A randomization and trial supply management system for adaptive clinical studies of TCM and its scientific research application in recurrent tuberculosis.

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Abstract — In recent years, a growing number of dynamic, double-blind and randomized trials for traditional Chinese medicine (TCM) have been designed with adaptive treatment regimens. The blind envelope or current randomization and trial supply management (RTSM) system have not met this requirement. Therefore, a more efficient platform for subject randomization and medicine dispensation was required. After we had done much research on dynamic TCM treatment trials' protocols, a new RTSM was designed and developed, which is suitable for TCM clinical trial during randomizing the groups for subject and medicine allocation in China. In a recurrent tuberculosis study of TCM, this RTSM system was involved in the management of subjects and medicines. By this system, a suit of TCM formulas or placeboes were assigned to patients based on their TCM syndrome diagnosis results by investigators at different visit points. The new RTSM system was convenient to operate, reduced operational errors, enhanced the management efficiency, and improved the data quality.

Keywords — randomization, trial supply management, traditional Chinese medicine, recurrent tuberculosis, adaptive treatment regimens

I. Background

In recent years, a growing number of dynamic, double-blind and randomized trials for Traditional Chinese Medicine (TCM) have been applied, in which the subjects are assigned to adaptive treatment regimens based on the TCM syndrome diagnosis results obtained at different visit points. Therefore, this type of clinical trials was complicated because of the changeable treatment regimen.

In general, randomized controlled trials (RCTs) should be designed using methods to randomly distribute subjects to different groups in order to minimize bias and balance potentially recognizable or unrecognizable confounders[1]. The traditional method uses a series of sealed envelopes containing the treatment information, so researchers could simply follow the numbers hidden inside the envelopes to assign different interventions and/or a placebo[2]. However, it is impossible to manipulate an adaptive trial using sealed envelopes because nobody can predict the subjects' disease process and predict all of the interventions in advance to place in the envelopes. In order to support these complex clinical trials design, a computer platform is required and it should allow researchers to modify the TCM treatment regimens based on changes in the TCM syndrome diagnosis at different consecutive visit points.

Thus, the best choice might be using a randomization and trial supply management (RTSM) system to manage subjects and medicines[3]. A parameter-driven RTSM can support a study "out of the box" by selecting or entering information regarding the visit schedule, treatment arms, dosing, etc. [4]. A list of random numbers or medicine numbers is entered into the RTSM and a random allocation algorithm is programmed before the first subject is enrolled. When the study is running, researchers can follow the patient enrollment process and the distribution of medicines by using the RTSM.

At present, even some existed clinical trials management systems used in China could support subject screening, random allocation, medicine dispensation, visit scheduling,

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and trial analytical reporting [5,6], they still couldn't allow the adjustment of therapeutic regimen functions, which is needed in dynamic TCM treatment studies. Therefore, we aimed to develop a new RTSM system which could support the complex study design of TCM, and it could be more effective and easier to access than current systems. Then, we describe the requirement analysis, infrastructure and key modules' design of the RTSM system. Furthermore, we gave a true example trial of TCM to explain how did the system work, and explained some challenges that we faced when using this system.

II. System Requirements

After we discussed with investigators and studied on some dynamic TCM treatment trials' protocols, the system requirements of RTSM were demanded. The RTSM system should cover the whole of the study process, including randomization, blind supplying and resupplying management to depots and sites, and drug dispensing. The functional reliability for supervising/controlling the trial procedure is explained as follows.

- The system checklist included inclusion and exclusion criteria for all subjects, and it notified researchers if any subject was ineligible.
- The system supported sampling, blocking, stratification, minimization and dynamic block algorithms.
- Researchers completed the TCM syndrome diagnosis during the first visit and entered the results into the system. The system randomly allocated a subject to a subgroup and generated the first numbers of treatments for the subject.
- A window was showed during the specific visit point or points up to different trial's protocol so researchers could answer questions about the TCM syndrome diagnosis results. Subsequently, the researchers received a new medicine number generated according to the diagnosis results.
- Whenever a subject dropped out of the study, the researchers updated the records for the subject's status in the system automatically.
- The system supported medicine resupplying, dosing and regimen adjustment, calling back medicines, and other procedures.
- The reporting modules automatically generated reports about subject enrollment, medicine consumption, and other details to help the principal investigator (PI) supervise the overall study.
- The system could restrict different levels of authorities for different end users, and a user could only access the data with permission.
- Two access methods were provided: web or telephone. The logical process for these two methods was the same, but the former one required an interactive web response and the latter one required an inter active voice response (IVR).
- The system supported multiple tasks, especially for IVR, and less than 16 users could call simultaneously.

III. Implementation

A. The system infrastructure

The RTSM system consisted of a web server, IVR server, email server, short message service (SMS) server, application server, and database server. End users could access the RTSM system by computer or telephone and receive feedback via email, fax, and SMS (Fig. 1). The main business functions were provided by a browser/client structure, and users could only employ various types of browser software to visit the RTSM system. In addition, randomization and medicine management functions were redeveloped and deployed on the IVR server based on computer telephony integration technology. The core business process operated on the application server and all of the data were stored in the data server. To ensure data security, the application and data servers were run in the background so they could not be accessed directly via the internet.

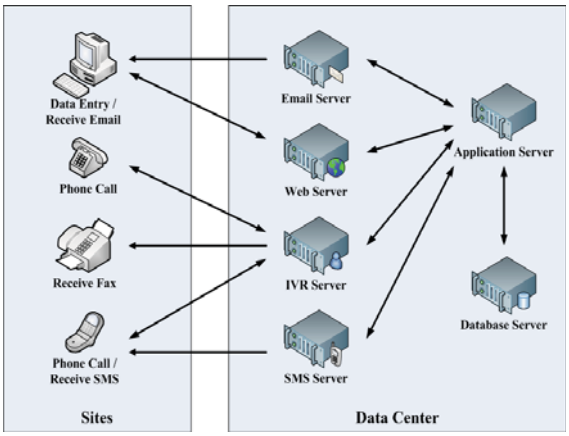


Fig. 1. Topological structure of the RTSM system.

B. Randomization algorithm module

In randomization algorithm module, we provided two methods to generate random numbers: 1) a statistician produced random numbers by SAS and uploaded them into RTSM system; 2) a statistician set up some parameters and the RTSM system created random numbers automatically. The first method just fit for static algorithm, such as blocked or stratified randomization, but the second method not only for static algorithm but also for dynamic random such minimization. Before a trial started, a list of random numbers was produced by SAS or set up by the parameters of RTSM system. After a subject was enrolled, the investigators entered the subject's name initials, date of birth or other special variable into the system. The RTSM system then automatically created a unique ID for the subject with the site ID captured from current investigator's site ID. Next, the random number from this site was assigned as *occupied status* and the subject was assigned as *randomized allocation status*. (Fig. 2)

Various programs can generate random numbers but SAS was chosen to create a list of random numbers because of its wide spread utilization in clinical research. For ethical reasons, the subject identities cannot be collected in clinical trials. However, some information related to each subject must be entered into the system in order to audit clinical data

sources. Hence, only the subject's name initials and date of birth were entered into the RTSM system.

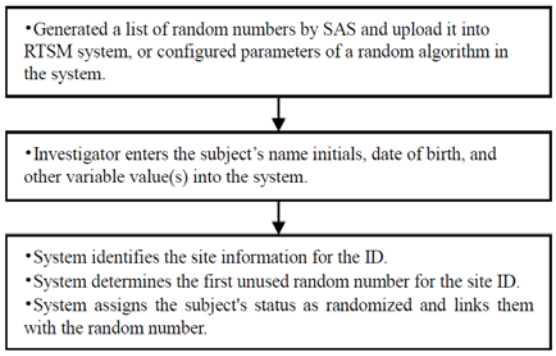


Fig. 2. Flow chart illustrating the subject randomization process.

C. Interview and medicine allocation module

According to a certain study protocol, the maximal amount of drugs for all participants based on drug dispensing visits could be calculated. All drugs were divided into different subgroups for different TCM syndrome diagnoses and interventions. However, due to the changeable TCM diagnosis during the clinical trial, at the beginning of the trial, it was extremely difficult to precisely estimate the dose for each subject. In order to adapt this dynamic intervention design and avoid wasting drugs, users can simply code a part of drugs (eg: 1/2 of all drugs) in advance and import them into the RTSM system.

After a specific type of medicine was delivered to a subject, the system checked the drug inventory at the current site immediately. If the inventory was lower than the limit which was set up in advance by the system, the system generated a drug order form and sent it to the sponsor or the drug depot for the overall study. In addition, while the study was ongoing, we regularly inspected the medicine dispensing records, subject enrollments, and TCM syndrome diagnoses so we could estimate the medicine supply required for the next treatment. (Fig. 3)

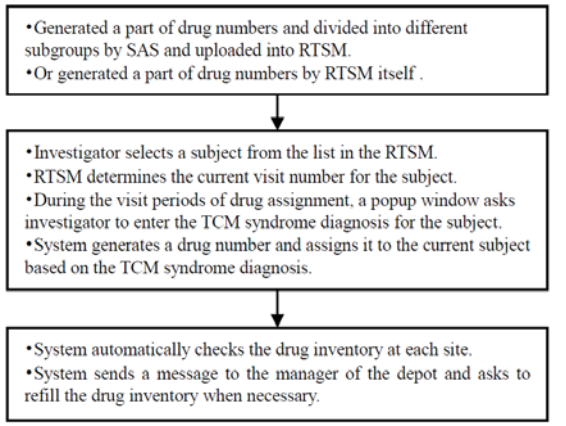


Fig. 3. Flow chart showing the subject interview and drug assignment process.

When a subject was in the interview window period, an investigator selected a subject to visit by entering a subject ID into the RTSM system. During the certain visits of drug assignment, the system automatically displayed a popup window and required investigators to answer a question about the TCM syndrome diagnosis result. Subsequently, the investigators received a new medicine number generated according to the diagnosis results. In the other visit points, the system only recorded the interview information and did not collect the diagnosis data.

D. System frontend

There were two versions for the frontend of the RTSM system: web-page and telephone access versions. The web-page version was developed using ASP.NET and the telephone access version was developed with a third-party commercial platform based on computer telephony integration. The backend of the RTSM system was developed in Microsoft SQL Server 2008 with core function modules prepared using database store procedures. Hence, different versions of the frontend could share the same business process. The RTSM system would popup a window in the web-page version as well as voice navigation for the telephone access version to allow entry of the TCM syndrome diagnosis during the predefined visits. Fig.4 was an example of how entry the TCM syndrome in the popup window for a subject, and in the main window, there were a list of subjects which shown the ID, date of birth, gender, current status, screen date, random date, random number, the last drug assignment number, investigator and available operations.

Fig. 4. Patient list form and TCM diagnosis form.

In telephone access version, all of the navigation points were linked to voice files. Therefore, we recorded adaptive differential pulse code modulation format voice files (.vox) in a study and uploaded them to the IVR server before the trial started. These voice files included the names of the trial groups, all the drug types, and the questions and the answers obtained during TCM syndrome diagnosis. The subject codes, randomized numbers, and drug codes were generated in real time, and these data could not be recorded as voice files in advance, so text-to-speech was employed to translate them into voice files.

IV. SCIENTIFIC RESEARCH APPLICATION IN RECURRENT TUBERCULOSIS

In 2015, after the RTSM system was developed and tested, a recurrent tuberculosis (TB) study treated by TCM based syndrome diagnosis was established in our RTSM

system. In this study, 812 TB patients from 14 hospitals were enrolled and followed up for 9 months. All these recurrent TB subjects were randomized into two groups, where the trial group were treated with TCM and chemotherapy (traditionalized Western anti-TB medication), and the control group were treated with chemotherapy and TCM placebo. During the first, third, and fifth visits, subjects were re-assessed and diagnosed to detect changes in the TCM syndrome, and physicians could adjust the TCM treatment regimen from time to time based on the diagnosis results. According to previous research, the TCM syndromes inmost recurrent TB patients were *Fei-Yin Deficiency*, *Yin-Deficiency and Fire-Hyperactivity*, and *Qi and Yin Deficiency*. The patients in the trial group with *Fei-Yin Deficiency* were treated with *Nourishing Yin and Moisturizing Lung* Formula Granules (Drug A), as well as *Nourishing Yin to Lessen Fire* Formula Granules (Drug B) for *Yin-Deficiency and Fire-Hyperactivity*, and *Shuang-Bai* Formula Granules (Drug C) for *Qi and Yin Deficiency*. The patients in the control group were given a TCM placebo plus chemotherapy(Fig. 5)

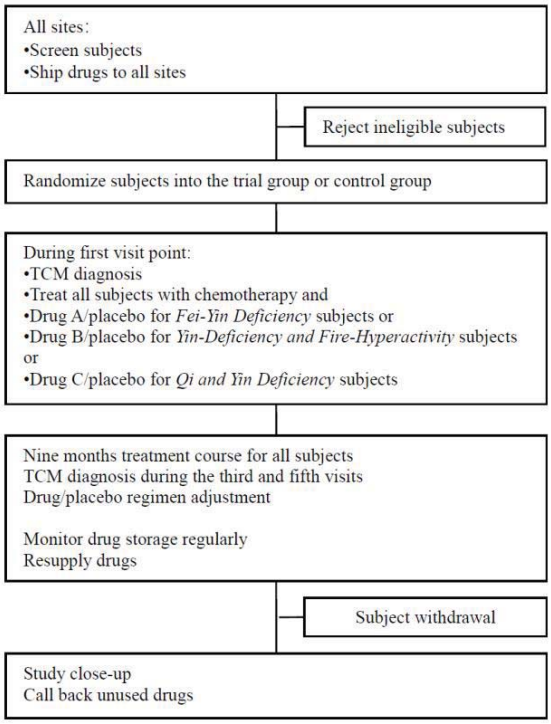
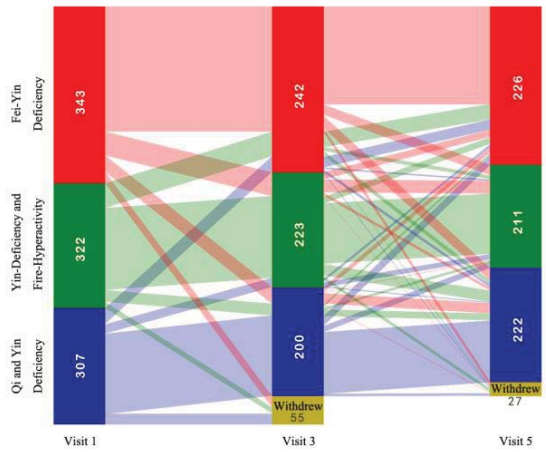


Fig. 5. Flow chart illustrating the recurrent TB study process.

Finally, 811 subjects were enrolled by this study and 2,277 drugs were dispensed to these subjects. In this computer platform, researchers could modify the TCM treatment regimens based on changes in the TCM syndrome diagnosis at three consecutive visit points. The TCM syndrome diagnosis results for the first, third, and fifth visits among the 811 subjects are shown in Fig. 6.



[a] 55 subjects withdrew from the study before visit 3 and 27 subjects before visit 5, so there were not TCM syndrome diagnoses of them.

Fig. 6.TCM syndrome distributions during the first, third, and fifth visits.

V. Discussion

A. Strengths and weaknesses

RCTs rarely use a central system for number randomization management and drug allocation, but a computer system is more efficient and convenient than blind envelopes if the study design is complex[7,8].Computer systems are essential for clinical trials because they can facilitate the balance of treatment groups, eliminate selection bias, increase the predictability of treatment allocations, and manage supplies needed by trials, including minimizing drug wastage via automated site restocking[9].The requirements for changes in drugs based on the TCM syndrome diagnosis during different visits in the present study inspired us to employ the RTSM system to manage subjects, number randomization, and drugs. The RTSM system satisfied the study's requirements after upgrading several modules within a limited time frame. In addition, clinical investigators can utilize the third component (professional organization) rather than designing and developing new software themselves. Table 1 shows the strengths and weaknesses of the RTSM system.

TABLE 1.STRENGTHS AND WEAKNESSES OF USING RTSM SYSTEM FOR CLINICAL RESEARCH.

Strengths	Weaknesses
• The third component and independent technical support team helped to reduce selection bias or other types of bias. • Capacity to support sufficient user numbers and facilitation empirical research. • Convenient to access in various ways such as websites, telephones, and mobile phone. • Complexity of the calculation process reduced. • Modules and functions can be built to support the whole randomization and drug allocation process. • Facilitates the blind assignment process.	• Computerized sites are necessary or other accessible ports such as telephones. • More training must be scheduled for some participants in a trial. • More roles are necessary in a clinical trial, such as technical supporter and system maintainer. • Has risks of system broken, so the risk plan or substitution plan is needed. • Separated from common clinical systems of hospitals, patients' information need to be double entered to RTSM and clinical systems of hospital.

B. Problems and challenges

One of major challenges for the RTSM system was to convert from the conventional blind envelope method to this centralized system for the clinician. Most RCTs are conducted to evaluate the effects of a medicine, so the treatment employs a "one size fits all" approach where a unique random ID number and drug number are assigned for each subject in the trial [10]. However, the aim of some TCM studies was to find the optimum treatment regimen and the investigators could adjust the medicines as the diagnosis changed. Therefore, a central system was employed in this study to manage the subjects and drugs, and all of the users were trained in the use of the RTSM system before participating in these study. We also provided a round the clock telephone hotline and trained a RTSM system assistant from the principal hospital to help the investigators while the trail was ongoing.

Even the Internet is very popular in China, most hospital information systems are separated from the Internet due to concerning information security[11,12].In December 2011, the National Health Commission of China issued guidance on the security level for the protection of information in the healthcare industry, where the key systems (e.g., hospital information system and electronic medical record system) were required to pass the third level of information security protection[13].According to this regulation, the work stations used by physicians have no way of accessing the internet directly, so they cannot use a web-based RTSM. Normally, one or two computers are provided to allow accessing the Internet in one office, which are physically separated from the hospital information system. Therefore, investigators are limited to use these shared computers to access the RTSM system. Thus, some investigators preferred to use a telephone to access the RTSM system because it was more readily available than the computerized link, although the operation of this method was more complicated. Based on a survey, we compared the time required to access the system by using a telephone with using a computer. Using a telephone, the overall process comprises patient enrolment, randomization, and allocation of the first drug required an average of 5 minutes and 10 minutes for a beginner, where as computerized access reduced the time by about 2 minutes to register each patient. In order to enhance the operational efficiency, we trained investigators and their assistants on site. In addition, some investigators optimized the process where assistants entered the data while the investigators interviewed the subjects, so the patients could undergo the screening assessments and visits more rapidly.

VI. Conclusions

In recent years, the number of dynamic TCM treatment trials has increased and their complicated trial designs have required computerized systems to facilitate their manipulation. The use of a computerized system for managing a study is determined by the complexity of a study. If a study involves multiple treatments, competitive enrollment, dynamic randomization, or drug supply management, a computerized system is preferable. In this type of study, the workflow and productivity are improved by using the RTSM system for managing the subjects and drugs. The RTSM system is convenient to operate, reduced operational errors, enhanced the management efficiency, and improved the data quality. However, it is extremely difficult to develop suitable software to meet the needs of all complex clinical trials. In the future, we will keep upgrading of this RTSM system to fit the more requirement of clinical trial.

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