CLINICAL TRIALS

Clinical Trials
1–10

DOI: 10.1177/1740774517706509
journals.sagepub.com/home/ctj
SAGE

Mobile access to virtual randomization for investigator-initiated trials

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Abstract

Background/aims: Randomization is indispensable in clinical trials in order to provide unbiased treatment allocation and a valid statistical inference. Improper handling of allocation lists can be avoided using central systems, for example, human-based services. However, central systems are unaffordable for investigator-initiated trials and might be inaccessible from some places, where study subjects need allocations. We propose mobile access to virtual randomization, where the randomization lists are non-existent and the appropriate allocation is computed on demand.

Methods: The core of the system architecture is an electronic data capture system or a clinical trial management system, which is extended by an R interface connecting the R server using the Java R Interface. Mobile devices communicate via the representational state transfer web services. Furthermore, a simple web-based setup allows configuring the appropriate statistics by non-statisticians. Our comprehensive R script supports simple randomization, restricted randomization using a random allocation rule, block randomization, and stratified randomization for un-blinded, single-blinded, and double-blinded trials. For each trial, the electronic data capture system or the clinical trial management system stores the randomization parameters and the subject assignments.

Results: Apps are provided for iOS and Android and subjects are randomized using smartphones. After logging onto the system, the user selects the trial and the subject, and the allocation number and treatment arm are displayed instantaneously and stored in the core system. So far, 156 subjects have been allocated from mobile devices serving five investigator-initiated trials.

Conclusion: Transforming pre-printed allocation lists into virtual ones ensures the correct conduct of trials and guarantees a strictly sequential processing in all trial sites. Covering 88% of all randomization models that are used in recent trials, virtual randomization becomes available for investigator-initiated trials and potentially for large multi-center trials.

Keywords

Central randomization, virtual randomization, mobile application, web interfaces

Introduction

The design of comparative clinical trials requires the specification of a method of allocating treatments to the trial subjects. Randomization has long been an important element in this design.[1] It entails the specification of random sequence generation, steps to be taken to ensure allocation concealment, and their implementation. Appropriate randomization provides unbiased treatment allocation and comparability of treatment groups and aids in providing unpredictability of subsequent assignments.[2]

Some time ago, the *conventional* way of *randomization* in clinical trials was based on lists that were generated by a statistician expert, printed and distributed to the sites. Such lists bear the risk that copies are deposited in the ward, operation theaters, and doctors' rooms to ensure accessibility on demand. Furthermore, paper-based lists encourage tampering. Inadequate and unclear allocation concealment has been shown empirically to exaggerate the effect of interventions by 41% and 30%, respectively.[3]

Therefore, *central randomization* has been suggested.[4] The investigator has to contact an independent centralized system, for example, phone an operator, that gives out treatment allocations based on the study

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and patient details. Further advantages of centralized randomization are as follows: verification of eligibility, enhanced study monitoring, and the possibility of using randomization designs in multi-center trials that cannot be carried out in a decentralized manner, such as without blocking by centers or using dynamic allocation methods.[5] Bland lists 19 institutions providing central randomization including telephone randomization and indicate fees up to about 15€ per subject.[6] In particular for investigator-initiated trials, such fees may not be affordable. The central randomization principle also depends on the availability of an operator, which might pose a challenge in particular when performing international trials spanning multiple time zones.

An alternative approach is *electronic randomization*, where the human operator is substituted by a web-based system, and the investigator retrieves the subject allocation via the Internet. However, the initialization of a web-based randomization system is quite elaborate. Users and roles need to be defined to support appropriate system access, trial and trial sites must be entered as well as the statistical protocol. Trial names and identifiers, users, roles and sites have already been defined in the electronic data capture system, as well as in the clinical trial management system.

Schrimpf et al.[7] have discussed different options to interconnect electronic data capture and randomization systems. Integrating the randomization into the electronic data capture system does not require data entry into two different systems and prevents failure. The authors refer to the commercial system secuTrial,[8] which implements basic randomization methods directly. However, this system architecture is claimed to suffer from limitations with respect to the diversity of randomization schemes.[7] Operating electronic data capture and randomization systems separately but with defined communication interfaces might be a solution, but it bears other issues of information system integration on all levels such as data, service, presentation, and semantics.[9]

Therefore, we aim at providing a web-based solution of randomization that (a) is low cost for the use in investigator-initiated trials, (b) avoids double data entry, (c) supports all major randomization methods, (d) allows a data manager (not having statistical expertise) to set up the system, (e) provides mobile access from patients' bed sites and operation theaters, and (f) computes the subject allocation on demand, that is, is not based on any central list. In the following, this approach is referred to as *virtual randomization*.

State of the art

In controlled clinical trials, a variety of procedures are used for the assignment of participants to treatment groups.[10] The most important methods are considered to be simple, blocked, and stratified block randomization while dynamic allocation procedures such as minimization are gaining popularity.[11,12] Simple randomization procedure is essentially equivalent to repeated tossing of a fair coin, while block randomization protects against sample size imbalance in the intervention groups by the use of random permuted blocks. Stratified randomization is used in order to circumvent imbalances in baseline characteristics between the intervention groups. This is achieved by generating separate randomization schedules for each group of patients that are defined by the levels of the prognostic factors that are thought to be strongly related to the outcome. However, stratified randomization can only be used with a limited number of factors. Dynamic allocation procedures are recommended to balance across many prognostic factors.[13]

Although several randomization programs are available today,[6,14] most of them are standalone programs and desktop applications to create allocation lists. We do not refer to such type of local systems as *electronic* randomization systems. Again, commercial software or services are available, where the allocation is displayed according to pre-computed lists that are stored within the system. In Table 1, we have summarized the features of the most popular randomization programs:[6,14]

1. *Research Randomizer*[15] is a freely available web service provided by the Social Psychology Network[16] to generate random numbers and to assign study participants to study conditions. It supports random sampling, random assignment and block assignment. It does not support allocation concealment or other aspects of a randomization service like centralized allocation.
2. *Randomization.com* is a free online program to generate randomization lists based on multiple randomization models.[17] Lists can be generated for cross-over trials as well, and the latest version also supports random block sizes when the list is generated using block randomization. Using the provided seed, previous randomization lists can also be easily reproduced.
3. *Random Allocation Software* is a free downloadable desktop program that provides simple and block randomization procedures.[18]
4. *MinimPy* is a free desktop application under general public license for allocation using minimization.[19] The program provides a network synchronization feature in order to support multi-center trials.
5. *RANDI2*[20] is an open source web-based randomization system that supports many randomization algorithms, free configurable patient properties, stratification, and definition and verification of inclusion criteria. Furthermore, it enables easy management of multi-center trials with an easy to handle user management.[21] It supports flexible extension of the system with new randomization

Table 1. Comparison of freely available, non-commercial randomization software.

Features software	Non-commercial	Central system	Seed control	Mobile access	System integration	Eligibility verification	Blinded trials	Multiple models	Dynamic designs
Research Randomizer[15]	X							X	
randomization.com[17]	X		X					X	
Random Allocation Software[18]	X							X	
MinimPy[19]	X	X			X				X
RANDI2[20]	X	X			X	X		X	X
secuTrial[8]		X			X	X	X	X	X
Our approach	X	X	X	X	X		X	X	

Central system: supports central randomization by providing controlled access to randomization lists; Seed control: provides user control over the seed for pseudo-random number generation; Mobile access: provides access to randomization through mobile applications; System integration: supports integration with a clinical trial management system or electronic data capture system; Eligibility verification: supports automatic verification if study subject is eligible to be randomized; Blinded trials: provisions are made to control access to treatment allocation information to different users; Multiple models: Provides several randomization models; Dynamic design: indicates if adaptive allocation designs are supported.

models and the management of centralized randomization.

6. *secuTrial* is a commercial, web-based, clinical data capture system with integrated randomization service.[8] This system provides all aspects of clinical trial randomization through web-based access. Since secuTrial has been used to compare with the other scientific publications,[7] we selected this system as an example of many other commercial solutions.

Methods

Conducting a controlled clinical trial, subjects need to be registered (enrolled) first and then the randomization system needs to work in conjunction with a separate system (such as the electronic data capture system providing the electronic case report forms). According to the listed features, we first determine the randomization designs we need to support, decouple statistical design in the trial protocol from the system implementation and suggest a system architecture that avoids double data entry and supports mobile access to virtual randomization.

Analyzing requirements for randomization schemes

Table 2 summarizes the results of analyzing three leading medical journals (*Lancet, NEJM*, and *JAMA*) in 2014 with respect to the randomization methods used in randomized clinical trials. According to Lin, Zhu, and Su, stratified blocked randomization and simple blocked randomization are used most commonly with 70% and 12% of 224 analyzed trials (*Lancet*: 92; *NEJM*: 57; and *JAMA*: 75), respectively.[11] According to these figures, 88% of all trials are satisfied providing simple or restricted randomization designs.

Decoupling statistical design from system implementation

The two most frequent randomization concepts (restricted and stratified) need the number/names of the study arms, sites, strata, and the number of times each treatment occurs in a block. Therefore, we seek statistical software that can be fed with the parameters and returns randomization lists. Furthermore, the software shall be free of charge (support of low-cost investigator-initiated trials) and must provide batch modes for automatic processing. The R Project for Statistical Computing is a free and open source software environment for statistical computing and graphics.[23] Since it compiles and runs on a wide variety of UNIX platforms, Windows and MacOS, it has been selected for virtual randomization.

Listing 1 (see Online Appendix) shows the comprehensive R code. It is based on only 11 parameters (Table 3). Each element within the stratification variable (StrataVar) is a set of possible categories. If the parameters StrataVar and CurrentStrata are not provided, a single randomization list is prepared. The parameter Index is indicating the subsequent element to be randomized within each strata. It is initialized with a vector of length equal to the number of strata and all elements are set to 1. The R script returns a list containing allocation (element of treatment or a permutation of treatment) and the updated Index indicator. The verbose mode prints extra information.

Designing the system architecture

The system architecture must support two use cases. During the trial preparation and setup phase, the investigator or data manager just needs to enter the stratification categories and their instances, which may include the sites, design, and type of randomization, and—if a blocked design is chosen—the number of times each treatment occurs in a block. This information is taken from the written trial protocol, where it has been provided by a statistician.

During the recruitment phase of the trial (trial conduct), subjects are allocated either using a computer connected to the Internet or a mobile device such as a smartphone. To bridge the use cases and interconnect

Table 2. Randomization methods used in RCTs.[11]

Randomization type	Randomization model	N	%
Simple	Simple randomization	14	6
Restricted	Random allocation rule	0	0
	Block randomization	27	12
	Stratified block randomization	156	70
Dynamic	Minimization	24	11
	Hierarchical randomization[22]	3	1

RCT: randomized controlled trial.

Table 3. Variables and parameters needed to implement simple and restricted randomization in R (see Online Appendix).

Parameter	R data type	Description
RandoDesign	Character	Indicates parallel or cross-over design
RandoType	Character	Indicates simple or blocked randomization
Arms	Character	The treatment arms of the trial
Sites	Character	The possible sites
StrataSite	Logical	Use/do not use sites as stratification variable
CurrentSite	Character	Actual site; must be one of the elements of sites; ignored if StrataSite is false
StrataVar	List	The stratification variables and their instances
Seed	Double	Seed of randomization
Repetitions	Double	Number of times each treatment occurs in a block (treatment per block)
Index	Double	Indicators of the next element to be randomized within each strata
CurrentStrata	Character	Stratification categories for which allocation is requested

the data manager as well as the research nurse with the R server, a core instance is needed. As a central core component, we suggest the use of either the clinical trial management system or the electronic data capture system, since both systems are connected with a database, provide user account management including access rights and roles, and already capture required information on trials, users, and sites. Using their application programming interfaces, the R server is connected.

Figure 1 depicts the resulting architecture. In the trial preparation phase, the data manager reads the parameters from the trial protocol and defines the virtual randomization. In the trial conduct phase, web-based and mobile access is provided for subject allocation. The web interfaces and the mobile apps are connected using the hypertext transfer protocol and representational state transfer web services, respectively.

The core component is connected to the database and the R server using structured query language, the Java R interface. The database is also used to store the randomization seeds and the number of subjects already randomized in each of the trials.

Selecting the core component

In previous works, we have developed a clinical trial management system, the so-called study management tool[24] as well as an electronic data capture system, the so-called framework for rare disease registries.[25] Both systems are implemented in Java and based on the Google Web Toolkit[26] that is a development toolkit for building and optimizing complex and powerful browser-based single page applications.

Both systems are connected with a structured query language database, which is used to store meta-information of trials including the name and type of studies, study sites, and study personnel. They allow the management of user roles and access levels.

Additionally, in the clinical trial management system, the study arms are modeled for cost calculations too. In both options, the R server is addressed using the Java R Interface protocol. It also provides a de-identification service[27] and assigns a screening number.

User acceptance testing

After completion of system integration, systematic user acceptance testing[28] has been performed. In sham studies, random allocation was carried out with the implemented random sequence generation models and the allocations provided by the system were checked against expected allocations. The following randomization models were tested: simple randomization without stratification, simple randomization within strata, restricted randomization using random allocation rule without stratification, random allocation rule within strata, blocked randomization without stratification,

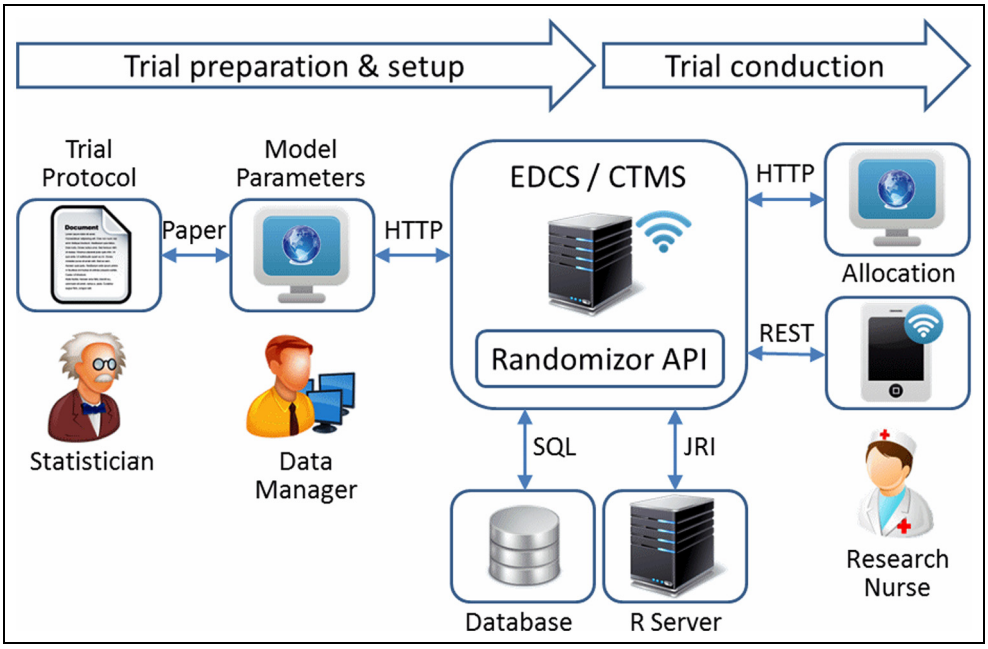

Figure 1. The system architecture supports the data manager and the research nurse in trial preparation and conduct, respectively. API: application programming interface; CTMS: clinical trial management system; EDCS: electronic data capture system; HTTP: hypertext transfer protocol; JRI: Java R Interface; REST: representational state transfer web services; SQL: Structured Query Language.

and blocked randomization within strata. For block randomized models, block sizes of 2, 4, 6, 8, and 9 were tested. Stratified models were tested using up to three stratification variables and maximum three levels per variable. All identified errors that occurred during the allocation process were corrected and the system was re-tested until no errors occurred.

Results

Individual password management and the user roles and access levels of the core system ensure appropriate control of access for defining and performing random allocation and accessing previous allocation information. Access to input and modify the randomization model is controlled by special rights in either of the core systems. The complete randomization list is not accessible throughout the entire study management tool system. Three use cases are considered.

Use case: trial setup

The randomization models are easily entered by the data manager using a web-based graphical user interface in which the study sites, treatment arms, and type of randomization have to be specified and, if applicable, the stratification variables and block size have to be specified (Figure 2). Access grants for specific users are also defined in the setup phase.

The example depicted in Figure 2 represents a multicenter trial (centers: Aachen & Witten) with two study arms (treatments pentaglobin and control) and the strata immunoglobulin status (IS_status) which is classified into low, medium, and high. The study has a parallel design and blocked randomization scheme, where the sites are used as strata. The number of treatments occurring in each block is 5. This yields an actual block size of 10.

In addition to the specific choices for random sequence generation, the randomization model setting also includes the option of whether allocation information should be available to all users with access to the study or only to a restricted subset of un-blinded users. In a double-blinded protocol, an email is sent to a specified person or persons and the user is notified that the randomization has been done successfully.

Once the model is defined, the system is set into operation mode. A study-specific randomization seed is generated, which is used for the randomization process. Thereafter, the statistical model itself cannot be altered anymore while sites still can be added.

Use case: web-based subject allocation

In the conduct phase of the trials, enrolled subjects are entered into the core system. The user selects the appropriate trial and subject, enters all strata parameters, and performs the virtual randomization. The allocated arm is returned instantaneously and—for non-blinded or simple-blinded designs—displayed directly to the user. Using the communication features of the core system, emails are sent automatically to the appropriate

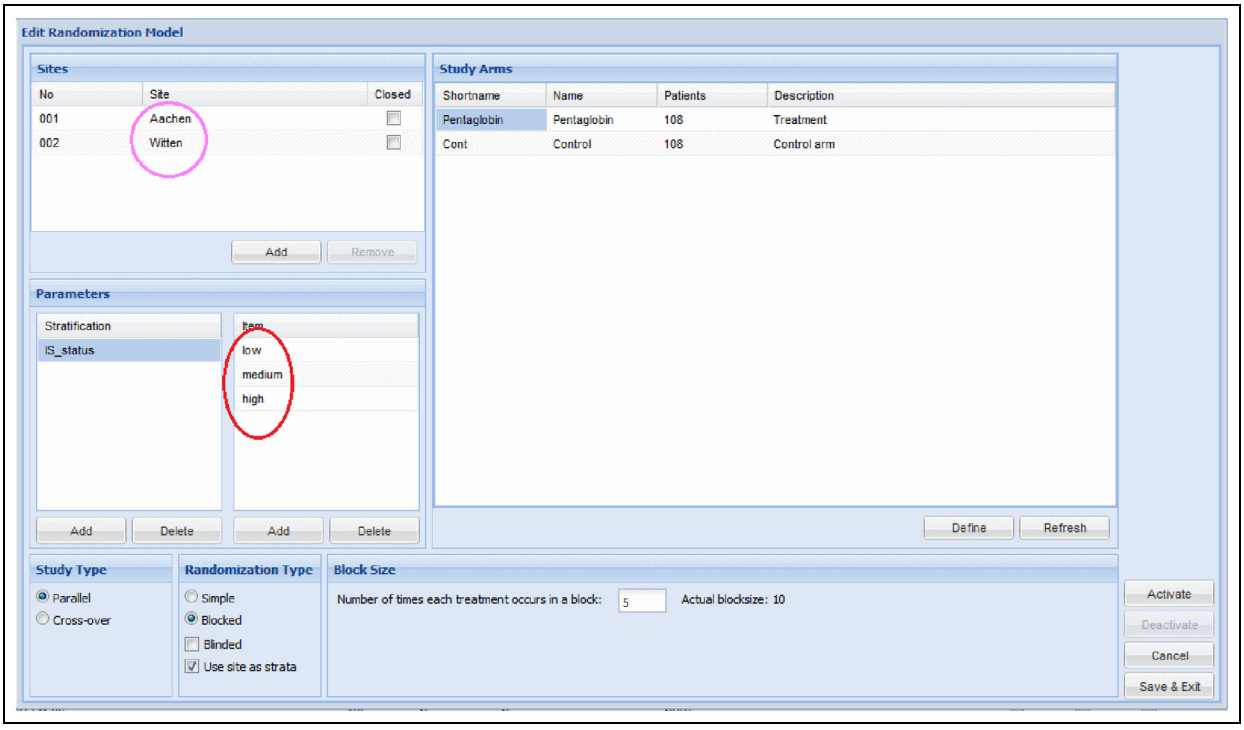

Figure 2. Google Web Toolkit–based graphical user interface for specifying the randomization model for a study, in this example, there are two sites (purple mark), two treatment arms, and one stratum of three instances (red mark) defined.

persons, for example, the pharmacist in charge of providing double-blinded study medication. This procedure also allows the reconstruction of allocation list in case of accidental loss of allocation information from the system.

Figure 3 exemplifies the web-based subject allocation using our clinical trial management system as core system. On the right hand part of the graphical user interface, the site and the immunoglobulin status (IS_status) are selected by the research nurse. Then, the nurse is required to press the "Random" button, and the resulting allocation is displayed on the screen (Figure 3(b)). The R call for this allocation is as follows:

random_allocation("Parallel","Blocked", Arms = c ("Pentaglobin", "Control"), c("Aachen","Witten"), StrataSite = TRUE, "Aachen", StrataVar = list (c("low", "medium", "high")), Seed = 1234, Repetitions = 5, Index = c(10,1,1,1,1,1), CurrentStrata = "low")

Use case: mobile subject allocation

In addition to the web-based randomization, mobile applications (apps) have been developed for Android and iOS using Java and Swift,[29] respectively. They allow randomization at patient sites, in the operation theater, or at any other place where computer systems are not available.

To perform study participant allocation, the user logs onto the app. The app does not allow allocation unless all the mandatory fields are completed by the user. These fields are as follows: study, status, screening number, inclusion date, study site, and, if applicable, the levels of stratification factors. Of course, data already stored in the core system are transferred automatically and does not need re-entry. Figure 4 shows a randomization performed on the Android app.

After successful randomization, a study-specific unique randomization number is assigned to the subject and displayed to the user, or, depending on the pre-set model settings (in double-blinded trials), group allocation information is sent via e-mail to the appropriate person.

Routine use

The randomizer tool is already in use for six trials that are managed by the Center for Translational & Clinical Research Aachen at Uniklinik RWTH Aachen, Aachen, Germany, and 156 study subjects have been allocated successfully without any delay or malfunction.

Discussion

The aim of this project was to create a tool that provides a user friendly access to patient allocation using virtual randomization. The main motivation was to support the study team that is responsible for

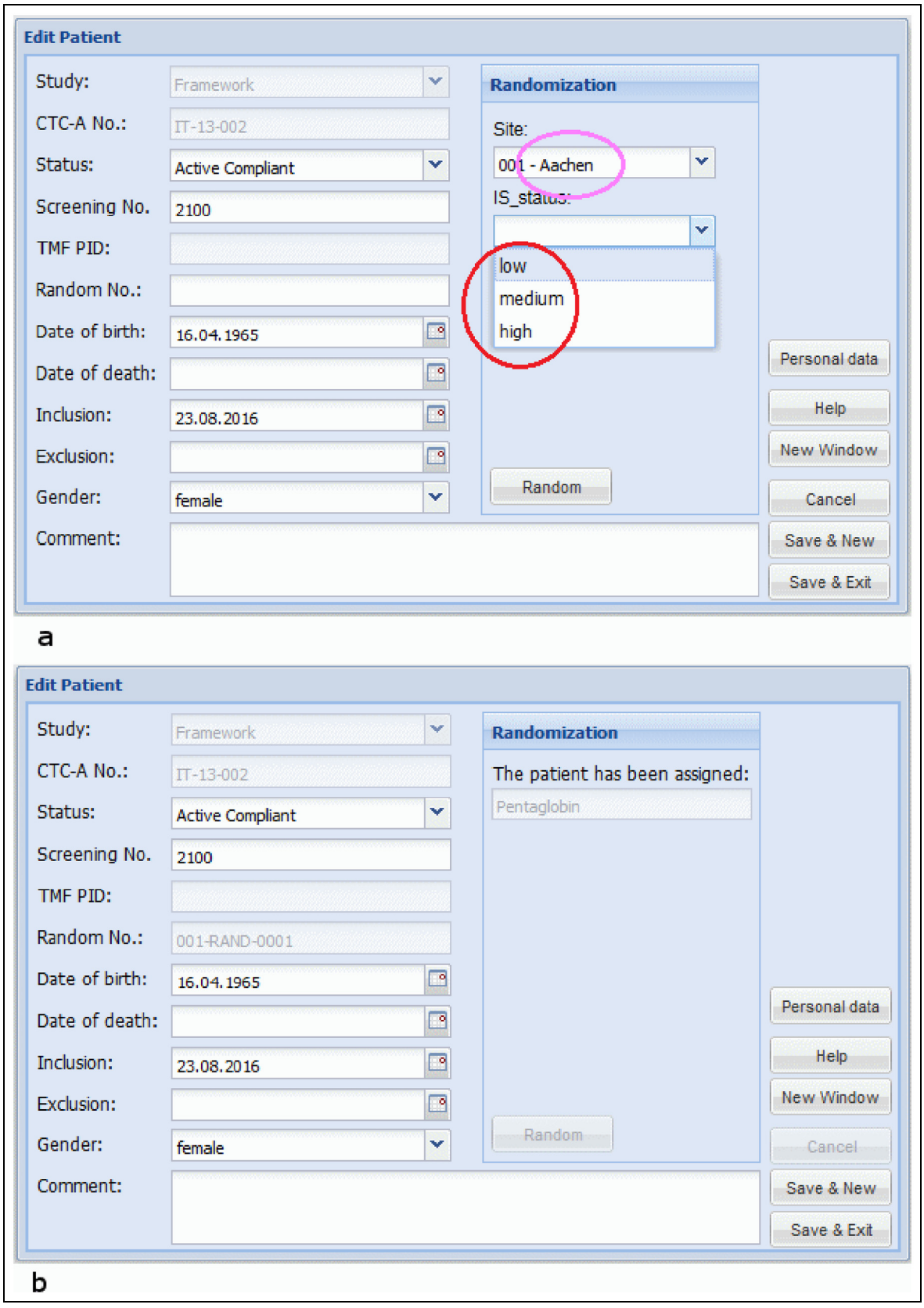

Figure 3. (a) Requesting a treatment allocation in the web-based application. (b) Information shown after successful assignment. Purple and red markings indicate site and stratification levels, respectively.

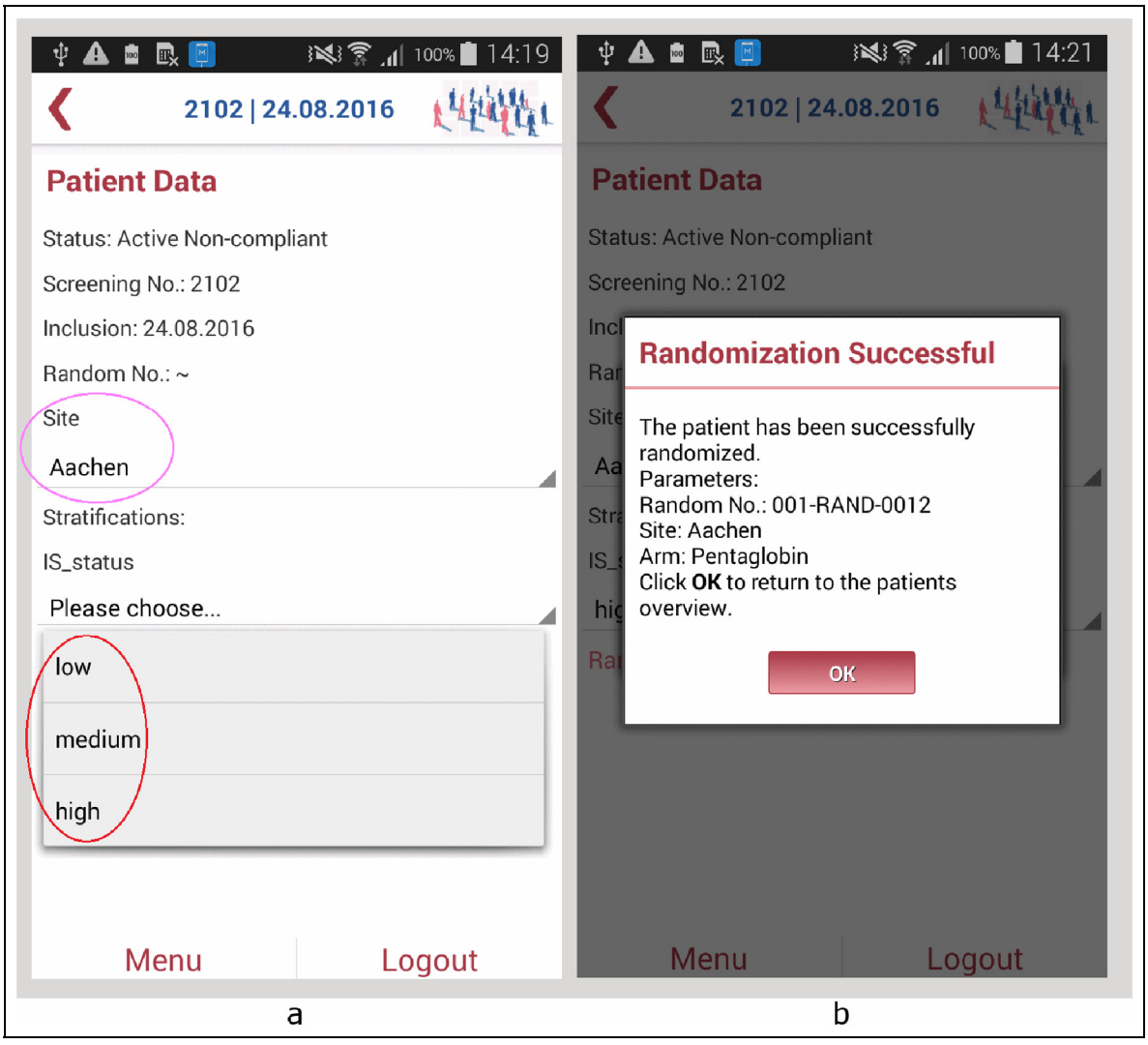

Figure 4. Random allocation on the Android application: (a) input screen and (b) output screen. Purple and red markings indicate site and stratification levels, respectively.

participant allocation. Desirable properties of randomization systems include the following: (a) availability of multiple randomization models, (b) support of centralized randomization, (c) control of access to treatment allocation information to ensure blinding of appropriate users, and (d) verification of eligibility to reduce the chance of allocation errors.

There are also advantages of integrating randomization systems with clinical trial management tools.[7] According to Schulz et al.,[3,4] inadequate and unclear allocation concealment exaggerates the effect of interventions by 41% and 30%, respectively. Although this might not solely be attributed to people having access to treatment lists, central randomization and the use of envelopes have been established as common methods to implement random allocation.[30] However, human-based services may be unaffordable in investigator-initiated trials lacking industrial sponsorship. Electronic randomization can be operated without manual interaction, once a web-based system has been set up. Evolutionary, the next step is virtual randomization, where the management of a randomization list is avoided. Each list entry is generated correctly on demand. This technology also supports mobile access.

A major advantage of web-based, centralized allocation systems is that they offer an improved maintenance of allocation concealment, which has been shown to be crucial to the validity of clinical trials.[4] The unavailability of a randomization list and the controlled access to allocations reduces the chances of guessing subsequent treatment allocations. Mobile randomization provides an opportunity for treatment allocation in special circumstances, where final eligibility of a patient depends on decisions made in special settings such as in the operating theater.

Another key contribution of this work is seen in the R script (see Online Appendix). This R code holds all particular expertise to define the statistics of 88% of all

trials. Therefore, it enables non-statisticians (e.g. a data manager) to initiate the virtual randomization for a certain trial simply following the description from the trial protocol. Note that in the setup phase, only the parameterization must be specified but all statistical syntax and semantics are hidden to the user setting up the model. This is a major advantage of virtual randomization over electronic randomization.

With respect to our R code (see Online Appendix), the number of strata is not limited. Sometimes when block sizes and/or number of stratification factors are too large, there may be a problem of over-stratification.[31] Extending the program accordingly will allow for an error check (or warning message) when that happens, which can be seen as another advantage of virtual randomization.

So far, we have linked the randomization system with our clinical trial management system. However, we have already suggested integrating the randomization system and the electronic data capture system (see Figure 1). As an advantage, randomization can be performed automatically if all required subject details have been entered into the electronic case report form of the trial. In addition, eligibility verification can be performed instantaneously and only those subjects that are eligible will be offered for mobile or web-based randomization. Furthermore, automatic randomization will be useful particularly for dynamic randomization schemes. So far, automatic randomization is used in randomized database studies.[32]

In our approach, we have used R as the statistical software. This however, can be easily exchanged by commercial software such as Statistical Analysis System or the Statistical Package for the Social Sciences. For instance, Hu et al.[33] have provided code segments for Statistical Analysis System in completely, stratified, and dynamic randomization grouping.

Although the introduction and endorsement of the Consolidated Standards of Reporting Trials statement has improved the reporting of clinical trials, the assessment of the methods of randomization is still hindered by the large proportion of unreported details.[34,35] A recent review provided evidence that 88% of the statistical designs in recent trial protocols are simple and restricted randomization,[11] which are supported with our system. However, the figure may be lower as in the future the frequency of dynamic randomization may increase.[12,13]

Further limitations of our tool are as follows: (a) in its current form it does not support adaptive randomizations designs, (b) cross-checking for relevant exclusion criteria has to be performed manually, and (c) backup plans have to be set up to handle situations if the system or the Internet connection is unavailable when an allocation is requested. Future work will focus on advanced system integration, and interfacing rare disease registries,[25] where subjects may participate in several clinical trials. To this end, we also plan to obtain user feedback from study personnel using the system.

Conclusion

We have provided an integrated allocation tool to conduct controlled clinical trials. Mobile access to virtual allocation lists improves protocol concealment and reduces the chances of human error.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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