

sealed envelope™

Randomisation

Version 11

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March 26, 2016

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Chapter 1

Overview

Sealed Envelope's comprehensive randomisation system allows investigators to randomise patients to clinical trials quickly and simply using their web browser and/or telephone.

The system can also be used by staff at trial coordinating centres to view and download randomisation data, add sites, view reports on randomisation activity and, where appropriate, view and update the randomisation code list to aid supply logistics activities.

Each system is configured individually for the trial it relates to. This means that some features described in this help may not be enabled for your trial.

This documentation applies to version 11, released 25th March 2016. The version number is shown in the footer of every page when logged into the randomisation system.

Chapter 2

Getting started

Investigator and randomisation accounts

If you will be randomising patients, an administrator for your trial will create your user account. Administrators are usually staff at the trial coordinating centre. The login details will be sent to your email address. This user account will normally be associated with your site and you will only be able to randomise and view randomisations at this site.

When you login, you will normally first arrive at a [summary page](#) showing the trials you have access to. You can also manage your account details and [change your password](#) here. You can get to the summary page at any time using the **Home** link.

Once you access a trial you will be able to see [previous randomisations](#) at your site and [perform randomisations](#) yourself.

Administrator accounts

When a randomisation system is set up, the first administrator account is created by Sealed Envelope and the login details are sent to that person's email address. The administrator should log in and create the [trial sites](#), unless the sites have been pre-coded by Sealed Envelope.

You do not need to add all your sites at once - you can come back later and add more sites as needed.

Next you should add some investigator accounts for each site so that randomisations can be performed by staff at the sites. You do this through the [user manager](#).

If your trial has a [code list](#) you should update the list to reflect the availability of treatment kits at each site. Randomisation cannot occur if there are no codes available at a site.

Finally check the specification page and randomisation form and report any discrepancies or errors to Sealed Envelope.

Chapter 3

Randomising

For trials set-up for internet randomisation a **Randomise** link will be shown in the top menu bar or a **Randomisation** form will be present in the CRF. Either route takes the user to the randomisation form that requests relevant subject information needed to perform the randomisation. The form will vary depending on the trial; each trial is individually configured. Administrative users may see a field to select the site the subject originates from. Investigators can only randomise for the site they are associated with and so will not see this option.

Once the form has been completed and submitted the user will be asked to review the information they entered and check it is correct. They can return to the previous screen to change items if any are incorrect. To continue, and generate a randomised allocation, the user must enter their password and click on the **Confirm** button. If the randomisation succeeds the user will be shown the randomisation code on-screen. For unblinded trials the code shown is the actual treatment group. Some trials may display multiple codes (for example where the amount of drug to be given depends on a subject's weight).

Randomisation may not succeed for trials with [code lists](#) if no randomisation codes are available for the site concerned. Depending on trial configuration, randomisation may also fail if a subject with the same details has previously been randomised (duplicate).

Subject ID Y8719 | Date entered study: 24 Mar 2016 | 1: UCL, United Kingdom

[Return to subject](#)

[Add Interviewers questions](#)

[Jump to form ...](#)



[+ Create a query](#)

Randomisation

The subject was successfully randomised.

Randomised to **Control** at 24 Mar 2016 17:51 GMT

[Edit this form](#)

This form was created at 24 Mar 2016 17:51 UTC by Sealed Envelope support (ID 1)

Randomisation

Identifier

Y8719

Date of birth

14/03/1969

[dd/mm/yyyy](#)

Currently taking antidepressant?

No

Does the patient meet all inclusion criteria?

Yes

Figure 3.1: Result of randomising a subject

Telephone randomisation

For trials set-up for telephone randomisation the user may randomise a subject using a touch-tone telephone by calling the trial specific telephone number. After authentication, the user will be asked a series of questions to collect stratification information and check eligibility. Once all information has been collected the randomisation will take place and the randomised group or code will be announced to the caller. Telephone randomisations can be viewed in the online system in the same way as randomisations carried out online.

Notifications

An email containing the randomisation code will be automatically sent out to all relevant users that have [notifications enabled](#). Relevant users are trial administrators and all investigators associated with the site that the randomisation originates from. Notifications are not sent to users with suspended accounts. Administrators can see the format of notification emails on the [specification page](#).

Manual randomisation

Occasionally, it may be necessary to randomise a subject outside the randomisation system. This is called a *manual* randomisation. To record the details of manual randomisations in the system an administrator should click the **Enter manual randomisation details** link at the bottom of the randomisation form. This will reveal extra fields: date and time of randomisation, and randomisation group or code. For blinded trials with a [code list](#) the code entered must match an unused code in the code list. However, no other validation is performed on the code: expiry date (if set) and site where the code is available are not checked. Once the form is saved the randomisation is recorded and clearly marked as a manual randomisation. If your trial uses minimisation for balancing treatment groups, then manual randomisations will be taken into account for future randomisations.

Randomisation limit

A randomisation limit is enforced that prevents further randomisations taking place once the limit is reached. The limit can be seen on the [specification page](#). Randomisations [marked as in error](#) do not count towards the limit.

Randomisation disabled

If an administrator has [disabled randomisation](#) it will not be possible to add a new randomisation form. The exception is that administrators can still record manual randomisations. Existing randomisation forms remain accessible for viewing and editing.

Randomisation form

The randomisation form behaves in the same way as other [Red Pill forms](#) with a few exceptions. Firstly, [validation overrides](#) are not enabled so that any errors in data-entry must be resolved before proceeding. Secondly, the [review step](#) is never disabled for the randomisation form, even if it is disabled for other forms in a Red Pill application.

Chapter 4

Viewing and downloading randomisations

Viewing

For trials set-up for internet randomisation only, clicking the **Randomisations** link in the top menu will display a list of randomisations. Administrators will see all randomisations, including manual randomisations and those subsequently marked as randomised in error, but Investigators can only see randomisations carried out at their site.

For trials with a randomisation form in the CRF, clicking the **Subjects** link in the top menu will display a list of subjects. Randomised subjects can be identified from the **Date randomised** column.



The screenshot shows a web interface for viewing randomisations. On the left, there is a search bar and a table with columns: Subject ID, Site, Date randomised, Randomisation code, and Status. The table contains three entries for Exmouth Hospital. On the right, a sidebar titled 'Randomisation details' shows information for Subject ID 2000/21, including Site (Exmouth Hospital, USA), Date randomised (24 Feb 2016 19:02 EST), and Randomisation code (SG6). Below the details are three links: 'View randomisation form', 'Mark as randomised in error', and 'Unblind'.

Subject ID	Site	Date randomised	Randomisation code	Status
2000/21	Exmouth Hospital	24 Feb 2016 19:02 EST	SG6	
2000/22	Exmouth Hospital	28 Feb 2016 10:50 EST	YH5	
2000/23	Exmouth Hospital	2 Mar 2016 05:19 EST	GR1	

Showing 1 to 3 of 3 entries

Randomisation details

Subject ID 2000/21
Site 1: Exmouth Hospital, USA
Date randomised 24 Feb 2016 19:02 EST
Randomisation code SG6

[View randomisation form](#)
[Mark as randomised in error](#)
[Unblind](#)

Figure 4.1: Viewing list of randomisations

The list can be restricted by typing in search terms and ordered by clicking on the row headers. Clicking one of the randomisations or subjects in the list displays more detail for that record. A

link will be displayed to [mark as randomised in error](#) if the subject has been randomised. Some trials may also have a link to [unblind the randomisation](#).

The unblinded treatment group will never be given out by the randomisation system for double-blind trials, except for when the unblinding procedure is followed.

Downloading

The full randomisation list can be downloaded in either CSV or Stata fixed format by clicking on the **Downloads** link in the top menu and choosing the randomisation form from the list of forms. See the [downloads documentation](#) for more information.

The data will vary by trial, but all trials will contain the following standard fields:

- id: primary key, unique id
- Subject id. In Red Pill applications this is the id of the subject that the randomisation belongs to
- Subject identifier: unique subject identifier, may be user entered or generated
- User who created row: the name and user id of the randomiser
- User who last updated row: the name and user id of the person who last edited the randomisation
- Date of study entry in the site's timezone. yyyy-mm-dd format
- Date & time of randomisation (UTC)
- Randomisation code: this will be the treatment group for unblinded trials
- Manual randomisation?: was this a manual randomisation?
- Date of manual randomisation
- Time of manual randomisation
- Timezone for date and time of manual randomisation
- Randomised in error?: was the subject randomised in error? 0=no, 1=yes
- Reason marked in error
- Date marked error (UTC): the date the randomisation was marked as in error
- Timestamp for row creation (UTC)
- Date & time of last update to row (UTC)
- Reason for editing row
- Notes
- Justifications for overriding validation: reasons for overriding validation errors

- Validation status: forms may be marked as 'Not validated', 'Validated', or 'Data unusable'
- Validation notes: notes recorded when changing the form validation status
- Date of study entry in the site's timezone. yyyy-mm-dd format
- Date withdrew
- Site: name of site
- Country
- Visit: the visit that the form is associated with

For blinded trials the data will *not* contain the treatment group, even if the randomisation has been unblinded.

Chapter 5

Editing randomisations

Randomisation forms may be [edited](#) but note the following:

- The treatment group or code can never be edited.
- Making changes to fields used to stratify the randomisation with random permuted blocks will have no effect on the blocking. In other words, randomisation is always stratified by the values recorded at the **time of randomisation**.
- Making changes to fields used to balance the randomisation with minimisation **will be reflected** in future randomisations. Randomisation with minimisation always takes into account the current values of balancing factors at the point of each randomisation.
- Inclusion and exclusion criteria can be changed to show that the subject was not eligible. Validation rules that prevent ineligible subjects being randomised are removed when editing an existing randomisation form.
- Whether a randomisation was performed manually or not cannot be changed.

Chapter 6

Randomised in error

Randomisations can be marked as *in error* by an administrator if necessary. Doing so excludes the randomisation from reports and, where minimisation is used, excludes the randomisation from the balancing algorithm when future randomisations are performed.

Randomisations should only be marked as in error when a mistake has been made, such as randomising ineligible subjects or randomising the same subject twice. Randomisations marked as errors would not normally be included in an intention to treat analysis, and consequently care should be taken not to introduce bias by inappropriate marking. A useful discussion of post-randomisation exclusions can be found in this paper:


Fergusson D, Aaron S, Guyatt GH, Hebert P. [Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis](#) *BMJ*. 2002; 325:652-654.

To mark a randomisation as in error the appropriate record should be viewed and the **Mark as randomised in error** link followed in the subject details section. Marking in error cannot be undone, so care should be taken to ensure the correct record is chosen by double checking the subject identifier shown in the heading. The user will be asked to enter a reason and their password to confirm the need for marking as in error.

After entering a reason and the correct password and clicking the **Mark as in error** button the record will be marked. The date and time, reason and user who marked the record as in error will be recorded in the details for the randomisation concerned. A red warning triangle will be displayed in the status column of the subject list for those marked in error.

Subjects

Search:

Subject ID	Site	Randomisation group	Date randomised	Status
S3365	Royal Albert Hospital	Control	21 Dec 2015 04:50 AEDT	

Showing 1 to 1 of 1 entries (filtered from 26 total entries)

Subject details

Subject ID	S3365
Site	2: Royal Albert Hospital, Australia
Randomisation group	Control
Date randomised	21 Dec 2015 04:50 AEDT
Date of withdrawal from follow-up	21 Dec 2015


 This randomisation was marked as randomised in error on 23 Dec 2015 22:35 AEDT. Reason given: "After randomisation but before treatment patient was found to be ineligible due to past drug use history" by Sealed Envelope support (ID 1).

Figure 6.1: A randomisation marked in error

Chapter 7

Maintenance and rescue codes

Maintenance codes

For some trials maintenance therapy may be given to subjects after randomisation, for instance every three months until the therapy period is finished. Where the trial is double blind it is therefore necessary to generate further codes that match the treatment allocation of the original randomisation code.

To generate a maintenance code for a randomisation the appropriate record should be viewed in the randomisation list and the 'Get maintenance code' link clicked on. The user will then be presented with the randomisation details and asked to enter a reason the code is needed and their password to confirm the need for a maintenance code.

After entering a reason and the correct password and clicking the 'Get maintenance code' button the user will be shown the next maintenance code on-screen, provided a suitable code is available for the site in the [code list](#). In addition an email containing the maintenance code will be automatically sent out to all trial administrators and all investigators associated with the site that the randomisation originates from, as long as they have notifications enabled. All maintenance codes that have been allocated to a subject can be viewed in the randomisation details. Each code and the date and time of allocation are shown at the bottom of the randomisation details.

Replacement codes

Replacement codes are a special type of maintenance code. For trials that don't require maintenance codes, the option to generate a replacement code may be presented. This works in exactly the same way as maintenance codes, and is useful in case a drug kit is damaged or lost after randomisation.

Rescue codes

Some double blind trials have rescue medication - usually a lower dose of the active treatment to be used for subjects showing signs of intolerance.

To generate a rescue code for a randomisation the appropriate record should be viewed in the randomisation list and the 'Get rescue code' link clicked on. The user will then be presented with the randomisation details and asked to enter their password to confirm the need for a rescue code. Following confirmation the user will be shown the rescue code on-screen (e.g. 'R2001'), provided a suitable code is available for the site in the rescue code list. In addition an email containing the rescue code will be automatically sent out to all trial administrators and all investigators associated with the site that the randomisation originates from, as long as they have notifications enabled.

Some trials may allow multiple rescue codes to be generated for the same subject. In this case the additional rescue codes will be appended to existing codes (e.g. 'R2001, R2003').

Chapter 8

Unblinding (code-break)

For some double-blind trials the option to unblind treatment may be offered. This option allows those authorised to unblind the treatment for a subject when it is felt necessary to do so on clinical grounds. Authorised users are administrators and those with an unblinding account. For some trials, investigators may also be allowed to perform unblinding.

To unblind a randomisation the record should be viewed by clicking in the subjects/randomisations list, then the **Unblind** link in the subject details section should be clicked.

The unblinding form will request the name and email address, mobile or fax number of the person to be unblinded.

The user will then be asked to enter a reason for unblinding and their password to confirm the need for unblinding.

After entering these details and clicking the 'unblind' button the user will **not** be shown the true treatment allocation on-screen. Instead an unblinded email, text message or fax will be sent to the designated person. An email stating that an unblinding has taken place will be automatically sent out to all trial administrators and all investigators associated with the site that the randomisation originates from, as long as they have notifications enabled. The date and time of unblinding, user who performed the unblinding and the designated person who was unblinded will be recorded in the details for the randomisation concerned.

The format of blinded and unblinded notifications can be viewed on the [specification page](#).



Subject ID 2000/21
Site 1: Exmouth Hospital, USA
Date randomised 24 Feb 2016 19:02 EST
Randomisation code SG6

By entering your password below you will reveal to a third party the true treatment allocation for the selected subject (shown above).

Please do not proceed unless it is absolutely necessary to unblind this subject. The unblinding will be recorded.

Person to unblind

Send message containing true treatment allocation to:

Name *

Email address

Mobile number

Figure 8.1: Unblinding a designated person


After unblinding

When a subject has been unblinded this will be indicated by an icon in the subject listing, and the subject details will include summary information.

Randomisation details

Subject ID	2000/21
Site	1: Exmouth Hospital, USA
Date randomised	24 Feb 2016 19:02 EST
Randomisation code	SG6

[View randomisation form](#)

 Unblinding history

Unblinded on 25 Mar 2016 07:01 EDT by Superuser (ID 1). Reason given: Patient SAE.
The true treatment allocation was sent to Jacob Benfield (email: jbenfield@example.com).

Figure 8.2: An unblinded subject record

Chapter 9

Code lists

Code lists are only relevant to double blind trials. The code list provides the link between the randomisation code and the true treatment group. It is used by the drug packager or pharmacist, for instance, to label the active and placebo treatments with the randomisation code - see the [FAQ](#) for more information. Here is an example of a code list in the randomisation system:

Block	Code	Site	Treatment group	On site?	Used?	Date used
1	QB2	UCL	Placebo	Yes	No	
1	AV3	UCL	Placebo	Yes	No	
1	QM9	UCL	Active	Yes	No	
1	FW0	UCL	Placebo	Yes	No	
1	KP8	UCL	Active	Yes	No	
1	EW3	UCL	Active	Yes	No	

The randomisation system does not display the treatment group, but it is useful for administrators to view the remainder of the code list because it shows the location of trial treatments and whether they are available for use.

Viewing a code list

For trials that have a code list, a **Code list** link will be shown in the left-hand sidebar to administrators. The list can be searched in the same way as the [randomisations](#). Some trials have expiry

dates on codes - these are shown in the list if this option is enabled.

Updating

Individual codes or blocks of unused codes can be assigned to different trial sites and marked as on site using the form provided. Only codes marked as **on site** and **unused** are available for randomisation. Multiple codes or blocks can be updated by specifying lists (e.g. 3,7,8). In addition, multiple blocks can be specified with ranges (e.g. 1-6).

Tip: check the 'Drug stocks' report frequently and make sure that sites have enough codes on site and available. If minimisation is being used, randomisation may fail unless all treatment groups are available on site.

For some trials, the expiry dates of blocks of codes may also be updated using the form provided. Only unexpired codes will be used for randomisation.

Notes may be added to codes in the list. This might be useful to record when kits are lost or damaged, or removed for testing etc.

Downloading

The full code list can be downloaded by clicking on the 'Download as CSV' link shown at the bottom of the code listing. The code list will be sent as a plain text comma separated value file. The field names are given in the first row. For example:

```
id,randomisationId,siteId,block,expiryDate,code,onSite,used,dateUsed,notes,siteName
1,7,23,2000,2019-11-29,2000/21,1,1,"2016-04-18 12:45:43",,Bath
2,6,23,2000,2019-11-29,2000/22,1,1,"2016-04-14 22:12:17",,Bath
3,,23,2000,2019-11-29,2000/23,1,0,,Bath
4,,23,2000,2019-11-29,2000/24,1,0,,Bath
5,8,23,2000,2019-11-29,2000/25,1,1,"2016-04-23 20:37:12",,Bath
6,,23,2000,2019-11-29,2000/26,1,0,,Bath
7,13,23,2000,2019-11-29,2000/27,1,1,"2016-04-28 22:59:45",,Bath
8,,23,2000,2019-11-29,2000/28,1,0,,Bath
9,,,2001,2018-12-30,2001/21,0,0,,,
10,,,2001,2018-12-30,2001/22,0,0,,,
```


The fields will necessarily vary depending on the trial but the following core fields will always be present:

id Unique index number (primary key)

randomisationId If used, the id of the randomisation record the code was assigned to

block Block id

code Randomisation code

notes Notes

onSite Is randomisation code on site and available for randomisation? 0=No, 1=Yes

siteId Site number - location or intended location of treatment linked to randomisation code

siteName Name of site

used Has randomisation code been used? 0=No, 1=Yes

dateUsed If used, Date and time randomisation code used (UTC)

Chapter 10

Sites

Trial sites (centres) must be added to the system before adding or randomising a subject, updating a code list, or creating investigator accounts. Sites must also be set to **Recruiting** before subjects can be added.

Administrators can add sites by clicking on the **Sites** link in the top menu, followed by the **Create a new site** link.

Site identifier

The site identifier can be any alphanumeric text and may be used in some trials to create a subject identifier of the form SNNN where S is the site identifier and NNN is a sequential number (either within or across sites). Note that once a subject is added to a site it is no longer possible to change the site identifier.

Timezone

The timezone of a site affects the display of randomisation dates and times generated by the system, such as date/time of randomisation, unblinding and marked in error. It is also used by validation rules such as checking whether a date is in the past. Other date/times, such as timestamps on forms, are usually displayed in GMT timezone (UTC).

Note that sites **cannot be deleted** if they have associated records, such as user accounts or subjects.

Create a new site

[Return to sites](#)

Site

Identifier*

Name*

Country

Timezone*

Recruiting*
 Yes
 No
It will not be possible to add subjects at this site if the site is not recruiting

Notes

Figure 10.1: Adding a new site

Chapter 11

Queries

Queries are intended to be used by administrators to raise questions about the form data for investigators to answer and for investigators to notify administrators of any issues they are aware of in completed forms. Queries can be linked generally to a subject, or more specifically to a particular form for a subject. Queries may only be closed by administrator users. Investigators can create new queries and add messages to existing queries.

Opening queries

A query can be opened either on the subject details panel or when viewing a form, by clicking on the **Create a query** link. The query must be given a title and an initial message. To link the query to a specific form in the CRF, choose the appropriate form from the related form drop-down control. Once it has been created, the query will be shown on the subject details panel and form specific queries will also be shown when viewing the form. In addition, if a form has an open query attached, an amber question mark symbol appears next to the form name in the subject details panel.

Note that creating a query or re-opening a closed query linked to a form will cause the form to be marked as **not validated**.

Create a query

Query

Related form
Baseline - Interviewers questions

Related question
Marital status

Title *

Message *

Re: Marital status

Create query

* required

This query relates to the following form:

Interviewers questions

Demographics and Clinical information, ECOG, Treatment Expectation

Figure 11.1: Creating a new query

Adding messages

Messages may be added to queries by investigators or administrators, forming a conversation thread. Administrators can close a query when the issue has been resolved. Administrators may also re-open a closed query by setting the action to 'Reopen' when adding a new message to it.

When viewing a query, printing the web-page will display an extra box that asks the investigator to write their response, with signature and date. This may be useful for the site's own records or workflow.

Email notifications

When a query is created or updated an email notification is sent out to:

- On creation: all administrators, and all investigators at the same site as the subject the query relates to;
- On update: all users who have participated in the query - that is the user who created the query and any user who has added a message to the query.

The format of the notification email is:

```
From: Sealed Envelope
Subject: [Trialname] Query updated
Date: Thu, 22 Oct 2015 15:43:22 +0100
To: joe@trialsite.org,admin@trialcentre.org
```

A query "Confirm date of birth" has just been updated by Joe Bloggs (ID 8). You can view the query here:

<https://www.sealedenvelope.com/Trialname/query/view/3>

Note, this message was auto-generated on Thu 22 Oct 2015 15:43 Europe/London (GMT +0100).

Listing queries

A list of queries grouped by site is displayed by clicking on the **Queries** link in the left-hand sidebar. The conversation thread for a query can be viewed by clicking on the query in the list. This view

Query ID 1: Matching screening?

Current status: Open

Sealed Envelope support (ID 1) on 22 Mar 2016 19:10 UTC Action: Open

Re: Date of birth different to date given at screening - please check.

Action *

None

Message *

Add message

* required

This query relates to the following form:

Randomisation

Figure 11.2: Viewing an open query

[Access](#) | [Logout](#) | [Sealed Envelope support \(ID 1\)](#)

Subject ID T1719 | Date entered study: 31 Jan 2016 | 1: UCL, United Kingdom

Query ID 1: Matching screening?

Current status: Open

Sealed Envelope support (ID 1) on 22 Mar 2016 19:10 Action: Open UTC

Re: Date of birth different to date given at screening - please check.

Action *

None 

Message *

* required

Please write your response above then sign and date.
Investigator name:
Investigator signature:
Date:

This query relates to the following form:

Randomisation

Figure 11.3: Response box shown when printing a query

also displays links for editing the query or viewing the related subject or form.

Chapter 12

Reports

Various reports summarising data-entry and randomisation activity and site status are available by clicking on the **Reports** link in the top menu. Clicking on a report title displays the report compiled from the live database so that it is always up to date. Report data can be downloaded as a plain text comma separated value file by clicking on the **Download as CSV** link. Reports may also be sorted by clicking on a column heading or filtered by entering search terms into the search box.

Completed forms

List of all completed forms and time delay between creation and last edit ("Edit delay"). All dates and times are shown in UTC. Click on a column heading to sort by that column.

[Return to reports](#) [Download as CSV](#)

Search:

Subject	Form	Time completed	Last updated	Edit delay, days	Validation status
T1719	Patient Questions	23 Mar 2016 12:51	23 Mar 2016 17:22	0	Not validated
S5050	Interviewers questions	23 Mar 2016 16:50	23 Mar 2016 16:50	0	Not validated
S5706	Interviewers questions	23 Mar 2016 16:48	23 Mar 2016 16:48	0	Not validated
S3365	Withdrawal	23 Mar 2016 11:48	23 Mar 2016 13:56	0	Not validated
S7008	Withdrawal	23 Mar 2016 12:55	23 Mar 2016 12:56	0	Not validated

Figure 12.1: Viewing a report

Chapter 13

Downloads

CRF data may be downloaded in either CSV or Stata fixed format via the **Download** link in the top menu. The download page shows a list of forms in the CRF and provides links to download the data for each form individually or for all forms (as a zip file).

Data dictionary

A data dictionary can be viewed which shows the fields for each table (there is one table per form). The field name, data type and label are displayed.

CSV format

The data for each form is provided in comma separated value format, which is a plain text file that can be opened in many spreadsheet or Statistical programs. The first row contains a header with the question labels for each column.

Every file contains a subject identifier field so that data stored in different forms can be linked together.

Form data downloads

[View data dictionary](#)

CSV files

These [CSV](#) format datasets can be imported into Excel, Numbers, Google docs, R etc.

Download individual form data:

- Subject
- Randomisation
- Interviewers questions
- Patient Questions
- Satisfaction of Care
- Concomitant medications
 - Medication - part of Concomitant medications
- Patient Questions
- Interviewers questions
- Patient Questions
- Serious Adverse Events
 - Section A - part of Serious Adverse Events
- Withdrawal

[Download all data](#)

Stata files

These datasets are ASCII (text) data in fixed format with a dictionary and can be imported into Stata using the `infile` command:

```
infile using SeWithdrawal_StudyCompletion.dct, clear
```

Figure 13.1: Form data download page

Form data dictionary

[Download form data](#)

Data types are specified as MySQL data types.

Subject

Database table name is **patient**.

Field name	Data type	Additional information
identifier	varchar(255)	Patient identifier
id	int(10) unsigned	
patientId	int(10) unsigned	Subject id
userIdentifier	varchar(255)	User who created row
lastUserIdentifier	varchar(255)	User who last updated row
invNo	int(10)	Telephone randomisation investigator number
dateEnteredStudy	date	Date of study entry yyyy-mm-dd
dateRandomised	datetime	Date & time of randomisation (UTC)
code	enum('Control', 'Intervention')	Randomised group
blockNumber	int(10) unsigned	Block number
blockSize	int(10) unsigned	Block size
blockSequence	int(10) unsigned	Sequence number within block
forced	enum('Control', 'Intervention')	First choice randomised group that was unavailable

Figure 13.2: Form data dictionary

Patient identifier	id	Subject id	User who cre	Timestamp for row creation (UTC)	Sex - Questions	Marital status - Questions	If
T5617	1	1	Sealed Envelo	2016-03-23 11:36:19	Male	Partner - Living with	
T1719	2	2	Sealed Envelo	2016-03-23 12:51:18	Female	Married	

Figure 13.3: Viewing CSV file in spreadsheet

Stata format

The data for each form is provided in Stata fixed format, which is a plain text file format with a dictionary 'header' that describes the format of the rows. Each row contains information from one saved form with a subject identifier field to identify the subject record it belongs to. The data can be easily imported into Stata using the [infile command](#).

For example, to import the data from a baseline form called *Interviewers questions*, the following `infile` command would be used in Stata:

```
infile using InterviewersQuestionsVER1_Baseline.dct, clear
compress
```

where `InterviewersQuestionsVER1_Baseline.dct` is the full filesystem path to the downloaded file. The `compress` command is recommended to reduce the storage space allocated to each variable.

Example

Some interview data has been downloaded in Stata fixed format. There are two rows below the dictionary header because only data on two subjects have been entered so far:

```
dictionary {
  str244 identifier `'"Patient identifier"'
  long id `'"id"'
  long patientId `'"Subject id"'
  str244 userIdentifier `'"User who created row"'
  str244 lastUserIdentifier `'"User who last updated row"'
  str244 created `'"Timestamp for row creation (UTC)"'
  str244 updated `'"Date & time of last update to row (UTC)"'
  str244 question1 `'"Sex - Questions"'
  str244 question2 `'"Marital status - Questions"'
  str244 question3 `'"If other, please specify - Questions"'
  str244 question4 `'"Have you had any previous episodes of depression? - Depression"'
  str244 question5 `'"If so, how many - Depression. Number (up to 2 digits)"'
  str244 question6 `'"Duration of current episode in weeks - Depression. Number (up to 3
  digits)"'
  str244 question7 `'"Are you using any treatments for depression at the moment? -
  Depression"'
  str244 question8 `'"Treatment/Medication Name - Depression"'
```

```

str244 reasonForEdit `Reason for editing row'
str244 notes `Notes'
str244 validationOverrides `Justifications for overriding validation'
str244 validationStatus `Validation status'
str244 validationNotes `Validation notes'
str244 _dateEntered `Date of study entry yyyy-mm-dd'
str244 _dateWithdrew `Date of withdrawal from follow-up - Withdrawal.'
str244 _site `Site'
str244 _country `Country'
str244 _visit `Visit'
}
"T5617" 1 1 "Sealed Envelope support (ID 1)" "Sealed Envelope support (ID 1)" "2016-03-23
11:36:19" "2016-03-23 11:36:19" "Male" "Partner - Living with" "" "Yes" "3" "3" "No"
"" "" "" "{}" "Not validated" "" "2015-12-27" "" "1: UCL" "United Kingdom" "Baseline"
"T1719" 2 2 "Sealed Envelope support (ID 1)" "Sealed Envelope support (ID 1)" "2016-03-23
12:51:18" "2016-03-23 12:51:18" "Female" "Married" "" "No" "" "2" "No" "" "" "" "{}" "
Not validated" "" "2016-01-31" "" "1: UCL" "United Kingdom" "Baseline"

```

The data is imported and compressed, and the output from Stata's describe command can be seen in the screenshot. The variable names and variable descriptions have been picked up automatically from the dictionary header.

```

obs:          2
vars:         25
size:        404 (99.9% of memory free)

```

variable name	storage type	display format	value label	variable label
identifier	str5	%9s		Patient identifier
id	byte	%12.0g		id
patientId	byte	%12.0g		Subject id
userIdentifier	str30	%30s		User who created row
lastUserIdent~r	str30	%30s		User who last updated row
created	str19	%19s		Timestamp for row creation (UTC)
updated	str19	%19s		Date & time of last update to row (UTC)
question1	str6	%9s		Sex - Questions
question2	str21	%21s		Marital status - Questions
question3	str1	%9s		If other, please specify - Questions

Figure 13.4: Form data imported into Stata

Category variables are stored as strings so can be tabulated without needing variable labels. Category variables can be [encoded](#) if storage space is an issue.

```
. tab question2
```

Marital status - Questions	Freq.	Percent	Cum.
Married	1	50.00	50.00
Partner - Living with	1	50.00	100.00
Total	2	100.00	

Figure 13.5: Tabulating imported form data

Conversion notes

During conversion into Stata download format, note the following changes that are made to the data:

- All strings are truncated at 244 characters
- Newlines are replaced by spaces
- Double quotes are replaced by single quotes

Stata with .do file format

This format provides a pair of Stata files per form: the raw data and a **.do** file to process the data. The data is imported by running the **.do** file within Stata. There are some differences to the Stata format described above to make analysis more convenient: categorical variables are stored as numeric values with value labels attached, and additional numeric variables are created for date fields.

Chapter 14

Audit trail

Clicking the **Log** link in the top menu bar displays the audit trail. The most recent 100 lines are shown by default; click the 'Show all' button to see the entire log. The audit trail is a plain text file which can be downloaded if required using the **Download** button. The log records all significant events and changes to the data including:

- Data entry and editing of forms
- Creation and adding messages to queries
- Creation and editing of sites
- Randomisations
- Movement of blocks within code lists
- Unblinding
- Downloads from the system such as reports in CSV format, CRF data, code list and the audit trail itself

An example extract from a log is shown below. The items shown in each row of the log are (from left to right):

- IP address of the user who initiated the event
- Name and user ID of the user
- URL
- Server date and time (including GMT offset)
- Notice level - usually this will be "INFO (6)"
- Message

Where applicable, the message contains information on the data before and after the event. Some events might generate several related messages - such as an explanatory note

Audit trail

Show all Download

This log captures all notable events and changes to the data. Only the 100 most recent lines are shown.

```
"Ms Coordinator (ID 2 - Administrator)" "/redpill/jump/crf/add/RandomisationVER1" [2016-03-23T11:34:19+00:00] INFO (6):
Randomisation to Control
"Ms Coordinator (ID 2 - Administrator)" "/redpill/jump/crf/add/RandomisationVER1" [2016-03-23T11:34:19+00:00] INFO (6):
Added form Randomisation for Subject S6310
192.168.33.1 "Sealed Envelope support (ID 1)" "/redpill/jump/markerror/get/22" [2016-03-23T11:35:37+00:00] INFO (6): Row in
crfRandomisationVER1 for: {"id": "22"}, changed From: {"lastUserIdentifier": "Ms Coordinator (ID 2 -
Administrator)", "error": "0", "errorReason": null, "errorDate": null, "updated": "2016-03-23 11:34:12", "reasonForEdit": null},
To: {"lastUserIdentifier": "Sealed Envelope support (ID 1)", "error": true, "errorReason": "\After randomisation but before
treatment patient was found to be ineligible due to past drug use history\ by Sealed Envelope support (ID 1)", "errorDate":
"2016-03-23 11:35:37", "updated": "2016-03-23 11:35:37", "reasonForEdit": "Randomisation marked as in error"}
192.168.33.1 "Sealed Envelope support (ID 1)" "/redpill/jump/markerror/get/22" [2016-03-23T11:35:37+00:00] INFO (6):
Randomisation number 22, code Control was edited
192.168.33.1 "Sealed Envelope support (ID 1)" "/redpill/jump/markerror/get/22" [2016-03-23T11:35:37+00:00] INFO (6):
Randomisation number 22, code Control was marked as in error
192.168.33.1 "Sealed Envelope support (ID 1)" "/redpill/jump/crf/add/InterviewersQuestionsVER1/1" [2016-03-
23T11:36:19+00:00] INFO (6): Row inserted to crfInterviewersQuestionsVER1: {"id": null, "patientId": "1", "userIdentifier":
"Sealed Envelope support (ID 1)", "lastUserIdentifier": "Sealed Envelope support (ID 1)", "created": "2016-03-23
11:36:19", "updated": "2016-03-23 11:36:19", "question1": "Male", "question2": "Partner - Living
with", "question3": null, "question4": "Yes", "question5": "3", "question6": "3", "question7":
"No", "question8": null, "reasonForEdit": null, "notes": null, "validationOverrides": "{}", "validationStatus": "Not
validated", "validationNotes": null}
192.168.33.1 "Sealed Envelope support (ID 1)" "/redpill/jump/crf/add/InterviewersQuestionsVER1/1" [2016-03-
23T11:36:19+00:00] INFO (6): Added form Interviewers questions for Subject T5617
```

Figure 14.1: Audit trail

"Edited form Eligibility Criteria Check At Recruitment for Patient SDN01"

plus a change in the data:

```
"Row in crfBaselineEligibilityCriteria for: {"id": "1"}, changed From: {"updated":
"2015-10-22 17:45:47", "reasonForEdit": null ..."
```

Example extract

```
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/crf/reviewadd/
BaselineEligibilityCriteria/1" [2015-10-22T17:45:47+01:00] INFO (6): Row inserted to
crfBaselineEligibilityCriteria: {"id": null, "patientId": "1", "userId": "1",
lastUserId": "1", "created": "2015-10-22 17:45:47", "updated": "2015-10-22
17:45:47", "reasonForEdit": null, "notes": null, "diagnosisOfIpfOrNsip": "No", "rhcMeanPap":
"Yes", "ageRange": "No", "dateWrittenInformedConsentGiven": "10\08\2008",
validationStatus": null, "validationNotes": null}
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/crf/reviewadd/
BaselineEligibilityCriteria/1" [2015-10-22T17:45:47+01:00] INFO (6): Added form
Eligibility Criteria Check At Recruitment for Patient SDN01
```

```
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/crf/reviewedit/  
BaselineEligibilityCriteria/1" [2015-10-22T17:48:40+01:00] INFO (6): Row in  
crfBaselineEligibilityCriteria for: {"id" : "1"}, changed From: {"updated" :  
"2015-10-22 17:45:47","reasonForEdit":null,"unstableUnderlyingLungDisease":null,"  
anySeriousComorbidity":null,"systolicBp":null}, To: {"updated" : "2015-10-22  
17:48:40","reasonForEdit" : "Adding some more answers","unstableUnderlyingLungDisease"  
: "No","anySeriousComorbidity" : "Yes","systolicBp" : "No"}  
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/crf/reviewedit/  
BaselineEligibilityCriteria/1" [2015-10-22T17:48:40+01:00] INFO (6): Edited form  
Eligibility Criteria Check At Recruitment for Patient SDN01  
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/contact/add/Individual" [2015-08-13T10  
:37:45+01:00] INFO (6): Row inserted to contact: {"id":null}  
1.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/contact/add/Individual" [2015-08-13T10  
:37:45+01:00] INFO (6): Row inserted to individual: {"id" : "52","title":null,"  
lastName" : "Kinnear","firstName" : "James","jobTitle" : "Layman","responsibility":  
null,"notes":null,"type" : "individual","qualifications":null,"regNo":null,"cv" :  
"0","cvDate":null,"delegationLogReceived" : "0","delegationLogReceivedDate":null}  
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/contact/add/Individual" [2015-08-13T10  
:37:45+01:00] INFO (6): Added contact James Kinnear
```

Chapter 15

Settings

A settings page is available to administrators that allows some features to be turned on or off to suit the requirements of your trial. Changes to settings are recorded in the [audit trail](#). There are some common settings (see below) and you may also have some trial specific settings.

Review step

The review step is turned on by default and introduces an intermediate step when saving forms. The user is required to review the form data and enter their password to confirm the information is correct before the data is saved to the database. The process is described in the [data entry section](#). Since investigator accounts normally do not have privileges to enter data once it is saved, the review step can help to prevent errors which would then require a [query](#) to resolve.

However, you may prefer to turn this review step off. In this case the form is saved immediately with no intermediate review page. This could be preferable, for instance, if you have data entry staff entering paper CRFs into a Red Pill database.

Note the review step is always enabled for randomisation forms

Settings

These are global settings that affect this application's behaviour. Changes to these settings will be recorded in the [audit trail](#).

Review step

- Off
 On

Enable the review step. If enabled, once a form has been completed without errors the "Save form" button will present the user with a review page. The review page allows the user to visually check that the data entered is correct and, if satisfied, complete the declaration by entering their password to save the form. If the review step is disabled the form is saved immediately without the need to complete the password declaration. Note the review step is **always enabled** for randomisation forms.

Subject delete

- Off
 On

Allow subject records to be deleted by an administrator. Deleting the subject will also delete all associated forms and queries. This cannot be undone so administrators should think carefully before turning on this setting or using this feature. Deleting randomised subjects is **strongly discouraged** because all randomised subjects must be accounted for.

Randomisation

- Off
 On

Enable randomisation. Manual randomisations can still be recorded by administrators when randomisation is disabled.

Save

Figure 15.1: Settings page

Subject delete

The ability to delete subjects is turned off by default. Deleting a subject will also remove all their CRF data, randomisation data and queries. The deleted data is shown in the audit trail but the action cannot be undone. You should consider very carefully whether to turn this feature on and use it. We recommend it is used only in exceptional circumstances.

We **strongly discourage** using the delete feature on randomised subjects because all randomised subjects must be accounted for.

If a subject was randomised in error [mark them as such](#) rather than deleting the record.

Randomisation

Randomisation systems and Red Pill systems with a randomisation form can turn randomisation on or off. When randomisation is disabled, administrator accounts can still record [manual randomisations](#). This may be useful, for instance, if offline randomisations have been carried out due to the Sealed Envelope website being unavailable.

This is a global setting - to stop randomisation at a specific site, edit the [site](#) and set *Recruiting* to **No**.

Chapter 16

Specification

The specification for a Red Pill application can be viewed by clicking the **Specification** link in the top menu. The specification is only accessible to administrator users. It shows the following information where relevant:

- Names of forms that can be completed multiple times per patient.
- The timetable used by the form scheduling feature, if enabled.
- Whether any of the forms can be patient self-completed, and information about custom text shown to the patient in the invitation email and after logging in.
- Details on randomisation method used, treatment groups, allocation ratio, strata, code list length, randomisation limit, data collected at randomisation (where relevant).
- Format of randomisation and unblinding email notifications
- User account privileges.
- Library version numbers.
- Server type (staging/production), review step setting and patient delete setting.

There may also be extra custom information specific to the study.

Chapter 17

Making changes to the specification

Once a Red Pill or randomisation system is in production, changes to the forms or other aspects of the system can only be done through a documented change control process. To initiate this process please download and complete a [Change Request spreadsheet](#) [Excel file].

The Change Request Log will require you to complete the following information:

Change # Sequential change number 1, 2, 3, ...

Visit Name of visit, e.g. *Baseline*

Form Name of form, e.g. *ECG results*

Item / Question The question to be added or changed, eg. *1. ECG - Has a baseline ECG been taken?*

Change type One of:

- New form
- New field
- Change field
- Other change

New or revised forms and fields might be required due to a change in the protocol or a mistake in the original specification. Other changes include changes to validation rules or user permissions etc.

If new field, please record response required When adding new fields, please list what type of response is expected. Please choose from:

- Single line text
- Paragraph text - a text box allowing long text entries
- Encrypted text - a text box whose value will be stored in an encrypted format

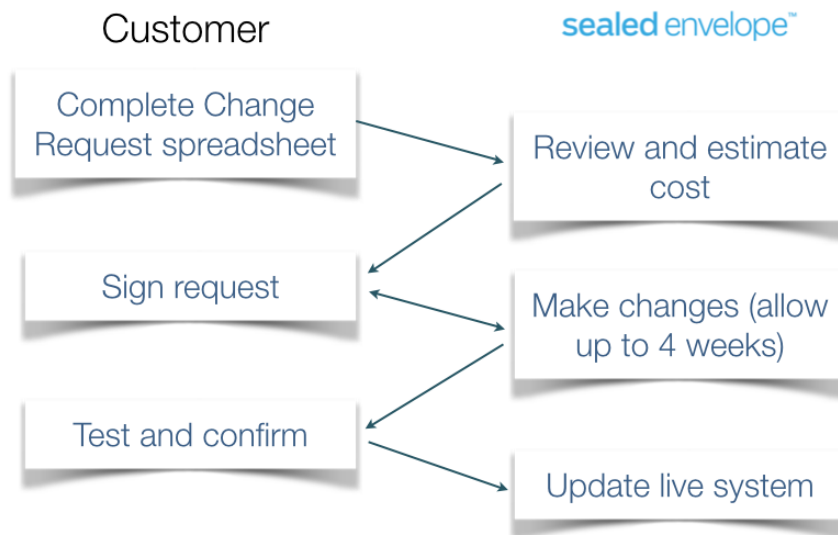


Figure 17.1: Flowchart for change request process

- Number
- Date
- Yes/No
- Category - please list all categories eg, Mild; Moderate; Severe
- Clock time - the time of day in 24hr clock format (e.g. 13:15)
- Elapsed time - a duration in hours and minutes (e.g. 30:50)
- Explanation - explanatory text (e.g. The following questions are about your health)

Change description The actual change that is required in the eCRF. e.g. *The drop down menu is missing a category and should be updated to include new option in drop down menu*

Once you have completed the form, please [send it to Sealed Envelope](#) for review. Sealed Envelope will review your list of changes and provide you with an estimate of how long it will take to configure these changes and provide you with a cost estimate to fulfil your request.

Chapter 18

Minimisation

Minimisation is a method of randomisation that allocates subjects to the treatment group that best maintains balance in stratifying factors. It is effective even at small sample sizes and with multiple stratification variables.

Example

The method is best illustrated by example. Suppose it is important to balance subject sex in a trial of a new drug, because women are expected to respond more strongly to the drug. It would be unfortunate if, by chance, more women received the new drug rather than placebo and more men were allocated to placebo rather than the new drug. For similar reasons we would also like to balance subject age, so that younger subjects, who are expected to have a better outcome, are evenly distributed to the placebo and drug groups.

The randomisations to the trial so far look like this:

Number	Sex	Age	Treatment group
1	Male	<30	Placebo
2	Male	30+	Placebo
3	Female	30+	New drug
4	Male	<30	Placebo
5	Female	<30	New drug
6	Male	30+	New drug

The next subject to be randomised is a man age 23.

To decide which treatment to allocate the subject to, the balance of treatments in the trial is compared for subjects with the same characteristics as the subject to be randomised. There are various ways of calculating the imbalance, but the most popular method¹ (and the one Sealed Envelope uses) is to simply sum the frequencies across the strata for each treatment. In this example the frequencies are:

Stratifying factor	Placebo	New drug
Male	3	1
<30	2	1
Total	5	2

Clearly in males and those under 30 there is an imbalance in favour of placebo so far. The next treatment allocation is the one with the lowest total score - in this case the next subject will be allocated to the new drug. Note that if the scores were tied, the treatment allocation would be chosen purely at random.

Incorporating a random element

Minimisation as described above is a largely deterministic procedure - given the characteristics of subjects in the trial and the subject to be randomised, the new treatment allocation is almost entirely predictable.

It is desirable to inject a random element into the procedure and, in fact, ICH E9 guidelines require it:

Deterministic dynamic allocation procedures should be avoided and an appropriate element of randomisation should be incorporated for each treatment allocation.

ICH Topic E9 Statistical Principles for Clinical Trials

The Sealed Envelope randomisation system defines a probability that a purely random allocation will be made, instead of using minimisation. So for each randomisation there is a chance (usually

¹Taves DR. Minimization: a new method of assigning subjects to treatment and control groups. *Clin Pharmacol Therapeut.* 1974;15:443-453.

around 30%) that the treatment will be chosen at random. This is equivalent to using a biased coin to determine the next treatment, with the bias in favour of the treatment that would make the treatment groups more balanced². If there are two treatments allocated in a 1:1 ratio, and a 30% chance of choosing the treatment at random, then the probability that the under-represented treatment will be chosen is 0.85 ($0.3 \times 0.5 + 0.7$). This probability can be viewed for your trial on the [specification page](#).

Factorial trials

In factorial trials, 2 or more treatments comparisons are evaluated in the same subjects. The most common design is the 2×2 factorial trial:

	Placebo	Aspirin
Placebo	x	x
β -carotene	x	x

where subjects are allocated to one of four treatment groups. In the above example these are:

- Placebo
- Aspirin alone
- β -carotene alone
- Aspirin and β -carotene

Suppose we want to make sure subject age is balanced between the four groups and the next subject to be randomised is aged under 30. The frequency table for allocations to each treatment group in subjects <30 years old is:

Age <30	Placebo	Aspirin	Total
Placebo	3	2	5
β -carotene	2	2	4
Total	5	4	9

To calculate the minimisation scores for each treatment group, the frequency in the relevant cell

²Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trials. *Biometrics* 1975;31:103-115.

plus the marginal totals are used:

- Placebo: $3 + 5 + 5 = 13$
- Aspirin alone: $2 + 5 + 4 = 11$
- β -carotene alone: $2 + 4 + 5 = 11$
- Aspirin and β -carotene: $2 + 4 + 4 = 10$

So in this case the next allocation will be to the aspirin and β -carotene group. As before, if scores are tied the treatment is chosen at random from the tied groups.

Chapter 19

Random permuted blocks

Blocking is a method of restricted randomisation that ensures the treatment groups are balanced at the end of every block. For example, here are two permuted blocks of 4 with treatment groups A and B:

[A B B A], [B A B A]

Random permuted blocks are blocks of different sizes, where the size of the next block is randomly chosen from the available block sizes. For example, here is a list of random permuted blocks of sizes 4 or 6:

[A A B A B B], [A B A B], [B B A A], [B A A B], [A B A B B A], [B A A A B B]

Stratification

Blocking can be used within strata, so that important prognostic characteristics (the stratification factors) are balanced between the treatment groups:

_____ | _____
_____ |

Men | [A B A B], [A A B B B A], [B B A B A A], [B A A B] |

Women | [B B A A B A], [A B B A], [B B A A], [A B B A] |

Using this list the frequencies after 9 men have been recruited and 5 women will be:

	A	B	Total
Men	4	5	9
Women	2	3	5
Total	6	8	14

Choice of block size

Block sizes must be multiples of the number of treatments and take the allocation ratio into account. For 1:1 randomisation of 2 groups, blocks can be size 2, 4, 6 etc. For 1:1:1 randomisation of 3 groups or 2:1 randomisation of 2 groups, blocks can be size 3, 6, 9 etc.

The treatment allocation is predictable towards the end of a block. For this reason block sizes should be kept confidential and not shared with those randomising. Large blocks reduce predictability, but will not restrict the randomisation as closely as small blocks. If interim analyses are planned at particular sample sizes, it is desirable that the treatments are balanced at these points. Having many stratification factors can lead to many incomplete blocks and thereby imbalance. Therefore choice of block size(s) should take into account the sample size, planned interim analyses and number of stratification factors.

You can experiment with different block sizes and stratification factors on our [simulation](#) page. This will show you how much imbalance to expect for various choices.

Chapter 20

Simulations

Sealed Envelope can carry out simulations of the randomisation system using an automated testing programme. The randomisations generated by this approach are available for download on the [specification](#) page.

How are the simulations produced?

A data specification document is provided to the automated testing programme. This defines the data to be submitted to the [randomisation form](#). The testing programme submits this data to the randomisation form to simulate a randomisation taking place. This process is repeated a set number of times (known as *replications* or *reps*) to produce the simulated dataset.

Data specification document

Here is an example of a data specification:

```
{
  "sample_size": 400,
  "fields": {
    "siteId": {
      "min": 1,
      "max": 10,
      "type": "int"
    }
  }
}
```

```

},
"dob": {
  "format": "d/m/Y",
  "min": "1 Jan 2000",
  "max": "31 Dec 2010",
  "type": "date"
},
"initials": {
  "type": "string",
  "length": 2
},
"eligible": {
  "value": ["Yes"],
  "type": "enum"
},
"gender": {
  "weight": [2, 1],
  "value": ["Male", "Female"],
  "type": "enum"
},
"consent": {
  "value": ["Yes"],
  "type": "enum"
},
"severity": {
  "weight": [1, 2],
  "value": [ "Low", "High"],
  "type": "enum"
}
},
"stubName": "mytrial"
}

```

It is possible to alter the data submitted to the form to more closely reflect the expected distributions of individual variables in your trial by changing the weight parameter on categorical variables. For example if you expect twice as many women to be recruited compared to men, the weighting on gender would be set to [1, 2].

You can ask Sealed Envelope to make these changes and re-run the simulation.

Analysing the simulated data

You can download the simulated data and import into a spreadsheet or statistics package for analysis. You can check, for instance, that the randomisation protocol is balancing the treatment groups within strata. If you want to make changes to the randomisation protocol or carry out more simulations you should contact Sealed Envelope.

Example

In this example a simulation has been carried out using the data specification above. The randomisation protocol was minimisation on gender, severity and age-group with a 25% chance that a purely random allocation will be made (equivalent to using a biased coin with an 87.5% chance of choosing the treatment that reduces imbalance). The analysis was carried out using Stata.

First we import the simulated dataset.

```
insheet using mytrialRandom.2012-10-31.150000.tsv
```

Now lets start exploring the dataset.

```
. tab gender
```

gender	Freq.	Percent	Cum.
Female	124	31.00	31.00
Male	276	69.00	100.00
Total	400	100.00	

We can see that gender has been allocated according to the weightings in the data specification (2:1 Male:Female).

```
. li initials gender severity dob agegroup in 1/5
```

	initials	gender	severity	dob	agegroup
1.	Q0	Male	High	08/08/2001	6.5 years or over
2.	MT	Male	Low	29/09/2002	6.5 years or over

3.		YZ	Male	High	06/12/2003	6.5 years or over	
4.		PK	Male	Low	15/11/2009	<6.5 years	
5.		MH	Female	High	29/09/2003	6.5 years or over	
+-----+-----+-----+							

Initials and date of birth (dob) have been generated with random strings and dates. The agegroup variable was calculated by the randomisation system from the date of birth so did not need to be included in the data specification.

```

. tab gender group

      |      group
gender |  Active  Control |  Total
-----+-----+-----
Female |      62     62 |    124
Male   |     138    138 |    276
-----+-----+-----
Total  |     200    200 |    400

. tab severity group

      |      group
severity |  Active  Control |  Total
-----+-----+-----
High    |     138    139 |    277
Low     |      62     61 |    123
-----+-----+-----
Total   |     200    200 |    400

. tab agegroup group

      |      group
agegroup |  Active  Control |  Total
-----+-----+-----
6.5 years or over |      94     96 |    190
<6.5 years |     106    104 |    210
-----+-----+-----
Total   |     200    200 |    400

```

The minimisation has clearly closely controlled the balance in the three minimisation factors. By way of contrast the balance within sites, which is not controlled by minimisation, can be seen to vary quite widely:

```
. tab siteid group
```

siteId	group		Total
	Active	Control	
1	20	22	42
2	21	23	44
3	22	23	45
4	14	17	31
5	16	6	22
6	18	22	40
7	18	26	44
8	26	27	53
9	25	18	43
10	20	16	36
Total	200	200	400

We can check the minimisation algorithm by calculating the marginal scores at each observation:

```
gen Active=0
gen Control=0
forvalues i=2/400 {
  foreach group of varlist Active Control {
    local total 0
    foreach factor of varlist gender severity agegroup {
      qui count if `factor'==`factor'[`i'] & group=="`group'" & _n<`i'
      local total = `total' + r(N)
    }
    qui replace `group'=`total' in `i'
  }
}
```

Control should be preferred by minimisation when its marginal total is lower than that for the Active group:

```
. tab group if Control < Active
```

group	Freq.	Percent	Cum.
Active	20	11.70	11.70
Control	151	88.30	100.00
Total	171	100.00	

The proportion allocated to Control in this situation is very close to the expected value of 0.875. We can test this:

```
. cii 171 151
```

Variable	Obs	Mean	Std. Err.	-- Binomial Exact -- [95% Conf. Interval]	
	171	.8830409	.0245759	.825158	.9270753

The 95% confidence interval is consistent with 0.875. The same analysis for the Active group is:

```
. tab group if Active < Control
```

group	Freq.	Percent	Cum.
Active	137	87.82	87.82
Control	19	12.18	100.00
Total	156	100.00	

```
. cii 156 137
```

Variable	Obs	Mean	Std. Err.	-- Binomial Exact -- [95% Conf. Interval]	
	156	.8782051	.0261849	.8163508	.9250541

So again the confidence interval includes the expected proportion 0.875.

Finally where the scores are tied, the group should be chosen at random:

```
. tab group if Active == Control
```

group	Freq.	Percent	Cum.
Active	43	58.90	58.90
Control	30	41.10	100.00
Total	73	100.00	

```
. cii 73 43
```

Variable	Obs	Mean	Std. Err.	-- Binomial Exact -- [95% Conf. Interval]	
	73	.5890411	.0575852	.4676846	.7029424

The confidence interval includes the expected value of 0.5.

Chapter 21

API

The randomisation API allows your server or database programme to perform randomisations using Sealed Envelope or download randomisations on demand. The API is not enabled by default - you must request access to this feature.

The API is used by the [Open Clinica Randomize](#) module to perform randomisation from within Open Clinica.