PhUSE 2017

Paper SD02

FlexRandomizer®: Easy Randomization in Real Time

Priyadarshan Shinde, Cytel, Pune, India
Mangesh Kulkarni, Cytel, Pune, India

ABSTRACT

Despite advances in clinical trial design methodology, it remains difficult to predict interim randomization needs at the outset of a trial. Even when possible, costly implementation and unanticipated biases can lead to the termination of promising research. Cytel's FlexRandomizer® provides randomization for both blind and double-blind studies, with a view to supporting the needs of decision-makers in real-time.

FlexRandomizer® is a highly secure, comprehensive web-based system that precisely performs randomization of both subjects and kits. It provides efficient centralized randomization methods for all phases of the trial. The system offers task-based workflow, study-centric user management, flexible role based control over study documents and randomization lists along with 21 CFR Part 11 compliance and features like audit trail. Audit trail, randomization, and kit lists can be downloaded and analyzed at any time by the study owner. The software has been fully validated and tested.

INTRODUCTION

Several factors need to be taken into account when conducting randomization in clinical trials. It is important to establish the requirements for the randomization like proportion of subjects to be allocated to each treatment group, stratification factors to be considered, block size to use, number of centers, how the seed will be defined and what outputs are required (e.g. schedule, randomization envelopes). Often these requirements are called as randomization protocol. In the randomization process, different study roles are required like randomization administrator, quality control, protocol manager.

FlexRandomizer® is a state-of-the-art enterprise web based application, which facilitates the randomization process in clinical trials. It has capability to integrate and communicate with external systems including those of the electronic data capture (EDC) and interactive response system (IxRS).

The software is designed and developed as a scalable SOA web service platform. Some of the typical services provided by the platform are:

- Authentication services
- Workflow services
- Notification services
- File and document repository services
- Audit Trail services
- Execution services

In this paper, the authors will explain the FlexRandomizer® features, regulatory and industry needs with two case studies.

REGULATORY NEEDS

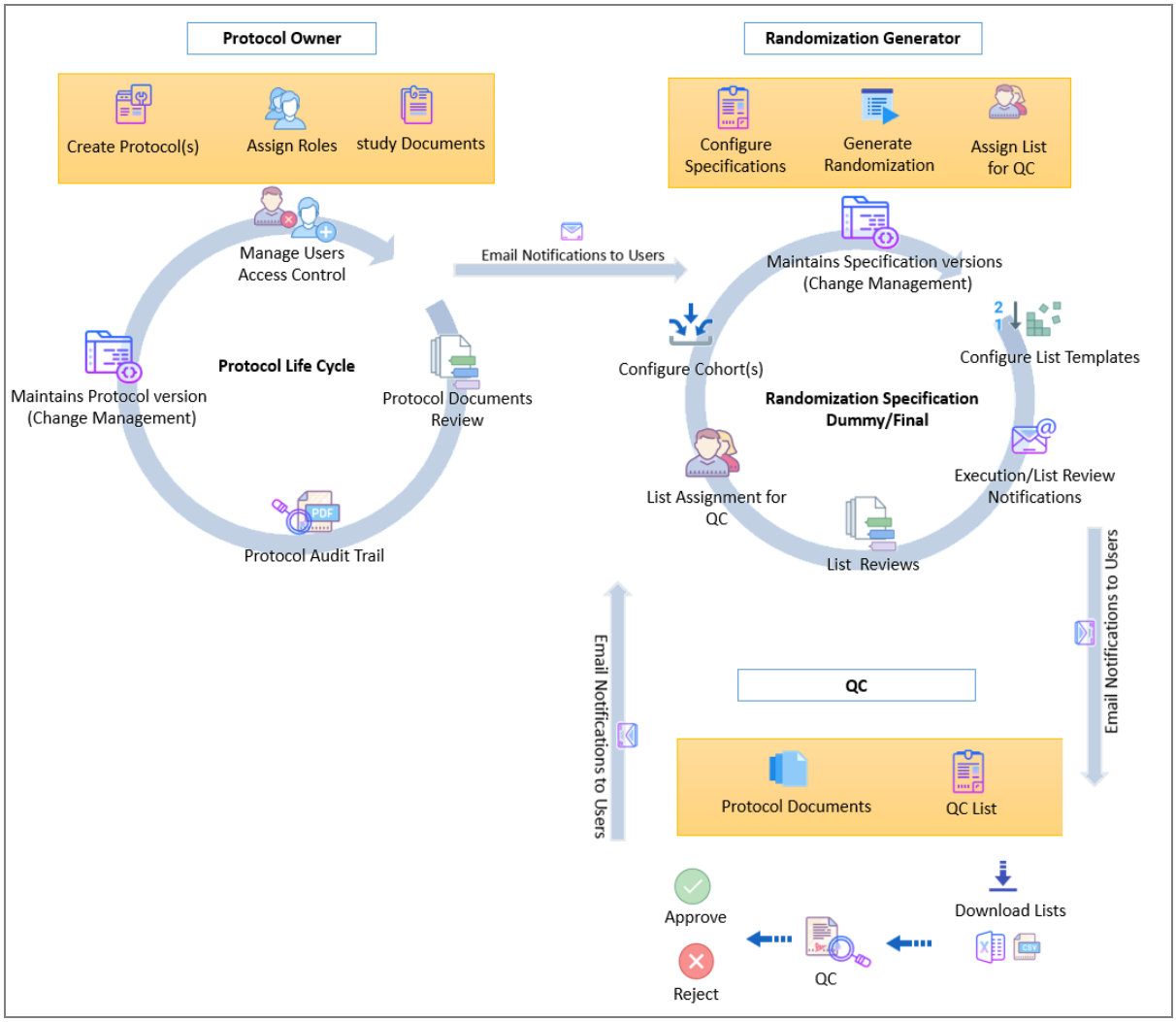
- Blinding and control of operational bias
- Controlled access to system functions
- Audit-ability and real-time inspections

INDUSTRY NEEDS

- Configurable workflow of randomization activities
- Control of who does what, and when.
- Ability to handle events and notify users in real-time

FLEXRANDOMIZER®

The following figure illustrates the different roles in a randomized clinical trial and the way FlexRandomizer provides a controlled access to the protocol creation, randomization, and QC of generated lists.



ICONS FROM HTTPS://ICONS8.COM

Fig1: Typical Workflow and Activities in FlexRandomizer

ROLE BASED ACCESS CONTROL

FlexRandomizer uses role based access control to the different operations in the system. It supports following predefined roles and their permissions.

- **FlexRandomizer Administrator:** Configures application settings, defines default system level starting seed for actual random number generation, manage users, generates system level audit trail report, and assigns protocol owner and administrator roles to one or more users.
- **Protocol Owner:** Defines protocol in the system, uploads protocol related documents, assigns randomization generator and QC roles to protocol users, and generates protocol level audit trail report.
- **Randomization Generator:** Configures randomization and kit specifications, defines list templates, and assigns generated lists for QC.
- **QC:** Performs quality checks for assigned lists.

DASHBOARDS FOR CONSOLIDATED VIEW

FlexRandomizer provides distinct dashboards for following major activities:

- **Protocol Dashboard:** Provides information of open, suspended, and closed protocols in the system
- **Generated Kit and Randomization List Dashboard:** Provides status of randomization runs
- **List File Dashboard:** Provides information of randomization and kit lists along with its QC status
- **Document Dashboard:** Provides access to protocol related documents
- **QC Dashboard:** Provides status of assigned QC lists

RANDOMIZATION CAPABILITIES

For subject randomization, FlexRandomizer has the following capabilities:

- **Block Randomization Method:** FlexRandomizer web services support four randomization methods – Block, Bias Coin, Minimization, and Random. Current version of FlexRandomizer user interface supports 'Block randomization' method.
- **Variable Block Sizes:** Biostatisticians recommend variable block sizes to reduce selection bias. FlexRandomizer accepts up to five different block sizes.
- **Stratification by Factor:** Clinical trials are often designed to analyze the effect of the treatment on subgroups of population having similar characteristics (factors). Stratification in randomization by these factors provides for these subgroups to get the specified treatment allocation in each subgroup.
- **Stratification by Sites:** Clinical trials often have subgroup of population having similar characteristics hailing from different geographical locations. Stratification by sites in randomization provides for these subgroups to get the specified treatment allocation in each subgroup
- **Mask ID:** Mask ID is used in randomization to prevent bias during un-blinded analysis.
- **Replacement Randomization:** Many studies need dropout to be replaced by an alternate subject. Replacement randomization provides additional randomization list for the replacing subjects.
- **Generate Randomization for One or More Cohort:** A cohort is a group of subjects that receive the same treatments and have randomization specifications. FlexRandomizer has the ability to generate lists for more than one cohort at a time.
- **Run Number:** FlexRandomizer has ability to generate additional runs of randomization when the initial randomization gets exhausted.

For kit randomization, FlexRandomizer has the following capabilities:

- **Kit ID:** Each assignment of a treatment needs to be packaged in a Kit. A unique identifying number is to be generated which is generally located on the outside of the kit.

LIST EXTRACTION CAPABILITIES

- **List Extraction in Multiple Files:** Often it is required to extract different types of lists for different study stakeholders. FlexRandomizer supports configuring multiple lists and extracting these at runtime.
- **Extract Lists as CSV or Excel File Types:** FlexRandomizer can extract lists as CSV and Excel file types for integration with different IxRS systems.
- **Configurable File Names and Columns:** FlexRandomizer has the ability to configure file names and column contents.

WORKFLOW CAPABILITIES

- **Dummy-Final Workflows**: Workflow capability provides easy enforcement of task sequences to be notified and executed by different role users.

CASE STUDY1: SUBJECT RANDOMIZATION

In this case study, we will discuss an example of subject randomization to two treatment arms with equal allocation i.e. 1:1 treatment ratio. The protocol has two stratification factors – Age and Gender. Sponsor requires a randomized list using block randomization method having variable block sizes of 4 and 8. Refer to the image below for the subject randomization request from the sponsor.

REQUEST FOR SUBJECT RANDOMIZATION

Sponsor Name: Dummy Sponsor
Protocol Number: DS453-235 Protocol version 1.0

Randomization Protocol: Subject Randomization	
Treatment Arms	1. XBA-VIA 2. Placebo
Treatment Ratio	1:1
Stratification Factors	Yes, 2 stratification factors as below 1. Age (<18, >= 18) Years 2. Gender (Male, Female)
Block Size(s)	4,8
Study requires Mask IDs	Yes Mask IDs will be started including a letter M followed by 4 digit random number from M0001 to M9999
Study requires Mask IDs & Treatment List	Yes
Study replacement strategy	Subjects who withdraw or are withdrawn during the study drug treatment period will not be replaced.
Total # of randomized subjects	960

Output File Specification:

1. The Mask ID list will only include the Mask ID and randomization number
2. The Mask ID treatment list will only include the Mask ID and treatment code
3. Following three randomization lists will need to be generated in CSV file format with file name as
   a. DS453-235-MASTER-RAND-LIST-DUMMY-V1.0-201701XX.csv
   b. DS453-235-MASKID-LIST-DUMMY-V1.0-201701XX.csv
   c. DS453-235-MASKID-TREATMENT-LIST-DUMMY-V1.0-201701XX.csv

Output file type	CSV

***Output file dictionary*: Comma separated data columns in the following order:** Stratum, Mask_ID, Rand_Num, Block_Num, Treatment, and treatment name.

Example List:

Stratum	Mask_ID	Rand_Num	Block_Num	Treatment	Trt_Name
<18 Years_ Male	Mxxxx	nnnn	1-nnn	Placebo	Placebo
>=18 Years_ Female	Mxxxx	nnnn	1-nnn	XBA-VIA	XBAVIA

Case study1: randomization specification requirements

FlexRandomizer requires valid login credentials for access. As discussed earlier FlexRandomizer system has three roles – Protocol Owner, Randomization Generator, and QC. To create a protocol in the system, login as protocol owner.

PROTOCOL OWNER

Following options are available for protocol owner role. These options are accessible from home page as well as from the menu.

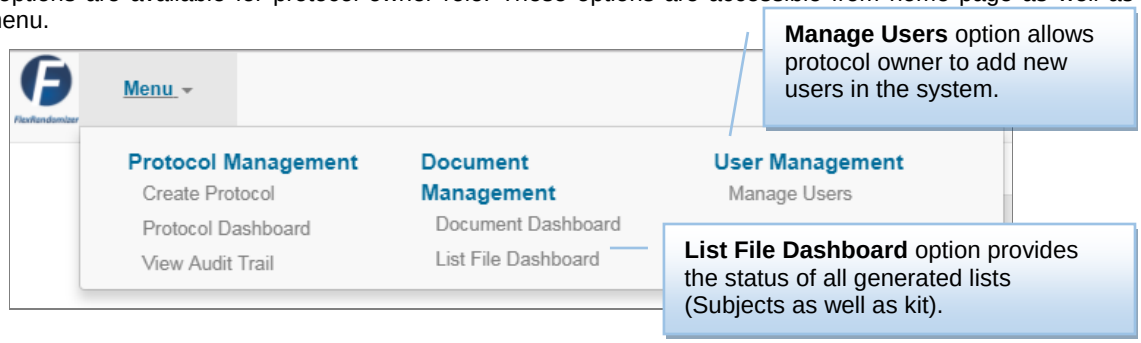


Fig2: Protocol Owner Options

"**Create Protocol**" option is used to create a new randomization protocol, this option invokes the protocol configuration page. Protocol Owner can describe protocol ID and protocol description. As specified above, the protocol ID is **DS453-235** and it is saved in the system. On successful saving, system enables options of assigning

users and uploading documents for the protocol. Fig3 shows the view on successful creation of the protocol in the system.

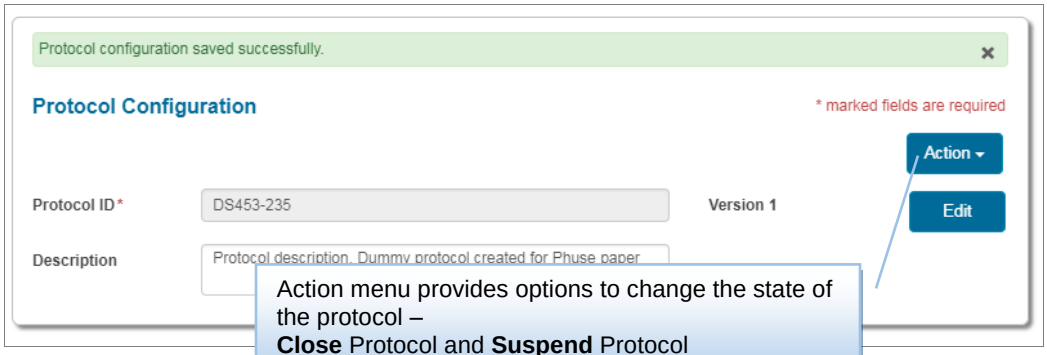


Fig3: Protocol Configuration

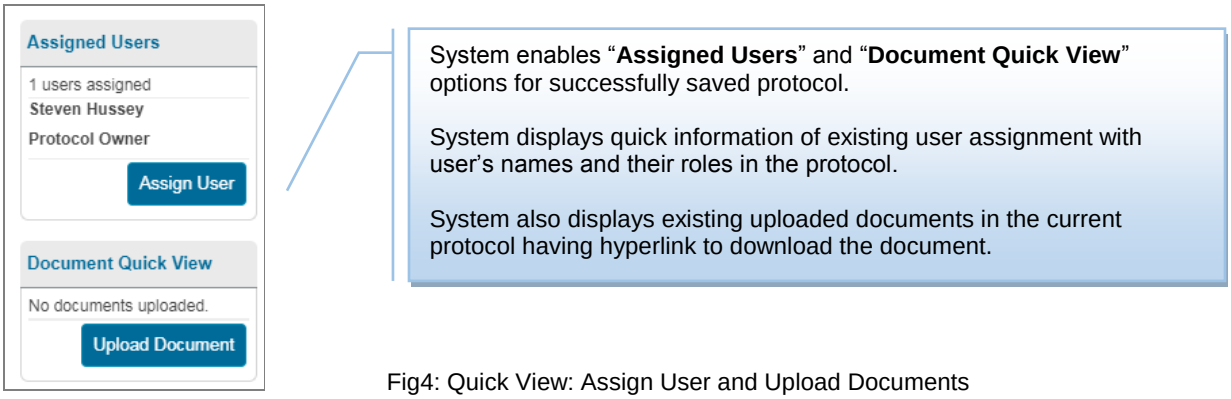


Fig4: Quick View: Assign User and Upload Documents

Protocol owner can upload protocol documents from "**Upload**" option available on **protocol dashboard** for a respective protocol or from "**Upload document**" option available on **document quick view** section. Upload document feature allows uploading any type of document (PDF, Excel, Word) in the system. These documents can be downloaded as a zip file. Protocol users can specify review comments on the document and these comments are visible to all the protocol users.

To configure users and their roles in the protocol, "**Assign User**" option is used to assign users to randomization roles. This option navigates to "**Assign Protocol User**" page. It displays summary of all assigned users to the protocol and provide options to assign new user and manage the existing user's access to the protocol.

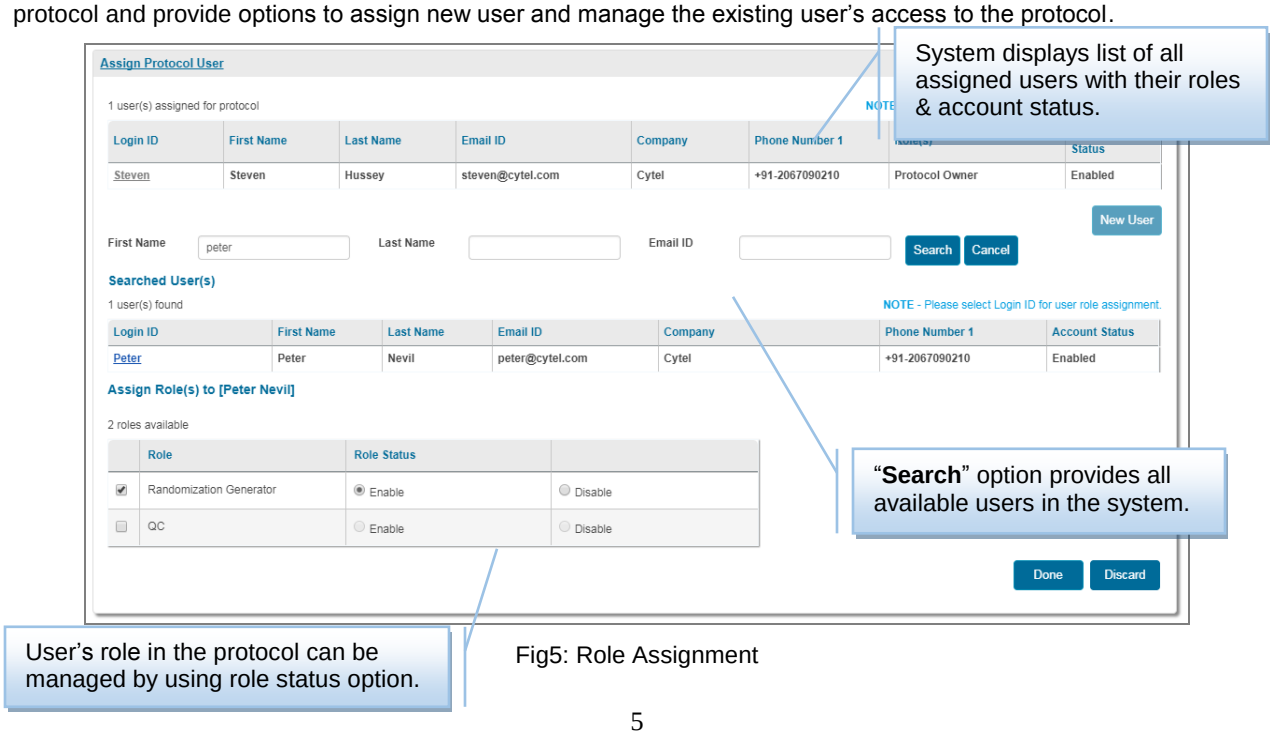


Fig5: Role Assignment

For this study, we have assigned randomization generator and QC roles to two different users. Refer below image (Fig6) for more details.

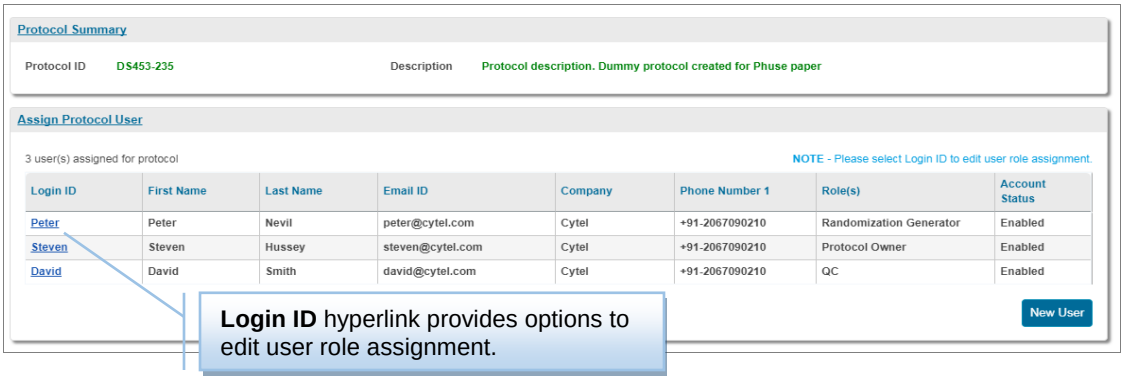


Fig6: Protocol Users

RANDOMIZATION GENERATOR

Randomization generator configures randomization specifications for a protocol. Protocol dashboard provides an option of navigating to protocol configuration page for a selected protocol.

Randomization generator defines treatments. Refer below image (Fig7) for treatment specification as per study request.

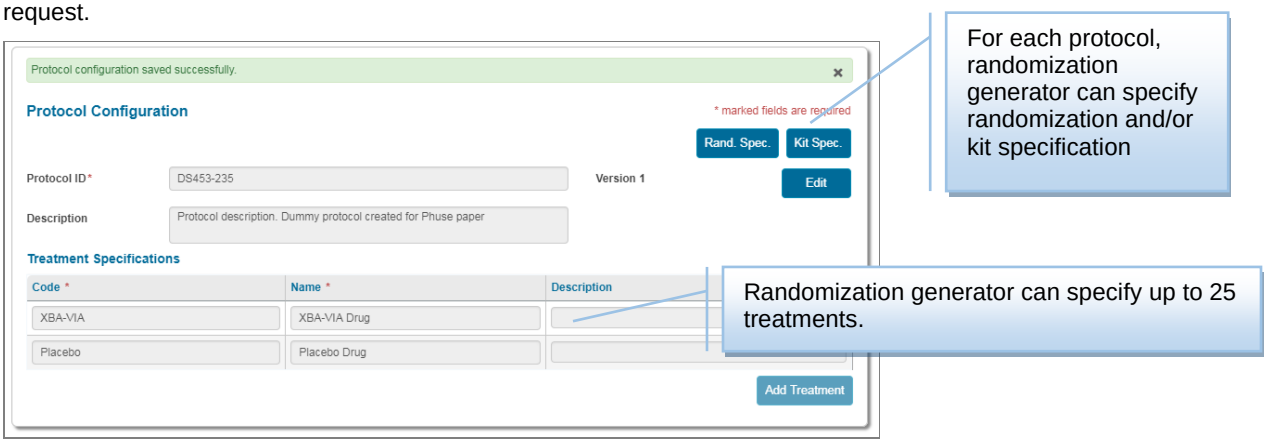


Fig7: Protocol Treatment Specification

As this case study requested for subject randomization, randomization generator navigates to **randomization specification** page using "**Rand Spec.**" option. Randomization specifications allow defining randomization method, No. of replacement randomization, Mask ID requirement, and Mask ID range. Study inputs specified as shown in below image (Fig8).

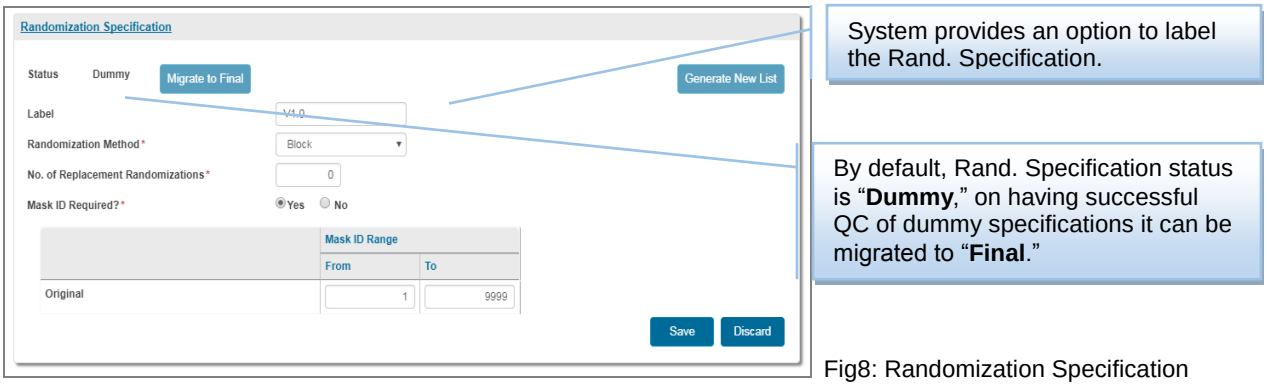


Fig8: Randomization Specification

After successful saving of randomization specification, system enables option for configuring cohorts. Randomization generator can configure a cohort from **cohort list** section. FlexRandomizer provides a facility to configure one or more cohorts for randomization specification. In a cohort, randomization generator can describe cohort ID, treatment specification, stratification factors, and site stratification requirements. User can select two or more treatments for a

cohort. He can also specify ratio of number of occurrences of a treatment in a block (Treatment Ratio) and block sizes. FlexRandomizer allows a user to define variable block sizes.

As this case study has two treatment arms having treatment ratio 1:1 and variable block sizes 4 & 8, these are defined in the system as shown in below image (Fig9). "**Edit Treatments**" option provides **Treatment Specification** section.

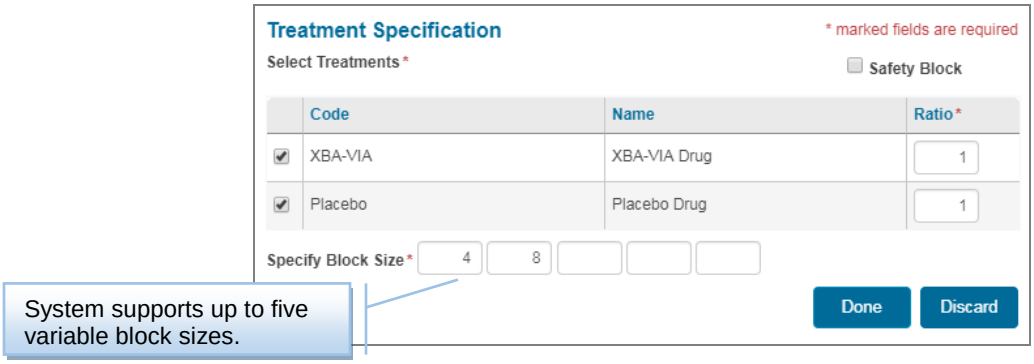


Fig9: Treatment Specification

Stratification Specification option gets enabled by selecting '*Stratify by factor*?' as '*Yes*'. As per study requirement, two stratum variables- Age & Gender along with their values are defined in the system as shown in the image below (Fig10). The system automatically generates the combination of stratum variables.

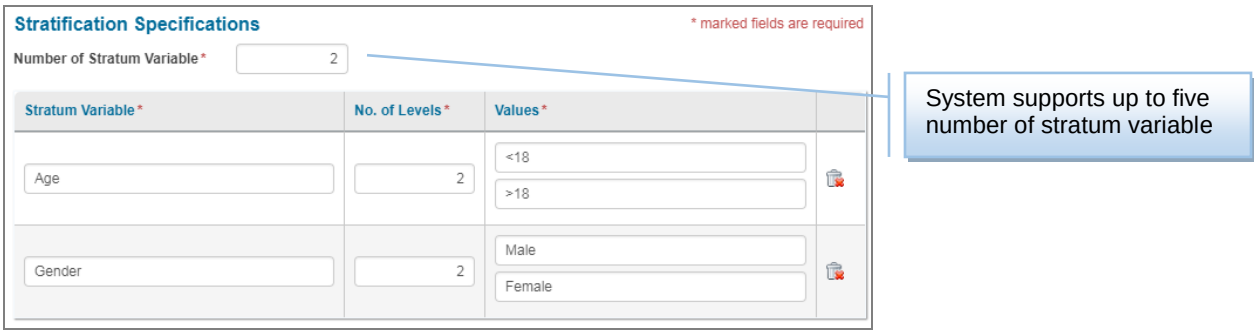


Fig10: Stratification Specification

On successfully saving of the first cohort, system enables the option for configuring '**Randomization File Template**'. This option is provided for configuring output files specifications. Case study requested three files with different file names and different data in each of the file. These file names require protocol ID, some custom text, randomization specification version, and date of generation in it. FlexRandomizer allows configuring dynamic file names. These are configured as shown in below image (Fig11)

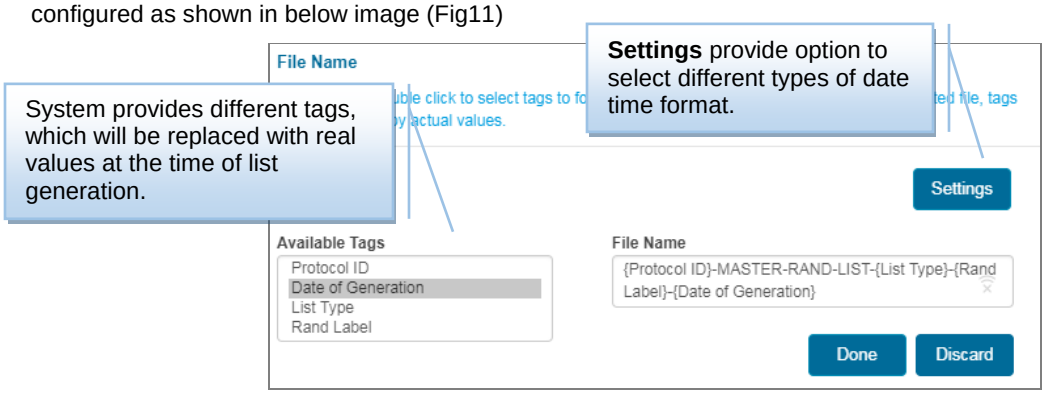


Fig11: File Name

Each output file needs specific columns into it. These columns can be composed using "**Add column**" option. FlexRandomizer provides columns with or without heading, and by default sorted with the specific field.

"Add column" option provides all available fields, which are required for a list. FlexRandomizer provides fields like Protocol ID, treatment code, treatment name, treatment description, cohort ID, stratum value, stratum label, site ID, site name, mask ID, sequence number, block number, list type, stratum number, stratum wise block number, and stratum wise sequence number.

This case study requested master randomization list having six columns. These columns can be added one by one-using "**Add Column**" option. Mask ID column requires four digit values and starting with a letter "M." For this, compose a column by concatenating two fields, one field is constant in which specify a constant value such as "M" and then Mask ID field in which specify the required number of digits in the column as four. Refer image (Fig12) below for the details.

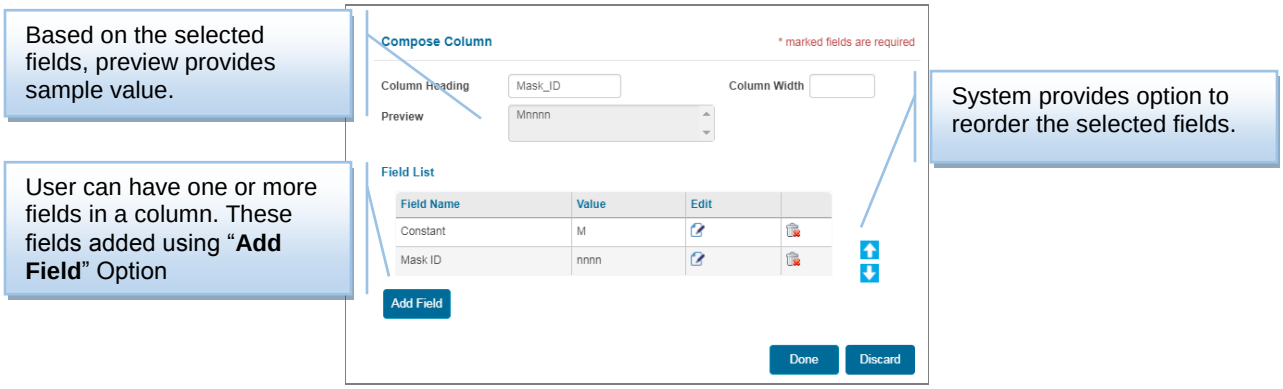


Fig12: Compose Column

Randomization File template section shows the list of configured templates as shown in below image (Fig13).

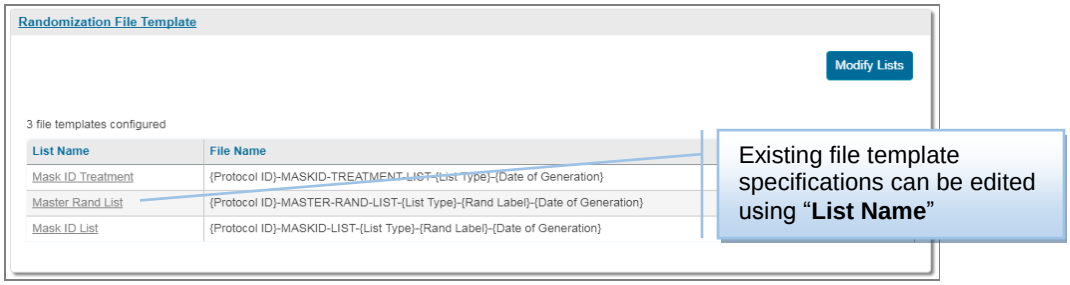


Fig13: File Templates

Randomization specification section enables "**Generate New List**" option. This option invokes the "**Generate Randomization List"** page as shown in below image (Fig14). It shows the list of all configured cohorts and summary of the cohort specification. FlexRandomizer provides an option for selecting starting seed. Starting seed can be selected as clock or fixed value as per the study requirement.

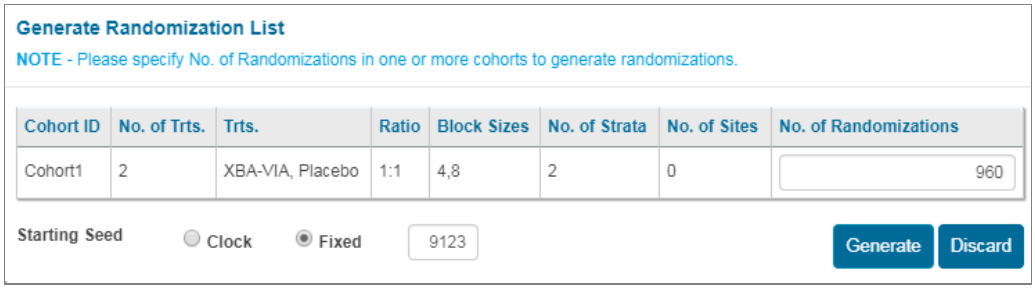


Fig14: Generate Randomization

FlexRandomizer sends email notification on completion of the list generation. **"Generated randomization lists"** dashboard shows the status of list generation request as shown in below image (Fig15). The dashboard provides an option to extract the list or discard the list.

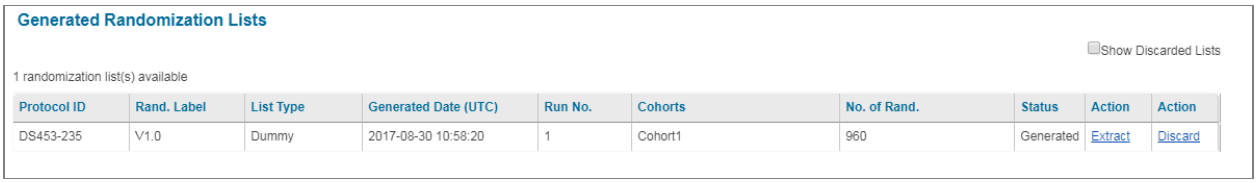


Fig15: Generated Randomization List Dashboard

Extract option allows extracting the generated randomization. It invokes "**Extract Randomization List**" page. System allows selecting list extraction for one or more cohorts. The system provides all configured templates for the protocol. As shown in below image (Fig16.) **Master Rand List** file specification is selected and assigned to QC.

Assign to QC option shows list of available QCs for the protocol. Randomization generator can select one or more QC and assign the list review task.

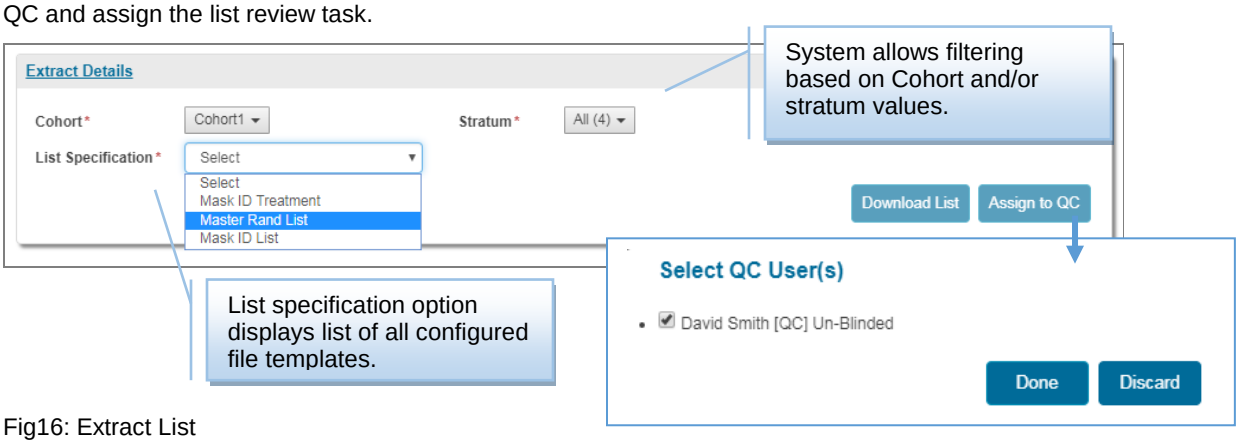


Fig16: Extract List

QC

QC user gets review task for each of the list. QC can download the list and verify it against the study randomization specifications. QC can approve or reject the list. With this system sends email notifications to randomization generator, and updates list dashboard for the current QC status. Refer to the image below for task and OQ dashboard (Fig17.).

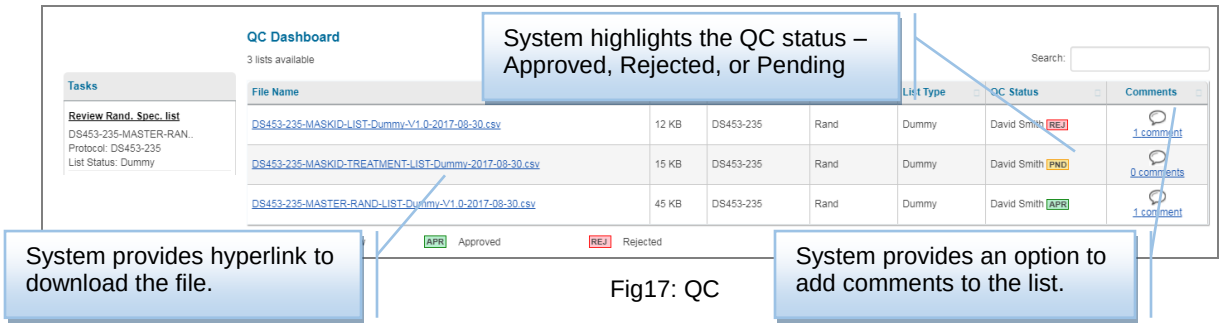


Fig17: QC

On QC approval, randomization generator migrates the specification to final and generates final lists. These lists also get extracted and assigned to QC for review. Below image (Fig18.) is shows generated list.

Stratum	Mask ID	Rand_Num	Block_Num	Treatment	Treatment Name
<18_Male	M5971	1	1	Placebo	Placebo
<18_Male	M7803	2	1	XBA-VIA	XBA-VIA
<18_Male	M5990	3	1	XBA-VIA	XBA-VIA
<18_Male	M2708	4	1	Placebo	Placebo
<18_Male	M2707	5	2	XBA-VIA	XBA-VIA
<18_Male	M9249	6	2	Placebo	Placebo
<18_Male	M3006	7	2	XBA-VIA	XBA-VIA
<18_Male	M2279	8	2	Placebo	Placebo
<18_Male	M7821	9	3	Placebo	Placebo
<18_Male	M6891	10	3	XBA-VIA	XBA-VIA
<18_Male	M6258	11	3	Placebo	Place
<18_Male	M7635	12	3	XBA-VIA	XBA-

Mask ID column extracted according to the specifications.

Fig18: Generated List

CASE STUDY2: KIT RANDOMIZATION

In case study2, we will discuss an example of a kit randomization for two treatment arms having a ratio of 1:1. Five digits kit ID is required in the range of 80000 to 89999. Refer to the image below for the detailed requirement of kit randomization request from a sponsor.

REQUEST FOR KIT RANDOMIZATION

Sponsor Name: Dummy Sponsor
Protocol Number: DS453-235

Randomization Protocol: Subject Randomization	
Treatment arms	1. XBA-VIA 2. PLACEBO
Treatment ratio	1:1
Kit Numbering Scheme	Kit numbers will be 5-digits in length using the range 80000 - 89999
Total # of kits	1200. (600 random kit numbers are to be generated for each treatment arm.)
Comments: For dummy list, you "Draft" labelling and production list use "Final" labeling. Change Draft into Final for the production kit list.	

Output File Specification:	
Output file type (Password protected)	Excel
Output file dictionary **: Comma separated data columns in the following order:** SPONSOR, PROTOCOL, VERSION, SEQUENCE, KIT TYPE (SHORT), KIT TYPE (LONG), KIT NUMBER	

Example List:

Sponsor	Protocol	Version	Sequence	Kit Type (Short)	Kit Type (Long)	Kit Number
Dummy Sponsor	DS453-235	DRAFT	001	2	Placebo	80937
Dummy Sponsor	DS453-235	DRAFT	002	1	XBA-VIA	80772
Dummy Sponsor	DS453-235	DRAFT	003	1	XBA-VIA	80199
Dummy Sponsor	DS453-235	DRAFT	004	2	Placebo	80230
Dummy Sponsor	DS453-235	DRAFT	005	2	Placebo	80379
Dummy Sponsor	DS453-235	DRAFT	006	2	Placebo	80421

Case study2: Kit specification requirements

Kit specifications can be configured using "**Add Kit Spec.**" option from **protocol dashboard** for the respective protocol. System allows specifying kit ID requirements, and provides an option of having randomized kit batch. For this study, inputs are defined as shown in the image below (fig19).

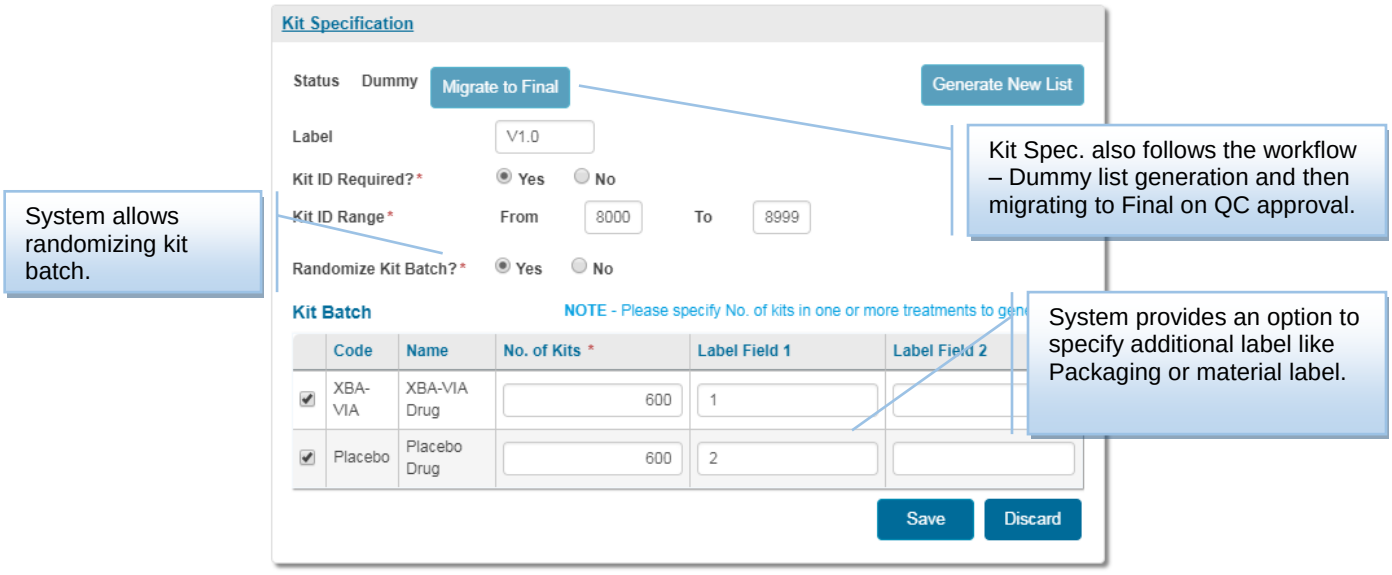


Fig19: kit Specification

Kit File template option enables configuration of output file template similar to subject randomization.

"**Generate New List**" option from kit specification page invokes the **Generate Kit List** page as shown in the image below (Fig20). This page displays the list of treatments configured for a kit batch. System allows selecting starting seed as Clock or Fixed.

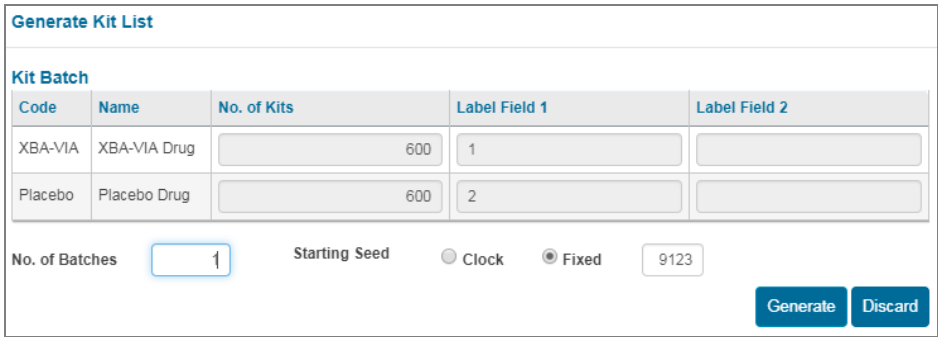


Fig20: Generate kit

FlexRandomizer sends email notification on completion of the list generation. "**Generated kit Lists"** dashboard shows the status of list generation request as shown in the image below (Fig21).

Protocol ID	Kit Label	List Type	Generated Date (UTC)	Run No.	Trts.	No. of Kits	No. of Batches	Status	Action	Action
DS453-235	V1.0	Dummy	9/1/2017 2:00:40 PM	1	XBA-VIA,Placebo	600,600	1	Generated	Extract	Discard

Fig21: Generated kit lists

Extract option allows extracting the generated kit list. It invokes "**Extract Kit List**" page as shown in following image (Fig22.). Select list specification and assigned for QC.

Fig22: Extract kit lists

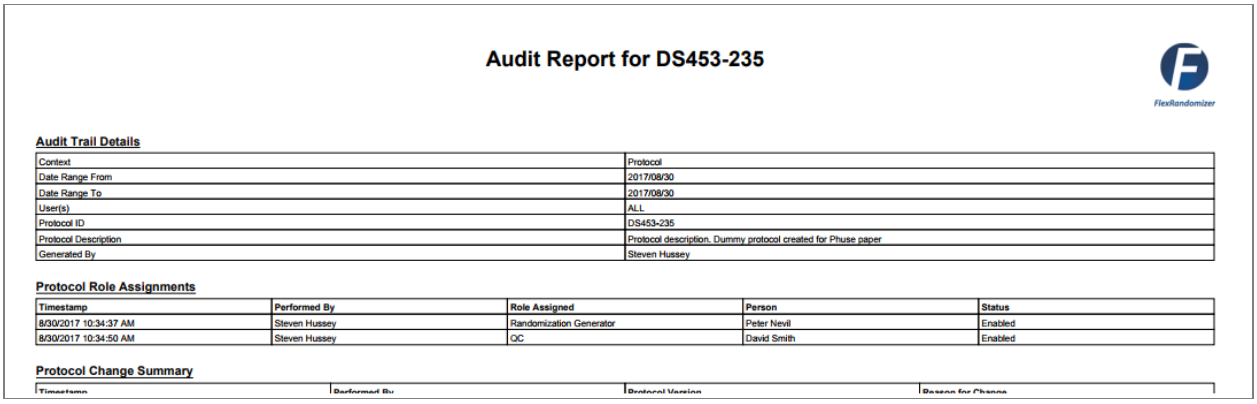
QC user of the protocol gets kit list review task. The list can be downloaded and verified against the study specifications. On QC approval, randomization generator migrates the kit specification to final and generates final lists. These lists also get extracted and assigned to QC for final review. The following image (Fig23.), shows generated kit list.

Sponsor	Protocol	Version	Sequence	Kit Type_Short	Kit Type_Long	Kit Number
Dummy Sponsor	DS453-235	DRAFT	00001	1	XBA-VIA	81193
Dummy Sponsor	DS453-235	DRAFT	00002	2	Placebo	84938
Dummy Sponsor	DS453-235	DRAFT	00003	2	Placebo	87173
Dummy Sponsor	DS453-235	DRAFT	00004	2	Placebo	86236
Dummy Sponsor	DS453-235	DRAFT	00005	1	XBA-VIA	82866
Dummy Sponsor	DS453-235	DRAFT	00006	2	Placebo	82707
Dummy Sponsor	DS453-235	DRAFT	00007	2	Placebo	89249
Dummy Sponsor	DS453-235	DRAFT	00008	2	Placebo	83006
Dummy Sponsor	DS453-235	DRAFT	00009	1	XBA-VIA	82279
Dummy Sponsor	DS453-235	DRAFT	00010	1	XBA-VIA	84282
Dummy Sponsor	DS453-235	DRAFT	00011	2	Placebo	86449
Dummy Sponsor	DS453-235	DRAFT	00012	2	Placebo	83593
Dummy Sponsor	DS453-235	DRAFT	00013	2	Placebo	88163

Fig23: Generated kit list

AUDIT TRAIL

Protocol owner generates protocol level audit trail report. This option is available on home page or from menu option. FlexRandomizer allows filtering the audit trail based on the users and/or the date. Audit trail report is downloadable in non-editable file format (PDF file format). Refer to the following image (Fig.24) for audit trail report.



Audit Report for DS453-235

FlexRandomizer

Audit Trail Details

Context	Protocol
Date Range From	2017/08/30
Date Range To	2017/08/30
User(s)	ALL
Protocol ID	DS453-235
Protocol Description	Protocol description. Dummy protocol created for Phuse paper
Generated By	Steven Hussey

Protocol Role Assignments

Timestamp	Performed By	Role Assigned	Person	Status
8/30/2017 10:34:37 AM	Steven Hussey	Randomization Generator	Peter Nevil	Enabled
8/30/2017 10:34:50 AM	Steven Hussey	QC	David Smith	Enabled

Protocol Change Summary

Fig24: Audit Trail

CONCLUSION

FlexRandomizer provides the following benefits:

- FlexRandomizer is a validated standard software system.
- Provides a platform that can standardize the workflow of randomized clinical trials.
- Provides centralized view to the study stakeholders to view progress of the trials.
- Addresses regulatory concerns of tracking trial changes, operational bias, and auditability.
- Provides wide range of options for list configuration and extraction.
- Provides a scalable platform having ability to connect to external systems.

REFERENCES

- FlexRandomizer user manual
- http://www.cytel.com/software/flexrandomizer

ACKNOWLEDGMENTS

The authors would like to thank all the colleagues at Cytel who gave their valuable inputs as and when required.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Please contact the authors at:

Priyadarshan Shinde Priyadarshan.shinde@cytel.com Work Phone: +91.20.6709.0210
Mangesh Kulkarni Mangesh.kulkarni@cytel.com Work Phone: +91.20.6709.0245
Fax: +91.20.6604.0120
Cytel Statistical Software & Services Pvt. Ltd.
6th Floor, Lohia-Jain IT Park, A Wing, Chandani Chowk, Paud Road, Kothrud,
Pune 411 038, India
www.cytel.com