의학박사 학위논문

Factors influencing the reliability of decentralized elements in clinical trials: results of three prospective studies

임상시험에 도입된 분산형 요소들의 신뢰성에 영향을 주는 요인들에 대한 연구: 전향적 연구 3건의 결과에 기반하여

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서울대학교 대학원

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허 기 영

Ph.D. Dissertation of Medical Science

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Abstract

Factors influencing the reliability of decentralized elements in clinical trials: results of three prospective studies

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Introduction: Randomized controlled trials have been a standard for demonstrating effectiveness and safety. However, increasing costs and low accessibility to patients became potential source of biases. Decentralized clinical trials (DCTs) are an approach that leverages digital technologies to reduce dependency on trial sites and study intermediaries. Despite the higher accessibility that DCTs can provide, data reliability of DCTs should be overcome. To evaluate the factors that influence the reliability of DCTs, three feasibility studies were conducted.

Methods: The informed consent process was evaluated in a 4-week DCT (*dynamic consent trial*) consisting of three visits with a two-week interval. Each subject reported the self-measured body

temperatures and entered a code for the virtual investigational drug daily on a mobile application. The number and proportion of consents to the total number of encountered protocol amendments were calculated and understanding of the study procedures was assessed by evaluating adherence to drug and procedures.

Adherence monitoring was evaluated in a 12-week DCT (*adherence monitoring trial*) with vitamin D-deficient adults. Subjects took vitamin D supplements for 12 weeks and were randomized to the following adherence monitoring methods: mobile application (App) only or App combined with smart watch groups (App + Watch). Treatment adherence records and serum 25(OH)-vitamin D levels were evaluated.

Integration of the DCT elements were evaluated in an open, *fully remote clinical trial* in participants who had functional constipation symptoms. Subjects were randomized to either receive *Lactobacillus* and vitamin C supplements or vitamin C alone in a 1:1 ratio, which were delivered directly to subjects. Subjects kept track of bowel diaries daily during the 1-week baseline and 2-week treatment period using mobile applications. Bowel symptoms and the validity of the records were descriptively evaluated.

Results: In the *dynamic consent trial*, study subjects gave consent to 95.7% of protocol amendments with median response time of 0.2

hours. A total of 90.8% and 97.6% of drug administration and body temperature measurements were performed whereas adherence to the schedule was 69.1% and 59.0%, respectively. Adherence to the schedule remarkably decreased after the major protocol amendment.

In the *adherence monitoring trial*, serum 25(OH) vitamin D levels were comparably increased until the first 7 weeks but became higher in App + Watch group in the later phase. The number of doses taken by pill count and the App was not significantly different in the early phase (p = 0.5534) whereas became different in later phase (p = 0.0225). In contrast, the corresponding concordance for the smart watch was not significantly different in both periods (p = 0.5898 and p =0.5839, respectively).

In the *fully remote clinical trial*, a total of 26.7% of subjects were enrolled outside of the metropolitan area. Two-week *Lactobacillus* treatments increased the number of defecations (+0.80 vs. +0.46 times per week) and decreased the defecation time (−3.94 h vs. −1.62 h) compared to the comparator group. Overall, 67.1% of bowel diary records were completed in accordance with the schedule, while 24.0% were retrospectively and 6.2% were prospectively completed.

Conclusion: The reliability of decentralized clinical trials depends on

proper understanding of patients supported by systematic modalities. Combination of multiple monitoring tools can improve the reliability of data.

*The results of the *dynamic consent trial* were published as follows: Huh KY, Moon SJ, Jeong SU, Kim MJ, Yang W, Jeong M, Kim MG, Lee S. Evaluation of a blockchain-based dynamic consent platform (METORY) in a decentralized and multicenter clinical trial using virtual drugs. Clin Transl Sci. 2022 May;15(5):1257-1268.

Keyword: decentralized clinical trials, data reliability, digital technology, wearable devices, patient centricity, feasibility study

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Chapter 1. Introduction

1.1. Study background

Randomized controlled trials (RCTs) have been considered as a standard method for evaluating effectiveness and safety of therapeutic interventions.[1] However, increasing costs for conducting an RCT is becoming an obstacle to research and a potential source of biases.[2] Study sites are condensed in limited areas where infrastructures for RCTs are well equipped. For example, more than half of the clinical trials in South Korea are conducted in Seoul (the capital city of South Korea) in 2017–2019[3] and top 5 trial sites accounted for ~30% of the total clinical trials.[4]

Diversity of study populations could be achieved with accessible clinical trials. Study population in clinical trials have been criticized for lacking representativeness to the whole population.[5–7] Low geographical accessibility has been considered a major cause.[8] A previous study revealed that only 8% of cancer patients participated in a clinical trial although approximately 50% of the patients were willing to participate.[6, 9] Inaccessible trial sites were part of the reason as conventional clinical trials were conducted in academic–affiliated hospitals located in limited areas.[6] Such biases can result in the biased treatment response and outcomes.[7, 10]

Decentralized clinical trials (DCTs) are a recent approach to

improve access to clinical trials.[11] The definition of DCT varies,[12, 13] but low dependency on trial sites and study intermediaries are key characteristics in common.[14] The Decentralized Trial in Atrial Fibrillation Patients (DeTAP) trial is a good example; study subjects were recruited through social media and mobile applications were used to facilitate study procedures.[15] The DCT design had advantage in the rapid recruitment and patient retention.[15]

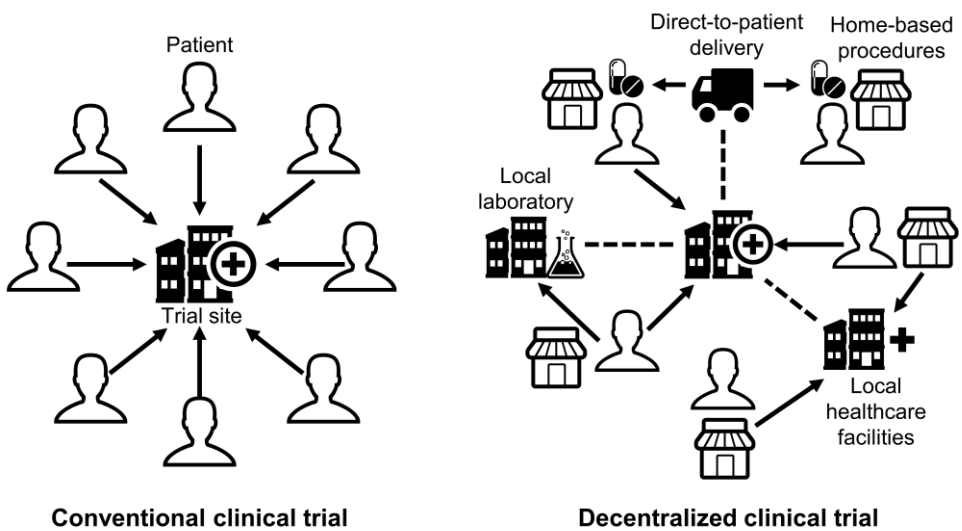

Figure 1. Schematic representation of a conventional clinical trial (left) and a decentralized clinical trial (right).

As DCT is not a dichotomous concept, adoption of DCT should be considered by element-by-element level.[16] It should be noted that not all face-to-face procedures in clinical trials cannot be fully

replaced by remote ones. In addition, when remote procedures are adopted, reliable data collection process must be provided for clinical decisions.[17] Therefore, what affects the reliability of the study procedures in a DCT must be evaluated at the early stage.[13, 16]

Despite the higher accessibility that DCTs can provide, data quality and integrity are subject to increased risk.[18, 19] DCT was recognized as a trial design by regulatory agencies that needs robust measures for data integrity.[19] Risks for data integrity can exist in study procedures (e.g., treatment adherence not assessed) or in study monitoring (e.g., unverified source data verification), all of which require the relevant mitigation plans.[20] As the implementation of DCT should be compatible with the local regulations and healthcare systems, identifying and dealing with the 'real-world' risk in feasibility studies are necessary.[15]

The process of informed consent is an important example. DCTs often involve electronic consents that are not conducted in a face-to-face manner.[21] In addition, continuous consent process in response to changes in the study would be required.[22] The changes necessarily require electronic systems which could be susceptible to data integrity risk.[23] Procedural burdens in electronic consent process and information overload should not be neglected.[24]

Therefore, balancing data integrity and procedural burden is not straightforward and needs to be investigated through feasibility studies.

Poor adherence also jeopardizes the data reliability in DCTs.[25] In particular, low adherence issue is problematic in the later phase of drug development, as the later-phase trials involve study procedures in routine medical practices.[25] Although adherence is often assumed ideal in clinical trials when not measured, actual adherence is reportedly less than 70%. The low adherence results in lower treatment effectiveness when analyzing the results.[26] As adherence can extensively influence the treatment outcomes, robust methods for measuring adherence are required in clinical trials, especially for DCTs.[26]

Recently, DCTs have been incorporating technological advances in information technologies. For example, blockchain is a data architecture characterized by immutability and traceability and has been integrated into clinical trials to ensure data integrity.[24, 27] Wearable devices, as another example, are comprehensively implemented as data acquisition and monitoring tools in DCTs.[28] Therefore, feasibility studies that integrate the principles of clinical trials and technological advances are required.

1.2. Purpose of Research

To investigate the factors that affect the reliability of DCTs, a series of feasibility studies were conducted. The focus of decentralization in each pilot study was (ⅰ) remote informed consent, (ⅱ) remote patient monitoring for treatment adherence, and (ⅲ) remote recruitment and direct-to-patient trial logistics. The studies aimed to evaluate if the introduction of the decentralized elements influenced the reliability of data collected in clinical trials, and which characteristics of the decentralized elements are attributable to. In addition, how the risks from decentralization could be mitigated was also explored. For this purpose, study subjects' behavior were monitored with minimal intervention from investigators to objectively assess the factors of interest. In addition, to evaluate the interactions in DCTs without posing unnecessary harms to study subjects, low-risk alternatives were used (e.g., mock drug or dietary supplements instead of drugs).

Chapter 2. Methods

Three feasibility studies involved different decentralized elements. Each study aimed to evaluate if the introduction of decentralized elements influenced the data reliability. The data reliability was operationally assessed by the predefined elements in each study. Purpose and brief summary of the conducted studies were provided in Table 1.

Table 1. Summary of the conducted studies

	Dynamic consent trial	Adherence monitoring trial	Fully remote clinical trial
Focus of decentralization	Remote informed consent	Remote patient monitoring for treatment adherence	Remote recruitment and direct-to-patient trial logistics
Study subjects	60 subjects	16 subjects	30 subjects
Study duration	4 weeks	12 weeks	3 weeks
Therapeutic area	Infectious disease	Endocrine disease	Gastrointestinal disease
Intervention	Virtual drug	Vitamin D supplements	*Lactobacillus* supplements
Assessment of data reliability	Subject's understanding to trial procedures	Concordance among treatment adherence measures	Appropriateness of efficacy outcomes Quality of study records
Trial registry no. (ClinicalTrials.gov)	NCT05047016	NCT05452512	NCT05520073

Part 1. Dynamic consent trial①

2.1.1. Study subjects

Adult subjects who were able to use web and mobile applications and without any cognitive impairment were enrolled. Subjects were required to measure the body temperatures by themselves and report the results through the applications.

2.1.2. Study design

The study was a 4-week trial consisting of three visits (i.e., screening and two follow-up visits) with a two-week interval. Subjects installed the application on owning smart phones and were given instructions on how to use the applications at the screening visit. At each follow-up visit, subjects visited the trial site and completed the questionnaires on the experience using the application. All other study procedures were conducted in home-based settings. (Figure 2a)

All informed consent process was conducted electronically using the installed mobile application. Subjects were informed of the study information in a *face-to-face* manner at the first visit. The other consents were conducted *remotely* in home-based settings

① The results of the *dynamic consent trial* were published in a peer-reviewed journal (Clin Transl Sci. 2022 May;15(5):1257-1268).

and study information was delivered via the mobile application.

Each subject reported the self-measured body temperatures and entered a code for the virtual investigational drug for coronavirus-19 (COVID-19) daily on the application. Virtual investigational drugs consisted of a subject number, study schedule, and a 4-digit drug code. Entering the drug code on the application was regarded as a dosing event. (Figure 2b) The scheduled dosing time was a 9 A.M. with a two-hour window period before and after the dosing time (i.e., 7 A.M.-11 A.M.). Subjects could call investigators using the chatting system in the application and records from the system was used in the analysis. (Figure 2c) The study was approved by the institutional review board of Seoul National University Hospital and Jeonbuk National University Hospital and was conducted in accordance with the Declaration of Helsinki. (*ClinicalTrials.gov* registration no. NCT05047016)

Each subject was requested to respond on the protocol amendments. A total of 2 major and 3 minor protocol amendments were prescheduled and effective dates for the amendments were set as Table 2. Subjects could be enrolled at any time and should follow the study protocol at the time of enrollment. (Figure 1d) The major protocol amendments involved changes in the schedule for body temperature measurement (i.e., morning to afternoon,

afternoon to evening). The minor protocol amendments were changes not related to study design or procedures (e.g., correction of typos).

Table 2. Summary of changes in the scheduled protocol amendments

Protocol version	Description of changes	Effective date (scheduled)
1.0	The initial protocol: scheduled time of the body temperature measurement between 8 A.M. and 11 A.M.	
1.1	Minor amendment; changes in the telephone number of the study personnel	7 days after the study initiation
2.0	Major amendment; changes in the scheduled time of the body temperature measurement (from 8 A.M.–11 A.M. to midday–3 P.M.)	14 days after the study initiation
2.1	Minor amendment; changes in the terminology in the introduction part (from 'consent system' to 'consent model')	18 days after the study initiation
3.0	Major amendment; changes in the scheduled time of the body temperature measurement (from midday–3 P.M. to 6 P.M.–9 P.M.)	30 days after the study initiation
3.1	Minor amendment; correction of typos	35 days after the study initiation

In addition, to simulate dropout events (e.g., due to serious adverse events), 4 subjects in each study center were randomly

selected and notified of dropout. The subjects should discontinue taking virtual drugs after the time of dropout. Other study schedules were conducted as originally planned (i.e., self-measurement of body temperature and follow-up visits). (Figure 2d)

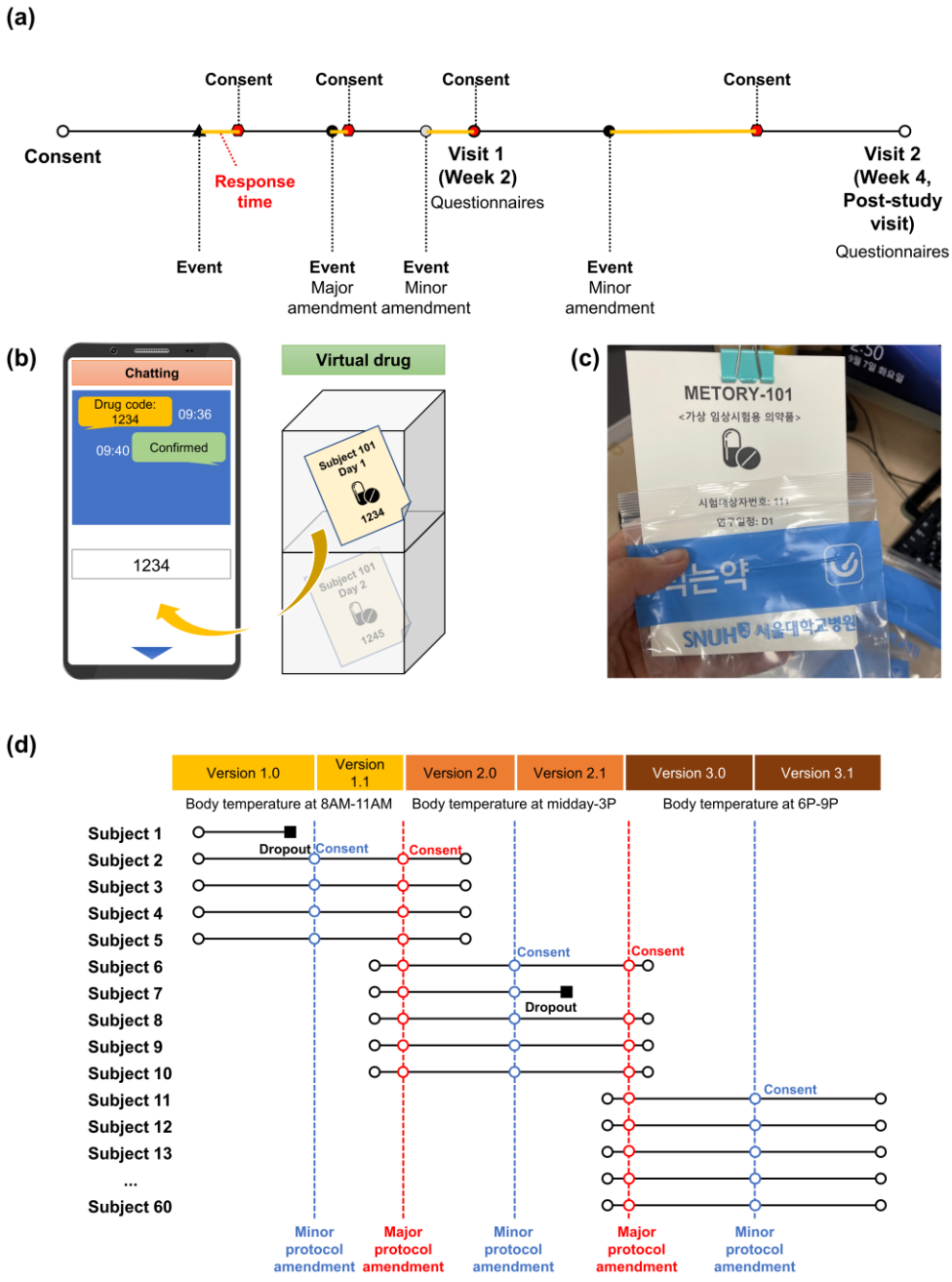

Figure 2. Study design. Schematic representation of the study schedule (a), administration of virtual drug (b), actual virtual drug used (c), and protocol amendments (d). (Adapted from Huh et al.[27])

2.1.3. Assessment of the consent process and understanding of the study procedures

The number and proportion of consents to the total number of encountered protocol amendments were calculated. Study completion rates were evaluated excluding scheduled dropouts. Response time was defined as the time difference between the time of protocol amendment and consent.

Understanding of the study procedures was assessed by evaluating adherence to drug and procedures. Drug adherence was assessed by the number of right drugs taken and whether the drugs were taken at the scheduled time window. Procedural was assessed by the number of body temperature measurements and whether the measurements were performed at the scheduled time window.

2.1.4. Statistical analysis

The sample size was not formally calculated considering the exploratory nature of the study. Continuous variables are summarized as the mean, standard deviation, median, minimum, and maximum. Count data were summarized as the mean and standard deviation of the proportions. R version 4.1.0 (R Core Team, Vienna, Austria) was used for visualization and statistical analyses.

Part 2. Adherence monitoring trial

2.2.1. Study subjects

Vitamin D-deficient adults defined as serum 25(OH) vitamin D concentration <20 ng/mL were eligible for the study. Subjects who had hypersensitivity to vitamin D, or history of hypercalcemia, sarcoidosis, or renal diseases (e.g., renal stone, chronic kidney disease) were excluded. Subjects who had serum calcium level exceeding the upper reference limit or estimated glomerular filtration rate <60 mL/min/1.73m^2 were also excluded. Subjects should not take any other vitamin D supplements at the screening and during the study period except for the allocated treatments.

Written consent forms were obtained from the subjects prior to any study-related procedures. The study was approved by the Institutional Review Board of Seoul National University Hospital (*ClinicalTrials.gov* registration no.: NCT05452512) and conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice.

2.2.2. Study design

An open, randomized, decentralized clinical trial was conducted. Subjects took vitamin D supplements and kept paper-based

medication diary daily for a week during the run-in period. After the run-in period, subjects were randomized to the following two groups: App only (using the electronic medication diary[29]) and App + Watch group (using both the electronic medication diary and the smart watch). Subjects should take the vitamin D supplements and keep the medication diaries until the last visit using the allocated monitoring methods.

Subjects in App + Watch group primarily used smart watch with artificial intelligence (AI)-based recognition and optionally used the attached mobile application to check the adherence. In addition, the application was used to record the medication records when the smart watch was not working. Technical support team was arranged to deal with the unexpected errors in the devices. (Figure 1)

Subjects took vitamin D supplements (1000 IU) for the 2 study periods consisting of 6-week self-administration each and remaining pills were counted at the end of each period. Blood samples for serum 25(OH) vitamin D, calcium, and phosphorus levels were collected biweekly for 7 times except for the screening.

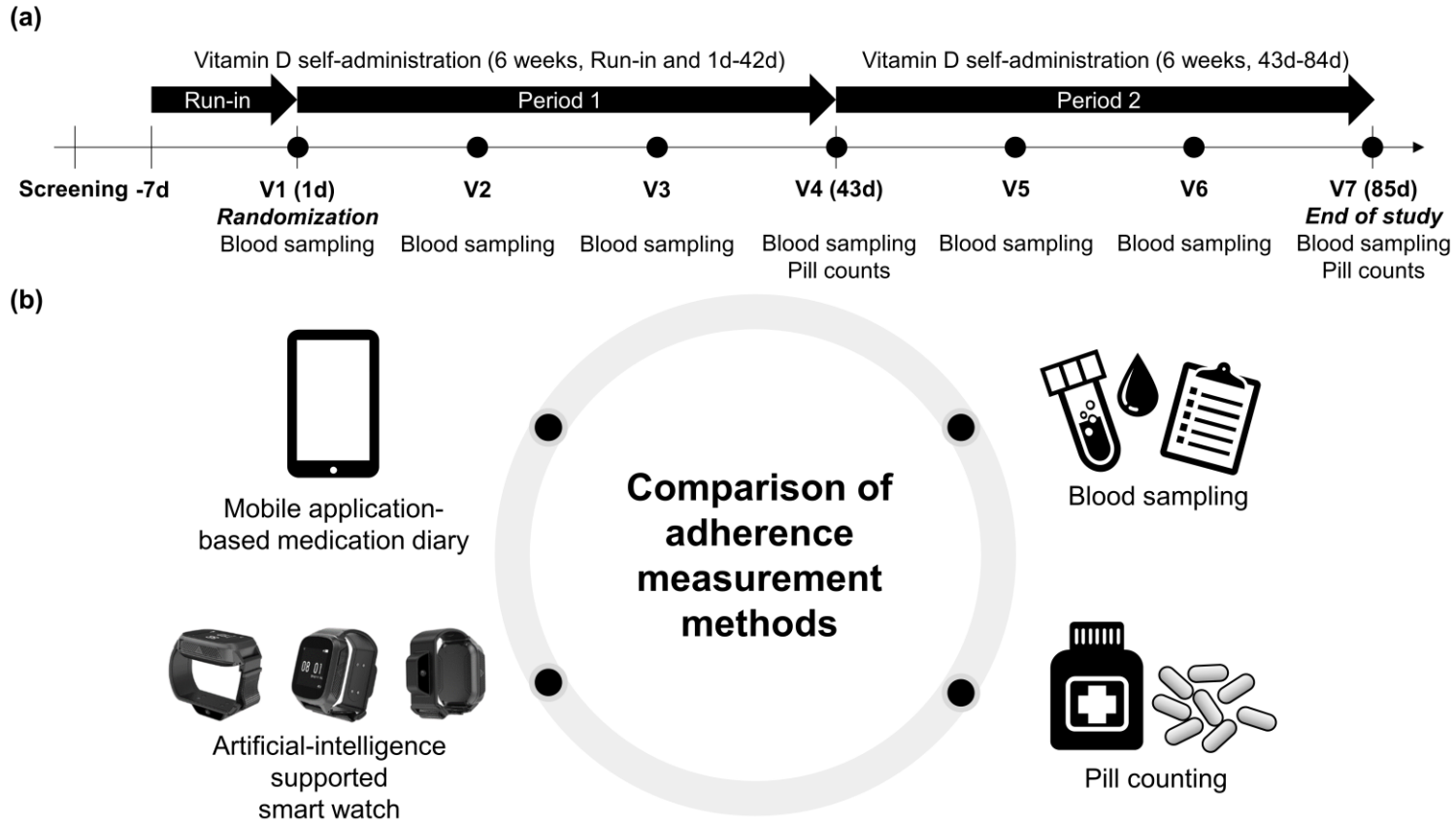

Figure 3. Schematic representation of the study design: study schedule (a) and comparison of adherence measurement methods (b).

2.2.3. Assessment of treatment adherence

Adherence to treatment was evaluated using the following measures: percentage of doses taken, taking adherence, timing adherence, drug holidays, and timing distribution index.[30] Doses taken was defined as the total number of doses recorded divided by the scheduled doses. Taking adherence was defined as the percentage of the days with correct doses (i.e., one tablet per day). Timing adherence was defined as the percentage of the days when the dose was taken within the treatment window (± 2 hours from the scheduled time). Drug holidays were defined as the percentage of the days when doses were not taken.

Timing distribution index was calculated using the hour of a dose was taken; the index was defined as the sum of absolute difference from the mode of the hour divided by the number of scheduled dates as the following formula: $\frac{\sum|h_i - mode(h_i)|}{n}$ (h_i, the hour of drug administration; mode(h_i), the most frequent hour; n, the number of the scheduled dates) Higher timing distribution index could be interpreted as higher variability in the drug administration time.[30]

If a subject was dropped from the study, the scheduled doses until the dropout date was used. To remove duplicity, data that

were recorded within 3 hours from the previous data in the same device (i.e., AI recordings from smart watch and the corresponding App) were considered same as the previous data.

2.2.4. Statistical analysis

Considering the exploratory nature of the study, sample size was empirically set as 8 in each group. Baseline characteristics between two groups were compared using Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. The number of drugs taken reported in each method was compared pairwise using Wilcoxon signed-rank test without the adjustment for multiple testing.

Part 3. Fully remote clinical trial

2.3.1. Study subjects

Adult subjects aged between 19 and 64 years who had at least one of the following functional constipation symptoms fulfilled for the past 2 weeks were enrolled (relaxed Rome III criteria for functional constipation[31]): straining with defecation more than 25% of the time; hard or lumpy stools more than 25% of the time; sensation of anorectal obstruction more than 25% of the time; sensation of

incomplete evacuation more than 25% of the time; manual maneuvers necessary to facilitate defecation more than 25% of the time; and less than three bowel movements per week.

Subjects who were pregnant, lactating or had hypersensitivity to supplements were excluded from the study. Subjects should sincerely keep track of medication and bowel diaries during the study period and were not allowed to take other *Lactobacillus* or vitamin C-containing supplements except for the study supplements. Study volunteers were recruited from the website of the Seoul National University Hospital clinical trial center.

Written consent forms were obtained from all subjects by the electronic consent platform prior to any study-related procedures. Subjects were identified by a mobile authentication system integrated in the electronic consent system.[32] Subjects were instructed for the study procedures by the delegated investigators via the teleconference system. After subjects agreed to participate in the study, subjects electronically signed the informed consent form, and the signed copy was recorded onto the blockchain platform. An electronic copy of the informed consent form was provided to the subjects. After giving consent to the study, subjects completed the web-based questionnaires, and the questionnaires were assessed for eligibility by the delegated investigators. The

study was approved by the Institutional Review Board of Seoul National University Hospital and conducted in accordance with the Declaration of Helsinki (*ClinicalTrials*.gov registration no.: NCT05520073).

2.3.2. Study design

The study was an open, fully remote, randomized clinical trial. Subjects were randomized to receive either treatment (*Lactobacillus* and vitamin C supplements) or placebo (vitamin C supplements alone) at a 1:1 ratio, which was delivered directly to the subjects' home. The study schedule consisted of 1-week baseline and 2-week treatment periods. During the baseline period, subjects should keep track of bowel diaries using the mobile application. After the baseline period, subjects took the allocated treatments (i.e., *Lactobacillus* + vitamin C or vitamin C) on their own daily for 2 weeks. During the treatment periods, subjects should keep track of both bowel diaries and medication diaries.

Treatment adherence was monitored through semiquantitative urine vitamin C measurement using home urine test strips (Self-Stik Vita-Check, Chungdo Pharmaceuticals, Chuncheon-si, Korea), which were also directly delivered to patients. Urine vitamin C measurements were performed 5 times (at Day 1 pre- and

postdose, Day 5, 9, and 13).

Exploratory fecal microbiome assessment was performed in subjects who agreed to give stool samples using validated stool collection kits (Gut Inside, CJBioscience Inc., Seoul, Korea).[33, 34] Stool collection kits were delivered directly to the subjects through a courier, and stool samples were collected at home. Collected stool samples were then delivered to the laboratory to perform fecal microbiome assessments. Detailed procedures were described in another study.[34]

After completing the study schedule, subjects submitted the patient experience questionnaire regarding participation in a DCT in an anonymous manner. Subjects could freely comment on the positive and negative aspects of DCT based on their experience. (Figure 4, Figure 5, and Figure 6)

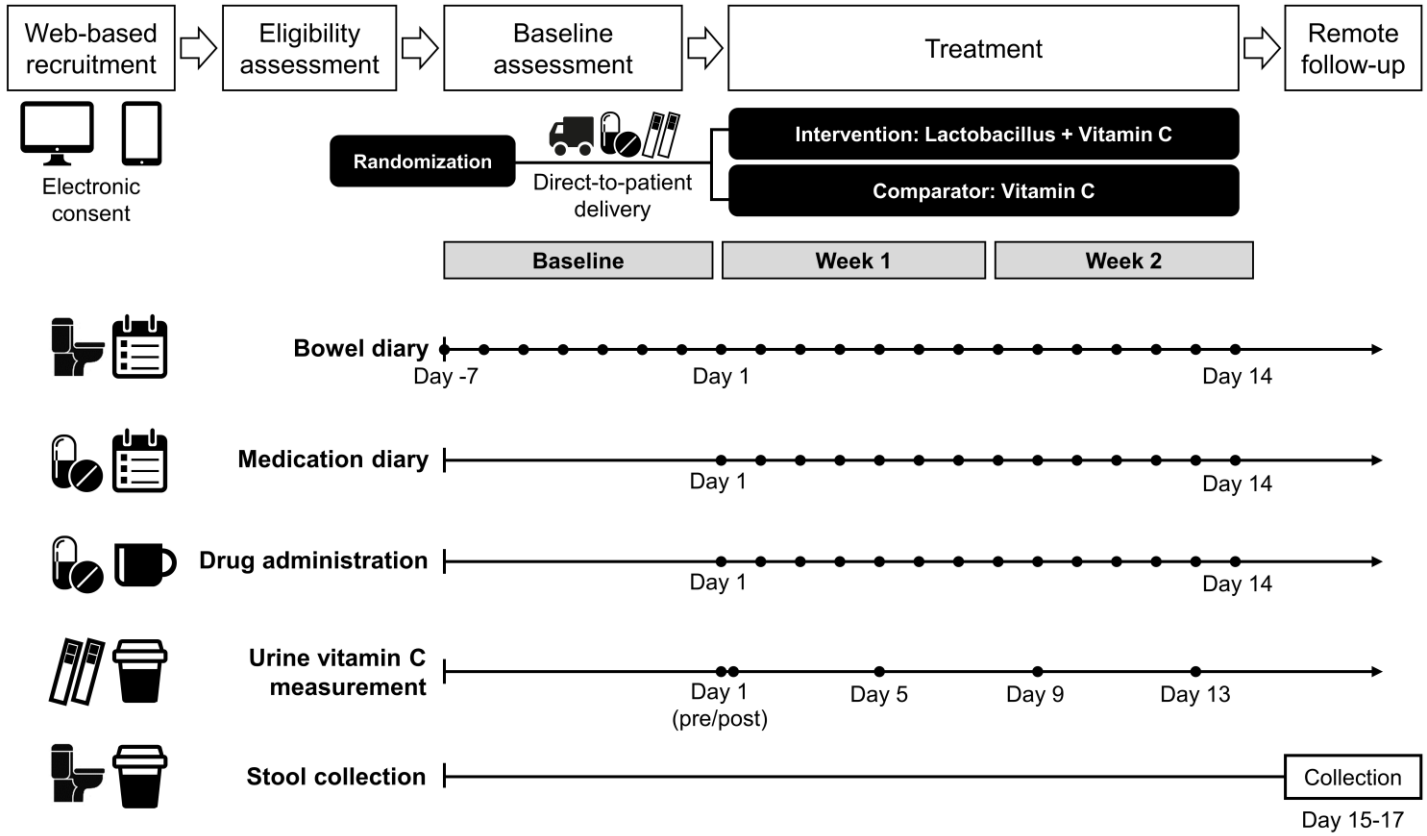

Figure 4. Schematic representation of the study design.

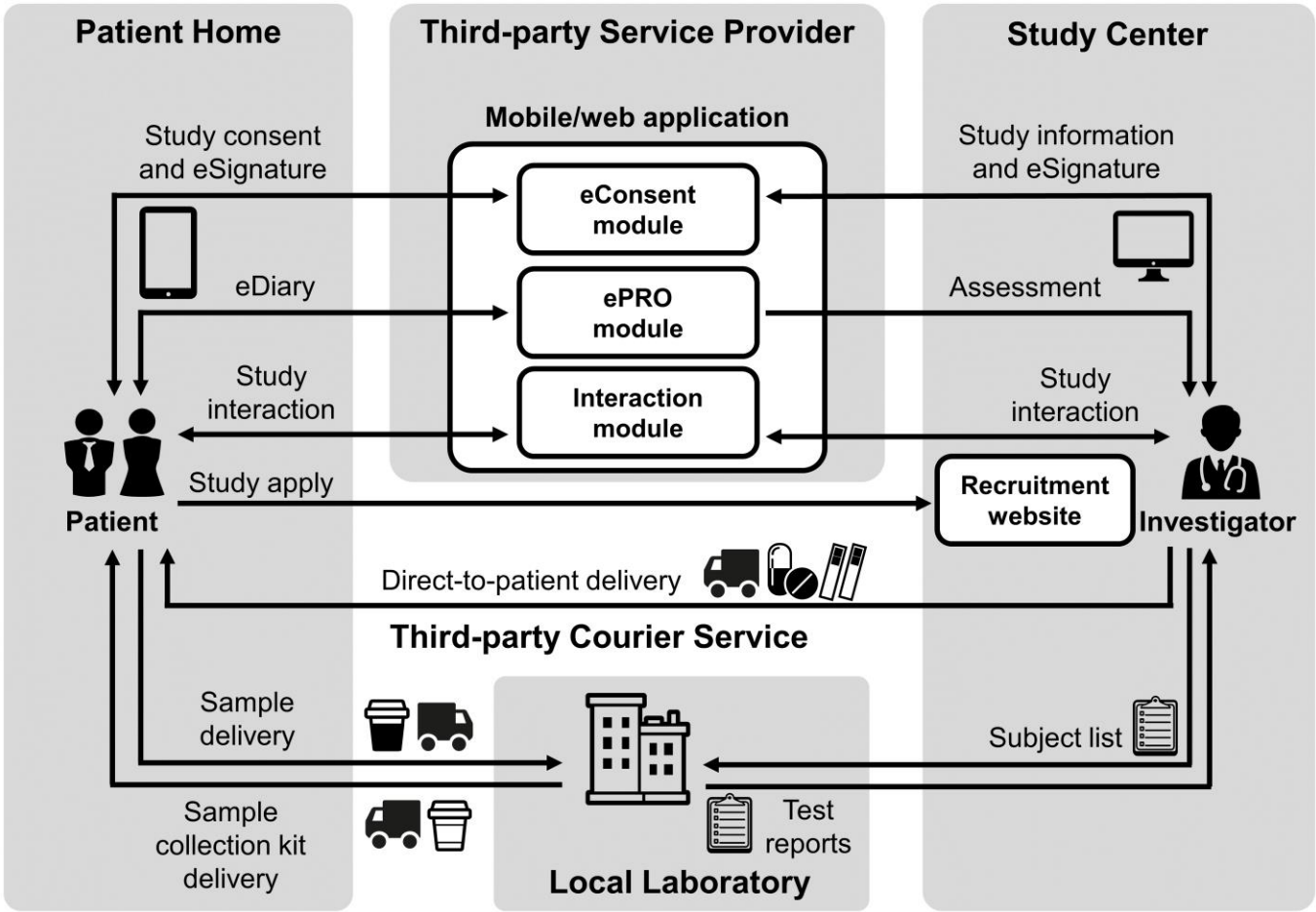

Figure 5. Schematic representation of the study procedures among stakeholders.

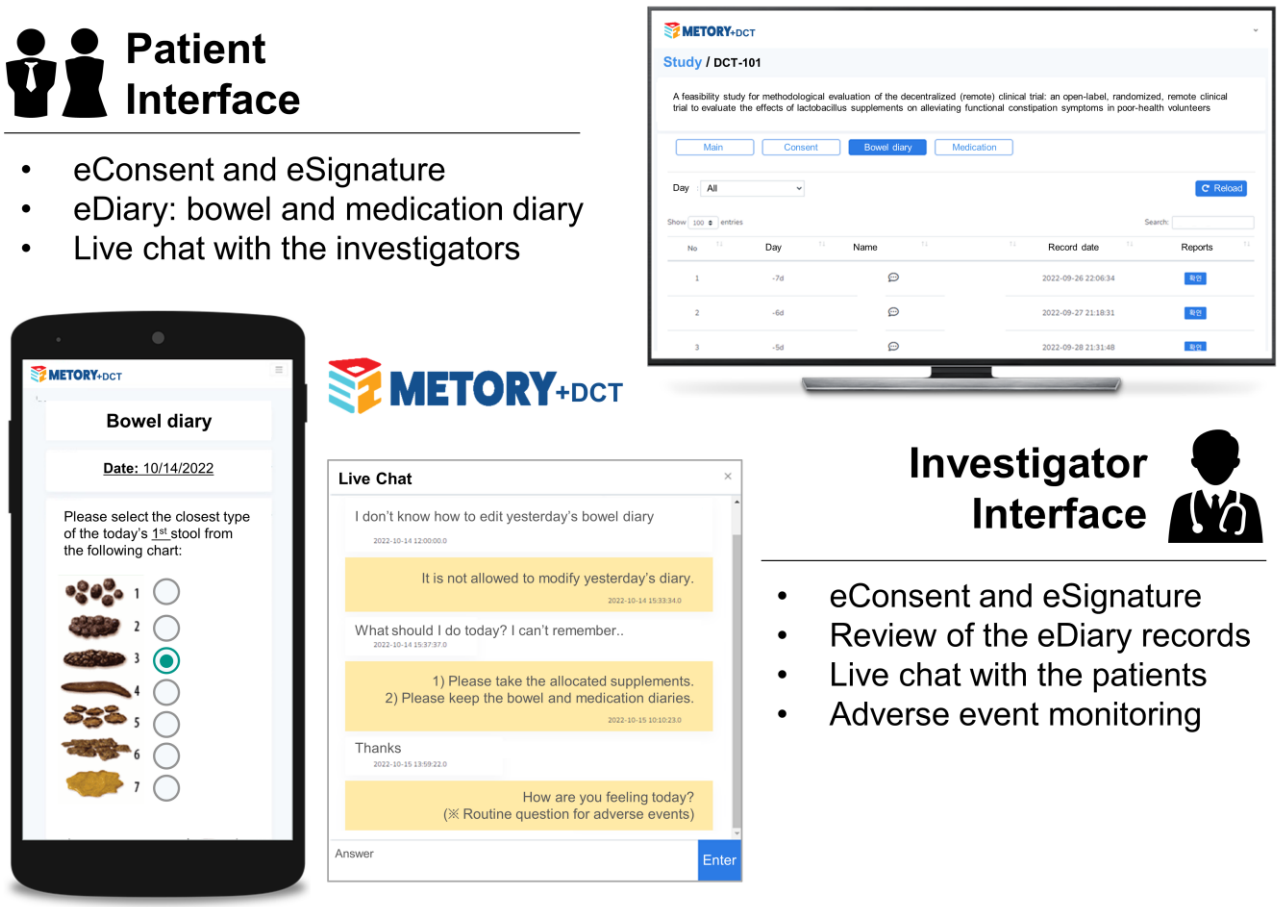

Figure 6. Illustrative presentation of the web and mobile application user interfaces.

2.3.3. Assessment of efficacy outcomes

Bowel symptoms were assessed weekly (i.e., baseline, week 1, and week 2) based on the records in electronic bowel diaries. The following bowel symptoms were evaluated: the total number of defecations, use of laxatives, stool consistency measured by Bristol Stool Chart, defecation time, the number of events for straining, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, abdominal pain/discomfort, and manual maneuvers to facilitate.

Exploratory analysis of the fecal microbiome was performed using the gut microbiome index (GMI).[34] The index quantifies the similarity of the microbiome profile to that of healthy Koreans and represents the probability of being a 'healthy' microbiome state. Details on the index were described in another article.[34]

2.3.4. Assessment of decentralized study procedures

To evaluate the quality of the data collection process, the timestamps of the electronic diary records were analyzed. We categorized the records into the following categories: correct, pre-recording, post-recording, and missing. 'Correct' denoted that the subject completed the electronic diary on the scheduled date; 'pre-recording' the records were generated before the

scheduled date; ‘post-recording’ the records were generated after the scheduled date; ‘missing’ the records were not entered.

Procedural adherence was assessed by the records reported from the participants as follows. ‘Correct’ denotes that the subject performed the urine test on the scheduled study day and proper times (e.g., pre- and post-dose test). ‘No detection’ denotes that urine vitamin C was not detected after administration, and ‘pre-dose detection’ vitamin C was detected at pre-dose measurement. ‘Performed incorrectly’ denoted that the subject performed the test not on the scheduled study day or unscheduled test (e.g., urine test on Day 2) was performed. ‘Missing’ denotes that the test was not performed.

Assessment of direct-to-patient procedures included shipping of the investigational products (IP) and test kits by investigators and stool collection kits by the contracted laboratory. The procedures were evaluated by the proportion of subjects who received IP, who received wrong IP, and the elapsed time to receive IP. The fecal microbiome analysis procedure was evaluated by the proportion of subjects who gave consent and the number of valid samples. All records were evaluated individually by study day, and the proportion of each category was calculated.

Patient opinions on the positive and negative aspects of

participating in the study were grouped by the similarity of the contents, and representative comments were quoted.

2.3.5. Statistical analysis

Given the exploratory nature of the study, the sample size was determined empirically, and statistical testing was not performed. Continuous variables were summarized descriptively with the mean and standard deviation unless the median and range were appropriate considering the distribution of data. Categorical variables were summarized by the proportion of each category in a subject, and the mean and standard deviation of the proportions were calculated. All statistical procedures were performed using R version 4.1.0. (R Foundation for Statistical Computing, Vienna, Austria).

Chapter 3. Results

Part 1. Dynamic consent trial

3.1.1. Subject disposition and consent process

A total of 60 subjects (30 subjects for each center) completed the study. The overall proportion of consent to each protocol amendment was 95.7 ± 13.2% (presented as the mean ± standard deviation). The median response time to each amendment was 0.2 h. (Table 3) The entire response to consent of each subject was presented in Figure 7.

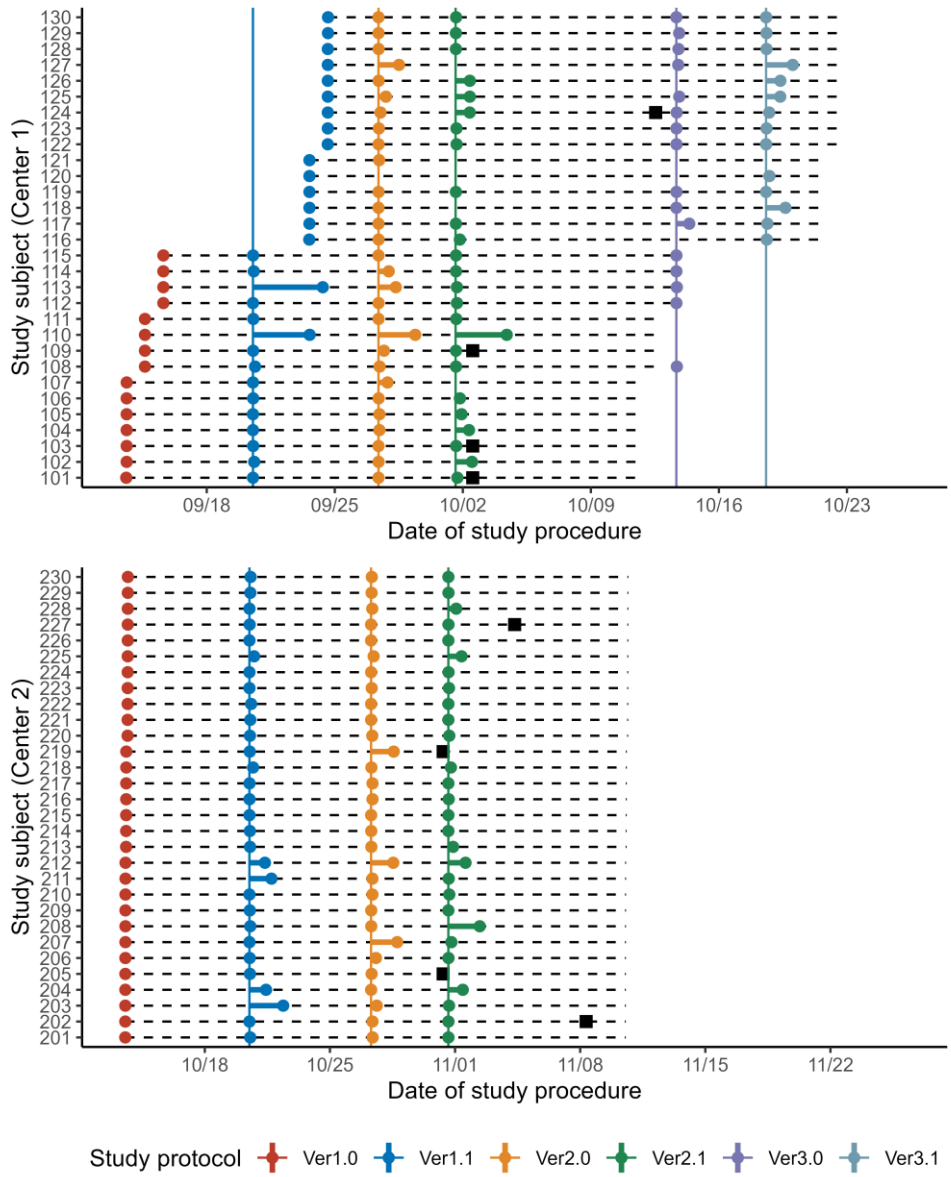

Figure 7. Summary of the responses to protocol amendments. Dots (●) represent each subject's consent and each protocol amendment is denoted as colors. Dashed horizontal lines represent scheduled study duration (28 days) of each subject and solid vertical lines represent the scheduled date of each protocol amendment. Black squares (■) denote scheduled dropout of each subject. (Adapted from Huh et al.[27])

3.1.2. Understanding of the study procedures

Overall, the subjects took 90.8% ± 19.2% of the allocated drugs (presented as the mean ± standard deviation, Table 3, Figure 8), while adherence to the schedule was 69.1 ± 27.0%. (Table 3, Figure 9) Subjects performed 97.6 ± 4.9% of the total body temperature measurements (Table 3, Figure 10), whereas adherence to the schedule was 59.0% ± 25.0%. (Table 3, Figure 11) In both study centers, adherence to the schedule remarkably decreased after the major protocol amendment where procedural schedules were changed (i.e., study protocol version 1.1 to 2.0, and 2.1 to 3.0). (Figure 11).

Table 3. Summary of response to study consent and adherence

	Center 1 (n=30)	Center 2 (n=30)	Overall (n=60)
Response to study consent			
Proportion of consents (%)	93.3 ± 17.3 (129/139)	98.3 ± 6.3% (118/120)	95.7 ± 13.2 (247/259)
Study completion rate (%)	100.0 (30/30)	100.0 (30/30)	100.0 (60/60)
Response time (h)	0.3 [0.0-91.6]	0.2 [0.0-43.3]	0.2 [0.0-91.6]
Drug adherence			
Administration of right drug (%)	89.6 ± 20.6 (753/840)	92.0 ± 17.9 (773/840)	90.8 ± 19.2% (1526/1680)
Adherence to the drug administration schedule (%)	75.7 ± 27.8 (636/840)	62.5 ± 24.9 (525/840)	69.1 ± 27.0 (1161/1680)
Procedural adherence			
Whether the body temperature was measured (%)	96.7 ± 4.2 (812/840)	98.5 ± 5.4 (827/840)	97.6 ± 4.9 (1639/1680)
Adherence to the procedural schedule (%)	50.5 ± 24.7 (424/840)	67.5 ± 22.6 (567/840)	59.0 ± 25.0 (991/1680)

Notes: Data are presented as mean ± standard deviation of the proportions in each subject (only overall values for study completion rate) and overall counts to total except for response time. Response time is presented as median [minimum-maximum].

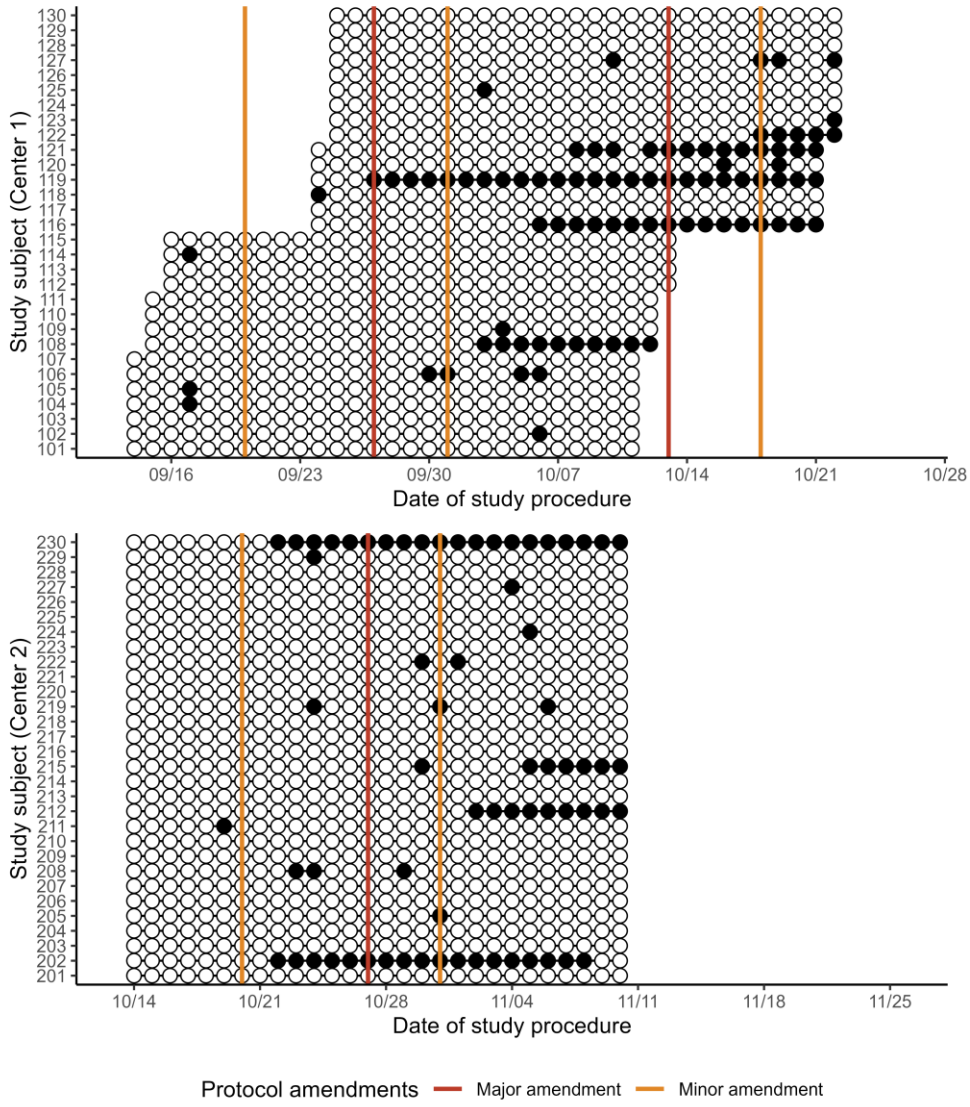

Figure 8. Summary of drug adherence: adherence to the right drug. White circles (○) represent the administration of the correct study drug while black circles (●) represent the incorrect conducts. Solid vertical lines represent the scheduled date of each protocol amendment. There were no changes to the administration of drug during the study. (Adapted from Huh et al.[27])

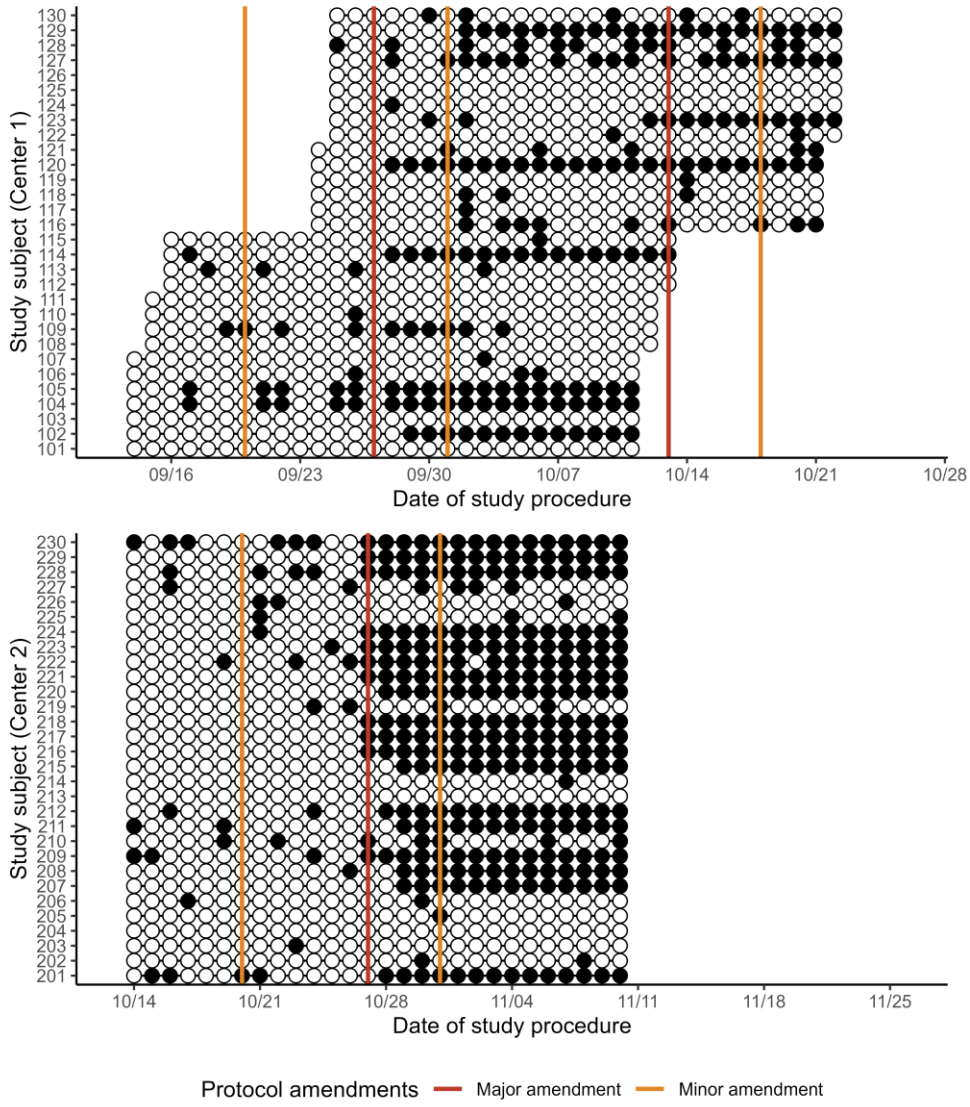

Figure 9. Summary of the drug adherence: adherence to the drug administration schedule. White circles (○) represent the administration of the study drug at the right schedule (within the scheduled time window) while black circles (●) represent the incorrect conducts. Solid vertical lines represent the scheduled date of each protocol amendment. There were no changes to the administration of drug during the study. (Adapted from Huh et al.[27])

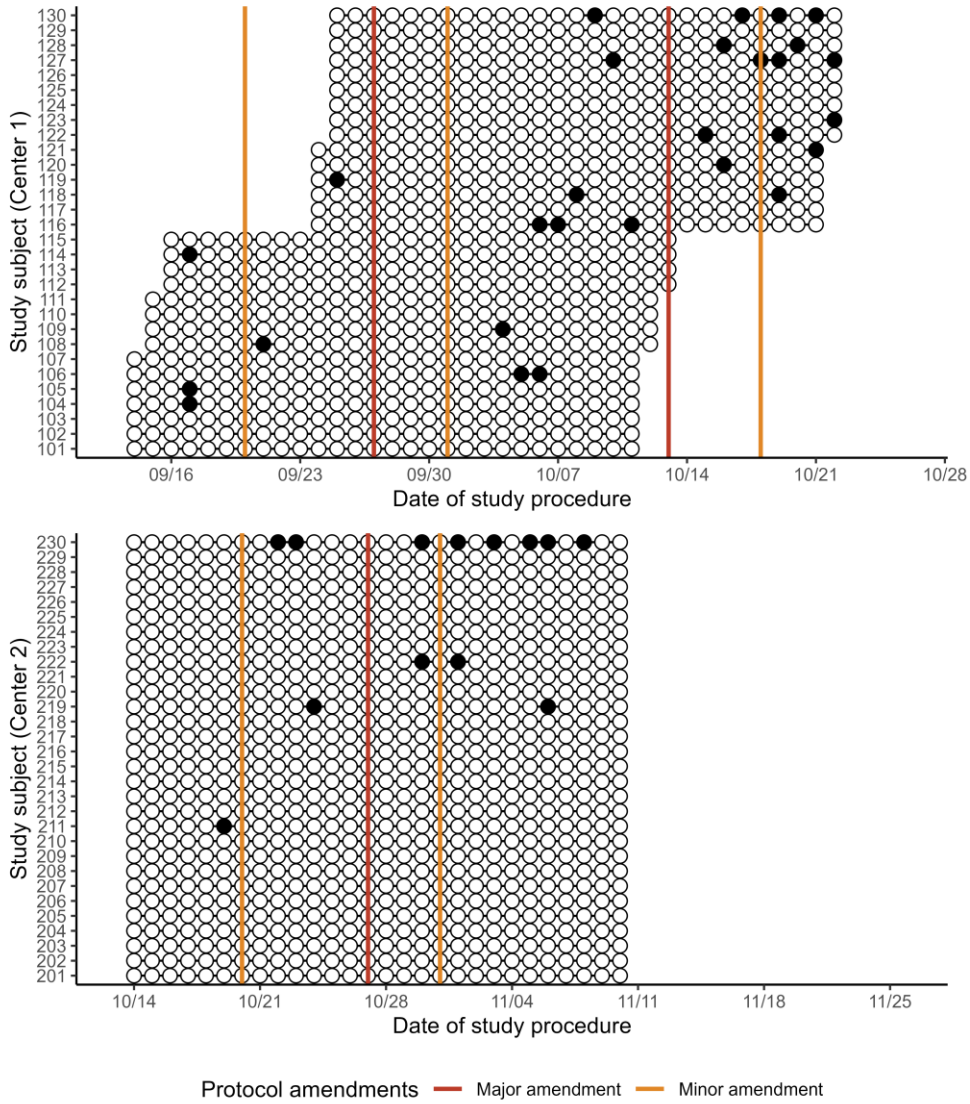

Figure 10. Summary of procedural adherence: whether body temperature was measured. White circles (○) represent the measurement of the body temperature while black circles (●) represent the missing measurements. Solid vertical lines represent the scheduled date of each protocol amendment. The scheduled time for body temperature measurements was changed at the major amendments. (Adapted from Huh et al.[27])

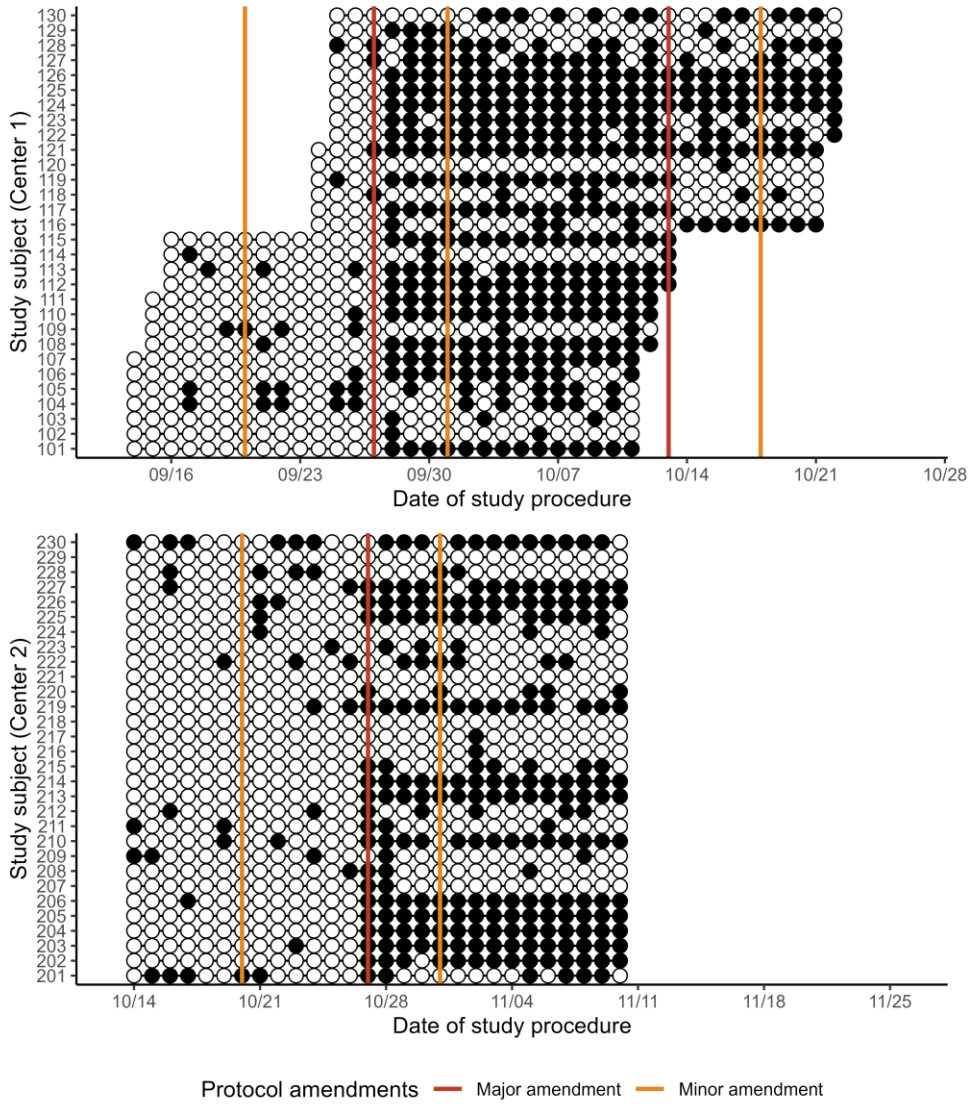

Figure 11. Summary of procedural adherence: adherence to the procedural schedule. White circles (○) represent the measurement of the body temperature at the right schedule (within the scheduled time window) while black circles (●) represent the incorrect conducts. Solid vertical lines represent the scheduled date of each protocol amendment. The scheduled time for body temperature measurements was changed at the major amendments. (Adapted from Huh et al.[27])

Part 2. Adherence monitoring trial

3.2.1. Subject disposition and demographics

A total of 16 subjects were enrolled and 13 subjects completed the study. One subject withdrew the consent at period 1 and two subjects were discontinued the study at period 2 due to coronavirus-19 infection. Data of the dropped subjects were analyzed until the date of the study discontinuation.

Most subjects were female (93.8%) and mean age was 38.1 years. Baseline serum 25(OH) vitamin D level was 16.6 ng/mL and no significant difference between two groups were noted. Baseline calcium and phosphorus levels were also comparable between the two groups. (Table 4)

Table 4. Baseline characteristics of the subjects

	App only (n=8)	App + Watch (n=8)	Total (N=16)	*p*-value
Gender				
Male		1 (12.5)	1 (6.3)	1.0†
Female	8 (100.0)	7 (87.5)	15 (93.8)	
Age	39.6 (9.1)	36.6 (12.9)	38.1 (10.9)	0.4932‡
Baseline serum level				
25(OH) vitamin D (ng/mL)	17.5 (2.3)	15.7 (3.1)	16.6 (2.8)	0.1889‡
Calcium (mg/dL)	9.4 (0.3)	9.5 (0.2)	9.4 (0.3)	0.4897‡
Phosphorus (mg/dL)	3.6 (0.4)	3.4 (0.4)	3.5 (0.4)	0.3395‡

†Fisher's exact test. ‡Wilcoxon rank sum test.
Note: Data are presented as mean (standard deviation) except for gender where number (percentage of subjects) are presented.

3.2.2. Serum 25(OH) vitamin D level

Overall, serum 25(OH) vitamin D levels were increased by 65.1% after 12 weeks of vitamin D supplementation. Serum 25(OH) vitamin D levels were continuously increased in both groups until the first 7 weeks and maintained approximately 25−30 ng/mL until the end of the study. The increasing trend was comparable in two groups until the first 7 weeks and became higher in the App + Watch group in the later phase. Serum calcium and phosphorus were maintained within the reference range in both groups during the study. (Table 5 and Figure 12)

Table 5. Summary of the serum 25(OH) vitamin D, calcium, and phosphorus levels

	App only (n=8)	App + Watch (n=8)	Total (N=16)
Serum 25(OH) vitamin D level (ng/mL)			
Baseline	17.5 (2.3)	15.7 (3.1)	16.6 (2.8)
V1	20.9 (2.2)	19.9 (2.8)	20.4 (2.5)
V4	27.7 (7.3)	27.5 (2.2)	27.6 (5.3)
V7	25.9 (6.6)	28.8 (7.0)	27.4 (6.7)
Serum calcium level (mg/dL) [Reference: 8.8-10.5]			
Baseline	9.4 (0.3)	9.5 (0.2)	9.4 (0.3)
V1	9.5 (0.2)	9.6 (0.2)	9.6 (0.2)
V4	9.4 (0.3)	9.7 (0.5)	9.5 (0.4)
V7	9.5 (0.3)	9.6 (0.4)	9.6 (0.4)
Serum phosphorus level (mg/dL) [Reference: 2.5-4.5]			
Baseline	3.6 (0.4)	3.4 (0.4)	3.5 (0.4)
V1	3.7 (0.7)	3.4 (0.2)	3.6 (0.5)
V4	3.4 (0.3)	3.7 (0.6)	3.5 (0.5)
V7	3.6 (0.5)	3.5 (0.3)	3.6 (0.4)

Note: Data are presented as mean (standard deviation).

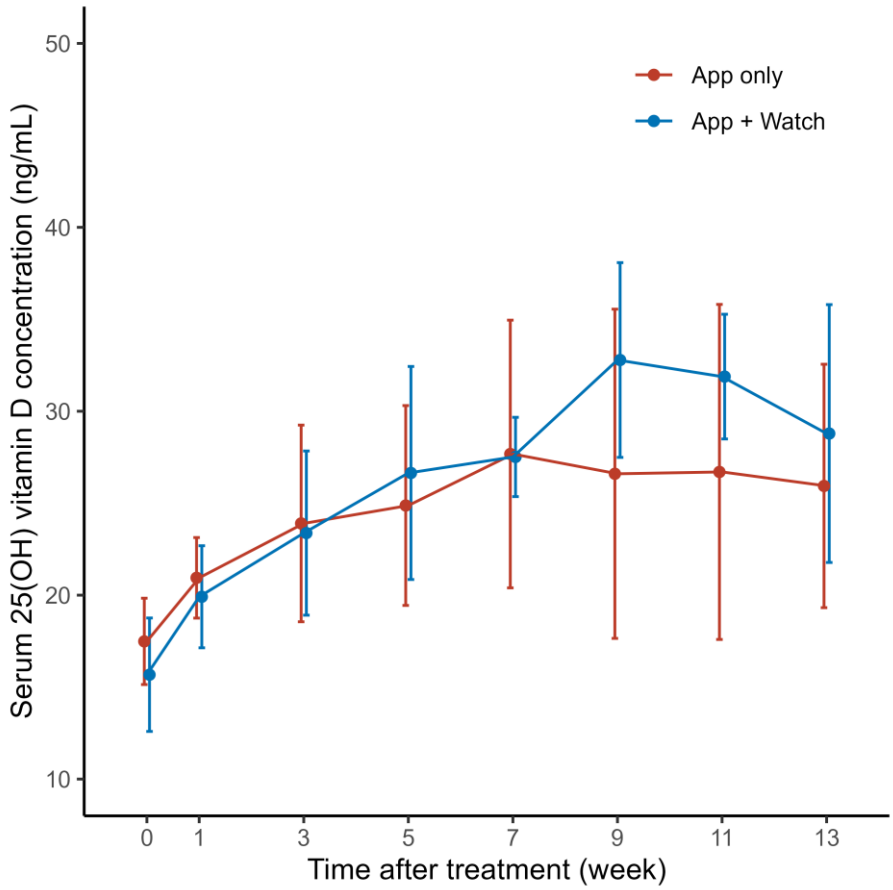

Figure 12. Changes in serum 25(OH) vitamin D concentration. Error bars denote standard deviation.

3.2.3. Treatment adherence and concordance assessment

The number of doses taken measured by pill count method and Smart App was not significantly different in the run-in and period 1 (p = 0.5534) whereas became significantly different in the period 2 (p = 0.0225). In contrast, pill count and watch AI/App were not significantly different in both the run-in and period 1 (p = 0.5898) and period 2 (p = 0.5839). However, records from the App were

not consistent with those from pill count or App. (Table 6 and Figure 13) Smart watch records reported by AI-based recognition were missing in several subjects and replaced by the attached application. (Figure 13)

Percentage of doses taken was higher in App + Watch (97.4%) than App group (84.3%). Similarly, taking adherence was also higher in App + Watch (95.6%) than App group (81.9%). Drug holidays were reported lower in App + Watch (3.5%) than App only group (16.9%).

In contrast, timing adherence was higher in App only (73.2%) than App + Watch group (68.9%). Timing distribution index was higher in App + Watch (1.6) than in App only group (0.7). Timing distribution index was markedly lower in the results from App (0.5) than those from Watch AI/App (1.6) in App + Watch group. (Table 7)

Table 6. Concordance assessment among adherence measures

	Run-in and period 1			Period 2		
	Pill count	App	Watch AI/App	Pill count	App	Watch AI/App
App only						
R1111	49	49		46	35	
R1112	50	46		41	38	
R1113	49	51		43	38	
R1114	50	33		38	9	
R1115‡	50	46		42	23	
R1116	42	49		41	41	
R1117	51	57		38	28	
R1118	50	40		42	29	
Concordance assessment						
Pill count -App†		0.5534			0.0225	
App + Watch						
R1121	49	34	49	41	1	41
R1122‡	.	23	24	.	.	.
R1123	45	39	49	43	35	43
R1124	50	49	49	60	39	42
R1125	45	25	48	41	.	43
R1126‡	50	47	49	38	27	28
R1127	50	49	49	42	40	42
R1128	50	24	51	42	38	43
Concordance assessment						
Pill count -App†		0.0223			0.0313	
Pill count-Watch AI/App†		0.5898			0.5839	
App-Watch AI/App†		0.0360			0.0313	

†Wilcoxon signed-rank test. ‡Dropped subjects. Data were assessed until the date of the study discontinuation.

Table 7. Summary of the adherence metrics

Adherence metric	Records	App only (n=8)	App + Watch (n=8)	Total (N=16)
Doses taken (%)	App	84.3 (18.9)	70.1 (29.0)	77.2 (24.7)
	Watch AI/App	.	97.4 (8.3)	97.4 (8.3)
Taking adherence (%)	App	81.9 (17.9)	69.2 (29.2)	75.5 (24.3)
	Watch AI/App	.	95.6 (7.7)	95.6 (7.7)
Timing adherence (%)	App	73.2 (16.7)	57.9 (31.0)	65.6 (25.3)
	Watch AI/App	.	68.9 (23.3)	68.9 (23.3)
Drug holidays (%)	App	16.9 (18.3)	30.3 (29.1)	23.6 (24.5)
	Watch AI/App	.	3.5 (7.8)	3.5 (7.8)
Timing distribution index	App	0.7 (0.6)	0.5 (0.6)	0.6 (0.6)
	Watch AI/App	.	1.6 (1.2)	1.6 (1.2)

Notes: To remove duplicity, data that were recorded within 3 hours from the previous data in the same device (i.e., AI recordings from smart watch and the corresponding App) were considered same as the previous data.
Abbreviations: AI, artificial intelligence; App, mobile application.

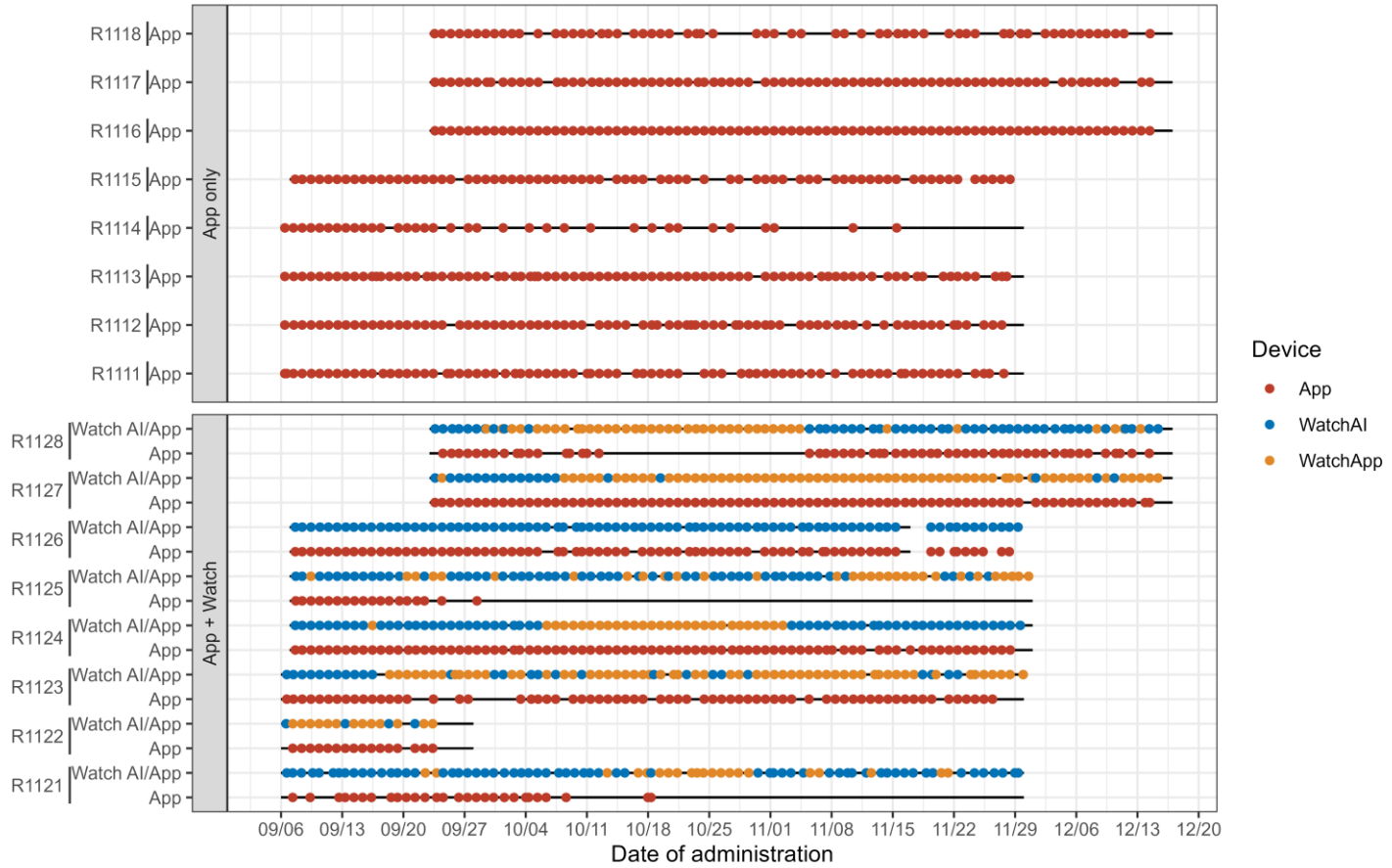

Figure 13. Medication records during the study period. Dots denote medication records and solid lines denote study duration.

Part 3. Fully remote clinical trial

3.3.1. Subject disposition and demographics

A total of 30 subjects were randomized and completed the study. The number of female participants (76.7%) was larger than that of male counterparts (23.3%). The gender distribution between the two treatment groups was not remarkably different. Participants ranged in all age groups between 20 and 65, giving a peak enrollment at the age group of 30–40 years (53.3%). Participants from Seoul, where the study center was located, accounted for the largest proportion (43.3%), while those outside of the metropolitan area accounted for 26.7%. (Table 8 and Figure 14)

Table 8. Demographics of the subjects.

	Lactobacillus Vitamin C (n=15)	Vitamin C (n=15)	Total (N=30)
Sex			
Male	3 (20.0)	4 (26.7)	7 (23.3)
Female	12 (80.0)	11 (73.3)	23 (76.7)
Age group (years)			
20-29	2 (13.3)	.	2 (6.7)
30-39	4 (26.7)	12 (80.0)	16 (53.3)
40-49	5 (33.3)	1 (6.7)	6 (20.0)
50-59	2 (13.3)	2 (13.3)	4 (13.3)
60-64	2 (13.3)	.	2 (6.7)
Location			
Seoul	7 (46.7)	6 (40.0)	13 (43.3)
Gyeonggi-do	6 (40.0)	3 (20.0)	9 (30.0)
Sejong	1 (6.7)	2 (13.3)	3 (10.0)
Gangwon-do	.	2 (13.3)	2 (6.7)
Chungcheongbuk-do	.	2 (13.3)	2 (6.7)
Gyeongsangnam-do	1 (6.7)	.	1 (3.3)

Note: The number of subjects (proportion, %) are presented.

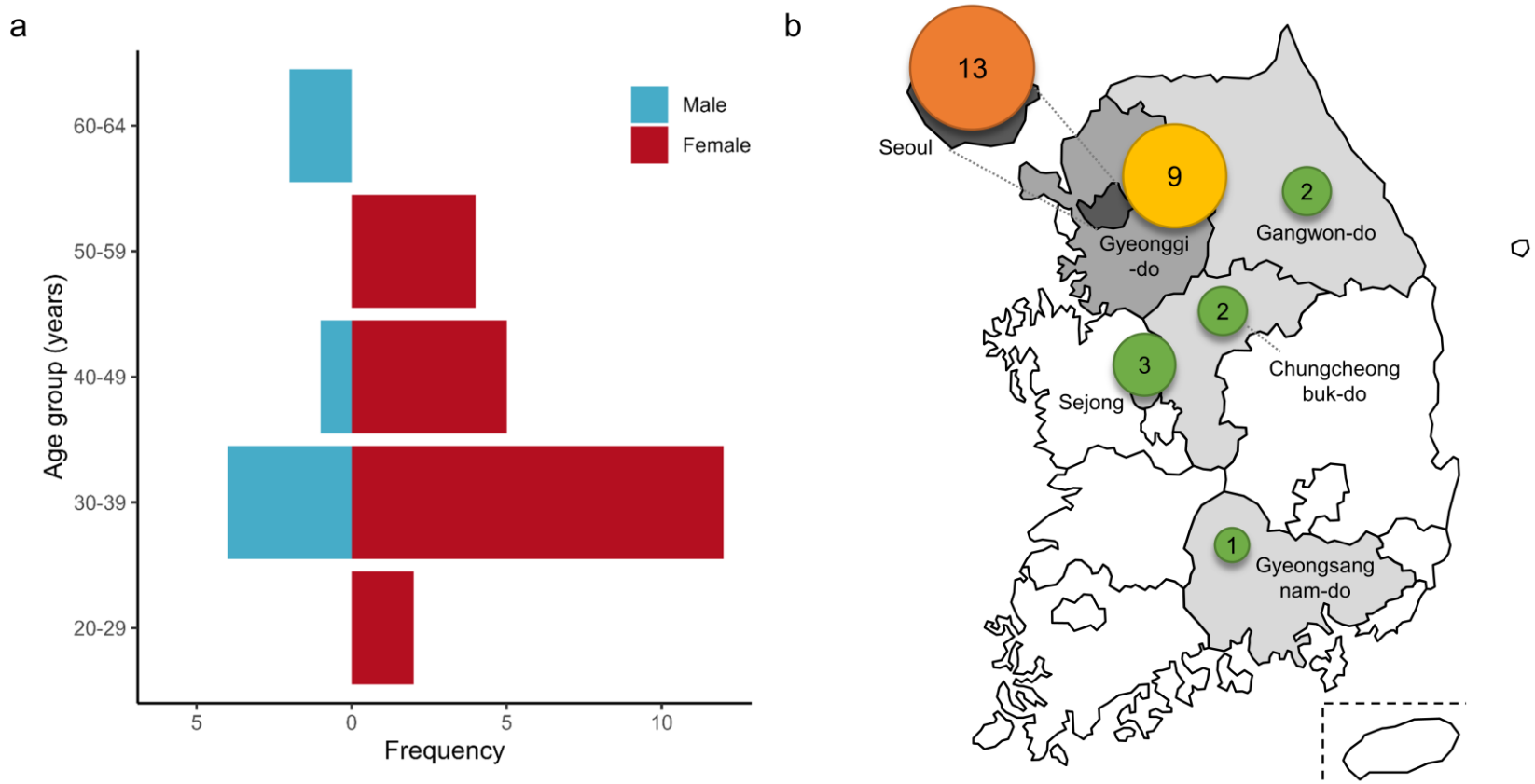

Figure 14. Age and gender (a) and geographical distribution (b) of the study subjects.

3.3.2. Efficacy outcomes

After the two-week Lactobacillus treatment, the number of defecations was slightly increased (+0.80 vs. +0.46 times per week, Figure 15a and Table 9), while the defecation time was decreased (−3.94 h vs. −1.62 h, Figure 15b and Table 9). Stool consistency was not remarkably changed after treatments. Other functional constipation symptoms were mildly alleviated after *Lactobacillus* treatments except for the sensation of anorectal obstruction/blocking. However, similar trends were also observed in the comparator group, and no remarkable difference between the two groups was observed. The use of laxatives and manual maneuvers to facilitate defecation were not observed during the study period. (Figure 15c, Figure 16, Figure 17, and Table 9) In the exploratory analysis of the fecal microbiome, GMI was higher in the *Lactobacillus* treatment group (55.0) than in the comparator group (41.6) after two weeks of treatment, but this difference was not decisive due to the small sample size. (Figure 15d)

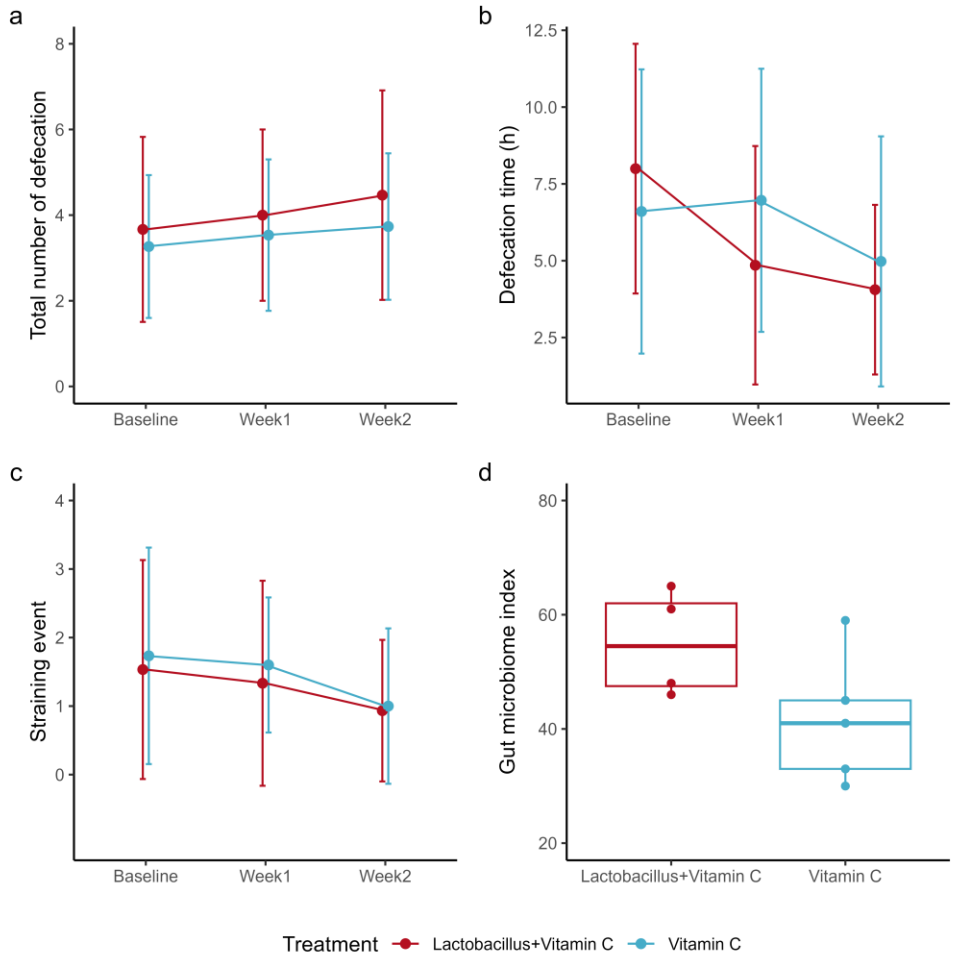

Figure 15. Summary of the efficacy parameters: the total number of defecations (a), defecation time (b), number of straining events (c), and gut microbiome index (index for the diversity of microflora) after two weeks of administration of the supplements (d). Dots and error bars in the scatter plots represent the mean and standard deviation, respectively.

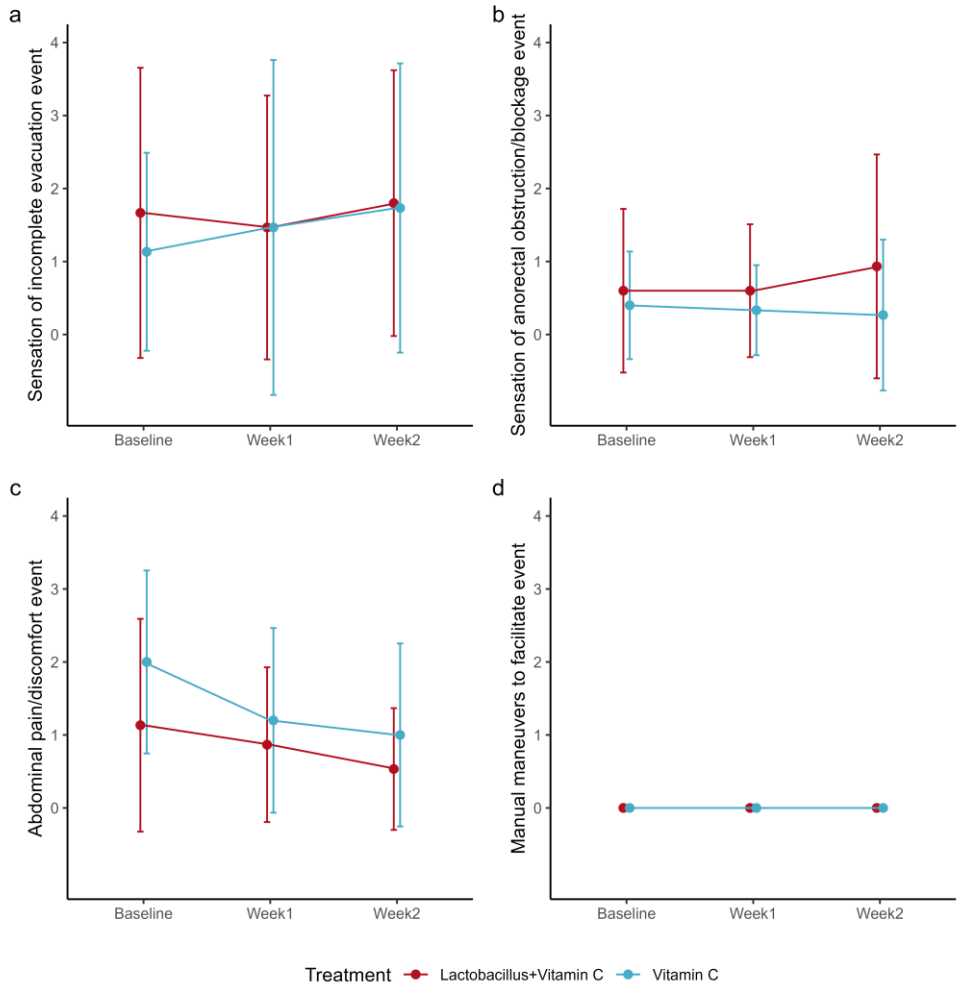

Figure 16. Summary of the additional efficacy parameters: the number of sensation of incomplete evacuation (a), anorectal obstruction/blockage (b), abdominal pain/discomfort (c), and manual maneuvers to facilitate events (d). Dots and error bars represent mean and standard deviation, respectively.

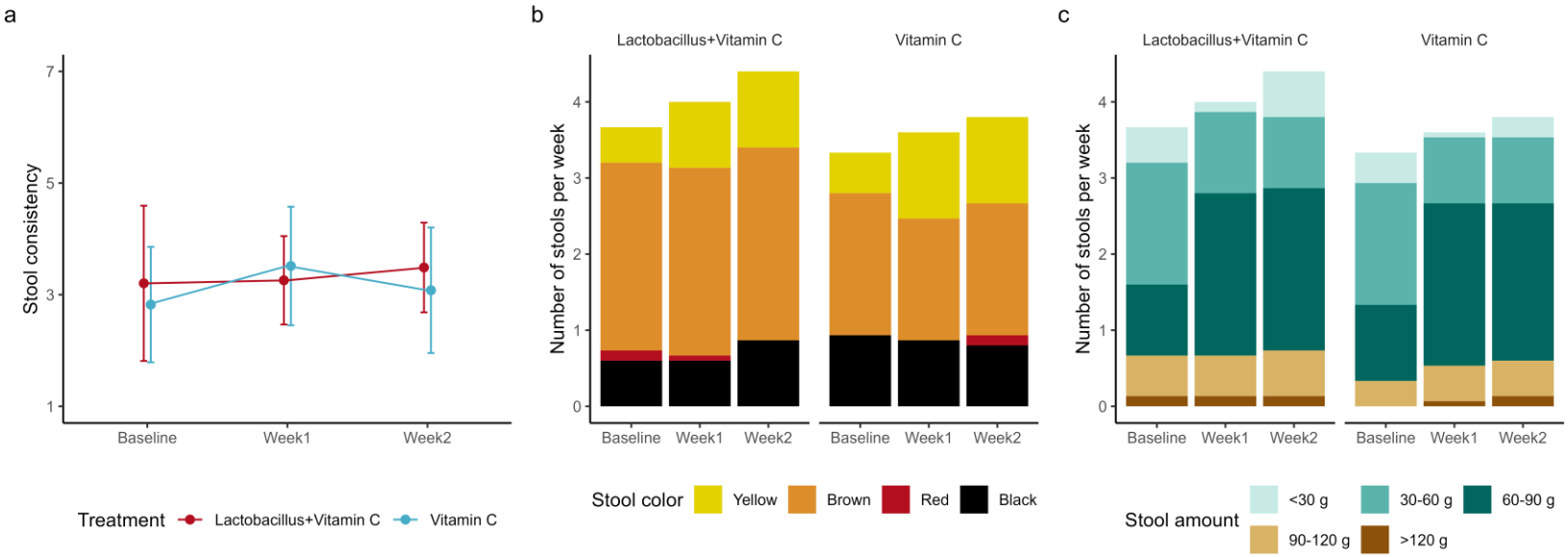

Figure 17. Summary of the additional efficacy parameters: stool consistency (a), stool color (b), and stool amount (c). Dots and error bars represent mean and standard deviation, respectively.

Table 9. Summary of the efficacy outcomes

	Lactobacillus+ Vitamin C (n=15)	Vitamin C (n=15)
Total number of defecation (#/week)		
Baseline	3.67 (2.16)	3.27 (1.67)
Week 1	4.00 (2.00)	3.53 (1.77)
Week 2	4.47 (2.45)	3.73 (1.71)
Use of laxatives (#/week)		
Baseline	0	0
Week 1	0	0
Week 2	0	0
Stool consistency		
Baseline	3.20 (1.39)	2.82 (1.03)
Week 1	3.26 (0.79)	3.51 (1.06)
Week 2	3.49 (0.80)	3.08 (1.12)
Defecation time (h)		
Baseline	8.00 (4.06)	6.60 (4.63)
Week 1	4.85 (3.88)	6.97 (4.28)
Week 2	4.06 (2.76)	4.98 (4.07)
Straining (#/week)		
Baseline	1.53 (1.60)	1.73 (1.58)
Week 1	1.33 (1.50)	1.60 (0.99)
Week 2	0.93 (1.03)	1.00 (1.13)
Sensation of incomplete evacuation (#/week)		
Baseline	1.67 (1.99)	1.13 (1.36)
Week 1	1.47 (1.81)	1.47 (2.29)
Week 2	1.80 (1.82)	1.73 (1.98)
Sensation of anorectal obstruction/blockage (#/week)		
Baseline	0.60 (1.12)	0.40 (0.74)
Week 1	0.60 (0.91)	0.33 (0.62)
Week 2	0.93 (1.53)	0.27 (1.03)
Abdominal pain/discomfort (#/week)		
Baseline	1.13 (1.46)	2.00 (1.25)
Week 1	0.87 (1.06)	1.20 (1.26)
Week 2	0.53 (0.83)	1.00 (1.25)
Manual maneuvers to facilitate (#/week)		
Baseline	0	0
Week 1	0	0
Week 2	0	0

Note: Mean (standard deviation) are presented.

Abbreviations: #, the number of events.

3.3.3. Evaluation of decentralized study procedures

Overall, 67.1% of bowel diary records were completed as scheduled, 24.0% were retrospectively (post-recording), 6.2% were prospectively (pre-recording), and 2.7% were missing. (Figure 18a and Table 10) Similarly, 63.8% of medication diary records were completed as scheduled, while 9.0% were retrospectively (post-recording), 15.5% were prospectively (pre-recording), and 11.7% were missing. (Figure 18b and Table 10). A total of 76.9% of vitamin C measurement records were performed as scheduled, and vitamin C was detectable after administration. However, 4.3% of the records were determined as pre-dose detection, and 12.4% were not properly conducted (e.g., not performed on the scheduled day; missing either pre- or post-dose tests) (Figure 16 and Table 10).

All subjects received the allocated treatments correctly with a mean delivery time of 21.3 hours. A total of 9 subjects agreed to give stool samples, and all samples were valid for fecal microbiome analysis. (Table 10)

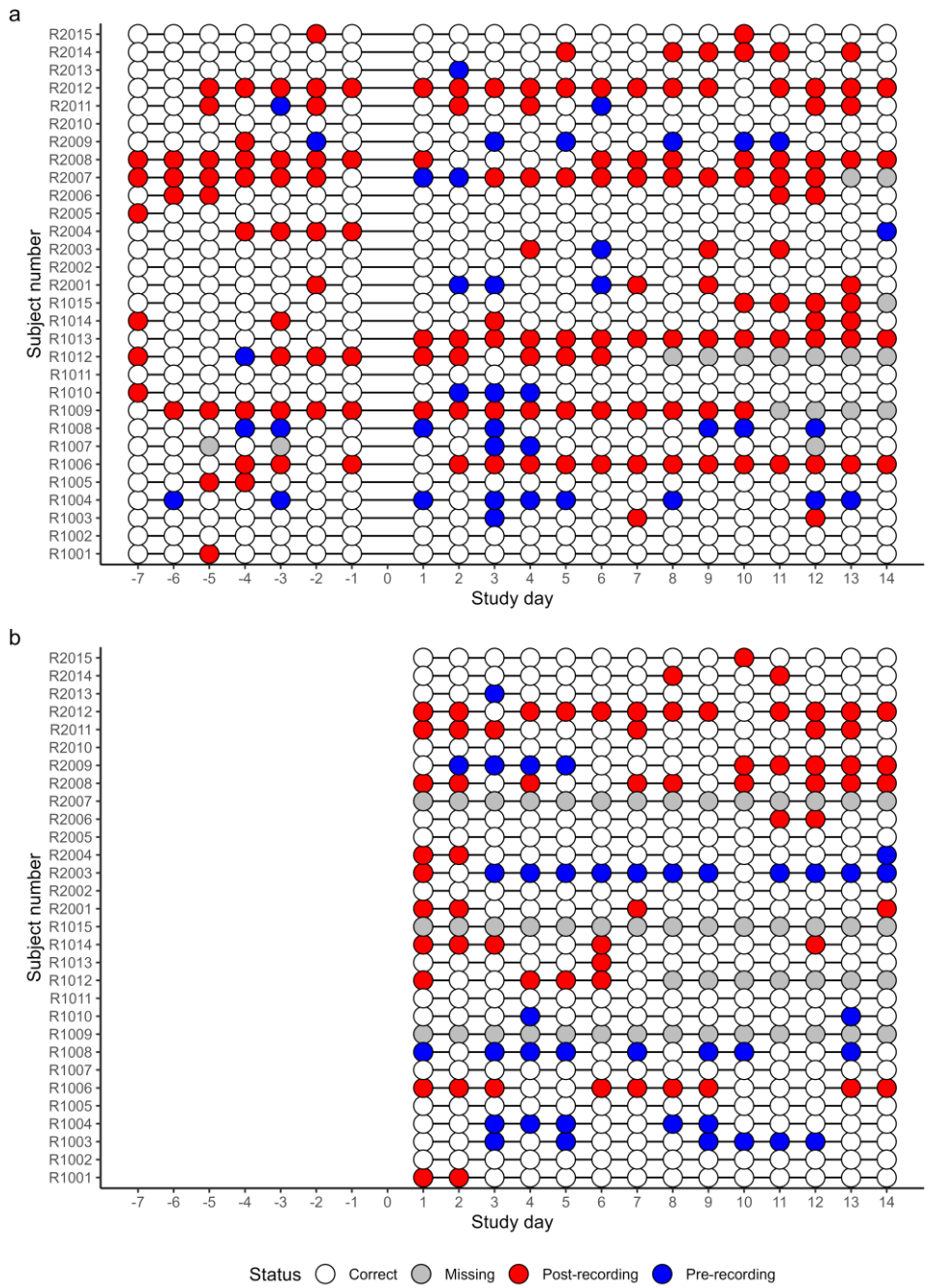

Figure 18. Evaluation of the electronic diary records: bowel diary (a) and medication diary (b). Pre-recording and post-recording are defined as the records entered before and after the scheduled date, respectively.

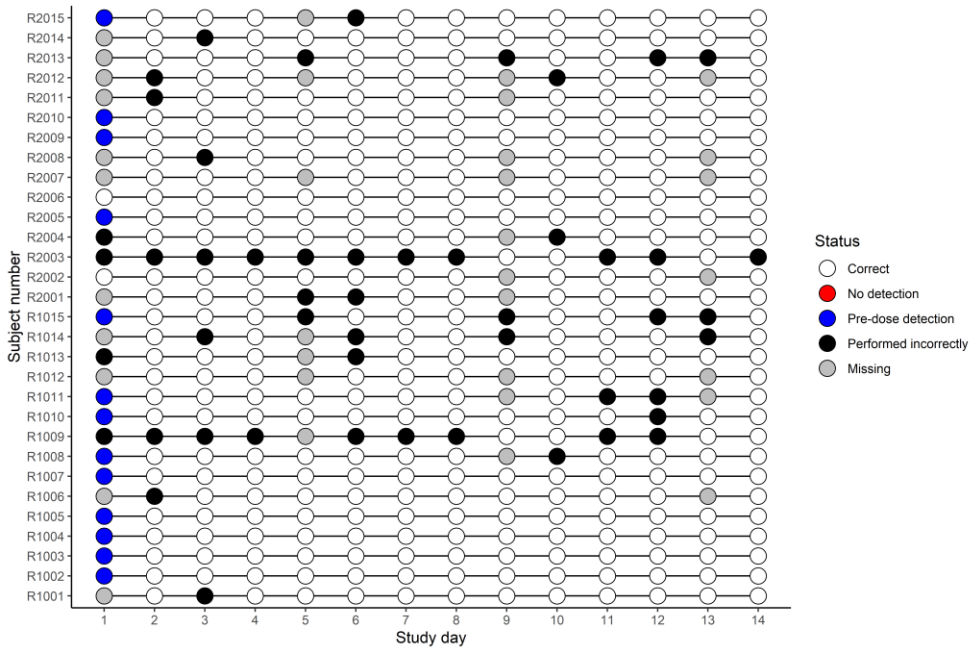

Figure 19. Evaluation of the urine vitamin C measurement records. 'Correct' denotes that the subject performed the urine test on the scheduled study day and proper times (e.g., pre- and post-dose test). 'No detection' denotes that urine vitamin C was not detected after administration, and 'pre-dose detection' vitamin C was detected at pre-dose measurement. 'Performed incorrectly' denotes that the subject performed the test not on the scheduled study day or unscheduled test (e.g., urine test on Day 2) was performed. 'Missing' denotes that the test was not performed.

Table 10. Evaluation of the decentralized elements

	Lactobacillus+ Vitamin C (n=15)	Vitamin C (n=15)	Total (N=30)
Bowel diary records (%)†			
Correct	65.7 (31.1)	68.6 (30.9)	67.1 (30.5)
Missing	4.8 (9.9)	0.6 (2.5)	2.7 (7.4)
Post-recording	22.2 (28.8)	25.7 (29.4)	24.0 (28.7)
Pre-recording	7.3 (13.3)	5.1 (7.9)	6.2 (10.8)
Medication diary records (%)†			
Correct	63.3 (36.1)	64.3 (35.3)	63.8 (35.1)
Missing	16.7 (36.2)	6.7 (25.8)	11.7 (31.3)
Post-recording	10.0 (18.9)	21.0 (26.1)	15.5 (23.1)
Pre-recording	10.0 (19.1)	8.1 (20.9)	9.0 (19.7)
Urine measurement records (%)‡			
Correct	77.6 (18.1)	76.2 (19.2)	76.9 (18.3)
Missing	6.7 (8.3)	10.0 (10.0)	8.3 (9.2)
Performed incorrectly	11.9 (17.4)	12.9 (20.6)	12.4 (18.8)
No detection	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Pre-dose detection	4.3 (3.6)	1.9 (3.3)	3.1 (3.6)
Direct-to-patient shipping procedures			
Who received the IP (n, %)	15 [100.0]	15 [100.0]	30 [100.0]
Who received the incorrect IP (n, %)	0	0	0
Time to receive IP (h)	21.5 (2.2)	21.1 (2.0)	21.3 (2.1)
Who agreed to collect stool (n, %)	4 [26.7]	5 [33.3]	9 [30.0]
Number of valid stool samples¶(n, %)	4 [26.7]	5 [33.3]	9 [30.0]

†Categories of the records were defined as follows: Correct, the subject completed the electronic diary on the scheduled date; Pre-recording, the records were generated before the scheduled date; Post-recording, the records were generated after the scheduled date; Missing, the records were not entered.

‡Categories of the records were defined as follows: Correct, the subject performed the urine test on the scheduled study day and proper times (e.g., pre and post-dose test); No detection, urine vitamin C was not detected after administration; Pre-dose detection, vitamin C was detected at pre-dose measurement; Performed incorrectly, the subject performed the test not on the scheduled study day or unscheduled test; Missing, denoted that test was not performed.

¶Pre-dose sample was not obtained due to logistical issue in the local laboratory.

Notes: Proportions of each category in subjects are summarized by mean (standard deviation) for the feces, drug administration, and self-vitamin C detection kit records. Time to receive IP was also summarized by mean (standard deviation). The other records are summarized by the number of subjects [percentages].

Abbreviations: IP, investigational product.

3.4.3. Participants' experience

Subjects commonly commented that the home-based procedures were convenient and lessened the burden of participation. (e.g., *"As all procedures were performed on the online, it was comfortable that we don't have to visit the study center"*) Several subjects commented that they participated in a clinical trial for the first time and that the overall experience was satisfactory. (e.g., *"It was the first time to participate in a clinical trial. I feel comfortable, as there were no restrictions on time and place. Remote consent process was also comfortable."*)

The user interface of the mobile application complained, in particular with notification of the study procedures. (e.g., "*I had to check the study schedules in the informed consent form during the study. It was not convenient and user interface was not intuitive"*) Several subjects complained the response to inquiries was not always prompt or found difficulty in contacting investigators using other routes when a system error occurred. Subjects also commented that they felt insufficiently notified of some study procedures (e.g., "*It was difficult to solve application errors or where to contact"*). *(e.g., "I want to know how the results of urine strip test were and why I should do such tests")* (Table 11)

Table 11. Selected quotes of the comments from the participants

Positive aspects
"As all procedures were performed on the online, it was comfortable that we don't have to visit the study center"
"It was easy to participate as I don't have to visit the study center and just use the mobile application. I feel threshold for participation was lowered. In addition, I was less embarrassed because I could do urine strip test by myself."
"It was the first time to participate in a clinical trial. I feel comfortable as there was no restrictions on time and place. Remote consent process was also comfortable."
Negative aspects or comments
"I found difficulty in entering the records as the scheduled date was not displayed but only study day (1d, 2d). I had to calculate the dates and sometimes entered the records in another date."
"I had to check the study schedules in the informed consent form during the study. It was not convenient and user interface was not intuitive."
"Notifications on 1:1 inquiry were not working well and keyboards were overlaid on the window where I write inquiries. Sometimes I could not enter inquires or inquiries were duplicated."
"Feedbacks on the complaints and application errors were not smooth."
"It was difficult to find how to solve application errors or where to contact."
"I was not sufficiently notified of the stool collection procedures."
"I want to know how the results of urine strip test were and why I should do such tests."

Chapter 4. Discussion

Patient recruitment and retention is one of the major advantages of DCT. During the early COVID-19 pandemic period, DCTs recovered faster from the recruitment than the conventional clinical trials.[35] Distant trial sites have been an obstacle to patient participation and the issues were overcome using patient-centered model in DCTs.[36] Participants in the trial commented in a similar context that DCT approach lessen the burden for trial participation. The participants also commented that home-based trial procedures were more convenient than those in conventional clinical trials.

Chronic diseases would be the most suitable therapeutic area for DCT design. Chronic diseases typically require everyday monitoring and treatment. Functional constipation, which was evaluated in our *Fully remote clinical trial*, can be managed through routine lifestyle modifications and pharmacological therapy.[37] Keeping track of bowel diaries is also required for treatment and can be readily done with use of electronic diaries.[38] The considerations comprehensively support the adoption of DCT design, as it enables study monitoring with little cost while reflecting real-world medical practices. Similarly, DCT approaches have been used in trials for other chronic diseases such as atrial fibrillation,[15]

Helicobacter pylori eradication,[39] Parkinson's disease,[40] type 2 diabetes.[41] All of the diseases could be benefited from implementation of DCTs.

The results of the study implied that decentralized elements could increase the retention of subjects. In the *dynamic consent trial*, overall response rate to protocol amendment was approximately 95.7% and all subjects completed the study. The finding was similar to that of a pilot study in patients with acute low back pain, where DCT design showed higher retention rate (89%) than conventional design (60%).[42] A randomized clinical trial in overweight volunteers also demonstrated that patient group using mobile application-based (93%) showed higher retention rate than paper-based counterparts (53%).[43] The findings supported the advantages of DCT in the retention of subjects.

It is pointed out that recruitment and data collection processes can be influenced by external factors other than the study design. Device heterogeneity is one example; Li *et al.* demonstrated that the device type of mobile phones (e.g., Android vs. iOS) significantly affected the data sharing patterns (e.g., providing barometer data) of participants.[40] Moreover, the layout of the recruitment website was also reported to influence participants' engagement and interest.[44]

Interestingly, more missing records were observed in the medication diary than in the bowel diary in our *fully remote clinical trial*. As the procedures were conducted in the same mobile application, the user interface of data collection system might be the cause. The findings suggest that the user interface for a software used in clinical trials can affect the reliability of data collection. Therefore, the user interface should be carefully designed with the early engagement of patients.[12, 13, 16]

In addition, we also found that the information given on the online platform without sufficient interactions could be missed or misunderstood. In the *dynamic consent trial*, large number of subjects stuck to the initial procedure (i.e., body temperature measurement in the morning) despite the changes in the protocol. Similarly, several subjects confused changes in body temperature measurement with those in drug administration. The findings suggest that study subjects can perfunctorily give consent without an accurate understanding of the content. These resulted in protocol deviations, which could expose subjects to unexpected risks in actual clinical trials.

It is noteworthy that the electronic form itself is not the determinant of poor understanding. In the *dynamic consent trial*, the overall procedural adherence was not critically low after the first

electronic consent conducted in a *face-to-face* manner. When delivered properly, electronic consent could provide comparable comprehension to paper-based consent.[45] The crucial factor for poor understanding might be the insufficient interaction in *remote* electronic consents. A previous study revealed that face-to-face interaction was more effective in improving comprehension than multimedia component or tests.[46, 47]

Patient-reported data in the *fully remote clinical trial* also raises reliability concerns. Retrospective records of bowel and medication diaries were found in 15.5-24.0% of the total records, and prospective records were found in 6.2-9.0%. The results are alarming as they can affect study outcomes. In addition, most participants did not accurately perform urine vitamin C measurements (e.g., missing post-dose measurement in the first day), which indicated that meticulous monitoring of study procedures are required. On the other hand, participants complained that checking study procedures on their own was difficult and demanded automatic alarm systems. The overall findings suggest systematic approaches to monitor trial procedures are associated with reliability of data in DCTs.[48]

Maintaining adherence until the later phase is a key to reliability in DCTs. In our *three trials*, we found that adherence to study

procedures was the highest at the beginning and decreased as study proceeds. Especially, instructions delivered solely on online were not perfectly understood to study subjects. This implied that multiple methods routes that can aid communication are required. Solutions can include multimedia-based approach such as audio or video component comprehension quizzes.[49, 50]

It was positive finding that multiple measures of monitoring can improve treatment adherence in the later phase. In the *adherence monitoring trial*, subjective reporting showed relatively low concordance in the later phase of the study. Missing data were increased in the later phase assessed by higher percentage of apparent "drug holidays". In contrast, combination of multiple methods (i.e., smart watch and app) reported were lower loss of data when combined. Although inconvenience of subjects should be also balanced, use of multiple modalities can contribute to more sensitive of data collection.

Monitoring itself can also enhance the adherence of the study subjects. Enhancing adherence to study procedures requires multifactorial approaches[51] and well-designed monitoring can be an important solution. In a previous study, smart-watch intervention group showed higher adherence rate (63.3%) than control group (43.2%) in allergic rhinitis patients.[52] Similarly, serum 25(OH)

vitamin D concentration, an important surrogate marker for efficacy, was well maintained in the watch group in adherence monitoring trial.

In addition, caregiver's role in clinical trials is also important. We found that several subjects incorrectly operate study procedures in a systematic and persistent manner in the *dynamic consent trial*. Similarly, completely missing medication records in the *fully remote clinical trial* were also observed. Such systematic and persistent procedural errors can be promptly detected and corrected by caregivers in real clinical settings. Therefore, the caregiver's role to report patients' status promptly would be critical in ensuring the reliability of DCTs. A previous survey on oncologists, investigators more relied on caregiver's report (45%) than self-report from patients (8%).[53]

In the *fully remote clinical trial*, direct-to-patient procedures were tried. Direct-to-patient procedures are often confronted by regulatory issues. Direct-to-patient shipping of investigational medicinal products is not allowed in several jurisdictions, while allowed in others with several limitations.[54] To overcome the issue, low-risk alternatives to direct-to-patient shipping were tried in our study. The procedures seem feasible and can benefit DCT designs. However, detailed management of the procedures should

be warranted as guided in Good Clinical Practice (e.g., identification of the recipients, storage and disposal of the products). The results of exploratory microbiome analysis also demonstrated that patient-centric collection procedures could yield analyzable data and could be utilized in further trials.[55]

Of note, estimating benefits from DCTs is complicated and still under debate. In a comprehensive review on DCT practices, there were conflicting views on the advantages and burden of DCTs.[56] DCTs reduced costs for staff training[57] and quality monitoring[58] while burden for technology use was increased.[59] The additional administrative burdens for trial sites were identified when the number of patients became larger.[16] Therefore, element-level assessment of benefits and burdens would be required in DCTs.

The study had several limitations. The small number of participants and short study duration limited the generalizability of the results. Lack of intervention arms involving traditional trial-related procedures restricted the direct comparison to DCT elements. The low-risk alternatives cannot fully reflect the characteristics of further DCTs in patients. In particular, absence of blood sampling procedures is a major drawback as evaluating the effect of decentralization on major clinical endpoints was not available.

Nonetheless, the study involved multiple DCT elements and could derive real-world considerations. Several elements in DCTs (e.g., blood sampling using local laboratory) were closely related to regulations in the local healthcare system and often not easily accessible. Considering the benefits of DCT elements to patients, risk-based approach for introducing DCT elements[60] with proper supervision would be suggested. Further investigations for various DCT scenarios will be warranted.

In conclusion, the reliability of decentralized clinical trials depends on proper understanding of patients supported by systematic modalities. Combination of multiple monitoring tools can improve the reliability of data.

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Abstract in Korean

서론: 무작위배정 임상시험은 유효성과 안전성을 입증하는 표준으로 자리매김해 왔다. 그러나 높은 비용과 환자에 대한 낮은 접근성으로 인한 편의(bias)가 발생할 가능성이 제기된 바 있다. 분산형 임상시험(decentralized clinical trial, DCT)은 디지털 기술을 활용하여 임상시험 실시기관과 연구 인력에 대한 의존을 줄이고자 하는 시도이다. 분산형 임상시험의 도입으로 인해 접근성이 증가했으나 자료 신뢰성 문제가 극복될 필요가 있다. DCT의 신뢰성에 영향을 미치는 요인을 파악하기 위해 3건의 타당성 평가 임상시험이 수행되었다.

방법: 동의 절차는 2주 간격의 3번의 방문으로 구성된 4주 기간의 DCT(*역동적 동의 연구*)에서 평가하였다. 시험대상자는 매일 자가로 체온을 측정하고 코드로 된 가상의 임상시험용의약품을 모바일 어플리케이션에 입력하였다. 연구기간 중 발생한 임상시험계획서 변경에 대한 동의 횟수와 동의율, 약품 복용과 연구 절차에에 대한 순응도가 평가되었다.

순응도 평가는 비타민 D 결핍자를 대상으로 한 12주의 DCT에서 평가되였다.(*순응도 평가 연구*) 시험대상자는 비타민 D 보충제를 12주 동안 복용하면서 모바일 어플리케이션(App only 군) 단독 사용과 어플리케이션과 스마트 워치를 함께 사용하는 (App + Watch 군) 순응도 평가군 중 하나에 배정되었다. 순응도 기록과 혈청 25(OH) 비타민 D 농도가 평가되었다.

DCT 요소의 결합은 공개 디자인으로 기능성 변비 증상을 가진 대상자에서 수행된 *완전 원격 임상시험*에서 평가되었다. 시험대상자는 유

산균 제제와 비타민 C를 병용 투여하는 군 혹은 비타민 C만 투여하는 군에 1:1로 배정되었고 해당 건강기능식품은 시험대상자에게 직접 배송되었다. 시험대상자는 1주의 기저치 평가와 2주의 중재기간 동안 배변일지와 복용일지를 모바일 어플리케이션을 통해 매일 기록하였다. 배변 증상과 기록들의 타당성에 대해 기술통계적 분석을 수행하였다.

결과: *역동적 동의 연구*에서, 시험대상자는 95.7%의 임상시험시험계획서 변경에 동의하였고 반응시간의 중앙값은 0.2 시간이었다. 투약과 체온 측정은 각각 예정된 절차의 90.8%, 97.6%가 수행되었으나 예정에 맞게 수행된 것은 각각 69.1%와 59.0%로 집계되었다. 순응도는 주요한 임상시험계획서 변경 후 크게 감소하였다.

*순응도 평가 연구*에서 혈청 25(OH) 비타민 D 농도는 첫 7주까지는 두 군에서 유사하게 상승하였으나, 연구 후반부에는 App + Watch군에서 더 높은 값을 나타내었다. 알약 개수 세기와 App을 통해 확인한 투여량은 연구 초반부에는 유의한 차이가 없었으나 (p = 0.5534) 후반부에는 유의하게 차이가 발생하였다 (p = 0.0225). 이와 달리 스마트워치로 얻어진 기록은 연구 전반부, 후반부 모두 유의한 차이가 없었다 (각각 p = 0.5898와 p =0.5839).

*완전 원격 임상시험*에서 26.7%가 수도권 외 지역에서 등록되었다. 2주의 유산균 투여는 대조군에 비해 배변 횟수를 증가시켰고 (주당 +0.80 vs. +0.46 회) 배변 시간을 감소시켰다 (−3.94 h vs. −1.62 h). 전체적으로 67.1%의 배변일지가 일정대로 수행되었으나 24.0% 기록은 후향적으로, 6.2%의 기록은 전향적으로 입력되었다.

결론: 분산형 임상시험의 신뢰성은 환자의 시스템적인 도구를 활용을 통해 확보된 환자의 올바른 이해에 의존한다. 복합적인 모니터링 도구 활용을 통해 자료의 신뢰성을 확보할 수 있다.

**역동적 동의 연구*의 결과는 다음과 같이 출판되었습니다. (Huh KY, Moon SJ, Jeong SU, Kim MJ, Yang W, Jeong M, Kim MG, Lee S. Evaluation of a blockchain-based dynamic consent platform (METORY) in a decentralized and multicenter clinical trial using virtual drugs. Clin Transl Sci. 2022 May;15(5):1257-1268.)

주요어: 분산형 임상시험, 자료 신뢰성, 디지털 기술, 웨어러블 기기, 환자 중심성, 타당성 평가 연구

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