Usefulness of Video-Based Observation and Self-Administration Patterns in Repeated-Dose Clinical Studies With Healthy Volunteers: A Retrospective Data Analysis

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Abstract

Background: It is imperative to maintain precise dosing records in repeated-dose pharmacokinetic studies involving healthy volunteers to ensure data validity. Conventional techniques, such as direct observation, self-reporting, and pill counts, often prove inadequate in terms of accuracy and practicality. Video-based monitoring systems have emerged as a promising alternative, offering enhanced accuracy and reduced burden on stakeholders. This study assesses the efficacy of an asynchronous video-based Self-Administration of the Investigational Product (SAI) monitoring system (VSMS) in ensuring accurate dosing in clinical trials with healthy volunteers in Korea.

Objective: The primary objectives of this study were to evaluate the usefulness of an asynchronous VSMS in validating subject SAI in a repeated-dose pharmacokinetic study and to explore patterns of subject compliance with planned dosing times, suggesting possible applications for such a system.

Methods: A retrospective analysis was conducted using data from 17,619 SAI events in repeated-dose clinical trials employing the VSMS between February 2020 and March 2023. The SAI events were classified into four categories: Verified On-time Dosing, Verified Deviated Dosing, Unverified Dosing, and Missed Dosing. Analysis methods included calculating the success rate for verified SAI events and analyzing trends in deviation between planned and actual dosing times (PADEV) over the dosing period and by push notification type. The mean PADEV for each subsequent dosing period was compared with the initial period using either a paired t-test or a Wilcoxon signed-rank test to assess any differences.

Results: The VSMS achieved a high success rate of 97%, with 99% of the classified as Verified On-time Dosing. An analysis of trends in dosing time deviations revealed a tendency towards delayed dosing in cohorts 1, 2, 6, 8, 12, and 14, while cohorts 3, 4, 5, 7, 9, 10, 11, and 13 exhibited a tendency to dose earlier than the planned time. A comparison of the initial and subsequent dosing periods revealed no significant differences in dosing time deviations for most cohorts. However, significant differences ($P < .05$) were observed on only 16% (13 out of 79 days). The analysis of the impact of push notification types revealed a trend towards the highest compliance with planned dosing times when both Dosing Notifications and Dosing Reminders were provided (average PADEV: -3.5 ± 31.3 minutes).

Conclusions: The VSMS effectively enabled real-time remote monitoring and verification of SAI events in early clinical trials. Additionally, the system facilitated control over subject SAI behavior through targeted push notifications and communication. Its utility is expected to grow with more data and experience.

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Abstract

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KEYWORDS

mobile health; medication administration; self-administration; pharmacokinetics; multiple-dose clinical trials; video-based monitoring

Introduction

Repeated dose studies in healthy volunteers are essential for obtaining basic information about the pharmacokinetics (PK) of a drug. These studies are performed during the development of a specific investigational product (IP) for which the dose of the active ingredient, formulation and route of administration has been determined. They include repeated dose escalation studies, drug-drug interaction studies, and some bioequivalence studies [1-3]. The changes in drug concentration that occur when an active ingredient is administered using a specific IP are usually described in terms of the time elapsed after administration, from which various PK relationships are defined. Therefore, whether the IP was actually administered and the time of administration are considered pivotal information to be obtained in such studies [4].

Historically, a variety of techniques have been employed to ensure precise dosing information in clinical trials. These include direct observation by investigators, self-reporting through diaries or questionnaires, and pill counts[4, 5]. Although direct observation is the most reliable method, it may be impractical and burdensome due to the necessity of frequent hospital visits, which increases costs and inconveniences participants[4, 6-10]. Self-reporting methods are susceptible to biases such as recall and social desirability biases, which can lead to inaccuracies[5, 6, 11-15]. While pill counts are a straightforward approach, they cannot confirm actual administration, making them less reliable for studies requiring precise dosing records[12]. The inherent limitations of existing methodologies have consistently underscored the necessity for novel approaches capable of addressing the demands of repeated-dose PK studies.

The advent of mobile technologies has brought about innovative methodologies for the monitoring of the IP administration in clinical trials[4, 16]. One such advancement is the utilization of video-based observation, which permits the remote assessment of Self-Administration of the Investigational Product (SAI)[4]. Video-based observation employs either synchronous or asynchronous methodologies. In the former, the investigator observes the SAI in real-time[6, 16-21], whereas in the

latter, the subject uploads a video of the SAI for subsequent review[4, 6, 16, 17, 22-25]. This technology offers a degree of verification that is comparable to that of direct observation while reducing the necessity for frequent hospital visits, thus enhancing the convenience of participants and reducing the costs associated with the trial[4].

This study was to assess the usefulness of an asynchronous video-based SAI monitoring system (VSMS) through a simple and straightforward outcome measure: “Was the investigator able to reliably verify SAI using the videos uploaded by the subject?”. This outcome measure is ultimately a direct indicator of whether the system performed as targeted, and was considered to be a composite of technical influences such as system reliability and socio-demographic influences such as digital literacy. In addition, if the results showed that the VSMS was sufficient to verify SAIs, it was planned to explore subjects' compliance with planned SAI times when utilizing these systems. These evaluations will enhance our understanding of the validity and reliability of asynchronous VSMS in a range of multiple-dose PK trial settings.

Methods

Ethical Considerations

This study employed a retrospective SAI dataset gathered through the use of DoseEase™ (CareSquare, Inc., Seoul, Korea), the inaugural asynchronous VSMS developed in Korea. The dataset did not include any personally identifiable information (refer section ‘Clinical Trials as the Data Source’ and ‘Dataset’), thereby eliminating the potential for a breach of subject privacy or confidentiality. Consequently, the informed consent procedure was not required. The study was reviewed and approved by the Institutional Review Board of The Catholic University of Korea Seoul St. Mary's Hospital (MC23EASI0052; approval date: 11 July 2023).

The system overview

The VSMS employed in this study comprises a web-based system for investigators and a mobile application for subjects. The web-based system allows investigators to 1) search for a QR code to match a subject to a specific subject number in the study; 2) view the SAI schedule, which should be assessed by calendar date; 3) view SAI-related videos uploaded by the subject; 4) determine if a valid administration is made and enter corresponding data; and 5) send subject feedback on the SAI.

The system is designed to allow the investigator to make the final confirmation about the SAI results, with outcomes recorded in one of four categories ((1)~(4));

(1) Verified On-time Dosing (VOD)

- The actual dosing time provided by the system is within the allowed SAI time window and the dosing behavior recorded in the video is appropriate.
- The actual dosing time provided by the system is outside the limits of the allowed SAI time window, but based on the video, it is verified that the appropriate dosing behavior occurred within the window (e.g., video recording started before the time window range, but the actual dosing occurs within the window). In this case, the investigator manually corrected the actual dosing time.

(2) Verified Deviated Dosing (VDD)

The actual dosing time provided by the system is outside the limits of the allowed SAI time window, and the appropriate SAI behavior is verified based on the video, but the timing is outside the window.

(3) Unverified Dosing (UD)

SAI cannot be verified via video due to technical issues, subject non-compliance with recording procedures (e.g., too dark recording environment, skipping oral cavity disclosure), etc. but there is evidence to believe the subject performed the SAI (e.g., subject statement from a phone call with the reason of inappropriate video recording)

(4) Missed Dosing (MD)

SAI cannot be verified via video and no evidence that the subject performed SAI can be obtained.

The mobile application is designed with a simple and user-friendly interface. The system may provide push notifications to subjects before or after the scheduled dosing time, as specified in the protocol. Upon opening the application, the subject is immediately instructed to start the video recording and proceed with the SAI. The server connection time, recording start time, and recording end time were always recorded based on the subject's mobile device time to ensure that the data remained accurate even in situations such as slow internet speeds or transmission failures. In these cases, the recorded video was sent to the server as soon as mobile network conditions improved. Of the stored time data, the recording start time was displayed on the investigator's web system as the default value for the actual dosing time. The recorded video was temporarily cached on the subject's mobile device and deleted once the transfer to the server was confirmed. The behavior of the system according to the SAI schedule and procedures, storage and management of SAI data, and processing of other communication-related information was handled through servers operated by the service provider, which complied with all applicable quality and regulatory standards.

Clinical Trials as the Data Source

The data presented in this study were derived from repeat-dose clinical trials in healthy volunteers that utilized DoseEase™ as a VSMS. These trials were conducted between February 2020 and March 2023 and the IPs were all self-administrable formulations (oral or ophthalmic). Trials that included groups with two or more different SAI schedules were also included in the analysis, and each group was treated as a separate cohort. The eligibility criteria for subjects across all trials were consistent and included the following: age between 19 and 55 years, a minimum weight of 50 kg for men and 45 kg for women, with a body mass index between 18.5 and 24.9, and confirmation of healthy condition in a comprehensive medical examination, which included an assessment of medical

history, physical examination, and laboratory tests. Subjects were excluded if they exhibited significant active disease at the screening stage or a history of prior disease that could affect the administration and absorption of the IP.

Before enrollment began for the clinical trial, the service provider received a protocol from the research staffs to set up the system that specified the followings;

- The number of subjects and the principle of subject numbering
- Cohort categorization according to dosing schedule
- SAI schedules by cohort and overall dosing schedule
- Allowable time deviations per SAI event
- Plan to deliver push notifications per SAI event.

The finalized system was piloted and validated by the investigators prior to the start of the trial.

At the first subject visit, the investigator accessed the VSMS web, retrieved and printed a QR code for each subject number, which was then scanned by the subject with that number using his or her mobile device (This was a key procedure to ensure that each subject was correctly identified without obtaining additional sensitive personal information). This registered the subject's device in the system at the same time as the VSMS application was installed on the subject's mobile device. This procedure was followed by training, which included 1-2 mock SAIs to familiarize the subject with the system. The mock SAI underscored the significance of securely positioning the mobile device and executing all procedures associated with the SAI (e.g., the IP preparation with a specified volume of water, the oral administration, and the disclosure of the oral cavity after dosing for oral administration) within the boundaries of the recording screen. At the visit immediately prior to the scheduled SAI, the subject received the IP for the number of scheduled SAIs before the next visit, after which the IP was managed by the subject at a location other than the hospital.

On days when SAI was scheduled, subjects were either alerted via push notification on the mobile

application or not, as specified in the protocol. The timing (before the planned dosing time [Dosing Notification, DN], after the planned dosing time [Dosing Reminder, DR], or both) and frequency of these alerts varied by cohort. As trained in advance, at their own available time (preferably within the allowable SAI time window specified in the protocol), subjects performed the SAI while recording a video. If mobile network conditions were adequate, the video was sent to the server as soon as it was recorded, at which point it was made available to the investigator. If the video was not uploaded after the planned dosing time, investigators were able to contact subjects by phone to remind them to perform SAI or to check for any technical issues.

For each SAI event, investigators evaluated the uploaded videos to assess whether the SAI was appropriate for each subject. A decision tree was provided to help investigator confirm SAI videos and related records into the appropriate category (Figure 1). For non-VOD cases, investigators were able to send proper feedback to the subject to improve compliance.

Dataset

The SAI dataset used the clinical trial protocol number as the study identifier (STYID) and the subject number assigned to the protocol as the subject identifier (SUBID). Each SAI record included the planned study day (STYDY, with the first dose day equal to 1), the planned dosing time (PTIME), the time the video recording started (STIME), and the investigator-confirmed actual dosing time (ATIME). The difference between PTIME and ATIME was defined as the dosing time deviation (PADEV). STYDY values of 15 or more were recorded as '≥15' since typical dosing duration was under 2 weeks. The investigator's final decision (SAIDC, categorized as VOD, VDD, UD, or MD) and the type of push notification delivery (PNTYP , categorized as none, DN, DR, or both) were also included as record items. All available data from subjects who dropped out before completing all procedures were included in the analysis.

Assessment and Statistical Analysis

The primary goal of a VSMS is to ensure that the subject's video-recorded SAI behavior is successfully transmitted to the investigator, who can then determine whether the SAI was properly performed. This goal cannot be achieved if the subject or investigator is unskilled in using the system, or if the data is incomplete due to technical problems with the system. Therefore, a VSMS may be considered ‘useful’ when it adequately fulfills its intention of use. In this study, the cases where the SAIDC is VOD or VDD are collectively referred to as validated dosing (VD), and the percentage of VDs among all SAI records (Success Rate [SR], %) is evaluated as a measure of usefulness. The SR was determined for each STYDY in which SAIs were performed in each cohort (considered separate cohorts if the same study included arms with two or more different dosing schedules). The SR by STYDY in the overall cohort and the SR over all STYDYs in each cohort were also calculated.

In addition, VSMS allows investigators to view SAI records in real-time, unlike other existing methods. This means that investigator-subject interaction is possible on a per STYDY basis, with features such as push notifications (DN or DR) and appropriate subject management to provide input on compliance. To assess the usefulness of this aspect, the trend of PADEV per STYDY was analyzed for each cohort. Only VD data records from cohorts with the SR of 90% or higher were used in this analysis (even VOD records may have deviations between PTIME and ATIME). In the first analysis, a paired t-test or a Wilcoxon signed-rank test (depending on the sample size) was performed on the difference between the mean of PADEV in the reference STYDY (the first three STYDYs in which SAIs were performed) and the mean of PADEV in each subsequent STYDY to assess whether the dosing trend identified early in the dosing period was maintained thereafter. In the second analysis, we performed a descriptive statistical analysis of the trend in dosing deviations over the entire SAI period according to the type of push notification provided, followed by t-tests of means between groups.

All statistical analyses were performed using R software (version 4.2.2. R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at 0.05, and all tests were two-tailed.

Results

Cohort characteristics

There were 10 trials included in the analysis based on the selection criteria, resulting in 14 unique cohort datasets. The cohort characteristics could be summarized based on IP characteristics, enrollment and completion rates, SAI schedule, push notification settings and allowed time window for SAI.

The route of administration was oral in 12 cohorts (86%) and ophthalmic in 2 cohorts (14%). The IPs were formulated in various forms, including tablets, capsules, and powders. High completion rates were observed in 13 cohorts (93%), with more than 80% of subjects completing the study, and some cohorts achieving 100% completion (Table1). The SAI schedules varied widely, ranging from 5 to 94 days, with daily frequencies varying from one to four times. Additionally, some cohorts had multiple daily administrations due to overlapping hospitalization or outpatient schedules. Push notifications were utilized in 11 cohorts (79%), with the majority (73%) employing both DNs and DRs to enhance compliance (Table2).

Table 1. Cohort characteristics

Cohort #	Dosing route	Formulation	Number of Subjects		
			Enrolled	Drop-out	Completed (%)
1	oral	tablet	90	8	82 (91%)
2	oral	tablet	15	3	12 (80%)
3	oral	tablet	23	4	19 (83%)
4	oral	capsule/ tablet	36	5	31 (86%)
5	oral	tablet	40	9	31 (78%)
6	oral	powder	44	1	43 (98%)

7	oral	capsule	8	1	7 (88%)
8	oral	powder	45	0	45 (100%)
9	oral	tablet	15	0	15 (100%)
10	oral	tablet	15	2	13 (87%)
11	oral	tablet	15	1	14 (93%)
12	ophthalmic	eye drops	16	2	14 (88%)
13	ophthalmic	eye drops	16	2	14 (88%)
14	oral	tablet	29	2	27 (93%)

Table 2. SAI-specific characteristics by cohort

Cohort #	SAI schedule			Dosing notification (min before the planned dosing time)	Dosing reminder (min after the planned dosing time)	Allowed time window for SAI (min)
	SAI Day	Number of total SAI Days	Number of SAIs per day			
1	2-4, 6-8, 10-12, 14-16, 18, 19	14	1	-60, -30, 0	15, 30, 45	±60
2	1, 2, 6, 7, 9 -11	7	1	NA	NA	±60
3	1, 2, 4 - 6, 10, 11	7	1	NA	NA	±60
4	1, 2, 12-15, 17-20, 24, 25	12	1	NA	NA	±60
5	1-4, 13-17, 21–23	12	1	-60, -30, 0	15, 30, 45	±60
6	1–32	32	2	-60, -15, 0	60, 110	±120
7	3, 5, 7, 9, 10, 12-14, 16-21, 23–30, 32-45, 47-60, 62-75, 77-90	78	1	-30, -5, 0	10, 20, 165, 665	±180
8	1-28	28	2	-60, -10, 0	60, 180, 350	-120 ~ 360
9	3-7	5	2[a],3	-30, 0	NA	±120
10	4-8, 11	6	2[a],3	-30, 0	NA	±120
11	5-9, 12	6	2[a],3	-30, 0	NA	±120
12	2-4, 8-96	92	1[a],2[a],4	-10, 0	10	NA
13	1-89, 92-96	94	2[a],3	-10, 0	10	NA
14	2, 3, 5, 6, 8, 9, 11	7	1	-30, 0	30	±60

SAI, Self-Administration of the Investigational Product

[a] SAI event and dosing by investigator performed on the same day

Fundamental Evaluation of Usefulness: Fulfillment of Intended Use

A comprehensive analysis was conducted on 17,619 scheduled SAI events across the 14 cohorts to evaluate the system's ability to fulfill its intended use. The analysis revealed a high SR of 97% (17,151 events), while 3% (468 events) were non-successful due to issues such as unclear video recordings or technical difficulties. Among the successful events, 99% (16,975 events) were validated by investigators as VOD, indicating that the actual dosing time was within the allowed SAI time window and the dosing behavior recorded in the video was appropriate.

A total of 127 SAI days were analyzed, with over 90% of subjects consistently reporting dosing videos on all SAI days. The majority of SAI days (95%) had more than 90% objective dosing data, with some days requiring additional verification via phone to ensure accurate data capture. This high rate of validated dosing (VOD + VDD) indicates that the system effectively supported the accurate SAI(Table 3, Multimedia Appendix 1).

Table 3. Success rate for SAI outcome determination using video sent from subjects

Cohort #	STYDY															Cohort Overall
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	≥15	
1	N/A	99	99	99	N/A	100	99	97	N/A	99	100	98	N/A	99	99	99
2	93	100	N/A	N/A	N/A	92	100	N/A	100	100	100	N/A	N/A	N/A	N/A	98
3	100	100	N/A	96	100	100	N/A	N/A	N/A	100	95	N/A	N/A	N/A	N/A	98
4	100	100	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	100	100	100	100	100
5	95	98	100	100	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	97	100	100	99
6	83[a]	91	95	93	97	91	89[a]	90	94	92	93	95	91	93	95	93
7	N/A	N/A	100	N/A	100	N/A	100	N/A	100	100	N/A	100	100	100	100	100

8	0[a]	92	92	94	97	96	94	97	98	97	94	97	99	97	97	93
9	N/A	N/A	87[a]	91	98	96	93	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	93
10	N/A	N/A	N/A	100	98	100	100	100	N/A	N/A	100	N/A	N/A	N/A	N/A	100
11	N/A	N/A	N/A	N/A	100	96	98	89[a]	96	N/A	N/A	79[a]	N/A	N/A	N/A	93
12	N/A	100	100	100	N/A	N/A	N/A	100	100	100	100	96	100	98	100	99
13	100	100	94	100	100	100	100	100	100	98	100	100	100	98	99	99
14	N/A	100	100	N/A	100	100	N/A	100	100	N/A	100	N/A	N/A	N/A	N/A	100
By STYDY	66	96	96	96	97	97	96	95	98	97	98	96	97	97	98	

All data is presented as a proportion of Verified Dosing (VD) with the decimal point discarded and expressed as an integer(i.e., Success Rate(SR)). SR(%) = (VD events / planned SAIs in each STYDY) * 100. N/A indicates days when SAI was not performed.

[a]Success rate is less than 90%

SAI, Self-Administration of the Investigational Product; STYDY, the planned study day with the first dose day equal to 1

Trends in dosing time deviations over time by cohort

The analysis of dosing time deviation (PADEV) across cohorts aimed to determine whether the trends observed during the initial dosing period were consistent with those observed during subsequent periods and whether these trends were maintained within each cohort.

Cohort 10 had the fastest mean PADEV during the initial period at -29.6 ± 65.8 minutes, and this trend remained consistent in subsequent periods, with a mean deviation of -27.2 ± 65.9 minutes. Similarly, cohort 8 had the slowest mean PADEV of 24.0 ± 50.5 minutes during the initial period and maintained a similar pattern thereafter with a deviation of 27.6 ± 53.1 minutes.

A trend toward delayed dosing was observed in cohorts 1, 2, 6, 8, 12 and 14, especially during the initial period. For example, cohort 1 had a mean deviation of 5.0 ± 44.0 minutes in the initial period, with subsequent deviations ranging from 1.9 ± 38.9 minutes to 14.8 ± 39.5 minutes. cohort 6 had an initial mean deviation of 11.3 ± 49.9 minutes, which increased to 21.5 ± 54.5 minutes in the second half.

Conversely, cohorts 3, 4, 5, 7, 9, 10, 11, and 13 tended to dose earlier than the planned time, and this trend was maintained over time. For example, cohort 3 had an initial mean deviation of -6.3 ± 27.8 minutes, which was followed by a deviation of -2.7 ± 27.5 minutes. cohort 7 had an initial deviation of -14.3 ± 30.9 minutes and remained at the same deviation of -8.3 ± 32.4 minutes afterward(Figure 2, Multimedia Appendix 2).

Tests of comparison between initial and subsequent dosing days showed no significant differences in dosing time deviations for most cohorts. However, significant differences ($P < .05$) were observed on 13 of 79 days (16%), indicating occasional deviations from the initial trend(Table 4). For example, cohort 12 had a significant difference on day 8 with a mean deviation of -13.3 ± 17.1 minutes compared to 1.8 ± 23.0 minutes in the initial period. The detailed results of the analysis are presented in Multimedia Appendix2.

Table 4. STYDY with a significant difference in mean PADEV from the reference period (the first 3 SAI days)

Cohort #	Proportion (%)[a]
1	0 (0/8)
2	0 (0/4)
3	25 (1/4)
4	0 (0/3)
5	0 (0/4)
6	40 (4/10)
7	0 (0/6)
8	9 (1/11)
9	0 (0/1)
10	67 (2/3)
11	0 (0/1)
12	13 (1/8)
13	25 (3/12)
14	0 (0/4)
Number of days with significant mean difference	13/ 79 (16%)

[a] Number of STYDYs with a statistically significant mean difference in PADEV from the reference period / Total number of STYDYs with planned SAI excluding the reference period
PADEV, deviation between planned and actual dosing time; SAI, Self-Administration of the Investigational Product; STYDY, the planned study day with the first dose day equal to 1

Trends in medication time deviations by push notification type

The cohorts could be categorized into three types based on their push notification strategies: Type 1 (DN only), Type 2 (both DN and DR), and Type 3 (no push notifications). The results by category are summarized in Table 5 and Figure 3.

For cohorts that received DN only (Type 1), which included cohorts 9, 10, and 11 with a total of 525 SAI data points, the average PADEV was -24.9 ± 63.0 minutes. This indicates a tendency to administer doses earlier than planned when only notifications were used.

The cohorts that received both DN and DR (Type 2), including cohorts 1, 5, 7, 12, 13, and 14, excluding cohorts 6 and 8 due to powder formulation, with a total of 11,297 SAI data points, had an average PADEV of -3.5 ± 31.3 minutes. This smaller deviation suggests that the combination of notifications and reminders was more effective in ensuring compliance to the planned dosing schedule.

The cohorts with no push notifications (Type 3), including cohorts 2, 3, and 4 with 639 SAI data points, showed an average PADEV of -1.3 ± 32.2 minutes. Despite the lack of notifications, these cohorts also maintained relatively small deviations, similar to Type 2.

Table 5. Distribution of the difference between planned and actual dosing time (PADEV) by push notification type and day

Distribution by STYDY	Type1 ;DN only (n=525)	Type2 ;DN + DR (n=11,297)	Type3 ;No DN/DR (n=639)
	Mean ± SD (min)		
1	N/A	-7.5 ± 28.0	-11.9 ± 27.2
2	N/A	-1.1 ± 26.4	0.4 ± 43.7
3	N/A	-2.8 ± 24.1	N/A
4	-39.5 ± 65.2	5.8 ± 48.3	-1.2 ± 29.3
5	-21.8 ± 60.0	-6.8 ± 19.9	-9.3 ± 26.3
6	-20.5 ± 63.1	0.6 ± 23.2	3.6 ± 50.9
7	-23.4 ± 66.9	-1.0 ± 33.0	8.7 ± 48.6
8	6.9 ± 67.0	3.9 ± 34.3	N/A
9	-27.4 ± 35.4	-2.6 ± 24.5	7.2 ± 16.0
10	N/A	-1.0 ± 22.9	2.4 ± 20.6
11	-59.4 ± 47.0	0.0 ± 27.3	9.2 ± 30.1
12	N/A	2.9 ± 42.9	5.9 ± 33.6
13	N/A	-3.9 ± 22.1	-5.5 ± 21.6
14	N/A	3.3 ± 36.8	7.1 ± 44.2
≥15	N/A	-4.5 ± 31.2	-3.1 ± 25.1
Total period *(P-value)*	-24.9 ± 63.0	-3.5 ± 31.3 (vs Type 1: <.001)	-1.3 ± 32.2 (vs Type 1: <.001) (vs Type 2: .09)

STYDY, the planned study day with the first dose day equal to 1; DN, dosing notification before the planned dosing time, DR, dosing reminder after the planned dosing time; SD, Standard Deviation

N/A indicates no corresponding data exists

Discussion

Principal Findings

This study evaluated the VSMS in the context of a repeated-dose PK study in healthy volunteers. Across the study cohort utilizing the system, the SR for reliable data acquisition of SAI events (VD)

was 97%, with 99% of these occurring within the allowed dosing window (VOD). Based on this performance, it was also possible to explore subjects' SAI behavior patterns when using the VSMS. The results showed that SAI behavioral trends observed in the early days of SAI were maintained in later periods, and that there were significant differences in SAI behavior patterns based on the settings of the push notifications.

The high level of SR recorded in this study indicates that the three essential requirements of VSMS were met. 1) technical reliability: the system operated without significant technical errors, ensuring that data capture and processing was accurate and reliable, 2) subject acceptability: participants were able to use the mobile-based application without difficulty, which is critical to maintaining high levels of compliance in clinical trials, 3) comprehensiveness for investigators: the system provided sufficient information in an appropriate manner to enable investigators to make informed decisions regarding the validation of SAI. Along with the intuitive user interface, user acceptability can be attributed in part to the initial training during the first visit, including a mock SAI session.

Although the system was asynchronous, the fact that the investigator was able to monitor video uploads in real-time during the dosing time window probably contributed to the fact that the majority of VDs were VODs. Deviated dosing could have been minimized by contacting participants who did not perform SAI by phone within the dosing time window.

While adherence is a common consideration in late-stage clinical trials, this concept does not enforce completion of all planned doses on time; therefore, how individual doses are assessed and recorded was not a primary concern, and the need for a system to obtain such specific data was not emphasized. In contrast, in a repeated-dose PK study, all actual dosing must be completed at the planned dosing time to accurately assess the PK characteristics of the steady state. In this setting, it is critical that the investigator witnesses and records the time of IP administration. VSMS provided the investigators with reliable dosing evidence even when subjects were not present at the study site, demonstrating that SAI is feasible in such studies. In addition, an outcome classification scheme

(VOD, VDD, UD, MD) that takes into account the various situations that can occur with SAI was presented, ensuring that all dosing behavior were appropriately categorized. Ultimately, the overall procedures and results demonstrate that VSMS has the potential to reduce direct costs by reducing the number of visits for subjects, while also reducing dropouts due to failed visits[6, 26,27].

The study observed that SAI behaviors established early in the trial were generally maintained throughout the study period. Only 16% of events showed statistically significant differences in dosing times compared to the initial SAI events. In the DN-only cohort, subjects tended to perform SAIs earlier than planned compared to the cohort with both DN and DR or the cohort without push notifications. While there was no statistically significant difference in the mean deviation between the cohort with both DN and DR and the cohort without push notifications, there was a more consistent trend in the variability or dispersion of daily deviations in the cohort with both DN and DR compared to the cohort without push notifications. Although push notifications were pre-set and remained constant throughout the study period in the cohorts included in these studies, given the nature of SAI behavior and the impact of push notifications, it is possible that better compliance could be achieved by adjusting push notifications based on the initial SAI pattern of the cohort.

Limitations

A notable limitation of this study is its retrospective design and the relatively small number of cohorts, which limits the generalizability of the findings. To reach more robust conclusions, the results must be validated through larger and more diverse cohorts. Moreover, prospective studies are necessary to provide higher-quality evidence of the system's generalizability and effectiveness.

Conclusions

The VSMS demonstrated potential as a useful tool for investigators in early clinical trials in healthy volunteers, offering the ability to remotely observe and monitor SAIs in real-time, evaluate them, and

confirm their status as valid IP administration. Furthermore, the system provided the opportunity to control subject SAI behavior through the use of appropriate push notifications and subject communication. These features could contribute to further improving the added value of clinical trials while ensuring compliant dosing with appropriate quality evidence in early phase trials where dosing records are critical. Such a system could be particularly useful in studies that require multiple doses per day, or where dosing must be maintained over an extended period of time. As additional data is obtained and experience is gained, the scope of use of VSMS is expected to continue to expand.

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Conflicts of Interest

none declared.

Abbreviations

ATIME: investigator-confirmed actual dosing time

DN: Dosing Notification before the planned dosing time

DR: Dosing Reminder after the planned dosing time

IP: Investigational Product

MD: Missed Dosing

PADEV: deviation between planned and actual dosing time

PK: pharmacokinetics

PTIME: planned dosing time

SAI: Self-Administration of the Investigational Product

SAIDC: The investigator's final decision on SAIs

SD: Standard Deviation

SR: Success Rate

STYDY: the planned study day with the first dose day equal to 1

UD: Unverified Dosing

VD: Validated dosing

VDD: Verified Deviated Dosing

VOD: Verified On-time Dosing

VSMS: video-based SAI monitoring system

Multimedia Appendix 1

The proportion of SAI outcome by category

Multimedia Appendix 2

Daily PADEV distribution and Statistical analysis results

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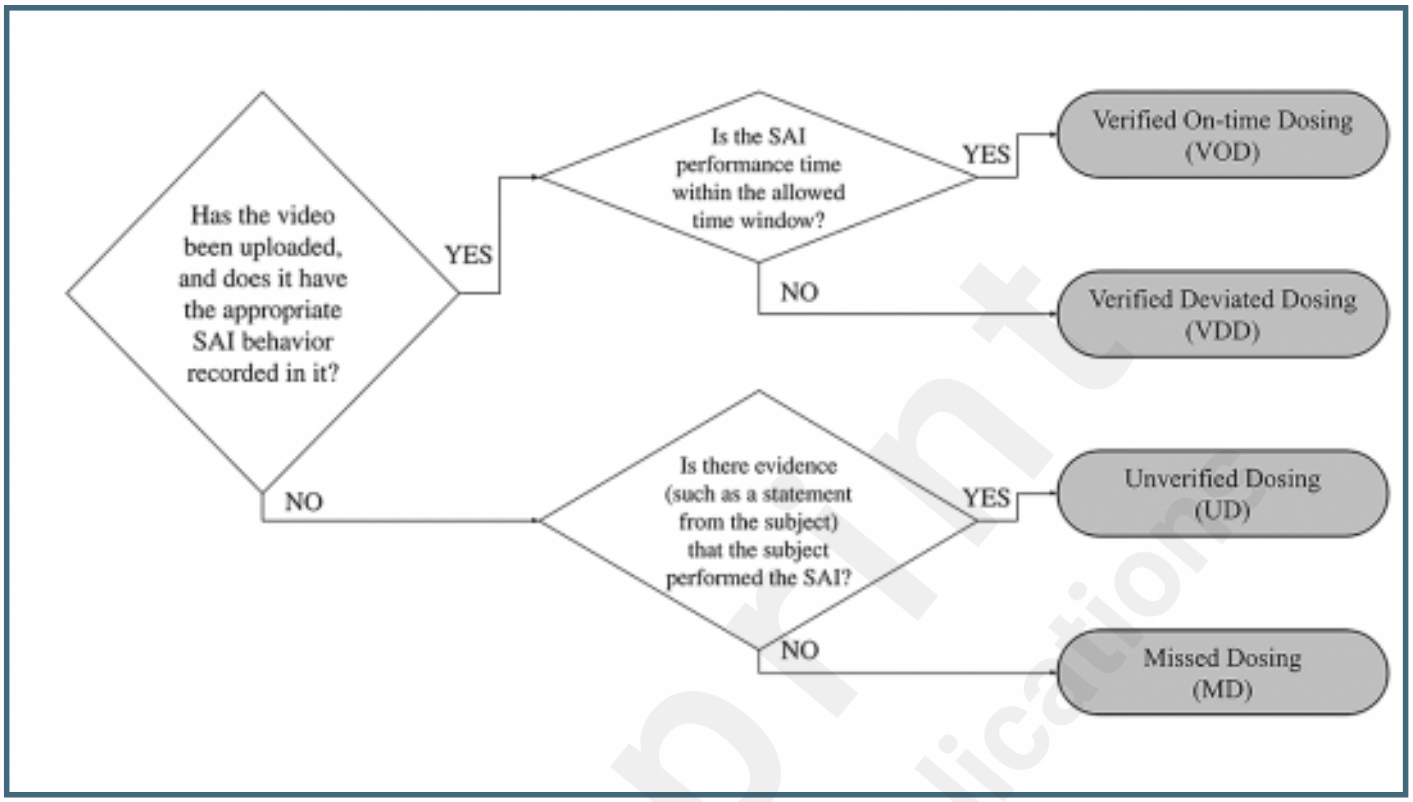
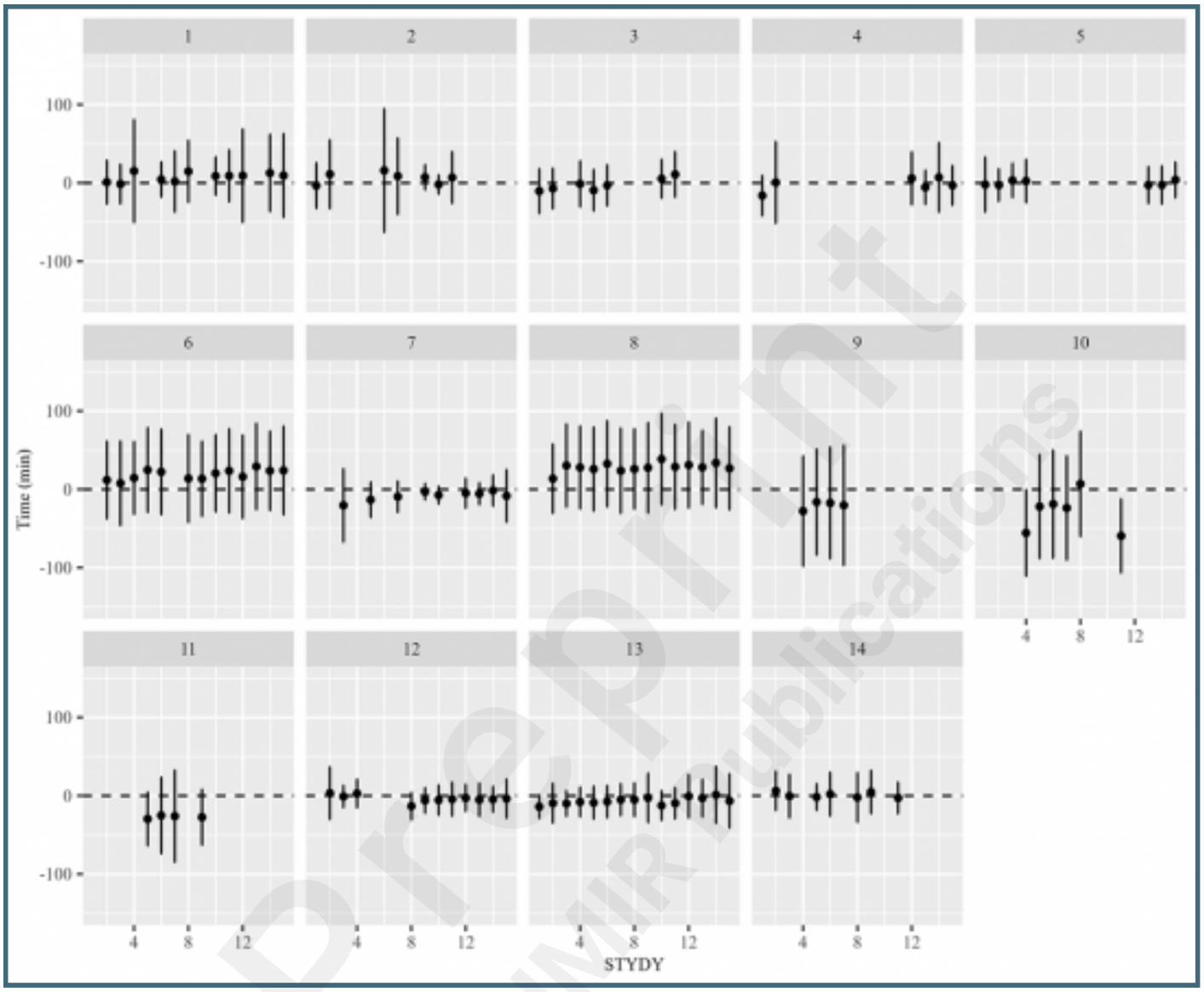
Supplementary Files

Figures

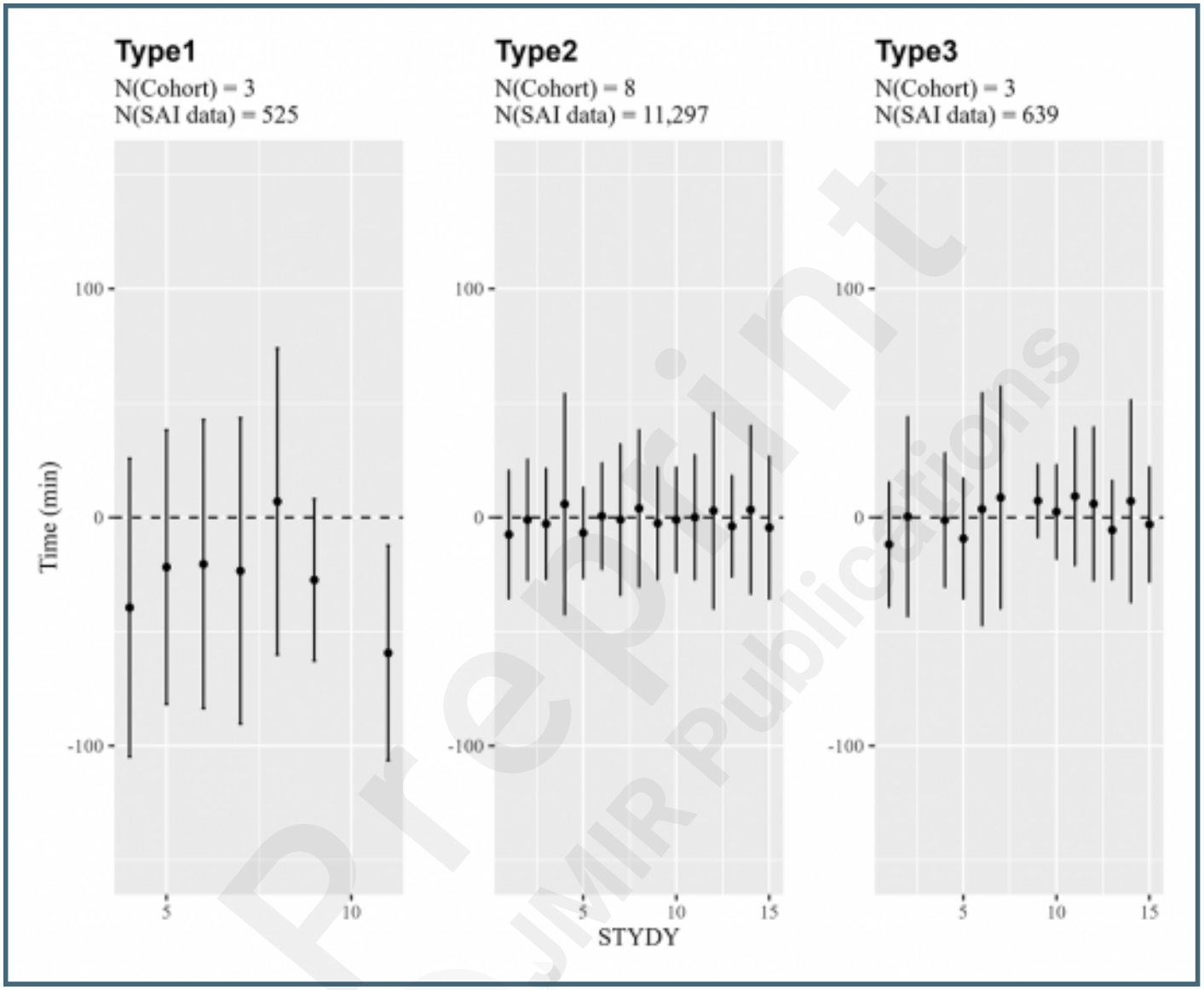
Decision tree for assisting investigators in SAI category confirmation. SAI, Self-Administration of the Investigational Product.



Distribution of the Mean PADEV by STYDY in each cohort. PADEV, deviation between planned and actual dosing time; STYDY, the planned study day with the first dose day equal to 1.



Distribution of the Mean PADEV by STYDY in each push notification type. Type 1 (DN only), Type 2 (both DN and DR), and Type 3 (no push notifications). PADEV, deviation between planned and actual dosing time; STYDY, the planned study day with the first dose day equal to 1; DN, Dosing Notification before the planned dosing time; DR, Dosing Reminder after the planned dosing time.



Multimedia Appendixes

All data is presented as a detailed proportion of SAI outcome with the decimal point discarded and expressed as an integer. VOD, Verified On-time Dosing ; VDD, Verified Deviated Dosing ; UD, unverified dosing; MD, missed dosing; SAI, Self-Administration of the Investigational Product; STYDY, the planned study day with the first dose day equal to 1.
URL: http://asset.jmir.pub/assets/f995516a42f4c8ba0e8088d26a549cc3.xlsx

a:The first three STYDYs in which SAIs were performed. b:Statistical Analysis was performed to see the mean difference from reference STYDY. SAI, Self-Administration of the Investigational Product; STYDY, the planned study day with the first dose day equal to 1.
URL: http://asset.jmir.pub/assets/5cda45d699798c810ceed5a28d5f7f12.xlsx