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Realization of simulations for blinded internal pilot study based on web ☆

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ABSTRACT

Misspecification of the designing parameters in the planning of a controlled clinical trial may yield an underpowered or an overpowered study. Internal pilot study, a kind of adaptive design, has gained increased attention for its allowing for sample size adjustment, especially blinded sample size adjustment that do not affect the type I error rate. Several methods were proposed to implement internal pilot design in recent years and some software emerges to simulate or implement it. But most of the software is only running on a stand-alone terminal or Client/Server(C/S) mode. We develop a system to simulate it based on Browser/Server(B/S) mode and realized on web. It allows the web users to input corresponding parameters from the web browser such as Internet Explorer to make simulations. The system was constructed with generic database schema design method and coded with Microsoft Visual Basic and Active Server Pages (ASP) programming languages. Web users on internet can use the system to make blinded variance estimate, sample size adjustment and randomization test for internal pilot study. The application of the simulation is demonstrated through an example. Not only blinded sample size adjustment is implemented but also a randomization test is performed. With applications of blinding one-sample variance for sample size recalculation and randomization test, the type I error rate is also controlled successfully.

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1. Introduction

Adaptive designs have long been proposed for economic, ethical or administrative reasons in clinical trials. Internal pilot study, also called internal pilot design or internal pilot, is a kind of adaptive design and mainly used to make sample size adjustment. It was based on the motivation that allowing for adjustment of the sample size during an ongoing trial can mitigate the hazards of an inadequate or an excessive sample size [1]. Stein firstly introduced the method in 1945 [2] and proposed the length of the confidence interval to be bounded by a predefined size. Wittes and Brittain [3] make further study on the topic of sample size reestimation procedures in the field of clinical trials. They firstly proposed the term "internal pilot" study which permits to adjust the planned sample size according to the unblinded result, for example, within-group variance from patients already recruited till the time of interim analysis.

Internal pilot design has regained special attention in recent years, especially in the recalculation of the sample size in clinical trials. It is well known that the sample size required for a clinical trial to assure a specified power depends on the significance level, the treatment effect to be detected, and the variance of the outcome. For the exact variance of the outcome in current trial is uncertain even at the end of the trial, it is often specified based on previous trials. However, the conditions of the previous trials and the current one are seldom exactly same with respect to many aspects and the variance is substantially affected by factors that are specific to the current trial, for example, inclusion/exclusion criteria; degree of standardization of measurement and number of equipment at collaborating centers [4]. Therefore, considerable uncertainties may exist about whether the assumed variance value is appropriate for the current trial when using only external information from previous trials for sample size calculation.

We focus on an example for illustrative purposes. A randomized, double-blind placebo-controlled clinical trial aimed to evaluate a new drug, Angiotensin II (AII) antagonists for the treatment of essential hypertension. The primary outcome variable was Supine diastolic blood pressure (SDBP). The fall of SDBP was measured at the end of the trial and was assumed to be normally distributed. A difference in fall of SDBP between the treatment and placebo groups of $\delta = 4$ mmHG was of clinical interest. According to previous studies, the common within-group variance of the fall was approximately 81, that is $\sigma_0^2 = 81$. Suppose that we wanted to make two-sided hypothesis to test the efficacy with significance

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level of $\alpha = 0.05$ and power of $1-\beta = 0.90$. Then the sample size needed to achieve the desired power is 106 subjects per treatment group. If the true variance is 50% larger than anticipated, the power decreases to 74.8%, while if the true variance is two-thirds as large as anticipated, the power increases to 97.6%.

Internal pilot design helps us re-estimate the variance of current trial and make sample size adjustment so as to yield the appropriate sample size and produce a test with the required power. It can be considered as the first stage of the two-stage adaptive design. When it is finished, we make an interim analysis for the patients recruited in it to re-estimate the variance of the outcome variable. Then the variance is used to recalculate the required sample size before the second stage starts. The sample size of the second stage is then re-determined according the newly recalculated sample size. When the second stage is carried out, the data of it are combined with those in the internal pilot. At last the pooled data are analyzed through hypothesis test.

There are many points of view about the sample size recalculation. Betensky and Tierney gave an excellent description about the different types of sample size adjustment procedures [5]. With the internal pilot study's drawing more and more attention, it is urged to develop software to make it easier to be simulated and implemented.

Some adaptive design software package or system had been developed, such as "Addplan V4.0" of ADDPLAN GmbH company [6] and Expdesign Studio of CTriSoft International Company [7]. All of them provide excellent function for simulation for the adaptive design. But all of them are only operated on stand-alone computer instead of web. There is not any web-based adaptive design having been reported so far. We have been engaged in the research of adaptive design, especially internal pilot design for its simulations or utilization in practical clinical trials. The simulation of blinded internal pilot design based on web is a part of our adaptive design project on web.

2. System overview

It is a web-based system specially developed for simulation and implementation of adaptive design. Simulation of the internal pilot study is one of its main components, which can be used to estimate the blinded variance, adjust sample size and make randomization test.

2.1. System architecture

The system is built and realized through B/S mode [8], coded with the active server page (ASP) programming method and Visual Basic(VB) Script language. It is running on the World Wide Web (WWW) Server and available on-line. The users can access the Web server as clients through Internet Explorer, the famous browser developed by Microsoft Corp, with the help of Secure Socket Layer (SSL) which provides the point-to-point communication security. The Web (WWW) Server is constructed through Internet Information Services (IIS) under WindowsNT. The server provides services and exchanges information with the users through Web Server and database. Database is created through Microsoft Access. No extra Database server is provided and the data files share the Web Server with the active page files. The schematic of this system is shown in Fig. 1.

2.1.1. The design of the system and the main page

The module design is the core of the system design. Two main modules were built up, registration of the users and its management module, and the realization of adaptive design module. The later is made of five separate modules: Introduction, Design, Example, Methods associated with adaptive design and Help. Five modules have different functions in which the design module is the most important one and internal pilot study belongs to it.

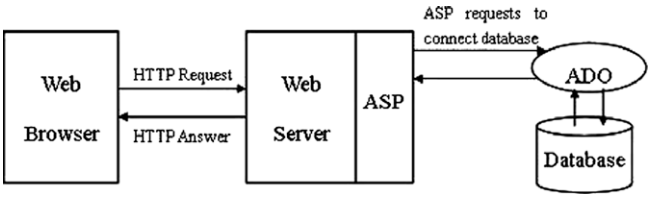

Fig. 1. Schematic of system architcture.

The main page of this system is designed with three main frame sets, top, left and right frame set. The top frame is mainly set at the aim of decoration so as to catch the eyes of the users. The left frame is specially designed and appears as hierarchical directories to show the five function modules and their sub-hierarchical directories. The contents corresponding to the items in left frame are shown in the right frame.

2.1.2. Web design of the internal pilot study

According to the procedure of internal pilot design, three modules are designed to support its simulation. The first one is variance estimation module which can be used to simulate the internal pilot study and compute the variance. The newly calculated variance is then used to recalculate the sample size of the clinical trial. The second one is the second stage simulating module which can simulate the second stage according to the recalculated sample size. The third one is data analyzing or hypothesis test module whose function is to analyze the data of the whole trial through randomization test.

Corresponding to the design procedures, two steps are designed on web to guide the users to perform simulation. The first step offers the opportunity for the users to input parameters to calculate the planned sample size of the clinical trial, see Fig. 2. The second step is used to realize the three modules described in the above passage, providing the interface to help users select simulating parameters for internal pilot study and simulate it; make sample size adjustment and analyze the data, see Fig. 3.

2.2. The management of this system

Two types of users, i.e., administrators and common users have different privileges. The administrators administrate the system at the side of server. Administrative tasks include accepting a new user's requesting registration, viewing, editing, and deleting the user's information and the database has been created by the users.

Managed by administrator, a common user can simulate internal pilot study in the following way:

(1) Access the web server at the side of browser. A new user must register when he/or she first accesses the main page and the system will give him/or her a unique user name. Then the user is allowed to login the system by inputting his/or her user name and password. In this way, the confusion among different users can be avoided.
(2) Click "New Design" in the left frame of the main page to unfold this directory. Then click its subdirectory "Internal Pilot Design". Next, click "Design and Analysis" which is subordinated to "Internal Pilot Design". Finally, click "Blinding Sample Size Reestimate and Analysis for Significance Test".
(3) Click hyperlink "here" in the right frame of the main page to enter "Scenario selecting".

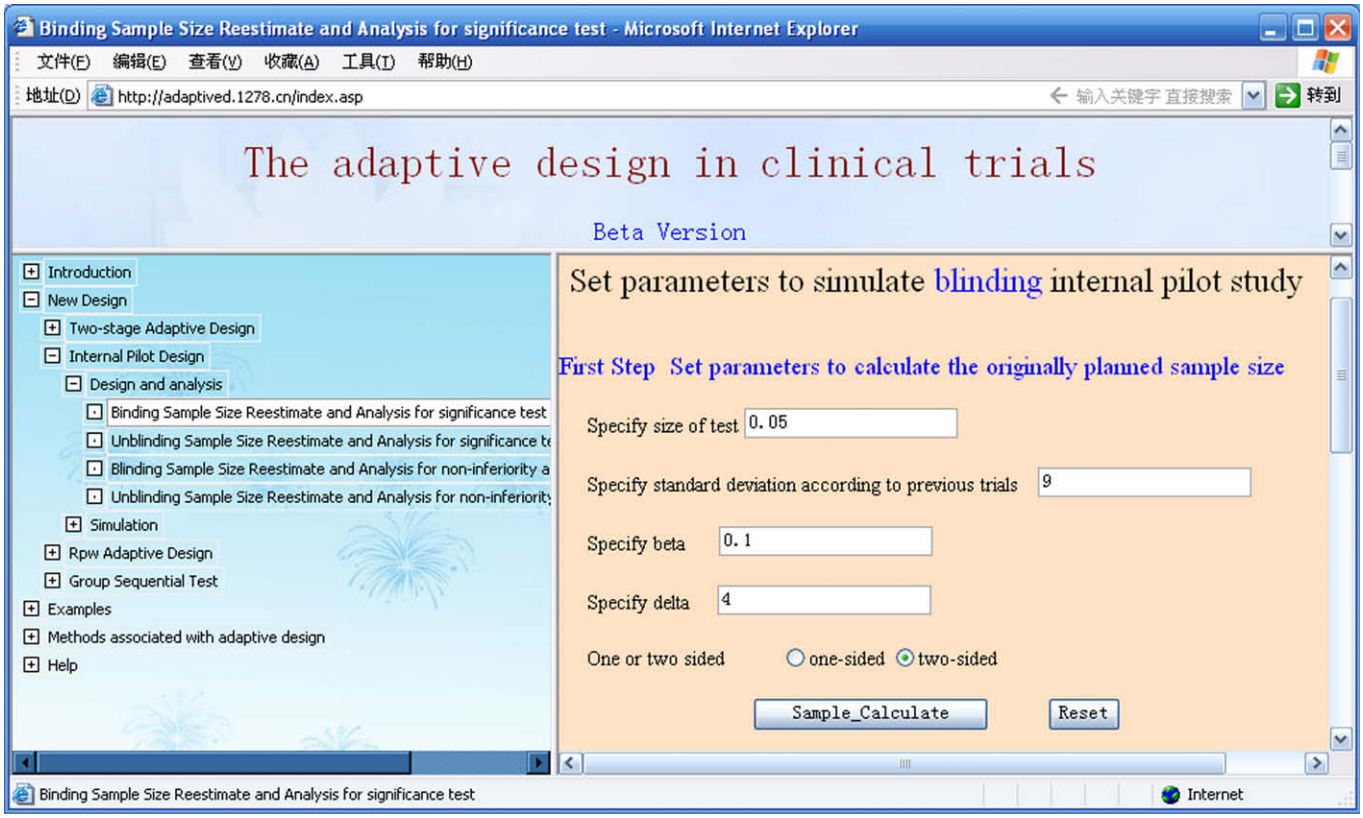

Fig. 2. The interface for inputting the parameters to calculate the initial sample size.

(4) Select "Two groups in *t*-test" and Click the "NEXT" button to enter "Select simulation or not" page.
(5) Click hyperlink "Simulating the process of internal pilot study under the condition of blinding" to enter the parameter setting page shown as Fig. 2.
(6) Input the parameters shown as Fig. 2 to calculate the original planned sample size.
(7) Input the parameters shown as Fig. 3 to simulate the internal pilot study, sample size adjustment and make final data analysis. For the specification of the parameters, refer to Sections 3.2.1 and 4.

Moreover, the users can brows the pages about adaptive design or make other kinds of simulations of adaptive design with the help of Web server.

3. Methods

3.1. Database design

Database design is the basis for the entire web design, which includes detailed data analysis, preparation of design specifications, database programming, database testing and validation. Microsoft Access 2003, a Relational Database Management System (RDBMS), has been chosen to build the database for system monitoring. A set of tables along with their columns' title and data type have been designed. Separate database is designed for the user information and internal pilot design, respectively.

Four tables in database are used for the simulation of internal pilot design: *Users*, *Plan-sample*, *Simulation_para* and *Simulation_data*. *Users* table is used to store the registering information about the users. *Plan-sample*, *Simulation_para* and *Simulation_data* tables are mainly used to store specified parameters and the intermediate calculated results from the first and second step shown in Figs. 2 and 3. The structures of the four tables are shown in Tables 1–4.

As illustrated in the above tables, *Plan-sample* table accepts the parameters specified by users in the first step and related with Foreign Key of username in *users* table. With these parameters the initial sample size of clinical trials with observed data in two treatment groups following normal distribution can be calculated. Users login in the main page for the first time must start from the first step in Fig. 2 to the second step in Fig. 3.

Some intermediate results in the first step such as the Alpha- or Beta-percentile of the standard normal distribution used to calculate the original sample size is stored in *Plan-sample* table to reserve for recalculating the sample size. The inputting interface is shown in Fig. 2.

Simulation_para is used to store and accept the simulating parameters input by users through interface shown in Fig. 3 in the second step so as to simulate the process of blinded sample size adjustment and make hypothesis test. Some useful intermediate results such as one-sample variance (OneS_Variance) and recalculated sample size (SS-sample) are also stored in this table.

With Some intermediate results stored in the tables, the users who have ever logged in the page previously and finished the first step need not have to start from the first one again when they re-login the page. They can ignore the first step and get the results from the table if the original sample size is the same as that in last time. They can only input the parameters for the second step and press "Sample Size Adjustment and Data Analysis" button directly to get the results.

The various issues associated with database, such as data redundancy and inconsistency, accessing data, data isolation, integrity problems, concurrent access of data and security problems have been carefully processed during database design. The

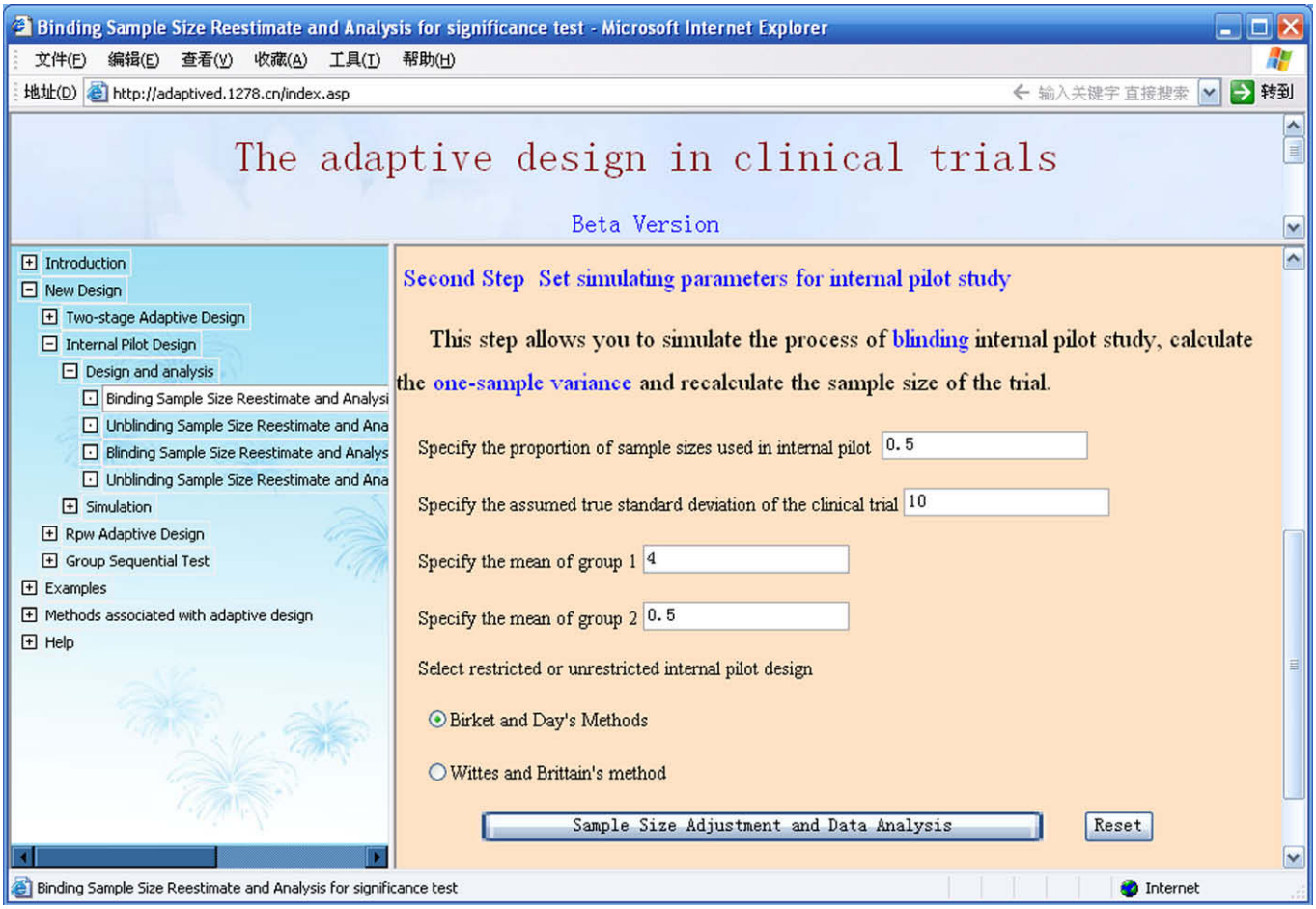

Fig. 3. The interface for inputting the parameters to simulate internal pilot study, make sample study size adjustment and randomization test.

Table 1
User information table (*user*)

Field name	Type	Length	Descriptions
UserName	Character	20	Store the users' name, primary key
userPW	Character	10	Store the password of the users
Email	Character	100	Store the Email of the users
Address	Character	255	Store the address of the users
Online	Boolean	1	Indicate the status that the user is on line or not

Table 2
Planned sample size calculating table used to store parameters for calculating the original sample size and some intermediate results (*Plan-sample*)

Field name	Type	Length	Descriptions
UserNames	Character	20	The users' name, foreign key
Alpha	Numeric	5.4	Type I error rate specified by the users
Sigma0	Numeric	6.3	
Beta	Numeric	5.4	Specified standard deviation according to previous trials
Delta	Numeric	8.3	Type II error rate specified by the users
Z-Alpha	Numeric	8.3	Interest of treatment difference between two groups Alpha-percentile of the standard normal distribution,
Z-Beta	Numeric	8.3	Intermediate results from integral Beta-percentile of the standard normal distribution
Plan_sample	Numeric	8.3	Intermediate results from integral the sample size initially planned

Table 3
Simulating table used to store parameters for simulating internal pilot and the second stage and some intermediate results (*Simulation_para*)

Field name	Type	Length	Descriptions
UserName	Character	20	The users' name, foreign key
PI	Numeric	5.4	The proportion of planned sample seize used as internal pilot
U1x	Numeric	10.3	The assumed mean of treatment group 1 of the trial
U2x	Numeric	10.3	The assumed mean of treatment group 2 of the trial
Sigma	Numeric	12.3	The assumed true standard deviation of the trial
OneS_Variance	Numeric	12.3	The one-sample variance calculated from internal pilot
SS-sample	Integer	8	The sample size recalculated for the second stage

Table 4
All simulating data from two stages (*Simulation_data*)

Field name	Type	Length	Descriptions
UserName	Character	20	Store the users' name, foreign key
Group-no	Integer	3	treatment group 1 or group 2
Value-OBS	Numeric	10.4	The observed values from internal pilot and second stage
RndID	Numeric	12.11	Random number used to rearranging the observed data

privilege of the administrators is set previously so that they can maintain or delete the records of the table in the database. The designed database provides accessibility through OLE DB database drive.

3.2. Program design

The system was coded with Microsoft Visual Basic and Active Server Pages (ASP) programming languages. Programming was based on the principles of internal pilot design proposed by Wittes and Brittain [3] and Birkett, and Day [9]. But sample size adjustment is carried out based on the formulation proposed by Kieser and Friede [10], in which sample size is calculated without unblinding internal pilot study. Program flow chart of the computation process is shown in Fig. 4.

3.2.1. Blinded sample size adjustment and randomization test

Sample size adjustment based on internal pilot is an effective way to avoid under- or over-power of the clinical trial. It firstly takes a proportion of the total sample size as an internal pilot to calculate the accurate variance of the current trial. Then use this variance to recalculate the sample size. If the internal pilot is kept blinded in accordance with the regulations of ICH E9 [11] during the sample size adjustment, the process is called blinded sample size adjustment, and the variance is virtually the one-sample variance which is used to recalculate the sample size. Based on the recalculated new sample size, the clinical trial continues to the second state until it is finished. Finally the data from the first and the second stage are combined and analyzed.

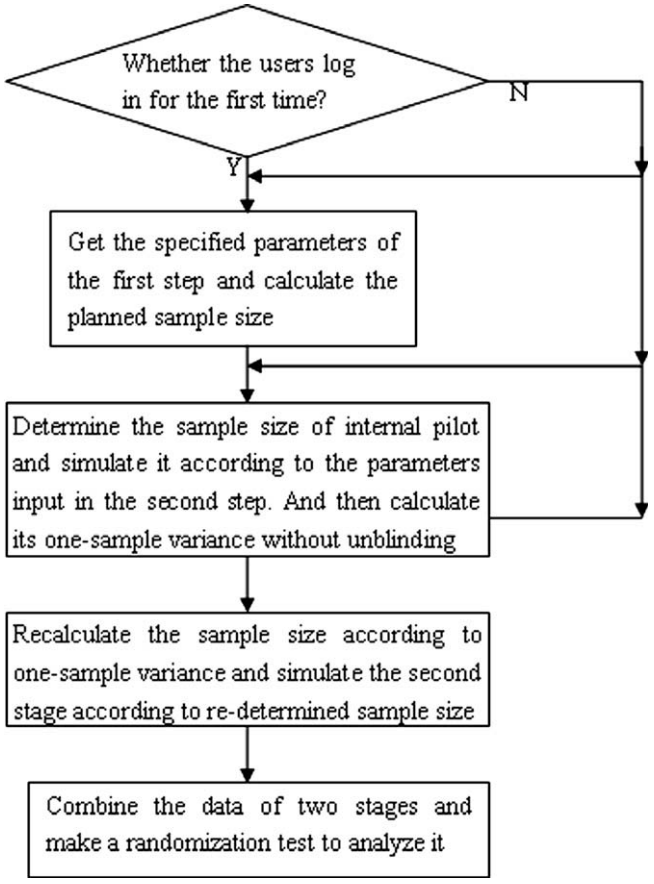

Fig. 4. Program flow chart for simulating internal pilot and making randomization test.

We still use the example described in Section 1 to illustrate the sample size adjustment. Suppose the study is designed to allow for two-stage sample size recalculation based on the variance from blinding internal pilot. Halfway through recruitment, without unblinding the treatment assignments, the variance is estimated from observations collected to that point, and an updated sample size is calculated. Suppose $S_{OS}^2 = 100$, then the recalculated sample size per group is 133. We can see that this estimate reflects a larger than anticipated variance. If the sample size adjustment were not made, the study would have been underpowered at the original sample size. If the newly calculated sample size is used to determine the sample size of the second stage and the hypothesis test is performed using data from both stages at the end of the second stage, the power will be close to the required power.

Due to the second stage's dependency on the first one, type I error probability may inflate if *t*-test is applied to test the significance and make inference [3], [9]. Many statisticians have proposed procedures to analyze the final data and control the type I error rate [10], [12–14]. Kieser and Friede [10] and Zucker et al. [12] mentioned that the randomization test could keep the type I error not being beyond nominal test level, but they did not give further study about it. Wang etc. have proved through a SAS macro [15] that using randomization test to analyze the final data can prevent the probability of type I error from exceeding nominal test level. So this method is still used to make significance test on our web system.

Two steps are designed to carry out the process of sample size adjustment and randomization test. The first step shown in Fig. 2 corresponds to the required sample size calculation in the planning phase of a clinical trial. All the parameters, such as the supposed variance σ_0^2 got from previous trials, type I error α, type II error β and the specified relevant treatment difference δ should be input in this step to calculate the originally planned sample size. The second step shown in Fig. 3 is the most important one. It contains three main functions controlled by Visual Basic program: firstly, providing the interface for users to input parameters to simulate the internal pilot for calculating variance; secondly, automatically making sample size adjustment and determining the sample size of the second stage and simulating it; thirdly, combining the data of the internal pilot with that of the second stage and making randomization test. All the parameters such as the proportion taken from total sample size as the internal pilot, denoted as π, the assumed true standard deviation σ and the respective mean μ_{1x}, μ_{2x} of group one and group two etc. should be firstly input in the second step, and then press the "Sample Size Adjustment and Data Analysis" button. The system will perform all the computation and show us the results in a web page.

3.2.2. Program design and technique for sample size calculation

In the process of sample size calculation and recalculation according to $N = \frac{2(Z_{1-\frac{\alpha}{2}}+Z_{1-\beta})^2}{\delta^2}\sigma^2$ and $\hat{N}_{\text{recalc}}(S_{OS}^2) = \frac{2(Z_{1-\frac{\alpha}{2}}+Z_{1-\beta})^2 S_{OS}^2}{\sigma^2}$, respectively [15], we need to determine the critical value Z_γ corresponding to γ-percentile of the standard normal distribution. However, there is no transformation function to turn γ-percentile into its critical value Z_γ in Visual Basic Script. Integration technique has been taken to realize the transformations. It is known that γ can be obtained by integrating the density function of the normal distribution over the region $(-\infty, Z_\gamma)$. The density function of the normal distribution with mean μ and variance σ^2 is

$$f(X) = \frac{1}{\sigma\sqrt{2\pi}} e^{\frac{(x-u)^2}{2\sigma^2}} (-\infty < x < +\infty) \quad (1)$$

The integration of $f(X)$ over region $(-\infty, Z_\gamma)$ is exactly the γ-percentile, that is:

$$\gamma = \phi(X) = \int_{-\infty}^{Z_\gamma} f(X) = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{Z_\gamma} e^{\frac{(x-u)^2}{2\sigma^2}} dx \quad (2)$$

Now γ is known. So we can inversely compute Z_γ according to $\gamma\sigma\sqrt{2\pi} = \int_{-\infty}^{Z_\gamma} e^{\frac{(x-u)^2}{2\sigma^2}} dx$ by calculating the accurate value of $\int_{-\infty}^{x} e^{\frac{(x-u)^2}{2\sigma^2}} dx$ through trapezia integration. When $\int_{-\infty}^{x} e^{\frac{(x-u)^2}{2\sigma^2}} dx = \gamma\sigma\sqrt{2\pi}$ holds true, the upper bound $x = Z_\gamma$ is exactly the value corresponding to γ-percentile. So $Z_{1-\frac{\alpha}{2}}$ and $Z_{1-\beta}$ can be computed with α and β input in the first step in Fig. 2. For σ_0 and δ are also input by the users, the planned sample size of the trial can be easily calculated. The programming code to fulfill the density integration and calculation of planned sample size is given in Appendix A.

3.2.3. Program design and techniques for trial simulation

Two independent standard normal variables, x_1 and x_2, have to be generated so as to simulate the internal pilot and the second stage. But there is no random function to generate normal distribution variables in Visual Basic Script. We have to generate the simulating data by the help of uniform random function and Box–Muller method [16,17], which provides the following transformation equations:

$$\begin{aligned} x_1 &= \sqrt{-2\log U_1}\cos(2\pi U_2) \\ x_2 &= \sqrt{-2\log U_1}\sin(2\pi U_2) \end{aligned} \quad (3)$$

where U_1 and U_2 are numbers on interval [0,1] and can be generated by random generating function Rnd in VB Script. Unfortunately, the use of Box–Muller transformation Eq. (3) to generate a pair of independent standard normals is computationally not very efficient for the computation of sine and cosine trigonometric functions. Besides that it can have numerical stability problems when X_1 or X_2 is very close to zero. The way to get around these time-consuming difficulty and numerical problem is to use an indirect computation of the sine and cosine of a random angle [18], that is, the polar form of the Box–Muller transformation. The polar transformation which is both faster and more robust numerically can be expressed in Eq. (4).

$$\begin{aligned} x_1 &= V_1\sqrt{\frac{-2\log S}{S}} \\ x_2 &= V_2\sqrt{\frac{-2\log S}{S}} \end{aligned} \quad (4)$$

where $\begin{matrix} V_1 = 2U_1 - 1 \\ V_2 = 2U_2 - 1 \end{matrix}$ and $S = V_1^2 + V_2^2$. The polar form is faster because it does the equivalent of the sine and cosine geometrically without a call to the trigonometric function library. From (4) we can obtain random variables following normal distribution. With the means of two treatment groups and the assumed true standard deviation input in the first step, the response variables can be easily generated. The algorithmic description of simulation and programming code generating a pair of independent standard normals is given in Appendix B. The generated observed data are stored in the *Simulation_data* table for analyzing.

3.2.4. Program design and technique for calculating one-sample variance

For the calculating of one-sample variance, the key point is to mix the simulating data of two groups up by ignoring the fact that they belong to different treatment groups. This was solved by using two-dimensional array. While the simulating data for internal pilot are generated, they are stored into both two-dimensional array and *Simulation_data* table. The data in the table reserve for the combining with that of the second stage to make hypothesis test. The data in the array are used to compute the blinded one-sample variance. Because there are no labels to indicate which treatment group the variables in the array belong to, the blinded one-sample variance is easily achieved with help of array algorithm. The program code for calculation of one-sample variance for internal pilot study is given in Appendix C. With one-sample variance computed, the sample size can be recalculated. The number of subjects recruited in the second stage is then re-determined according to the recalculated sample size. With the newly determined sample size, the second stage is simulated similarly with the internal pilot.

3.2.5. Program design and technique for randomization test

A randomization test is a distribution-free test in which a reference distribution is obtained by calculating almost all possible values of the test statistic under rearranging the labels on the observed data points. Mean difference is chosen as the test statistic for randomization test. The algorithm is described as follows:

1. Subjects from the internal pilot and the second stage are re-randomized Ns times.
2. Compute mean differences from these Ns simulations and the observed mean difference from original observed outcome. These mean differences constitute the reference set.
3. Compare the original test statistic with the reference set.
4. The proportion of mean differences in the reference set that is as or more extreme than the observed mean difference is the randomization test *p*-value.

Because the original simulating data are stored in the *Simulation_data* table, we need to access the database to read the data out to make randomization test. Two ways can be used to connect the database through ADO(ActiveX Data object) provided by Microsoft: ADO Connection object and ADO Command object. The former is relatively easier to be implemented but needs more time; and the later is more complicated but needs relatively less time. As far as the randomization test is considered, it needs to permute the data many times. The common way to perform the randomization test is to permute the data in the table of the database and then calculate the test statistics, but that will spend much time, especially when a great many of users access the WEB server simultaneously. In order to decrease the time to perform randomization test, we use the GetRows() method of ADO Record object to read the data out and write them into two dimensional array of VB Script. So we can implement the randomization test through array operation.

We firstly generate a random number "randnumber" following uniform distribution, randnumber$\sim$U [0,1], and then re-randomize the observations according to the random number on the condition that subjects in group 1 is equal to that in group 2. If the randnumber $\leqslant 0.5$, then the variable in the array which represents a special observation is supposed to be reassigned to group 1, otherwise, it is reassigned to group 2. All the mean differences (including that of original data) between two groups at Ns times of re-randomization are calculated. Then the proportion of mean differences in the reference set that is as or more extreme than the observed mean difference is the randomization test *P*-value. The times of re-randomization in our Visual Basic program are determined according to Manly who suggested that 1000 iterations of the data are sufficient to test hypothesis at a 5% level of significance and 5000 iterations are sufficient to test at a 1% level [19]. So 5000 iterations are chosen to perform randomization test. The programming code to carry out randomization test is given in Appendix D.

The advantage of array operation is obvious. On one hand, it can avoid the much time expenditure of access database frequently which makes the process slower. On the other, array operation itself is much faster than database operation. Generally speaking, if there are 100 thousand records in the table of database, we need to extract the records one by one. The average spending time is about

3 s by the use of ADO Connection object and 2 s by the use of ADO Command object. Neither ADO Connection object nor ADO Command object can completely solve the problem of the long time of implementation. The use of the function GetRows() can extract all the records for one time and store them into the array. The data of array is stored in memory, which is the fundamental solution to the time spending in accessing the records of database one by one. So the randomization test can be finished in reasonable time.

4. Simulations and results

The clinical trial mentioned in Section 1 was simulated in our system. According to the description we have known that $\delta = 4$, $\sigma_0 = 9$, $\alpha = 0.05$ and $1-\beta = 0.90$. Therefore, we input the parameters in its corresponding text area in the first step shown in Fig. 2 and pressed the "Sample_Calculate" button to calculate the original sample size. The system showed us that 106 subjects should be recruited per treatment group. Then we entered the second step shown in Fig. 3 to simulate internal pilot study, made sample size adjustment and randomization test. If half of the original sample size was taken as the sample size of internal pilot, that is $\pi = 0.5$, 53 subjects per group would be chosen for internal pilot. We further assumed that the mean fall of the SDBP for group one and two is $\mu_{1x} = 4$ mmHG, $\mu_{2x} = 0.5$ mmHG and the true standard deviation $\sigma = 10$ to generate normally distributed simulating data. The simulating parameters in the second step should be input as shown in Fig. 3. If we selected the first radio button for restricted design, that is, Birket and Day's Methods and clicked the "Sample Size Adjustment and Data Analysis" button, the system would show us the results of the sample size adjustment and randomization test. The output page told us that one-sample variance of internal pilot study is 100.254848081141 and the recalculated sample size is 132 instead of 106 per group, reminding us that 79 further subjects should be taken in each group instead of 53 for the second stage. The system determined the subjects for the second stage automatically and did not need the users' interference. It also output the simulating data of two stages and the *P* value of randomization test. The message "The *P* value of randomization test is 0.011" in the browser window told us that the *P* value of our example was 0.011. H0 was thus rejected at the significance level 0.05.

In the second step of the simulations, if we let $\mu_{1x} = 4$, $\mu_{2x} = 3$, $\sigma = 10$ to generate normally distributed data, the One-sample Variance was 107.863826605668 and the recalculated sample size is 142 per group. The newly calculated sample size for the second stage is 89. The *P* value of randomization test is 0.262. H0 was thus accepted at the significance level 0.05.

One-sample variance, recalculated sample size and *P* value of randomization test etc. in the output page may be different from the above results when the user presses the "Sample Size Adjustment and Data Analysis" button, even with the same parameters input as that shown in Fig. 3. For example, with the parameters shown as Fig. 3, the One-sample variance, recalculated sample size and *P* value of randomization test in the output page are 108.491282942088, 143 and 89, respectively when the user presses the "Sample Size Adjustment and Data Analysis" button for first time. The three numbers become 114.713269017178, 151 and 97, respectively when the user clicks the back button of the Internet Explorer to back to the previous page and presses the "Sample Size Adjustment and Data Analysis" button for the second time. Every time the user repeats to click the back button and press the "Sample Size Adjustment and Data Analysis" button, he/or she will get different results about the one-sample variance, recalculated sample size and *P* value. Two reasons can explain that. One is that the data of the internal pilot and the second stage are randomly generated. The other is that the randomization test needs to randomly resample the data and assign them to the two groups for many times. It's the difference of the randomly generated data and permuted data sets that result in the variability of the output.

The simulating results of the output can be used as the reference for the purpose of planning and conducting a clinical trial based on sample-size adjustment. On one hand, simulating results give the researchers opportunities to redesign the clinical trial. For example, before the researchers begin a real clinical trial, they can firstly make simulations with the planned parameters. If they find that the results do not satisfy them, they can change the parameters such as the mean difference between two groups, the proportion of the internal pilot etc. and implement simulating again and again until they get the satisfied results. Then they can commence the real trial with the parameters resulting in the satisfied results. On the other, the process of simulating is similar with the process of real clinical trials, which can help the researchers plan and design a specific trial.

5. Discussions

Sample size adjustment through interim analysis is an efficient tool to meet the desired study power even under misspecification of the variance in the planning phase. Two-stage designs with blinded internal pilot study are appealing in recalculating the sample size because the recalculation is performed without breaking the blind which is in accordance with the regulations for drug approval.

Combining the data used for variance estimate from internal pilot study with that from the second stage in the final analysis changes the distribution of the test statistic from that of a fixed sample, because the statistic depends on the variance estimate through the final sample size. The effect of this dependence likely increases in smaller samples, such as those commonly used in laboratory studies and many phase II clinical trials, which results in the inflation of test size. Randomization test is undoubtedly the elegant and sensible choice to solve this problem because it's a nonparametric test and does not need to use the variance of the final sample size. So the inflation caused by the variance of the adaptive design does not exist any more. It is not only highly intuitive and easy to apply in practice, but also valid under very mild conditions and thus provide protection against departures from model assumptions. It can be as powerful as their parametric counterparts at the same time works especially well in situation where the initial sample size was small. For its using the control of the type I error probability is guaranteed for any arbitrary blind sample size adjustment strategy. So sample size adjustment becomes easier with the use of blinded sample size adjustment and randomization test.

A permutation test is special case of a randomization test. If the number of possible permutations is small, we can calculate all the permutations which are called the exact permutation test. A typical full permutation test is too time-consuming and is just impossible in personal computer. An alternative to the full permutation test is a randomization test. It uses a Monte Carlo approach to select a random subset of the total number of permutations, so that the computations can be done in a reasonable amount of time, even for large data sets. For the test statistic of the randomization, we determined it according to Manly [19] who suggested that we can choose the mean difference or the usual *t*-test statistic as the measure of discrepancy for two groups. So we choose mean difference as the test statistic in our VB Script program. In order to verify the results, we exported the data into another database and imported the database in SAS system and then chose *t*-test statistic as test statistic to make randomization test. The results from *t*-test statistic calculated from SAS program are in accordance with those output from using mean difference as test statistic in VB Script program.

The method for adaptive design used in the described simulation based on web refers to blinded sample size adjustment and randomization test. The inflation of type I error rate can be successfully controlled with the using of blinded variance and randomization test. A randomization test usually spends a lot of time for the many permutations of the data. The applications of the array arithmetic and the extracting function GetRows() in Visual Basic Script help us solve this problem because they can avoid accessing the database frequently. So randomization test based on web can be finished in a reasonable time.

The system described in this paper can be used to facilitate the utilization of internal pilot study in practical clinical trials. It is designed for the purpose of simulating the adaptation process of sample size recalculation and final data analysis. It can help the researchers with planning and conducting a clinical trial based on sample-size adjustment with blinded internal pilot study. It incorporates the key features of planning and conducting sample size re-estimation for an adaptive clinical trial within a user-friendly interface. The achieved performance by using data generation to re-estimate the sample size by one-sample variance and make hypothesis test as well as the possibility of changing parameters without changing other assumptions are features which allow flexible and quick simulation of sample size adjustment without unblinding internal pilot. The web-based system accounts for the process of sample size adjustment in an interactive way. Its use can assist researchers to design a specific trial, especially when they can not ensure the variance of the clinical trial or the adaptation parameters of sample size adjustment.

On the other hand, realization of simulations for internal pilot study based on web is consistent with the development of electronic data capture (EDC). With EDC becoming widespread and popular, web-based system becomes more and more popular in the field of clinical trials because it provides the interface to transmit the relevant patient information over the Internet. Simulating internal pilot study on web is just the outset. Implementing EDC in adaptive design for clinical trial is our ultimate goal.

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Appendix A

Programming code in VB Script for integration of normal distribution density

```
<%'definition of the exponential part of the density function of normal distribution
Function efdensity(sigma,u,x)
  x1 = (x−u)^2*(−1)
  x2 = 2*(sigma^2)
  efdensity = Exp(x1/x2)
End Function
  'Calculate the Zγ corresponding to γ −percentile through integration
  Function integral_Zvalue(gama,sigma,u,x,h)
  Dim s,pi,h
's is used to store the sum of the little trapezia area pi takes the value of 3.1415926
'H is height of the trapezia to be integrated
s = 0
pi = 3.1415926
  Do
    s = s+(efdensity(sigma,u,x)+efdensity(sigma,u,x+h))*h/2
    x = x + h
    Loop Until s ⩾ gama *(sigma*Sqr(2*pi))
    S_total = s/(gama *(sigma*Sqr(2*pi)))
    integral_Zvalue = x−h
  End Function%>
```

The following program code is used to calculate the planned sample size for the trial.

```
<%@ language = "VBScript"%>
<% Alpha = Request.Form("Alpha") 'read in the Alpha value input by users
  Sigma0 = Request.Form("Sigma0") 'read in the Sigma0 input by users
  Beta = Request.Form("Beta") 'read in the Beta value input by users
  Delta = Request.Form("Delta") 'read in the Delta value input by users
  Onetwo = Request.Form("oneT") 'determin one or two-sided test
  If Onetwo = "one-sided" Then
  Z_Alpha = integral_Zvalue(Alpha,sigmaStandard,0,−5,0.0001)
  Else  Z_Alpha = integral_Zvalue(Alpha/2,sigmaStandard,0,−5,0.0001)
End If
  Z_Beta = integral_Zvalue(Beta,sigmaStandard,0,−5,0.0001)
N_init_cal = 2*(Z_Alpha + Z_Beta)^2*Sigma0^2/Delta^2
  Plan_sample = cint(N_init_cal) 'the planned sample size of the trial
%>.
```

Appendix B

Algorithmic description and programming code in *V*B Script for generating a pair of independent standard normal variables

```
<%'Function for generating two variables of independent standard normal distribution
Function Gaussian-gen()
  Dim flag,S,V1,V2,count,Gaussian-gen_tem
  flag = 0
  count = 0
  If flag = 0 Then
    Randomize
    Do
   'Rnd is the routine function to obtain a random number uniformly distributed in [0,1], so V1 and V2 is uniformly distributed in [0,1]
    V1 = 2.0* Rnd −1.0
    V2 = 2.0* Rnd −1.0
    S = V1^2 + V2^2
    count = count + 1
    Loop While S ⩾ 1.0
    fac = sqr(−2.0*log(S)/S)
    Gaussian-gen_tem = V1* sqr(−2.0*log(S)/S)
    Gaussian-gen = V2* sqr(−2.0*log(S)/S)
    flag = 1
    Else
    Gaussian-gen = Gaussian-gen_tem
    flag = 0
    End If
    End function%>.
```

Appendix C

Programming code in VB Script for calculation of the one sample variance from internal pilot study

```
<%@ language = "VBScript"%>
<% Dim suby, temp, Gmean, SSos, Pilot_sample
  'suby: the sample size of the internal pilot and also the upper subscription of the array y
  'Gmean: grand mean of the internal pilot study
  'SSos: one sample variance of the internal pilot
  Pilot_sample: the sample size per group of internal pilot
  PI = Request.Form("PI") ' Pilot_sample=PI*plan_sample, specified by users
  U1x = Request.Form("U1x") ' read in the mean of group 1
  U2x = Request.Form("U2x")' read in the mean of group 2
  Pilot_sample = PI*plan_sample
  suby = 2*Pilot_sample
  Dim y()
  Redim y(suby) 'y is the outcome of the observation
  temp = 0
  'generate simulation data for internal pilot study
  For i = 0 to 2*Pilot_sample−1
  If i ⩽ Pilot_ample−1 Then
  y(i) = U1x + Sigma*gasdev(2007 + i)
  vElse y(i) = U2x + Sigma*gasdev(2007 + i)
  End If
    temp = temp + y(i) 'sum of data for simulations
  Next
    Gmean = temp/suby 'Grand mean of simulations
  temp = 0
    For i = 0 to 2*Pilot_sample−1
    temp = temp + (y(i)-Gmean)^2
  Next
  SSos = temp/(2*Pilot_sample−1) 'Variance for simulation%>
```

Appendix D

Programming code in VB Script for implementing randomization test

```
<% Dim Simu_num, Rcount, Array_rec_Original, Dmean, Array_rec_random, Darray_mean
'Simu_num: re-randomized times of the original data
'Rcount: the number of extreme value of mean differences for Simu_num simulations
'Array_rec_Original: observations from the original data
'Dmean: the mean difference between two treatment groups of the original data
'Array_rec_random: observations after sorting by the random number
'Darray_mean: mean differences from these Simu_num simulations
'db: storing the database and its path
UserName=Session("UserName")
db = "/internal_pilot/database/internal.mdb"
Set Conn = Server.Createobject("adodb.connection")
Conn.open "driver={microsoft access driver (*.mdb)};dbq="&server.mappath(db)
'Read out the original data (stored in Simulation_data) and compute its mean difference
Set Rs = Conn.Execute("Select avg(Value-OBS) from Simulation_data where trim(UserName) = trim('"+UserName+"') group by Group-no")
Array_rec_Original = Rs.Getrows()
Dmean = Array_rec_Original(0,0)−Array_rec_Original(0,1)
Response.write("<p>The original mean difference between the two groups is "&Dmean&"</p>")
Rs.close
Set Rs = Nothing
'Read out the data and sort them by random number(RndID)
Exec = "Select Value-OBS from Simulation_data where trim(UserName) = trim('"+UserName+"') order by RndID"
  Set Rs = Server.Createobject("adodb.recordset")
  Application.Lock
  Rs.open Exec,Conn
  Application.UnLock
  Array_rec_random = Rs.Getrows()
  Rs.close
  Set Rs = nothing
  Conn.Close
  Set Conn = Nothing
  ' Following is the randomization test
  Rcount = 0
  Simu_num = 5000
  For i = 1 to Simu_num
  sum_group1 = 0 'the sum of the outcome re-randomized to group 1
  number_group1 = 0 'the number of subjects re-randomized to group 1
    sum_group2 = 0 'the sum of the outcome re-randomized to group 2
  number_group2 = 0 'the number of subjects re-randomized to group 2
  For j = 1 to Ubound(Array_rec_random,2)
  Randomize
  randnumber = Rnd
  If number_group1 > int(Ubound(Array_rec_random,2)/2) Then
    sum_group2 = sum_group2 + Array_rec_random(0,j)
    number_group2 = number_group2 + 1
  Else If number_group2 > int(Ubound(Array_rec_random,2)/2) Then
  sum_group1 = sum_group1 + Array_rec_random(0,j)
    number_group1 = number_group1 + 1
  Else If randnumber ⩽ 0.5 Then
  sum_group1 = sum_group1 + Array_rec_random(0,j)
  number_group1 = number_group1 + 1
Else sum_group2 = sum_group2 + Array_rec_random(0,j)
  number_group2 = number_group2 + 1
 End If
    End If
    End If
  Next
  Mgroup1 = sum_group1/number_group1
  Mgroup2 = sum_group2/number_group2
  Darray_mean = sum_group1/number_group1-sum_group2/number_group2
  If Darray_mean> = abs(Dmean) or Darray_mean<=(−1)*abs(Dmean) Then
  Rcount = Rcount + 1
  End If
  Next
  Pvalue = Rcount/(i−1)%>
```

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