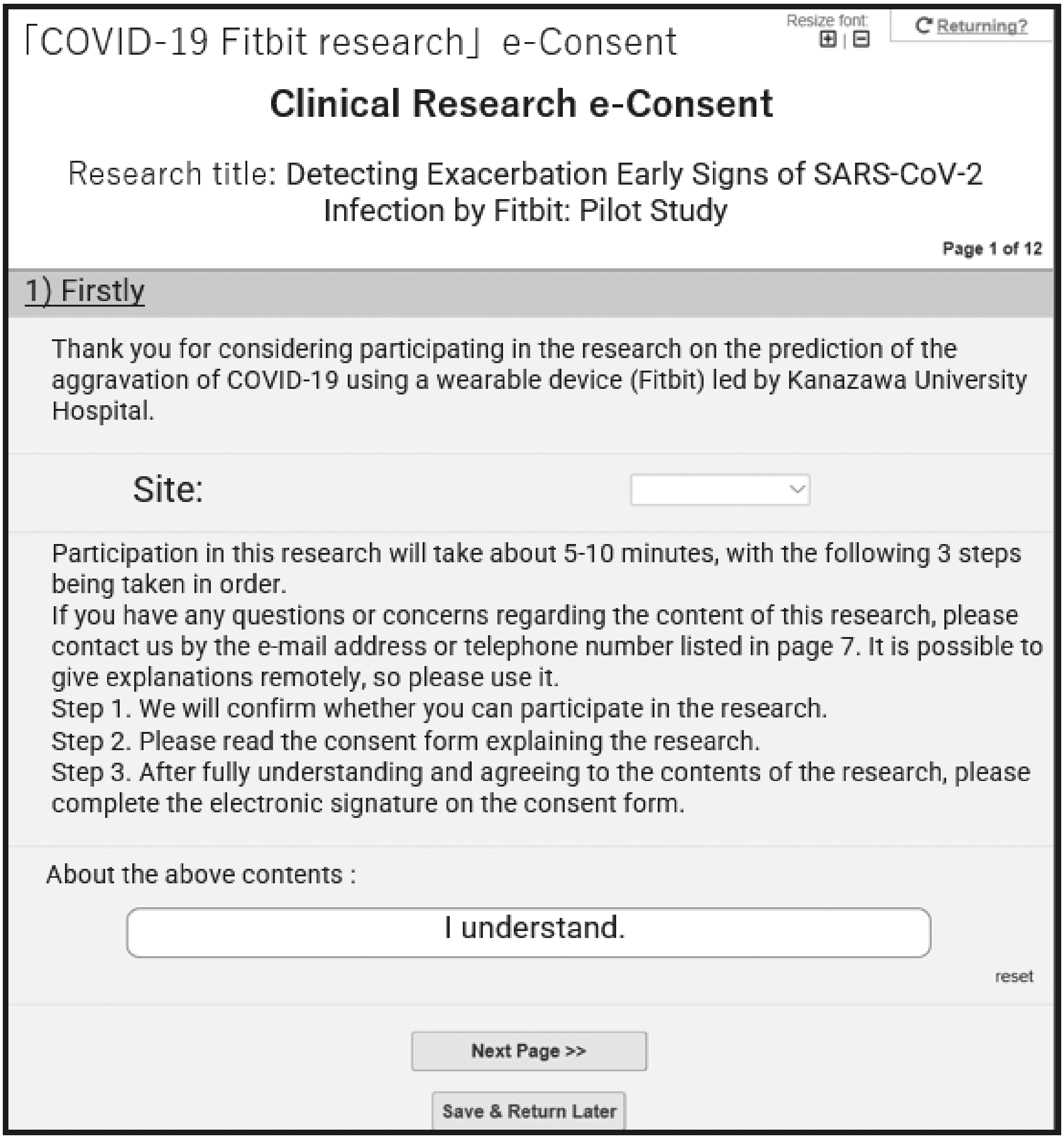
2）Minor problem 2:

＜Request＞

"Please include the investigator's contact phone number and e-mail address in the e-Consent form so that participants can contact the investigator immediately if they have any questions."

＜Solution＞

The investigator's contact phone number and e-mail address were clearly indicated on the e-Consent form, and the PDF of the e-Consent form which was automati-



「COVID-19 Fitbit research」 e-Consent

Clinical Research e-Consent

Research title: Detecting Exacerbation Early Signs of SARS-CoV-2 Infection by Fitbit: Pilot Study

Page 1 of 12

1) Firstly

Thank you for considering participating in the research on the prediction of the aggravation of COVID-19 using a wearable device (Fitbit) led by Kanazawa University Hospital.

Site:

Participation in this research will take about 5-10 minutes, with the following 3 steps being taken in order.
If you have any questions or concerns regarding the content of this research, please contact us by the e-mail address or telephone number listed in page 7. It is possible to give explanations remotely, so please use it.
Step 1. We will confirm whether you can participate in the research.
Step 2. Please read the consent form explaining the research.
Step 3. After fully understanding and agreeing to the contents of the research, please complete the electronic signature on the consent form.

About the above contents :

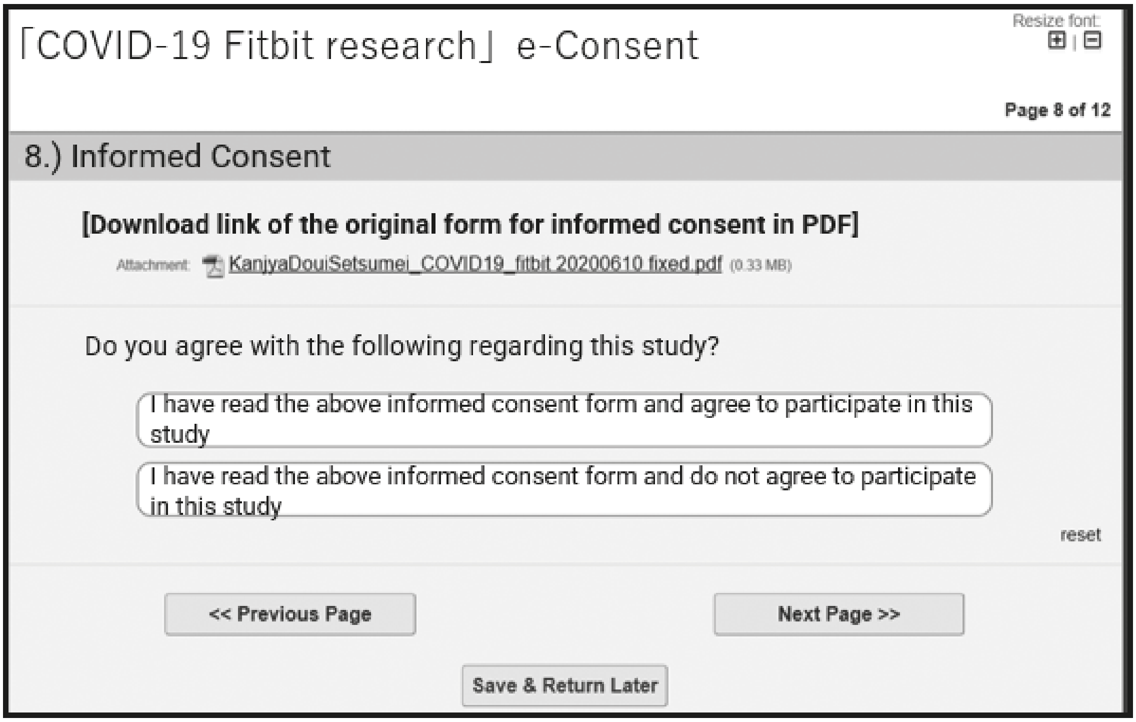
I understand.

Figure 3　Layout of the column for "I understand" set up for each e-Consent page in the pilot study. The actual consent form is described in Japanese

cally sent to the participant after consent, so that if participants had any questions about the explanation, they could contact the investigator at any time.

The elderly who have difficulty in operating electronic equipment such as smartphones, when giving informed consent, inquired about button operations on smartphones, how to write signature, etc. There were no questions regarding young people.

3) Minor problem 3:
＜Request＞
"After the participant gives e-Consent, a digitally signed e-Consent form should be automatically sent to the participant, and the participant should be able to download and save the PDF of the original consent form."
＜Solution＞
We set up the system so that the e-Consent form digitally signed in the entry page is automatically sent to the participant's e-mail address, and the participant can down-



「COVID-19 Fitbit research」 e-Consent

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8.) Informed Consent

[Download link of the original form for informed consent in PDF]

Attachment: KanjyaDouiSetsumei_COVID19_fitbit 20200610 fixed.pdf (0.33 MB)

Do you agree with the following regarding this study?

I have read the above informed consent form and agree to participate in this study

I have read the above informed consent form and do not agree to participate in this study

reset

Figure 4　Layout of the column for "Consent agreement" in the pilot study. The actual consent form is described in Japanese.

load a PDF of the original consent form containing the data that they entered (**Figure 5**).

4) Minor problem 4:
＜Request＞
"I want to be notified by e-mail when a new e-Consent is initiated."
＜Solution＞
We configured the system to automatically send a notification e-mail to site manager when the e-Consent entry was completed.

3　Inquiries from participants, investigators and other medical staffs during production use

During production use, we collected inquiries from study participants via investigators and examined whether there were any issues that should be improved in e-Consent. As a result, we received the inquiries as below, which were considered as minor problems. Therefore, there were no major problem and 1 minor problem from the participant during production use.

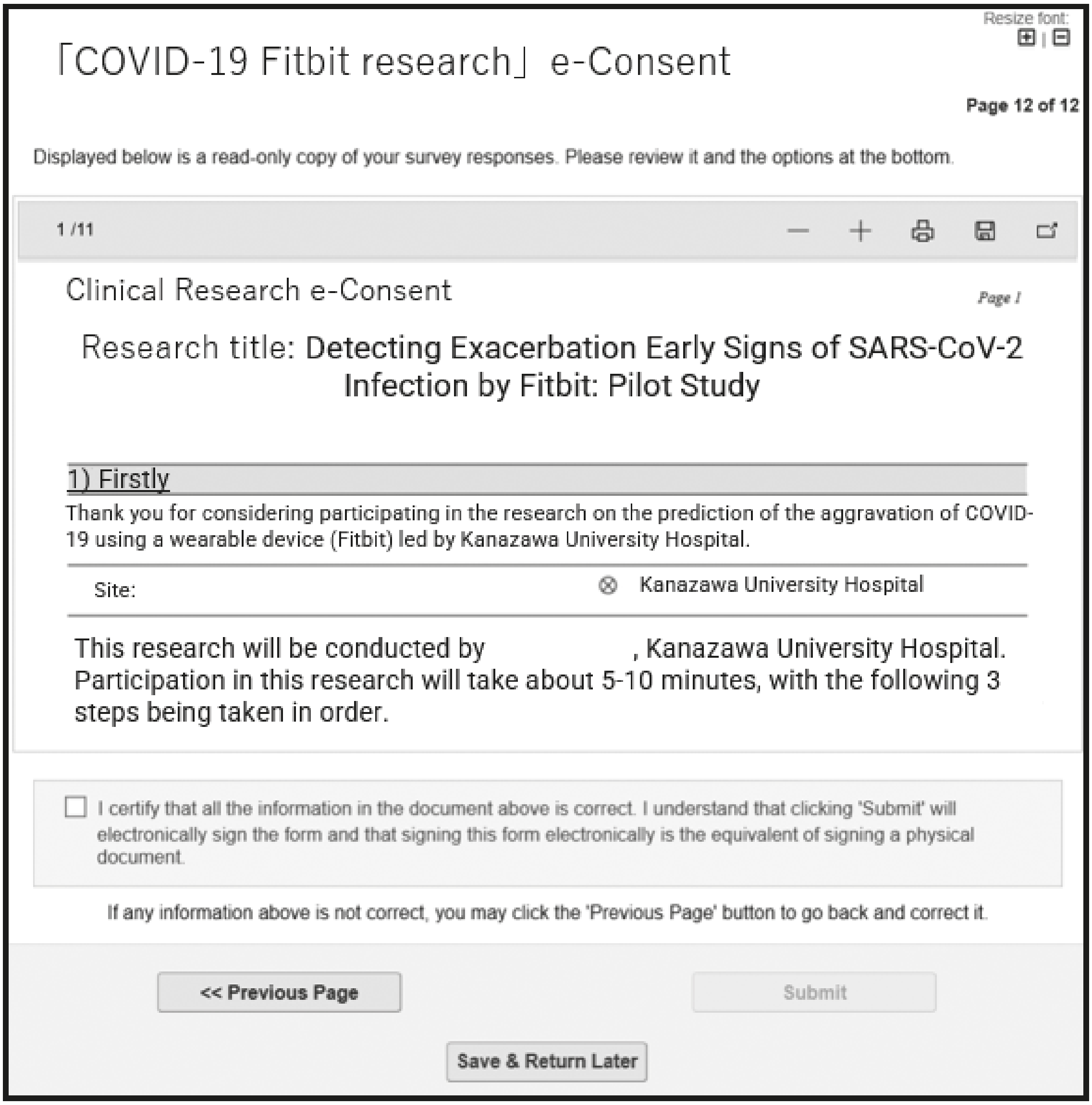
1) Minor problem: operating problems for electronic equipment in the elderly people

Elderly people who have difficulty with electronic devices asked questions about how to operate e-Consent buttons on smartphones, how to write signatures, etc., but there were no inquiries from young people. We answered these questions and found that there is no need to improve e-Consent because it is currently a global social problem among the elderly associated with the digital divide.

There were no inquiries from investigators and other medical staffs for the e-Consent in REDCap during production use.

There were no cases of failure to complete informed consent in the study due to difficulty using e-Consent during production use. Although there were cases in which Fitbit and smartphones did not work well so that they could not be used in the pilot study, regardless of the main purpose of this study, e-Consent. We were able to obtain informed consent with all participants with no problem for e-Consent in REDCap.

In summary, there were no major problem or minor problems that could not be dealt with in the e-Consent in REDCap, so that the e-Consent in REDCap can be considered a feasibility.



「COVID-19 Fitbit research」 e-Consent

Displayed below is a read-only copy of your survey responses. Please review it and the options at the bottom.

Clinical Research e-Consent

Research title: **Detecting Exacerbation Early Signs of SARS-CoV-2 Infection by Fitbit: Pilot Study**

1) Firstly

Thank you for considering participating in the research on the prediction of the aggravation of COVID-19 using a wearable device (Fitbit) led by Kanazawa University Hospital.

Site:	⊗ Kanazawa University Hospital

This research will be conducted by , Kanazawa University Hospital. Participation in this research will take about 5-10 minutes, with the following 3 steps being taken in order.

☐ I certify that all the information in the document above is correct. I understand that clicking 'Submit' will electronically sign the form and that signing this form electronically is the equivalent of signing a physical document.

If any information above is not correct, you may click the 'Previous Page' button to go back and correct it.

Figure 5　Layout of the PDF page for the original consent form including the entered data in the pilot study. The actual consent form is described in Japanese

Discussion

This study is the first to verify the applicability of e-Consent operation using REDCap in Japan, specifically the design of e-Consent in REDCap and the actual operation of e-Consent in clinical research. The results on this study suggest that e-Consent in REDCap can be used and applied in clinical research, and the possibility of using e-Consent in REDCap in future academia-led clinical research in Japan has been identified. On the other hand, we also identified the following issues that need to be considered in the future, when e-Consent in REDCap is used on a larger scale like multicenter study.

Site settings for personal information management in e-Consent

Currently, the protocols for handling personal information in Japan have become stringent because of the enactment of the Act on the Protection of Personal Information.10,11) Therefore, the problem faced by the investigators at all sites in any multicenter observational study regarding accessibility of personal information of all participants, needs to be addressed as early as possible. We established a new role of “site manager” as a unique operational solution in this issue. The coordinating investigator was delegated as the site manager during the assignment of the site manager, on the ground that the personal information of the participants used for the study must be protected as a requirement of the “Ethical Guidelines for Medical and Health Research Involving Human Subjects.” Since the participants are patients, the coordinating investigator of study is considered to be the most suitable candidate for this role; the participants themselves disclose their personal information directly to the coordinating investigator for protecting their personal information from third parties. The pilot study was conducted at two sites, and the site manager managed the personal information of participants enrolled at their respective sites while conducting the observational study; thus, there was no leakage of personal information to investigators at the other site.

A system specification of REDCap is that only one URL can be generated for the e-Consent form issued for a single project. Therefore, the creator of REDCap, Vanderbilt University, uses the“Single site hosts e-Consent for all sites” method in a multicenter study, and a Coordinating Center at Vanderbilt University Medical Center（VUMC）manages all sites.[12,13)]

The VUMC method necessitates the transfer of a list of participants’ names, e-mail addresses, and other personal information to the coordinating center in charge of site operation in advance; however, this approach cannot be replicated in Japan because of the Act on the Protection of Personal Information. Especially in the pilot study, it is necessary to carefully handle sensitive personal information of COVID-19-positive patients. Therefore, we adopted an operational solution to manage the participants’ personal information by establishing the role of the site manager. As the pilot study was conducted at only two sites, it was relatively easy to establish the role. However, this solution may not be easily applicable in large multicenter studies.

Unless an enhanced version of REDCap for multicenter studies is developed, it will be necessary to devise a customized solution to this problem. The limitations of the REDCap system need to be appropriately addressed while setting up the site. If the coordinating investigator becomes the site manager, they will need to constant access to a computer, centrally managing a large number of sites. This is quite an encumbrance for the investigator-physician and would be extremely difficult to manage. It is thought that sites can be managed more efficiently by organizations, such as data centers. However, according to the Act on the Protection of Personal Information, when sites are coordinated by data centers, it is necessary to consider the operational procedures/guidelines and determine how the non-physician staff should handle the personal information of the participants, such as by masking data that can be identified as personal information when collating the informed consent forms.

Features required for REDCap to use e-Consent

1）Update of the e-Consent entry page because of revisions in the consent form

If the consent form is revised during clinical research because of a revision in the study protocol or for other reasons, the e-Consent entry page of the operating database need to be updated. Owing to the limitations of REDCap’s specifications, database updating corresponding to the upgrades in the consent form version is required, it is necessary to suspend the e-Consent entry page, participant enrollment entry page, and case report data entry page, as the update needs to be verified in the production environment. In addition, to prevent participants from accidentally selecting the old version of the e-Consent, it is necessary to set the default so that the latest version of e-Consent will be automatically selected when designing the database.

2）Language of the e-Consent entry page

Since some of the e-Consent entry pages are displayed in English, they need to be translated into Japanese. In the pilot study, the data center created a data entry guidance in Japanese, and the participants referred it, to view and enter relevant data on the e-Consent entry page. However, considering the actual operational results, we believe that simply preparing guidance in Japanese is not sufficient. Currently, the system default message that pops up during the REDCap operation is also in English. In particular, when the participant selects “No” for Consent agreement on the e-Consent entry page or when the e-Consent final confirmation is reflected in the input content, the descriptions are in English. These descriptions may be difficult for the Japanese participants to understand, even if explained in the guidance. An adaptation needs to be developed that enables investigators to change the language directly on the e-Consent entry page to Japanese.

In the pilot study, what has been done and what should be improved for compliance with "Ethical Guidelines for Life Sciences and Medical and Health Research Involving Human Subjects"?

The "Ethical Guidelines for Life Sciences and Medical and Health Research Involving Human Subjects",[14] which came into effect on June 30, 2021, in Japan, allows e-Consent only when the following three conditions are met: secure identification, adequate opportunity to ask questions and receive answers, and document delivery in response to requests for access to the consent statement. Therefore, e-Consent is expected to become increasingly important. In the pilot study, we discussed the following in anticipation of the implementation of the new guidelines.

1　Secure identification

In the pilot study, we set the protocol such that the URL address of the study-specific webpage where the e-Consent form can be accessed, is handed over to the the participants only by the investigator in-person at the time of confirmation of COVID-19 positivity. However, even though the participant's identity was confirmed by providing the URL address, when accessing the e-Consent form, it could not be confirmed that the same participant had accessed the e-Consent form because it was not an in-person session. Conducting e-Consent using video conferencing tools would be more reliable. However, it is difficult to respond in real time, so it may be more feasible to send an e-mail to the participant's smartphone or tablet to confirm their identity. Their identity and their ability to respond can be confirmed when they reply to the verification e-mail.

2　Adequate opportunity to ask questions and receive answers

The e-Consent form for the pilot study had an "I understand" confirmation box on each page（each item of consent, such as "about study content," "about study period," "advantages and disadvantages of participating in study" etc.）, so that if the participants did not understand the explanation on that page, they could not proceed to the next page. In addition, the contact phone number and e-mail address of the investigator were clearly indicated on the e-Consent form, so that if participants had any questions about the explanation, they could contact the investigator at any time. Actually, the elderly participants who have difficulty in operating smartphones did inquire about some questions, but none of the participants were unable to participate in the study due to problems with the use of e-Consent in REDCap. It was assumed that anyone who can normally operate a smartphone or tablet can give informed consent with e-Consent in REDCap. It is necessary to create a dedicated manual and take measures such as easy-to-stumbling operations and easy-to-understand designs in future, for the elderly people who are unfamiliar with digital devices such as smartphones and tablets. However, as e-Consent is not obtained in-person/face-to-face, there is a possibility that participants may click on the "I understand" confirmation box without fully understanding the content of the explanation. There is also a possibility that participants may forego the opportunity to ask questions by refraining from contacting the investigators. As noted above, obtaining e-Consent via video conferencing tools would allow the investigator to monitor the participant's understanding of the content and to answer their questions, if any.

3　Document delivery in response to requests for access to the consent statement

In the pilot study, after the e-Consent was given, the e-Consent PDF file containing explanatory text was automatically sent to the participant's e-mail address, and a download function was provided on the e-Consent form（**Figure. 5**）to deliver the completed form to the participant. In the case of withdrawal of consent, no measures were set on e-Consent, but the option to consent withdraw on the REDCap EDC Discontinuation page was set.

Considering the need to comply with the new guidelines and to address the above three points（1,2,3）, it is necessary to devise ways to identify participants and answer their questions in non-face-to-face situations. These issues need to be addressed in future studies.

In conclusion, although e-Consent systems are currently being implemented around the world, they are uncommon in Japan, not only in investigator-initiated observational studies, but also in industry-sponsored clinical trials, because of legal restrictions. However, with the COVID-19 pandemic, the e-Consent has become more relevant because it has been demonstrated to prevent the spread of infection when conducting clinical research. Based on the solutions to the operational and systemic problems of e-Consent obtained through REDCap for a pilot study, we consider it necessary to devise better ways to implement e-Consent in the future. It is desirable that e-Consent use becomes more commonplace, and it is essential that it complies with the revised Act on the Protection of Personal Information in Japan.

Conclusions

Non-face-to-face informed consent could be obtained from study participants in Japan using the e-Consent in REDCap. Although there was one major problem, and some minor problems with e-Consent in REDCap which we noticed and collected, we solved for each by our solutions. And we were able to obtain informed consent with all participants with no problem for e-Consent in REDCap. Therefore, informed consent using e-Consent in REDCap is enough to replace the traditional face-to-face method of obtaining informed consent for clinical research including observational studies. However, regarding the issue of site settings, the solution used in our pilot study can be used in the case of the study for a single site or a small number of multisite. In the case of a large number of multisite clinical study, site settings should be managed by an organization such as a data center or some other way should be devised for handling of e-Consent upgrades due to system updates.

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【Conflicts of Interest】

The authors declare no conflicts of interest associated with this manuscript.

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