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Rooibos™: Automated schedule broadcast software for clinical pharmacology studies

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Pharmacokinetic blood sampling is a prerequisite for successful early clinical trials. It is essential to take samples at the precise designated times to ensure the reliability of the clinical trial data; however, investigators have encountered difficulties in conducting procedures with limited manpower. We have recently developed automated schedule broadcast software (Rooibos™) to manage the precise scheduling of procedures for clinical trial centers. Rooibos™ is platform independent because it is programmed in the Java language. It generates scheduled times based on a reference time. It alarms at the scheduled times and pages subjects and alerts staff to prepare for the upcoming procedures. Rooibos™ can also group subjects when multiple clinical trials are conducted simultaneously in one or more clinical trial wards. This software may be applied to any study involving procedures that must be performed at designated times.

Introduction

A clinical trial is defined as any investigation in human subjects intended to discover or verify the effects, adverse reactions and pharmacokinetics (PK) of investigational products.[1] Every clinical trial has a protocol, or action plan, for conducting the trial. The plan describes what will be done in the study, how it will be conducted, and why each part of the study is necessary.[2]

Clinical pharmacology is the study of the pharmacokinetics and pharmacodynamics of a drug's effect on humans. PK studies are intended to define the time course of a drug and, where appropriate, its major metabolite concentrations in blood and other body compartments.[3] These studies should be performed according to procedural directions at precise times to ensure high reliability. When both PK and pharmacodynamic (PD) data are to be obtained during a clinical pharmacology study, the sampling strategy should be optimized for both PK and PD measures.[4] The blood draws for pharmacokinetic samples should take priority over all other activities and should occur at the scheduled time point before any other procedure.[5]

In general, clinical pharmacology research is designed for the analysis of multiple blood samples acquired over time. During PK sampling, there are typically heavy workloads and busy workflows for investigators to conduct all treatments within a limited time. There could also be timing errors when investigators read time visually on a clock. These factors may cause time-deviation, decreasing the accuracy of the study. To perform the intended procedures (such as blood draws, vital sign measurements, and so on) at the desired times, both investigators and subjects should prepare in advance for upcoming procedures.

Although clinical trials have adopted information technologies (IT) for study planning, patient management, data analysis and so on, there has as yet been no IT solution to support conducting clinical pharmacology studies. We have recently developed automated schedule broadcast software, Rooibos™, to assist in the timely performance of clinical pharmacology procedures in studies. This article briefly introduces the development process and functions of Rooibos™.

Methods

Environments

Rooibos™ is written in the Java programming language. It utilizes many of the library functions in Java 1.8.0, including the Java Advanced Windows Toolkit (AWT) and Java Swing, to provide a common Graphical User Interface (GUI). The Java programming language is a multi-platform language that enables binary Java byte codes to run on various operating systems with JVM (Java Virtual Machine).[6] To run Rooibos™ on Linux or Windows operating system, JVM and a sound system are required, as shown in Figure 1. We have developed and tested Rooibos™ on Windows 7 32 bits.

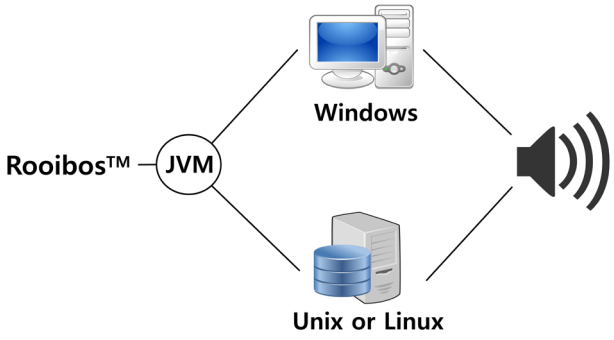

Figure 1. System Configuration.

Input Setting

Rooibos™ was designed to reflect the actual process of clinical trials. Subject, group, reference time, interval, schedules, and announcement time for subject paging and preparation were carefully selected as input values (see Fig. 2).

"Subject" is a range of subject numbers for clinical trials. "Interval" is an interval of reference time between a subject and the next subject. "Group" in the people icon at the top is used to assign each subject to a group. "Calling" is the paging time for a subject to return to the nurses' station. The "Calling" function can be disabled by unchecking if the procedure is to be performed on a bed. "Preparing" is the alert time for the clinical investigator to prepare for the procedure. When "Preparing" is checked, the counting function is automatically activated to broadcast the countdown time 5 seconds before the scheduled time. "Reference Time" is the starting time when the first subject, namely subject number 1, undergoes a procedure. Reference time is usually the dosing time. "Schedules" is a table for each blood sample setting. The columns "Hour" and "Min" are collecting times based on the reference time. Therefore, the first row, "0.0 : 0", indicates a reference time. The column "Group" in the "Schedules" table is used to select a group for the sample collecting time. The column "Calling(min)" is used to set calling time specifically for the sample collecting time. With all these input values, the calculated scheduled times appear in the scheduled time table on the right.

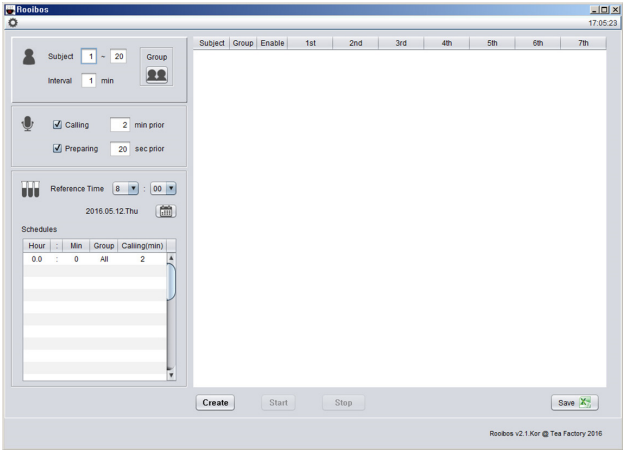

Figure 2. Main window of Rooibos™.

Schema and algorithm

Rooibos™ consists of 4 functional parts: Scheduler, Time Synchronization, Search, and Broadcast (see Fig. 3). Scheduler is used to make, show, edit, and save all scheduled times. Time Synchronization synchronizes the internal clock of the software with the operating system (OS) clock. Search is used to search for a scheduled time with respect to the current time. Broadcast sends the appropriate sound to the speaker.

As shown in Figure 4, Rooibos™ receives input values through user typing or reading a file through the GUI and checks whether the input values are valid. When an investigator clicks the "Create" button, Scheduler generates the scheduled times based on the input values and displays them on screen. When the "Start" button is clicked, Rooibos™ searches the current time in the scheduled times database every second until all scheduled times are broadcasted.

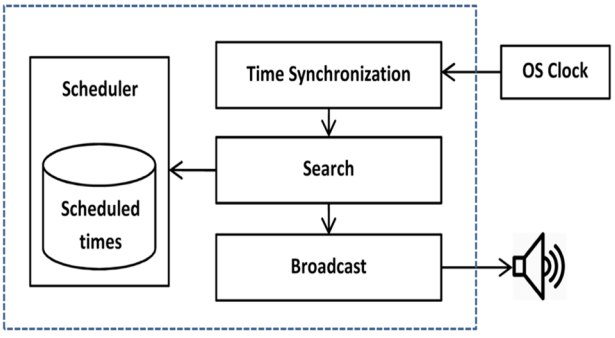

Figure 3. Schematic representation of Rooibos™.

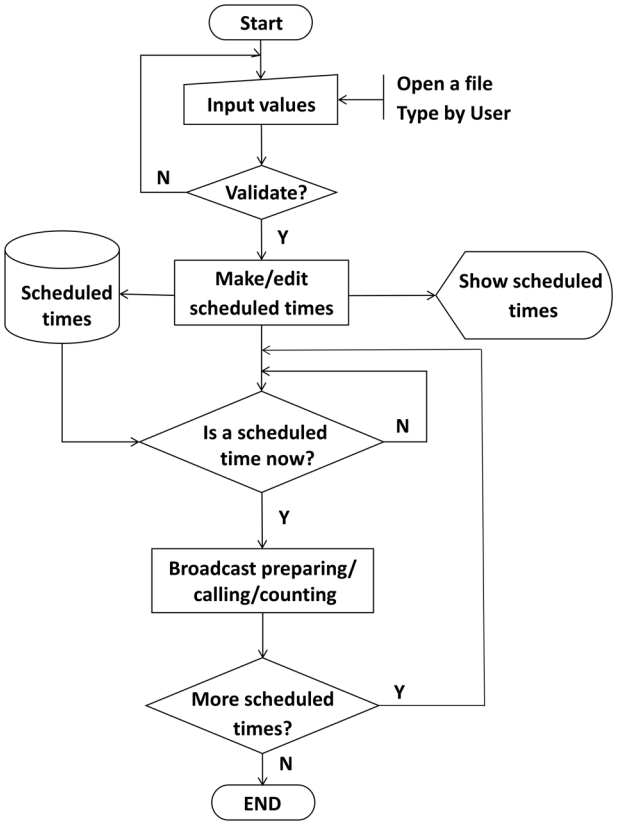

Figure 4. Rooibos™ algorithm.

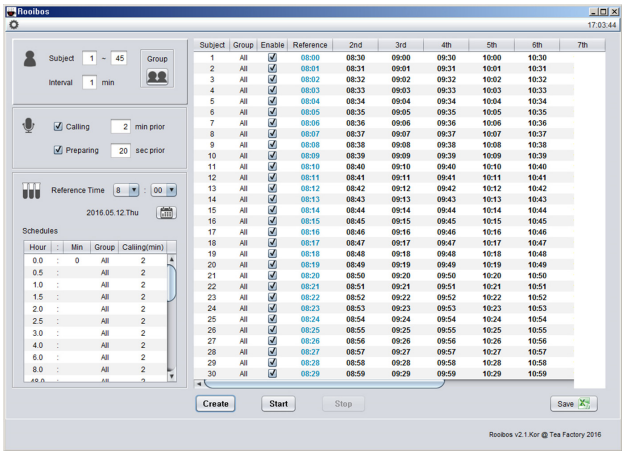

Figure 5. Schedule setting example for one group.

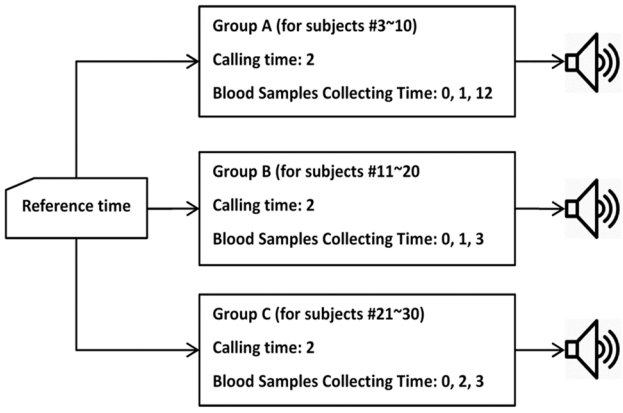

Figure 6. Multi-group schema.

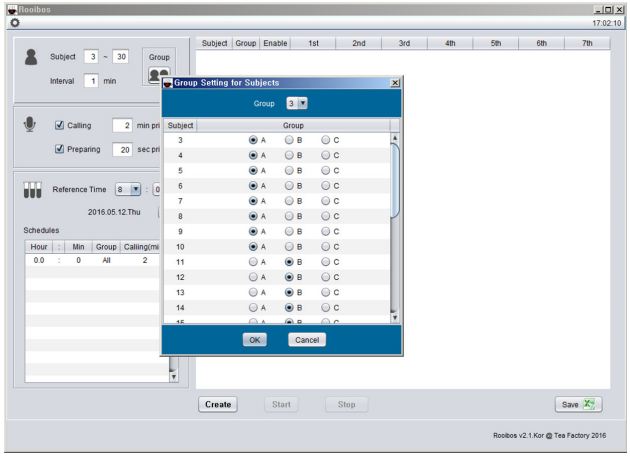

Figure 7. Group selection.

RESULTS

Application to clinical trials

Rooibos™ has been developed based on the above schema and algorithm. An example is shown in Figure 5: our previous clinical study, conducted as a 2x2 crossover design. Blood samples were collected before dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72 and 96 hours after oral administration.[7]

These blood sample collecting times, including the dosing time, are set in the schedule table located on the left side. All scheduled times, calculated from the schedule table, are shown in the columns of scheduled time table on the right side. The first row of the schedule table is matched to the column "Reference", and the second row is matched to the column "2nd" of the scheduled time table.

If there are two or more clinical trials, each clinical trial can be set as a group. For example, Figure 6 shows a clinical trials plan for three groups. "Reference time" and subject number 1 are global values to maintain consistency for all groups. In Figure 7, subjects are assigned to three groups from the plan in Figure 6. If all subjects are assigned to the three groups, each row of the "Group" column in "Schedules" table shows a checkbox to select groups, enabling broadcast to call the selected groups at each sample collecting time (see Fig. 8). After clicking the button "Create", scheduled times are shown on the scheduled time table

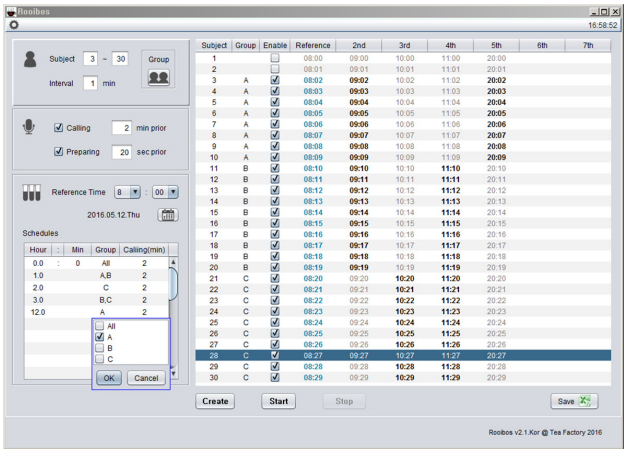

Figure 8. Schedule setting example for multiple groups.

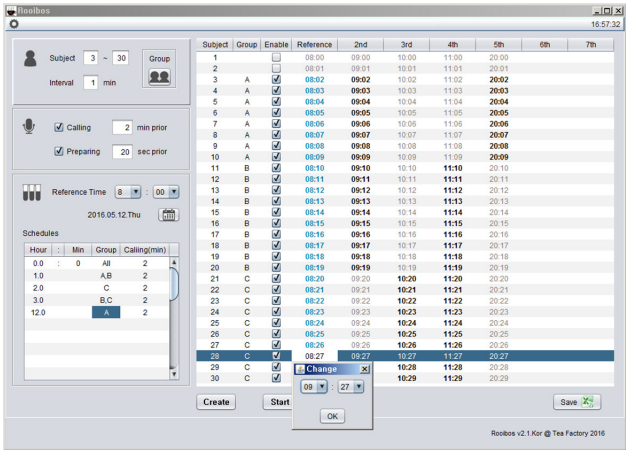

Figure 9. Changing a reference time.

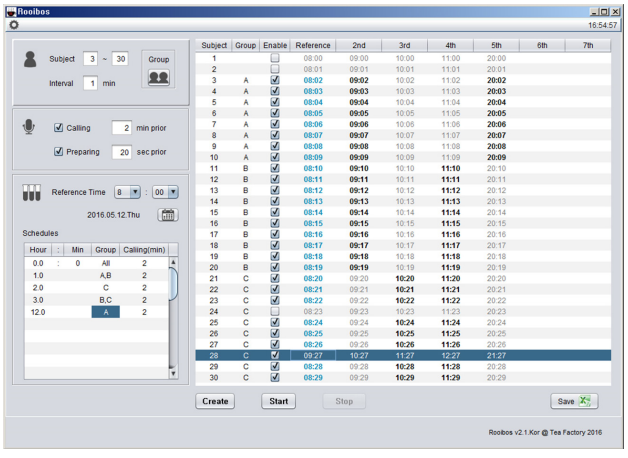

Figure 10. Disabling broadcast of a subject.

on the right. The reference time for each subject is shown in sky blue in the "Reference" column. Because the subject number ranges from 3 to 30, the two rows for subject number 1 and 2 are in gray, which means uneditable and disabled. Broadcast would then start from subject number 3.

If the dosing time of a subject is delayed, the reference time for the subject should be changed as shown for subject number 28 in Figure 9. When a reference time is changed, other scheduled times on the same row are changed automatically in relation to it. Additionally, if a subject is dropped from the clinical trial, all scheduled times for the subject can be disabled by unchecking the check box on the subject's row: see Figure 10, where all scheduled times for subject number 24 are disabled.

Run

When "Create" is clicked, the scheduled times for the clinical trial are generated in the scheduled time table on the right side. When "Start" is clicked, Rooibos™ starts to search the scheduled times against the current time every second to determine whether to broadcast preparing, calling, or counting for a scheduled time. Figure 11 shows the broadcast action in text. For the

08:00:05	**Calling Number 3, please come to a station.**
08:01:05	**Calling Number 4, please come to a station.**
08:01:40	**Preparing for Number 3.**
08:01:55	**55**
08:01:56	**56**
08:01:57	**57**
08:01:58	**58**
08:01:59	**59**
08:02:00	**BEEP**
08:02:05	**Calling Number 5, please come to station.**
	...
08:20:05	**Calling Number 23, please come to station.**
08:20:40	**Prepare for Number 22.**
08:20:55	**55**
08:20:57	**57**
08:20:58	**58**
08:20:59	**59**
08:21:00	**BEEP**
08:21:40	**Prepare for Number 23.**
08:21:55	**55**
08:21:56	**56**
08:21:57	**57**
08:21:58	**58**
08:21:59	**59**
08:22:00	**BEEP**
08:22:05	**Calling Number 25, please come to station.**

Figure 11. Broadcast action in text.

first scheduled time, "8:02 AM", the calling broadcast would be played automatically approximately 2 minutes before, saying, "Calling Number 3, please come to the nurses' station". At 20 seconds before 8:02 AM, the preparing broadcast for subject number 3 would be played, which says "Preparing for Number 3", and at 5 seconds before 8:02 AM, count down would begin, saying "55, 56, 57, 58, 59, BEEP". For subject 24, neither calling nor preparing would be played because it is disabled. All scheduled times can be exported to Excel files, and the settings can be saved for future use.

Discussion

In this paper, we have demonstrated how Rooibos™ can assist the process of automated schedule broadcasting for managing clinical pharmacology studies.

There are several clinical trial management solution (CTMS) systems available to the public. These CTMS systems have functions such as study planning, site engagement, patient engagement, study conduct, management, and data analysis. However, these CTMS systems focus on research management from a sponsor perspective, and do not include functions to control or direct a study systematically for clinical trials.

Rooibos™ has been developed to improve the reliability of clinical trials by increasing their accuracy and decreasing the investigator workload. It has the following features:

1. Broadcasts countdown time to conduct procedures at an exact scheduled time.
2. Broadcasts the relevant subject's number to report to the nurses' station by each scheduled time.
3. Broadcasts the relevant subject's number to prepare for the procedure.
4. Eliminates space limitations: Rooibos™ can manage several clinical trials in one space or manage subjects in separate rooms.

In particular, Rooibos™ is useful for a study, such as a bioequivalence test, that involves timing performance of procedures such as blood sampling for many subjects at the same time. Implementing Rooibos™ can help to collect blood samples precisely on schedule. If a study includes a large number of participants, Rooibos™ can help to manage all subjects as one group or separate groups. If several studies are in progress in one room at the same time, Rooibos™ helps to manage the tests by grouping the subjects.

Additionally, because it is programmed in the Java language, Rooibos™ can be installed without extra cost on any platform. After implementing Rooibos™, the process of conducting clinical trials is managed systematically, and researchers can focus more on procedures than on constantly checking a timer or clock.

This software can be applied to any study involving procedures that must be performed at designated times.

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Conflict of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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