

sealed envelope™

Red Pill and Randomisation

Version 17

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Chapter 1

Overview

Red Pill is an online application for collecting and managing case report form (CRF) data on subjects recruited to a clinical trial or other research study. This type of system is sometimes called electronic data capture (EDC). Red Pill can also be used to collect data directly from [subjects themselves](#), known as electronic patient reported outcomes (ePRO).

Randomisation is an integral part of Red Pill, and is also offered as a standalone component. This 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 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.

Note that all data shown in this help is fictional and for illustrative purposes only.

This documentation applies to version 17, released Aug 2017. The version number is shown in the footer of every page when logged into Red Pill.

Chapter 2

Accessing the system

The [Access](#) application is the gateway for Red Pill systems. Systems set up before 2015 have Access URLs that are specific to a client - e.g. www.sealedenvelope.com/abc_trialsunit. Systems set-up after 2015 generally have the same common URL: www.sealedenvelope.com/access. In either case the URL will be contained in automated emails sent out when a new user account is created.

Users are requested to authenticate themselves by providing their log-in credentials. See the [Access](#) help for more information.

Chapter 3

Getting started

Investigator accounts

If you will be randomising or entering CRF data on subjects, 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 be able to view and add data for subjects at this site. Depending on a trial-wide setting controlled by administrators you may also be able to edit data.

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 [enrolled subjects](#) at your site and [enter data](#) yourself. For randomisation only systems you will be able to see [previous randomisations](#) at your site and [perform randomisations](#) yourself.

Administrator accounts

When a Red Pill 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 randomisation and data entry can be performed by staff at the sites. You do this through the [Access](#) application. Check the [settings page](#) and make any adjustments to suit your trial.

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 case report forms and report any discrepancies or errors to Sealed Envelope.

Chapter 4

Subjects

Subject records can be viewed by clicking on the **Subjects** link in the top menu. This shows a list of all subjects entered into the study to date. An amber question mark in the status column of the subject listing indicates that there is an open query for that subject.

The screenshot shows a web interface for viewing subject records. On the left, a table lists subjects with columns for Subject ID, Site, Randomisation group, Date randomised, and Status. Subject T5617 is highlighted with an amber question mark icon in the Status column. On the right, a 'Subject details' panel shows information for T5617, including Site (UCL, United Kingdom), Randomisation group (Intervention), and Date randomised (27 Dec 2015 10:24 GMT). Below this, there are sections for 'Queries' (with a 'Create a new query' link), 'Open queries' (with a link to 'Query ID 2: Forms due'), 'CRF' (with a 'Baseline' section due on 27 Dec 2015 and a 'Mark as data missing' link), and a list of data points with 'Add', 'View', and 'Edit' links for each.

Subject ID	Site	Randomisation group	Date randomised	Status
S3365	Royal Albert Hospital	Control	21 Dec 2015 04:50 AEDT	⚠
S5706	UCL	Intervention	23 Dec 2015 18:19 GMT	
T5617	UCL	Intervention	27 Dec 2015 10:24 GMT	?
S5050	Royal Albert Hospital	Intervention	31 Dec 2015 02:41 AEDT	
S4470	Royal Albert Hospital	Intervention	2 Jan 2016 02:44 AEDT	
S4622	Royal Albert Hospital	Control	2 Jan 2016 15:16 AEDT	
S4445	UCL	Control	5 Jan 2016 04:30 GMT	
S8040	UCL	Control	8 Jan 2016 11:23 GMT	
S2309	UCL	Intervention	9 Jan 2016 12:21 GMT	
S6369	Royal Albert Hospital	Intervention	14 Jan 2016 06:32 AEDT	
S6306	Royal Albert Hospital	Intervention	16 Jan 2016 19:49 AEDT	
S7291	Royal Albert Hospital	Intervention	20 Jan 2016 05:55 AEDT	
S5799	UCL	Intervention	19 Jan 2016 22:55 GMT	
S6913	UCL	Intervention	24 Jan 2016 05:45 GMT	
S2949	Royal Albert Hospital	Control	27 Jan 2016 03:02 AEDT	
S6310	Royal Albert Hospital	Control	29 Jan 2016 00:48 AEDT	
T1719	UCL	Control	31 Jan 2016 13:24 GMT	?
S6165	Royal Albert Hospital	Control	3 Feb 2016 04:01 AEDT	
S2478	Royal Albert Hospital	Intervention	8 Feb 2016 02:07 AEDT	
T5511	UCL	Control	8 Feb 2016 04:18 GMT	
S7928	UCL	Intervention	9 Feb 2016 20:13 GMT	
S4983	Royal Albert Hospital	Intervention	12 Feb 2016 21:58 AEDT	

Subject details

Subject ID: T5617
Site: 1: UCL, United Kingdom
Randomisation group: Intervention
Date randomised: 27 Dec 2015 10:24 GMT

[Mark as randomised in error](#)

Queries

[Create a new query](#)

Open queries

[Query ID 2: Forms due](#)

CRF

Baseline
Due: 27 Dec 2015 [Mark as data missing](#)

Randomisation Add [View](#) [Edit](#)

Interviewers questions Add [View](#) [Edit](#)

Patient Questions Add [View](#) [Edit](#)

Satisfaction of Care Add [View](#) [Edit](#)

Concomitant medications Add [View](#) [Edit](#)

6 Week Follow-up

Figure 4.1: Viewing an individual subject record

Adding subjects

New subjects may be added to the list at any time by clicking on the **Add a subject** link in the top menu. This opens the study entry form which requests a subject identifier and date of study entry. Note that at least one [site](#) must be created before any subjects can be added.

Some trials may be configured such that subjects are randomised into the trial. If this is the case a subject can be added via the [Randomise](#) link in the top menu. Check the [specification page](#) to see if this is the case.

Deleting subjects

Subjects may be deleted by administrative users providing the [delete subject](#) setting is enabled. A delete subject option is shown in the 'Subject details' section. The user will be asked to confirm they wish to go ahead. Deleting the subject will also delete all associated forms and queries. This cannot be undone so administrators should think carefully before deleting.

Searching

The search box filters the subject list to match the entered terms. Note that form data is not searched. Multiple search terms narrow the focus, e.g. 1 2 finds rows that match 1 *and* 2. Putting search terms in brackets performs a wider search for any matches, e.g. (1, 2, 3) or (1 2 3) finds rows that match 1 *or* 2 *or* 3.

Subject details

Clicking on a subject in the list shows subject details from the study entry form, any queries and provides links to [add](#), [view](#) and [edit](#) the forms for that subject grouped by visit.

Schedule

For visits at specific timepoints (for instance 30 days after study entry) the due date is shown. Overdue forms are highlighted in red. If the Withdrawal form has been completed and the subject marked as withdrawn from follow-up, then any visits due after the date of withdrawal will not be shown as overdue. All uncompleted forms in these visits will become inaccessible. Forms that were completed before the subject was marked as withdrawn will remain accessible and may be viewed and edited in the normal way.

Baseline

Due: 9 Feb 2016 [Mark as data missing](#)

Randomisation		Add	View	Edit
Interviewers questions		Add	View	Edit
Patient Questions		Add	View	Edit
Satisfaction of Care		Add	View	Edit
Concomitant medications		Add	View	Edit

6 Week Follow-up

Due: 22 Mar 2016 (*subject withdrew on 11 Feb 2016*)

Patient Questions	Add	View	Edit
--------------------------	-----	------	------

Figure 4.2: A follow-up visit due after subject withdrew

Missing forms

Sometimes forms within a visit are not available because, for instance, the subject did not attend a follow-up appointment, the data was not collected or was lost. Forms within visits can be marked as missing using the **Mark as data missing** links. Marking the data as missing in this way causes all uncompleted forms in the visit to become inaccessible and they will not be shown as overdue. Forms that were completed before a visit was marked as missing will remain accessible and may be viewed and edited in the normal way.

12 Week Follow-up

Due: 12 Apr 2016 [marked as missing](#)

Interviewers questions

Add View Edit

Patient Questions

Add View Edit

Figure 4.3: A follow-up visit marked as missing

Subject-entered forms

A subject invitations section may be displayed to invite the subject to self-complete some forms in the CRF if [subject entered forms](#) are enabled.

Form status

A green tick next to a form name indicates that it has been marked as [validated](#). An amber question mark symbol next to a form name indicates that the form has an open query.

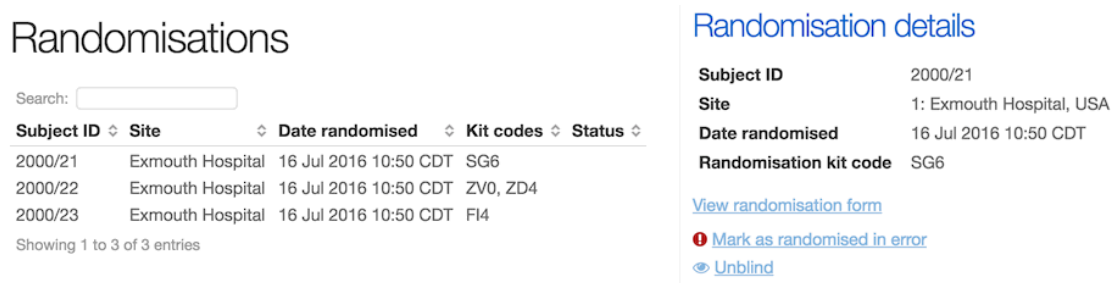
Chapter 5

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 for Subject ID, Site, Date randomised, Kit codes, and Status. The table contains three entries for Exmouth Hospital, all dated 16 Jul 2016 10:50 CDT. On the right, a sidebar titled 'Randomisation details' shows information for Subject ID 2000/21, including the site (Exmouth Hospital, USA), date, and kit code (SG6). Below the details are links for 'View randomisation form', 'Mark as randomised in error', and 'Unblind'.

Subject ID	Site	Date randomised	Kit codes	Status
2000/21	Exmouth Hospital	16 Jul 2016 10:50 CDT	SG6	
2000/22	Exmouth Hospital	16 Jul 2016 10:50 CDT	ZV0, ZD4	
2000/23	Exmouth Hospital	16 Jul 2016 10:50 CDT	F14	

Showing 1 to 3 of 3 entries

Randomisation details

Subject ID: 2000/21
Site: 1: Exmouth Hospital, USA
Date randomised: 16 Jul 2016 10:50 CDT
Randomisation kit code: SG6

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

Figure 5.1: 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 randomisations 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.

For blinded trials the data will *not* contain the treatment group, even if the randomisation has been unblinded. Kit codes assigned to randomised subjects can be determined by downloading the code list and joining on the `patientId` field (= Subject id).

Chapter 6

Data entry of forms

Forms can be completed by clicking on the **Add** link shown on the subject details section next to the name of the form. At the top of every form is a banner reminding the user of which subject they are entering data on. Date fields can be completed manually or by using the date-picker that appears when a user clicks on the calendar icon.

Tip: When entering dates or times manually, just type the numbers – the / or : will be filled in automatically.

Validation

Validation (e.g. range checking) is carried out on the form to reduce errors. There are two types of error messages - those in the form of popup warning messages and those displayed in red on the form. The popup message alerts may warn the user of a value that may be incorrect (such as a high blood pressure) or give some other message. The user must dismiss the alert before proceeding.

Red error messages require either a change to the value entered or providing a justification for overriding the validation check before proceeding. Validation checks may not be overridden on [subject entered forms](#).

Some fields are always required - these are displayed with an adjacent red asterisk - whilst others may become required or not applicable depending on the answers to previous questions. Other

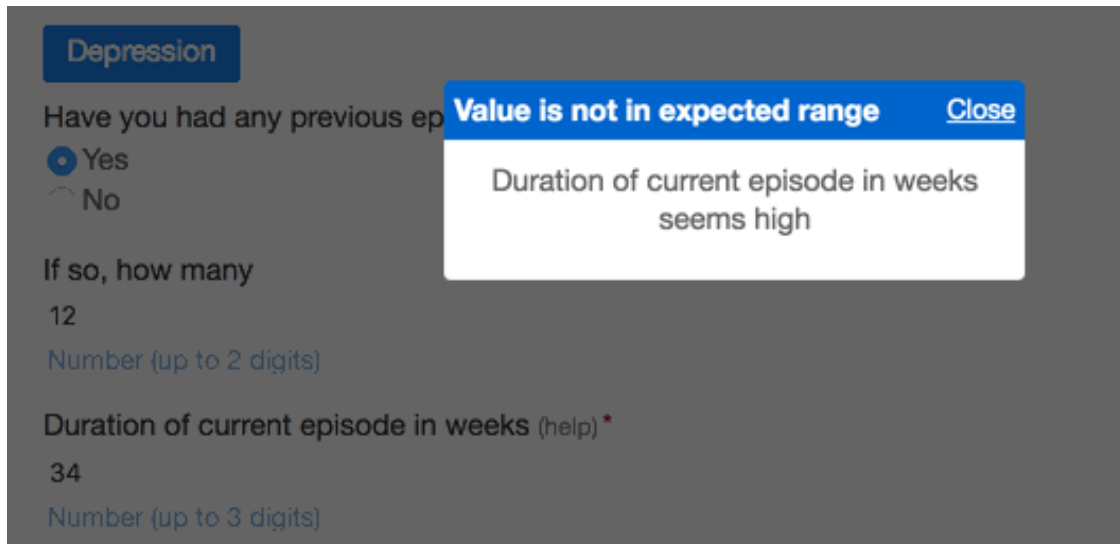


Figure 6.1: Popup warning message

fields are optional and may be left blank if desired.

Repeating sections

Some sections of a form can be added multiple times. This is used, for instance, to record all the hospital admissions for a subject. A button, such as **Add hospital admissions** will be shown on the parent form. Clicking this button goes to a subform which can be added as many times as necessary. The subforms are saved along with the parent form.

Likert scales

Sections that capture Likert scale responses are laid out in a grid. Validation and overriding work in the same way as for other sections.

Day 4 Telephone Follow-Up

1. Which day telephone follow-up? 4

2. Was it possible to conduct a telephone follow-up? *

Yes

No

2. a) Date of call/final attempt *



This field is required.

dd/mm/yyyy

Justification for overriding validation "This field is required.":

Figure 6.2: Overriding form validation

Hospital admissions

Did your child stay at hospital overnight during the last 7 days? (reset)

Yes
 No

If 'Yes' please provide details below:

Hospital admissions

Hospital admissions

Name of hospital
Bath

Reason for visit
High temperature

Date of admission
04/01/2017
dd/mm/yyyy

Date of discharge
05/01/2017
dd/mm/yyyy

[Edit](#) [Delete](#) 

Hospital admissions

Name of hospital
Bath

Reason for visit
Surgery

Date of admission
07/01/2017
dd/mm/yyyy

Date of discharge
09/01/2017
dd/mm/yyyy

[Edit](#) [Delete](#) 

[Add Hospital admissions](#)

Figure 6.3: A form with subforms

Satisfaction of Care

Overall care

On a scale of 0-10 (0 being least 10 being most), how satisfied are you with:

	0	1	2	3	4
Your overall care? *	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The continuity of your care? *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
Your supportive care? *	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Your information needs being met? *					
This field is required.					
Justification for overriding validation "This field is required.":	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Figure 6.4: A Likert scale section

Encrypted PII fields

Fields containing personally identifiable information (PII) that have been configured in the CRF builder to be stored in an encrypted format are shown with a small padlock symbol below. PII fields can be viewed and edited through the web interface like any other field, but they will be in encrypted format when [downloaded](#). Sealed Envelope support can provide instructions on how to decrypt this data after download if necessary.

Review step

Once the form has been completed without errors the **Save form** button will usually present the user with a review page. Here the user can visually check that the data entered is correct and, if satisfied, complete the declaration by entering their password to save the form.

This review step may be disabled for some systems, in which case the data is saved immediately.

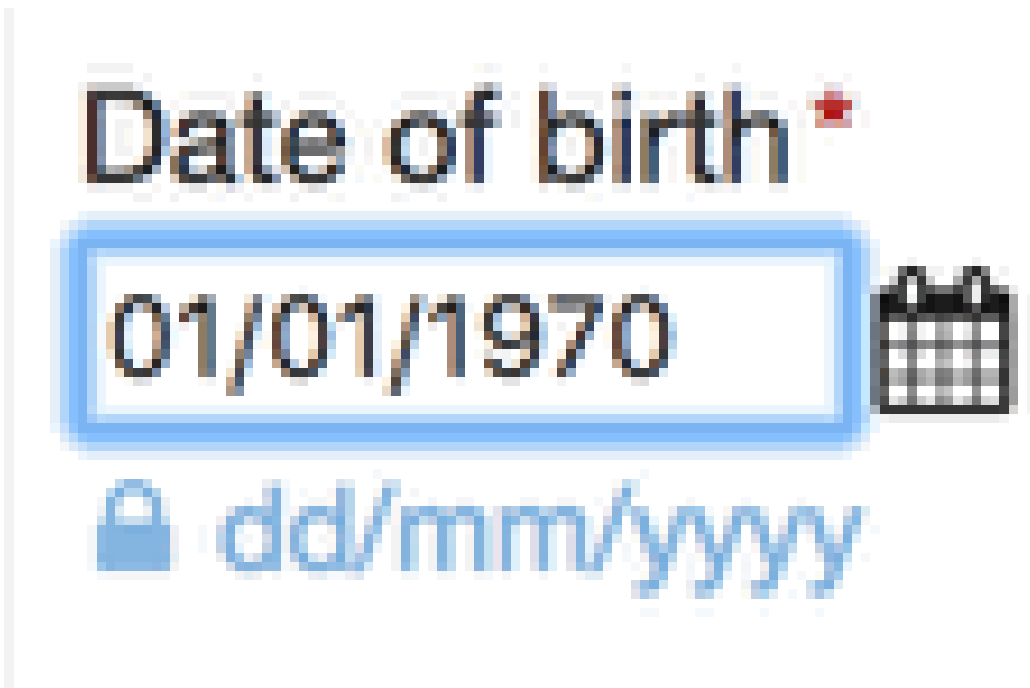


Figure 6.5: An encrypted field

If there are errors the user may return to the previous page to make changes. Once the declaration has been successfully completed the form is saved to the database.

Auto-saved drafts

Once data entry is commenced most forms are auto-saved periodically.

Study entry forms (or the randomisation form when subjects are randomised into the study) are never auto-saved.

Edits to existing forms are not auto-saved.

A message indicating a draft has been saved is shown periodically at the top of the form. This allows the user to navigate away from the form and return to it later without losing data. When returning to a form that has a saved draft, the user is shown a message and given the option to load the draft data or ignore it. If the draft is ignored and data-entry started again the original data will no longer be available.

There is only one draft per form/subject and it is accessible to all users (not just the author of the draft).

If the user navigates away from the page before saving the data, a pop-up message is shown to warn the user that the data has not been permanently saved yet. This is because, even though a draft may exist, it could be lost by the actions of another user.

Form completion messages

After a form has been saved, the user may be prompted to complete other forms based on the answers they have given. For instance, an event form may be required if a stroke has been recorded. If the form contains any of these rules and they are triggered by the data recorded, the user will see a message asking them to complete the related forms. A query will also be automatically opened to remind the user to complete the required forms.

Thoughts that you would be better off dead, or hurting yourself in some way
Several days

Any problems

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people
Somewhat difficult

Notes
-

Investigator's declaration

By entering my password below I declare that the information presented in this form accurately reflects the medical records, including the results of tests and evaluations performed on the dates specified.

Name
Sealed Envelope support (TB) (ID 51)

Date
19 Jan 2017

Password

[Back](#)

Figure 6.6: Reviewing a form before saving

Demographics and Clinical information, ECOG,
Treatment Expectation

Draft saved

Questions

Sex *

Male

Female

Figure 6.7: Saved draft message

Interviewers questions

Demographics and Clinical information, ECOG, Treatment Expectation

Questions

Sex *

Male

Female

Marital status

Choose ...

Draft exists [Close](#)

There is a draft version of this form saved by Sealed Envelope support (TB) (ID 51) on 19 Jan 2017 18:12 UTC. [Load draft](#) / [Ignore](#).

Figure 6.8: Load draft dialogue

Interviewers questions

Depression and ECOG

This form was saved.
Based on your answers the following forms are now due: Serious Adverse Events. Please complete these forms if you haven't already done so

Open queries

Query ID 4: Forms due

[Edit this form](#)

This form was created at 23 Mar 2016 16:50 UTC by Sealed Envelope support (ID 1)

Depression

Are you using any treatments for depression at the moment?

No

Treatment/Medication names - list all

-

Did an SAE occur?

Yes

Figure 6.9: Reminder to complete related forms

Repeating forms

Most forms can only be completed once per subject, but some can be entered multiple times. Repeating forms are normally used for events (like SAEs) that can occur multiple times per subject. As repeated forms are entered, they are listed in the subject view with a sequence number.

Other forms

Due: at any time [Mark as data missing](#)

Serious Adverse Events	Add		
Serious Adverse Events (#1)		View	Edit
Serious Adverse Events (#2)		View	Edit
Withdrawal	Add	View	Edit

Figure 6.10: Repeat entry forms

Chapter 7

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 7.1: 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 using an emergency procedure, such as giving the next treatment allocation from a pre-defined backup list. 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 list

Some randomisation methods rely on a predefined randomisation list, whereas dynamic methods (such as minimisation) do not use a randomisation list. The randomisation method is shown on the [specification page](#). The total number of unused allocations in the randomisation list will be displayed if applicable, and a report, **Allocations available in the randomisation list**, will show the number of used and available allocations by the levels of each strata. Randomisation will not be possible if there are no allocations available for the stratification factors that apply to the subject being randomised. Contact Sealed Envelope support if this happens as it will be necessary to extend the randomisation list.

Randomisation Form

Randomisation

Some errors occurred! See below for details.

No allocations available in the randomisation list for the selected strata

Randomisation details

Initials *

AH

Figure 7.2: No allocations available when randomising a subject

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 8

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

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


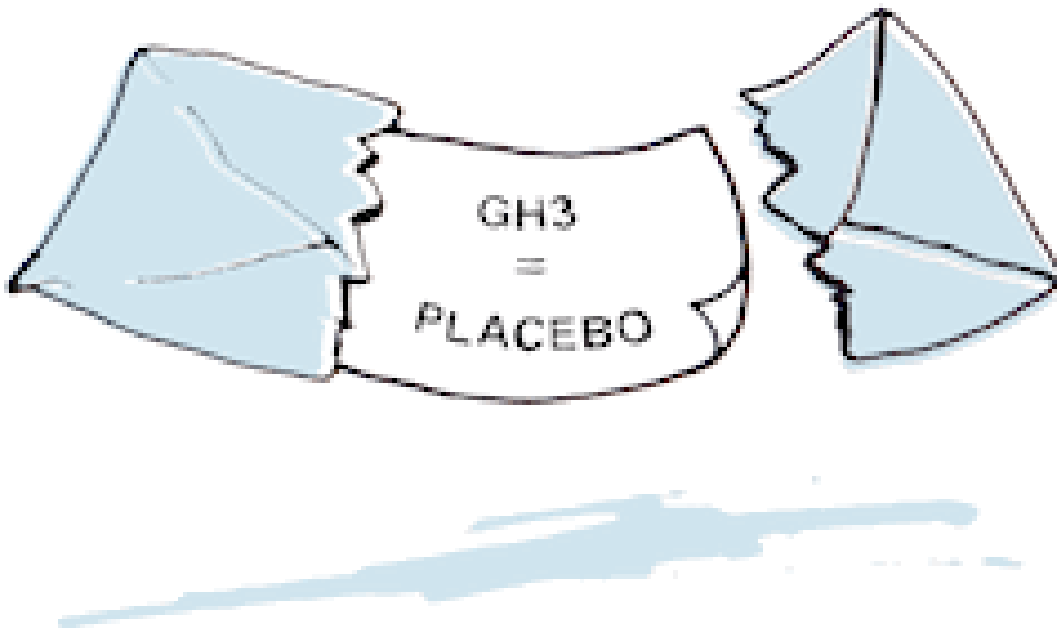
 This randomisation was marked as randomised in error on 23 Dec 2015 22:35 AEDT. Reason given: "After randomisation but before treatment patient was found to be ineligible due to past drug use history" by Sealed Envelope support (ID 1).

Figure 8.1: A randomisation marked in error

displayed in the status column of the subject list for those marked in error.

Chapter 9

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.



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 9.1: Unblinding a designated person

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](#).

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 9.2: An unblinded subject record

Chapter 10

Subject entered forms

Subject entered forms are forms which can be self-completed by the subject (ePRO). See the [specification page](#) to see if this feature is enabled and information on email templates, reminders and information shown to subjects when logging in.

Inviting subjects

Subjects must be invited to complete their forms by completing a subject invitation form. To do this the subject must be selected from the [subject list](#) and the **Invite subject to complete forms** link used. This link will only be shown to investigators and not administrators or other roles as it leads to a page that potentially contains personally identifiable information (subject email and, optionally, mobile number).

Completing the subject invitation form enrolls the subject and allows them to complete certain forms themselves. The form to invite the subject requires their personal email address and, optionally, mobile number. These fields are stored in an encrypted format in the database. Invitations and reminders will be sent by email and also by SMS if a mobile number is given. Unique links to complete forms online are included in both emails and SMS messages. These links expire after a set time period which is configurable for a study. Links can be turned off so that notification emails and texts act as simple reminders to complete paper forms. The number of reminders sent if forms are not completed and time delay between reminders is also configurable for a study. These details can be viewed on the [specification page](#).

An optional memorable word can be entered which will be required by the subject to enter their forms. The time of day at which automatic invites and reminders will be sent can also be customised for each subject. Deactivating a profile prevents further invitations and reminders from being sent and subjects will not be able to enter forms, even using an unexpired link.

Invite schedule

Once the subject invitation form has been completed the invite schedule is displayed. This shows when invites and reminders will be automatically sent. It shows whether a subject has logged in and how many forms they have completed. If a subject completes all forms due at the visit any remaining reminders will be cancelled. Links are provided to manually trigger invitations, which is useful to invite a particular subject earlier or later than scheduled. The invite schedule can be viewed by administrators but links for manual invitations are not displayed.

Note that invitations are still sent out and forms can be entered by subjects for visits that have been marked as missing.

Subject list

Subjects with an active invitation to complete forms are denoted by a green icon of a person in the status column of the [subject list](#). Subject entered forms are also shown with this icon in the subject details section.

Report

A subject invitation [report](#) is available to administrators. This shows for each invited subject when each visit is due, whether the subject has logged in and the number of forms they have completed out of the total due.

Subject invitation

Subjects can be invited to complete certain forms in the CRF (see schedule below). Subject S2478 has not yet been invited. Complete the form below to enrol the subject to receive invitations to enter their own forms. A welcome email will be sent. Invitations will be sent automatically to the subject's email address (and optionally their phone via SMS) for scheduled visits when they become due. Invites for unscheduled visits have to be sent manually.

Invitation details

Email*

Mobile number

Send links in invitations?* Yes No

Links are needed to allow the subject to enter forms themselves online. Invites that do not contain links act as simple reminders to complete paper forms. Links will expire 7 days after being sent.

Memorable word

If you enter a memorable word, subjects will be asked for it before entering forms. Subjects cannot reset the memorable word so will need to contact you if they forget it.

Send time*

In subject's timezone (Australia/Melbourne)

Active?* Yes No

Invites are only sent when this profile is active

* required

Form schedule




Visit	Form	Due
Baseline	Patient Questions 	On day of study entry
6 Week Follow-up	Patient Questions 	6 weeks after study entry
12 Week Follow-up	Patient Questions 	12 weeks after study entry

Figure 10.1: Subject invitation form

Invite schedule

Baseline:

- ✓ Invite due on 1 Feb 2017 16:58 GMT sent automatically on 1 Feb 2017 17:01 GMT
- ✓ Invite sent manually on 1 Feb 2017 17:36 GMT
Subject logged in
- ✗ Reminder due on 8 Feb 2017 16:58 GMT was cancelled
All subject entered forms have been completed for this visit
- ✗ Reminder due on 15 Feb 2017 16:58 GMT was cancelled
All subject entered forms have been completed for this visit
- ✗ Reminder due on 22 Feb 2017 16:58 GMT was cancelled
All subject entered forms have been completed for this visit

1/1 subject entered forms completed

6 Week Follow-up: [Send now](#)

- ⌚ Invite will be sent on or after 15 Mar 2017 16:58 GMT
- ⌚ Reminder will be sent on or after 22 Mar 2017 16:58 GMT
- ⌚ Reminder will be sent on or after 29 Mar 2017 16:58 BST
- ⌚ Reminder will be sent on or after 5 Apr 2017 16:58 BST

12 Week Follow-up : [Send now](#)

- ⌚ Invite will be sent on or after 26 Apr 2017 16:58 BST

Figure 10.2: Subject invitation schedule

Subjects

Search: ⓘ

Subject ID	Site	Randomisation group	Date randomised	Status
01921	UCL	Control	1 Feb 2017 16:58 GMT	

Showing 1 to 1 of 1 entries

Subject details

Subject ID 01921
Site 1: UCL, United Kingdom
Randomisation group Control
Date randomised 1 Feb 2017 16:58 GMT

[Mark as randomised in error](#)

Queries

[Create a new query](#)

Attachments

There are currently no attachments.

[Upload an attachment](#)

Subject invitations

Subject has been invited to complete forms.

[View details](#)

CRF

Baseline

Subject invited ([details](#))

Due: 1 Feb 2017 [Mark as data missing](#)

Randomisation		Add	View	Edit
Interviewers questions		Add	View	Edit
Patient Questions		Add	View	Edit
Satisfaction of Care		Add	View	Edit

Figure 10.3: Subject list

What the subject sees

Once a subject goes to the URL in their email or SMS invitation and, optionally, enters their memorable word they will see a list of forms to complete. Clicking on the name of the form takes them to that form where they can complete their answers. Unlike [data entry of forms](#) by investigator and administrator accounts, subjects cannot override the validation checks on fields. They also will not see the review step - once they press the save button the form is saved immediately and cannot be viewed or edited by the subject. Entered forms are shown as completed in the list of forms.

JUMP



Thanks for taking part in this research study. Please complete all of these forms.

Please complete the following form:

1. [Patient Questions](#)

Figure 10.4: List of forms as seen by the subject

The subject can return to complete the forms at any time until the unique link in their email expires. Once all the forms are completed a thank you message is displayed.

JUMP



Thanks for taking part in this research study. Please complete all of these forms.

The form was successfully saved.

Please complete the following form:

1. Patient Questions — completed ✓

Thank you for completing this form. Please [logout now](#).

Figure 10.5: Completed forms as seen by the subject

Security

In addition to the [security measures applied to all Sealed Envelope systems](#) the following aspects apply to subject entered data:

- Only investigator accounts can view the subject's email address and/or mobile number
- The subject's email address and/or mobile number are encrypted at rest (AES-256 CBC)
- Subjects are sent unique links to complete forms that expire after a set period
- Subjects cannot view their forms, only add them. Draft saving is not enabled.
- An optional memorable word can be specified by the investigator that is used as a challenge when a subject accesses a unique link

Chapter 11

Viewing forms

Forms are viewed by clicking on the **View** link next to the selected form shown on the patient details screen. The most recent version of the form is displayed. If the form has been edited a history bar will be shown, allowing past versions of the form to be displayed. Changes to the form compared to the previous, older, revision are highlighted in yellow when navigating through the history. The exception to this is repeating sections within forms - changes to these are not highlighted.

Patient Questions

[Edit this form](#) This form was created at 23 Mar 2016 12:51 UTC by Sealed Envelope support (ID 1) and last edited at 23 Mar 2016 17:22 UTC by Sealed Envelope support (ID 1)

Form history: < [Previous version](#) | [Next version](#) > Version saved by Sealed Envelope support (ID 1) at 23 Mar 2016 17:22 UTC

Patient Health Questionnaire (PHQ-9)

Over the past 2 weeks, how often have you been bothered by any of the following problems?

Little interest or pleasure in doing things

Not at all

Feeling down, depressed, or hopeless

Not at all

Trouble falling or staying asleep, or sleeping too much

Not at all

Feeling tired or having little energy

More than half the days

Poor appetite or overeating

Not at all

Figure 11.1: Viewing a form that has been edited

Chapter 12

Editing forms

Completed forms may only be edited by users with administrator accounts or investigator accounts when the [investigator edit setting](#) is turned on. Forms are edited by clicking on the **Edit** link next to the selected form shown on the patient details screen, or by clicking on the **Edit this form** link shown when viewing a form. The form is displayed in the same way as when adding the form but with some extra fields for recording validation status and reason for editing. The user may change any of the values in the form and they must complete the reason for editing field before reviewing and saving the form.

Validation status

When editing a form, the validation status can be set to 'Validated' provided there are no open queries for the form. Once a form is marked as validated, a green tick appears next to the form name in the patient details. If a query is added to the form after the form has been marked as validated, the validation status will automatically be changed to 'Not validated'. It is up to the trial coordinating team to decide what constitutes a validated form. It may, for instance, be as a result of a formal monitoring visit, or alternatively visual check against the source data by someone who did not enter the data.

Completed forms may not be deleted. However, the validation status may be set to 'Data unusable' to indicate that the whole form should be disregarded.

Any problems

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people

Somewhat difficult ▾

Notes

Validation status *
Not validated ▾

Validation notes

Reason for edit *
Response to query #24

Save form

Figure 12.1: Editing a form

Chapter 13

Editing randomisations

Randomisation forms may be [edited](#) by viewing the form and clicking on the 'Edit this form' link.

Study ID 04-1290 | Date entered study: 30 Jan 2017 | 04: Helsingør, Denmark

[Return to subject](#) [Create a query](#)

Randomisation

Randomised to **XP7** at 30 Jan 2017 13:31 CET

[Edit this form](#)

Randomisation

Study ID

04-1290

SS-NNNN, where SS is 2-digit site number and NNNN is 4-digit sequence number

Figure 13.1: Viewing a randomisation form

Randomisation forms have the following special features:

- 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 14

Obsolete forms

If changes are made to the CRF after data collection has started, Red Pill keeps track of the different versions of the same forms. The previous version () will be marked as obsolete in the interface.

If the form was completed for a particular subject, it will still be accessible for viewing and editing. The latest version will also be available for data-entry.



Figure 14.1: Subject with obsolete form

However, for subjects where the original version was not completed, only the latest version will be accessible.

The [overdue forms](#) display always operates on the latest version of each form. Therefore, forms will be shown as overdue unless the latest version has been added. If it is not possible to collect the newer version of a form for a subject (perhaps because it was too long ago), the forms can be marked as data missing.

v2	Demographics	Add	View	Edit
	Physical examination	Add	View	Edit

Figure 14.2: Subject without obsolete form

Downloads

Data from all versions of a form will be available for [download](#). The datasets will have a version suffix, e.g. DemographicsVER1, DemographicsVER2. The datasets will only contain rows for subjects where the specific version of a form was completed for them.

CSV files

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

Download individual form data:

- Subject
- Study entry
- **v1** **obsolete** Demographics
- **v2** Demographics
- Physical examination

Figure 14.3: Download page showing different versions of a form

Chapter 15

Overdue forms

An overview of overdue forms for all subjects may be viewed by clicking the **Overdue forms** link in the left-hand side bar. Each subject is shown as a row in the table, with a cell for each form in a visit with a time-point.

Note that visits without time-points are not shown

Completed forms are shown in green, overdue forms in red. Forms that will never be completed because the subject withdrew or did not attend a visit are shown in grey. Blue cells indicate that the form is not applicable to that subject - for instance because a form is only collected on subjects with a baseline abnormality. Clicking on a cell displays the name of the associated form. The table may be filtered by entering terms in the search box.

The percentages of forms completed, overdue etc are shown in the summary by site and overall. Note that percentages are calculated excluding forms that are not yet due in the denominator. So although 100% of forms may be shown as done today, this may change in the future as forms become due.

Overdue forms

[View a summary](#)

Detail by subject

Key ■ Form completed ■ Form overdue ■ Not due yet ■ Form missing

Visits **A:** Baseline **B:** 6 Week Follow-up **C:** 12 Week Follow-up

[Download as CSV](#)

Click an entry to display the form and visit name.

Search:

Subject	Site	A			B			C		
T5617	UCL	■	■	■	■	■	■	■	■	
T5511	UCL	■	■	■	■	■	■	■	■	
T1719	UCL	■	■	■	■	■	■	■	■	
S8040	UCL	■	■	■	■	■	■	■	■	
S7928	UCL	■	■	■	■	■	■	■	■	

Figure 15.1: Overdue forms detail

Summary by site

Key ■ Form completed ■ Form overdue ■ Form missing ■ Subject withdrew ■

Number and percentage of forms by status excluding forms not yet due.

Site	■	■	■	■	■
UCL	21 30%	43 61%	4 6%	3 4%	0 0%
Royal Albert Hospital	16 19%	62 73%	4 5%	3 4%	0 0%
Total	37 24%	105 67%	8 5%	6 4%	0 0%

Figure 15.2: Overdue forms summary

Chapter 16

Code lists

Code lists are only relevant to double blind trials. The code list provides the confidential link between the kit codes 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 kit code - see the [FAQ](#) for more information. Here is an example of a code list in the randomisation system:

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

Terminology

A consistent terminology is used throughout the randomisation system, although in practice different trials may use alternative terms.

Kit

A *kit* is a unit of the investigational product or placebo that will be given to a single subject. In practice a kit may be a vial, a bottle containing pills, a pack containing multiple vials etc. Multiple kits may be given to the same subject, for instance at scheduled follow-up visits or because the original kit has been lost or damaged.

Code list

The code list shows the current location and details about all the kits in the trial. A kit is a unit of the investigational product or placebo that will be given to a single subject. In practice a kit may be a vial, a bottle containing pills, a pack containing multiple vials etc.
Use the form to update selected rows in the code list. Only new, unexpired kits at site will be available for randomisation or assigning to subjects so you must keep this list up to date. The [drug stocks report](#) is useful for monitoring stock levels at sites.

Update selected - 0 row(s)

Update batch
 Update expiry date
 Update buffer
 Update status
 Update location
 Update notes

Batch
 Expiry date
 Buffer
 Status
 Location
 Notes

[Download as CSV](#)

Select	Seq. no	Kit Block	Kit code	Batch	Expiry date	Buffer, days	Status	Location	Site	Last update	Notes
	<input type="text" value="Search seq. no"/>	<input type="text" value="Search kit block"/>	<input type="text" value="Search kit code"/>	<input type="text" value="Search batch"/>	<input type="text" value="Search expiry date"/>	<input type="text" value="Search buffer, days"/>	<input type="text" value="Search status"/>	<input type="text" value="Search location"/>	<input type="text" value="Search site"/>	<input type="text" value="Search last update"/>	<input type="text" value="Search notes"/>
<input type="checkbox"/>	1	1	AZ4		31 Dec 2035	7	New	Site	Exmouth Hospital	13 Jul 2016 16:09 BST	
<input type="checkbox"/>	2	1	AL8		31 Dec 2035	7	New	Site	Exmouth Hospital	13 Jul 2016 16:09 BST	
<input type="checkbox"/>	3	1	LN6		31 Dec 2035	7	Dispensed (Randomisation)	Site	Exmouth Hospital	13 Jul 2016 16:09 BST	
<input type="checkbox"/>	4	1	OV5		31 Dec 2035	7	New	Site	Exmouth Hospital	13 Jul 2016 16:09 BST	
<input type="checkbox"/>	5	1	RS4		31 Dec 2035	7	New	Site	Exmouth Hospital	13 Jul 2016 16:09 BST	
<input type="checkbox"/>	6	1	WW7		31 Dec 2035	7	New	Site	Exmouth Hospital	13 Jul 2016 16:09 BST	
<input type="checkbox"/>	7	1	AY9		31 Dec 2035	7	New	Site	Exmouth Hospital	13 Jul 2016 16:09 BST	
<input type="checkbox"/>	8	1	RJ9		31 Dec 2035	7	New	Site	Exmouth Hospital	13 Jul 2016 16:09 BST	
<input type="checkbox"/>	9	2	KU6		31 Dec 2035	7	New	Site	Luton Hospital	13 Jul 2016 16:09 BST	
<input type="checkbox"/>	10	2	EJ4		31 Dec 2035	7	New	Site	Luton Hospital	13 Jul 2016 16:09 BST	

Figure 16.1: Code list page

The *kit code* is unique code assigned to a kit. The kit code will be printed on the packaging and given out by the randomisation system. The format of a kit code is usually numeric or alphanumeric (e.g. 7210 or AT6). Some trials may have different types of kit, such as different bottle sizes, different dosages or rescue medication. If your trial does not have different kit types you won't see kit types in your code list.

A *kit block* is an administratively convenient block of kits and is used in the [dispensing policy](#) (see below). Kits are often shipped in whole blocks and the blocks are balanced to represent the randomisation ratio. For instance, a block of 4 in a trial with 1:1 ratio will contain 2 active and 2 placebo treatments. Note, however, that the kit blocks in the code list are not related to the block sizes chosen to balance the randomisation if [random permuted block randomisation](#) is in use.

Randomisation kit code is the kit code given out at randomisation.

Sequence number

The sequence number is used to order the code list in a consistent, reproducible manner. It has no other function - in particular do not assume that kits are given out in sequence number order (see [dispensing policy](#) below).

Batch

Batch is optional but is intended to record the manufacturer's lot or batch number.

Expiry

Kits must be given an *expiry date* and that date must be in the future before they can be dispensed (kits will not be dispensed on the date of expiry). Kits will not be dispensed in the *buffer* days leading up to the expiry date either. This is to prevent kits being dispensed that may expire during the period of their use.

Viewing a code list

For trials that have a code list, a **Code list** link may be shown in the top menu to administrators. It will not be shown for trials that are not shipping kits to sites such as trials where the drug is made up in the pharmacy on demand using bulk supplies.

Expired kits and those without an expiry date are greyed out. The list can be filtered and sorted using the controls in the table headings.

Updating

Kits can be selected using the checkboxes to the left of the list, or by clicking anywhere on a row. Shift-click and Control/Command-click can be used to select multiple rows.

Update selected - 4 row(s)

Update batch Update expiry date Update buffer Update status Update location

Batch Expiry date Buffer Status Location

 31/12/2020 📅 days New Site

Site

3: Site 3

First Previous 1 2 3 4 5 ... 17 Next Last

Select ▼	Seq. no	Kit Block	Kit code	Batch	Expiry date
	<input type="text" value="Search seq. no"/>	<input type="text" value="Search kit block"/>	<input type="text" value="Search kit code"/>	<input type="text" value="Search batch"/>	<input type="text" value="Search expiry date"/>
<input checked="" type="checkbox"/>	1	1	90001		
<input checked="" type="checkbox"/>	2	1	90002		
<input checked="" type="checkbox"/>	3	1	90003		
<input checked="" type="checkbox"/>	4	1	90004		
<input type="checkbox"/>	5	2	90005		
<input type="checkbox"/>	6	2	90006		

Figure 16.2: Updating a code list

Selected rows are updated using the form above the code list. This takes the user to a confirmation screen showing the actions that will be carried out and any warnings for unusual changes. Warnings are shown when:

- Changing batch, expiry date, expiry buffer, status or notes for a dispensed kit
- Moving kits between sites
- Changing status from **Dispensed** to any other value
- Changing status of a previously dispensed kit to **New** as this will remove the link to the subject the kit was dispensed to
- Changing location from **Site** to any other value as this will remove the link to a specific site

If a warning is shown the user will be required to enter a reason for making the change. This reason will be recorded in the [audit trail](#).

It is not possible to change the kit type, location or site if a kit has been dispensed.

Update list

Please confirm that you wish to update the code list.

The following code(s) will be updated: 90001, 90002, 90003, 90004, 90005, [and 4995 more codes](#).

The following actions will be performed

- Update expiry date to 31/12/2020
- Update buffer to 7 days

Update list

Cancel

Figure 16.3: Confirmation of changes to code list

Deallocating a kit from a subject

Sometimes it may be desirable to deallocate a kit from a subject, such as when a subject was randomised in error or withdraws before the kit is used. This can be done by updating the kit in the codelist and changing the status from **Dispensed** back to **New**. This makes the kit available again

for use at the site. Kits deallocated in this way are still shown when viewing the original subject along with the date of deallocation.

Dispensing policy

Kits are assigned to subjects at [randomisation](#) and during [follow-up](#) according to a dispensing policy. The default policy is to assign kits which:

- Match the subject's randomised treatment group
- Have not expired and are not within the expiry buffer before the expiry date
- Have a status of **New**
- Have a location of **Site** and are at the same site as the subject
- Come from lower kit block numbers

Kits are chosen at random from the pool of eligible kits (with lower numbered kit blocks preferred) to reduce the chance of treatment information being gleaned from the order in which kits are used. Note this means that kits are *not allocated in sequence number order*.

The dispensing policy for particular trials can vary from the default policy. Extra factors such as follow-up visit, kit type or patient characteristics may be taken into account. You should check the [specification page](#) for your trial to see if this is the case.

Stock levels

It is the administrators responsibility to update the code list to reflect the real world location of kits and make sure sites have enough stock available for randomisation and follow-up visits as appropriate. The drug stocks report shows the number of new, unexpired kits available at each site. It will also show warnings for sites where there are fewer than 2 kits available for any treatment group. Randomisation may fail if there are insufficient kits available at site.

A low stock email notification will be sent to all administrators and notification accounts when the number of new, unexpired kits available at a site drops below a preset threshold. The default threshold is 6 but can be changed on request.

Drug stocks

New, unexpired kits marked as on site in the code list by site. Make sure you have enough kits available at each actively recruiting site. Note that kits without an expiry date and those within the buffer zone before expiry are shown as expired as they will not be chosen for randomisation. Click on a column heading to sort by that column.

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

Search:

Site	Total kits	Kits dispensed	Expired	New, unexpired kits on site	Warnings
Exmouth Hospital	5	1	0	4	One or more treatments has fewer than 2 kit(s) available!
Luton Hospital	31	0	1	27	

Figure 16.4: Drug stocks report

Downloading

The full blinded code list can be downloaded by clicking on the 'Download as CSV' link shown at the top 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,patientId,code,kitBlock,kitType,batch,expiryDate,expiryBuffer,kitStatus,dispensedVisit,location,siteId,dateUpdate,notes,siteName
1,3,SG6,1,,2035-12-12,0,Dispensed,Randomisation,Site,2,"2016-07-14 17:02:24",,"Luton Hospital"
2,2,ZV0,1,,2035-12-12,0,Dispensed,Randomisation,Site,2,"2016-07-14 17:02:24",,"Luton Hospital"
3,1,FI4,1,,2035-12-12,0,Dispensed,Randomisation,Site,2,"2016-07-14 17:02:24",,"Luton Hospital"
4,,ZD4,1,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital"
5,,XB3,2,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital"
6,,HC3,2,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital"
7,,KG0,2,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital"
8,,YH5,2,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital"
```

The fields present are:

- id Sequence number
- patientId If the kit has been dispensed, the id of the subject the kit was assigned to. Use this field to link kits to other [subject data](#)
- code Kit code

- `kitBlock` Kit block number
- `kitType` Type of kit (optional)
- `batch` Manufacturer's batch or lot number (optional)
- `expiryDate` Expiry date (*yyyy-mm-dd* format)
- `expiryBuffer` Buffer period in days before the expiry date when kit will not be allocated
- `kitStatus` Current status of kit - one of 'Unmade', 'New', 'Dispensed', 'Quarantined', 'Lost', 'Damaged' or 'Destroyed'
- `dispensedVisit` Visit when kit was allocated, such as 'Randomisation', 'Follow-up' etc
- `location` Current location of kit - one of 'Manufacturer', 'Distributor', 'Site', 'Other'
- `siteId` ID of site where kit is located. Will be blank if not at a site or if the kit can be used at all sites
- `dateUpdate` Timestamp of when kit information was last updated (UTC, *yyyy-mm-dd hh:mm:ss* format)
- `notes` Notes (optional)
- `siteName` Name of site

Chapter 17

Assigning kits

Double blind trials use a [code list](#) to automatically assign kit codes at randomisation. Kits can also be assigned at a later time by administrators or investigators, at follow-up visits, for instance, or to replace lost or damaged kits.

Not all trials with a code list can assign kits. This feature will not be available in trials where the drug is made up in the pharmacy on demand using bulk supplies.

How to assign a kit

To assign a new kit to a randomised subject, first locate the subject in the [randomisations](#) or [subjects](#) list. A link to assign a kit code is shown. This takes the user to a form to complete with the reason for assigning a new kit. Depending on the trial, this form may also have options for selecting visit, kit type or number of kits required. The user must enter their password to confirm the action and a new kit code(s) will be chosen from the code list and shown to the user.

The kit is chosen according to a dispensing policy in the same way as at randomisation. If insufficient kits are available an error message will be shown when trying to assign a kit.

Assign kit code

Kit code ZV0 was assigned

The following kit code(s) have been assigned:

Kit code	Kit type	Expiry date	Date/time assigned	Reason
ZV0		12 Dec 2035	16 Jul 2016 16:51 BST	"Original kit was mislaid by patient" by Superuser (ID 1)

Figure 17.1: Result of assigning a kit code

Failed kit assignment at randomisation

Occasionally, if a subject is randomised at a site with low stock levels, a suitable kit may not be available that matches the chosen treatment group. In this case the subject will be shown with a warning message that no kits have been allocated. A kit should be manually assigned as soon as the site is re-supplied.

Notifications

An email notification will be sent out to the same recipients as for randomisations. The format of the email can be seen on the [specification page](#).

Viewing assigned kits

Assigned kits are shown in the kit codes section of the randomisation or subject details. All kits assigned are shown in the **Kit codes** column of the [randomisations](#) or [subjects](#) list. The list can be searched to find the subject a specific code was assigned to.

Randomisation details

Subject ID 2000/21
Site 1: Exmouth Hospital, Algeria
Date randomised 25 Aug 2016 17:15 BST
Randomisation kit code

[View randomisation form](#)

No kits have been assigned! This may be because no suitable kits could be found at randomisation. Assign a kit code manually when more stock becomes available.

 [Mark as randomised in error](#)

 [Unblind](#)

Kit codes

 [Assign kit code](#)

Figure 17.2: Subject without assigned kit

Kit codes

 [Assign kit code](#)

Kit code	Kit type	Expiry date	Date/time assigned	Reason
FI4		12 Dec 2035	25 Aug 2016 17:15 BST	Randomisation by Ms Admin (ID 2)
SG6		12 Dec 2035	6 Sep 2016 12:36 BST	"Original kit was mislaid by patient" by Superuser (ID 1)

Figure 17.3: Randomisation with assigned kits

Deallocated kits

If a kit has been deallocated from a subject in the [code list](#), it is still shown in the assigned kits section along with the date of deallocation.

Randomisation details

Subject ID 2000/23
Site 1: Exmouth Hospital, Algeria
Date randomised 25 Aug 2016 17:15 BST
Randomisation kit code

[View randomisation form](#)

⚠ This randomisation was marked as randomised in error on 6 Sep 2016 12:39 BST.
Reason given: "Mix-up with screening results - patient not eligible" by Superuser (ID 1).

[Unblind](#)

Kit codes

Kit code	Kit type	Expiry date	Date/time assigned	Reason
SG6		12 Dec 2035	25 Aug 2016 17:15 BST (deallocated 26 Aug 2016 11:34 BST)	Randomisation by Ms Admin (ID 2)

Figure 17.4: Randomisation with deallocated kit

Chapter 18

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 it is not possible to change the site identifier if a site has associated records, such as user accounts, subjects, kits in the code list or allocations in a randomisation list stratified by site.

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, subjects, kits in the code list or allocations in a randomisation list stratified by site.

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 18.1: Adding a new site

Chapter 19

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 section 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 19.1: 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).

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 19.2: Viewing an open query

23/03/2016

JUMP | Query ID 1 | View Randomisation | Subject T1719

[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 19.3: Response box shown when printing a query

Listing queries

A list of queries grouped by site is displayed by clicking on the **Queries** link in the top menu. The conversation thread for a query can be viewed by clicking on the query in the list. This view also displays links for editing the query or viewing the related subject or form.

Chapter 20

Subject attachments

If subject attachments are enabled, documents associated with a subject can be uploaded for storage in the subject's CRF.

Note: It is **essential** that documents containing personally identifiable subject information are not uploaded.

The [specification page](#) will list details of the maximum file size allowed for an individual attachment and the remaining the space available for attachments.

Permissions

Every role with access to the subject view may download the attachments. Investigators can upload new attachments, and Administrators can delete existing attachments.

Uploading attachments

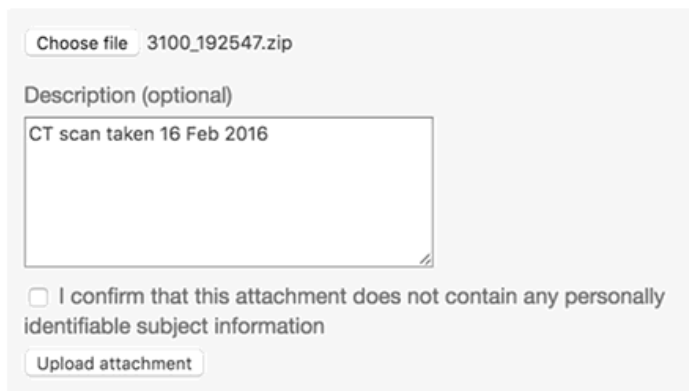
The subject record will have an Attachments section with a link to **Upload an attachment**. Following the link leads to the Attachments page for that subject, and a form where the file to be uploaded and an optional description can be specified.

Attachments

You have used 0% of the 5.0 GB space you have available for storing attachments.
Individual attachments can have a maximum file size of 1.0 MB.

Upload an attachment

Please ensure that you do not upload any attachments containing personally identifiable subject information.



The screenshot shows a web interface for uploading an attachment. At the top, there is a button labeled "Choose file" followed by the filename "3100_192547.zip". Below this is a section titled "Description (optional)" with a text area containing the text "CT scan taken 16 Feb 2016". Underneath the text area is a checkbox with the text "I confirm that this attachment does not contain any personally identifiable subject information". At the bottom of the form is a button labeled "Upload attachment".

Figure 20.1: Uploading an attachment

Submitting the form will store the attachment in the subject's CRF.

Viewing and downloading existing attachments

Once attachments have been uploaded for a subject the subject view will display a link to download the attachment.

The Attachments page will contain a table detailing the attachments for that subject.

Deleting an attachment

Administrators can delete existing attachments. To delete an attachment follow the **Delete** link from the table on the Attachments page. This leads to a confirmation page where clicking the **Delete attachment** button will remove the attachment from the subject's CRF.

Note: Deleted attachments are removed from the filesystem so this action cannot be undone.

Running out of space

Contact support@sealedenvelope.com to increase the space available for storing attachments.

Subject details

Subject ID	S4470
Site	2: Royal Albert Hospital, Australia
Randomisation group	Intervention
Date randomised	2 Jan 2016 02:44 AEDT

[Mark as randomised in error](#)

Queries

[Create a new query](#)

Attachments

 3100_192547.zip

[Upload or view existing attachment](#)

Figure 20.2: An attachment listed in the subject view

Existing attachments

Attachment	Size	Uploaded by	Uploaded at	Description	Delete
3100_192547.zip	746.6 kB	Sealed Envelope support (ID 1)	24 Mar 2016 15:14 UTC	CT scan taken 16 Feb 2016	Delete

Figure 20.3: Table of attachment details

Delete an attachment

You will not be able to undo this action so please double check the details below before proceeding.

Attachment details

Attachment 3100_192547.zip
Size 746.6 kB
Uploaded by Sealed Envelope support (ID 1)
Uploaded at 24 Mar 2016 15:14 UTC
Description CT scan taken 16 Feb 2016

Delete attachment

Figure 20.4: Deleting an attachment

Chapter 21

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
S7028	Withdrawal	23 Mar 2016 12:55	23 Mar 2016 12:55	0	Not validated

Figure 21.1: Viewing a report

Chapter 22

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.

Encrypted PII fields

Fields containing personally identifiable information (PII) that have been configured in the CRF builder to be stored in an encrypted format will be downloaded with AES-256 encryption applied. This means these fields cannot be viewed or analysed without decryption. Decryption can be carried out using common decryption tools such as [OpenSSL](#). Contact Sealed Envelope support for further instructions.

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 22.1: 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 22.2: Form data dictionary

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.

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

Figure 22.3: Viewing CSV file in spreadsheet

Every file contains a patient identifier field (`identifier`) and subject ID field (`patientId`) so that data stored on the same subject in different forms can be linked together. In general the `id` field should be ignored - it simply records the order forms were added to the database and is not related to the subject.

Subforms

Subforms store the data from repeating sections of forms. These are downloaded as separate files from the parent form. Records should be linked to the parent form via the column labelled `Parent record`. Foreign key: `<parent-table-name>.id`. This should be matched to the `id` field in the parent table. Although subforms also contain the subject ID field, and this could be used to match records to the parent form, it is not recommended in case the parent form is repeatable.

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 22.4: 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.

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


```
. 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 22.5: Tabulating imported form data

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 23

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)

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 23.1: Audit trail

- 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

```
"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 24

Settings

A settings page is available to administrators that allows some features to be turned on or off to suit the requirements of a trial. Changes to settings are recorded in the [audit trail](#). There are some common settings (see below) and there may also be 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, administrators 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 data entry staff are 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 24.1: Settings page

Investigator edit

By default investigators cannot edit forms - only add them and view them. This setting enables investigators to also edit forms after they have been saved. In addition it allows investigators to mark forms in a visit as missing.

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. Administrators 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.

Form delete

Allows an administrator to delete forms. The deleted data is shown in the [audit trail](#). Randomisation forms cannot be deleted - the [randomised in error](#) feature should be used instead. Study entry forms may not be deleted either - the subject must be deleted to remove this form.

The form delete setting will not be shown for randomisation only systems

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 ran-

dominations. 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 25

Specification

The specification for a Red Pill or randomisation 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, showing when visits are due and the forms within each visit.
- Whether any of the forms can be self-completed by subjects, and information about custom text shown to the subject in invitation emails and after logging in.
- Details on randomisation method used, treatment groups, allocation ratio, strata, blinding, code list length, randomisation limit, data collected at randomisation (where relevant).
- Format of randomisation, unblinding and kit assignment email notifications.
- If [attachments](#) are enabled, the maximum file size allowed and percent of storage allowance used.
- The format of all notifications and a description of who they will be sent to.
- User account privileges for different roles.
- Library version numbers.
- Server type (staging/production), database version, current value of [settings](#).

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




Specification

Multiple forms

The following forms can be completed as many times as required.

- Serious Adverse Events

Form schedule

Visit	Form	Due
Baseline	Randomisation	On day of study entry
	Interviewers questions	On day of study entry
	Patient Questions 	On day of study entry
	Satisfaction of Care	On day of study entry
	Concomitant medications	On day of study entry
6 Week Follow-up	Patient Questions 	6 weeks after study entry
12 Week Follow-up	Interviewers questions	12 weeks after study entry
	Patient Questions 	12 weeks after study entry
Other forms	Serious Adverse Events	at any time
	Withdrawal	at any time

Subject entered forms

Subjects may be invited to complete the following forms:

- Baseline visit: Patient Questions
- 6 Week Follow-up visit: Patient Questions
- 12 Week Follow-up visit: Patient Questions

Figure 25.1: Specification page

Chapter 26

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:

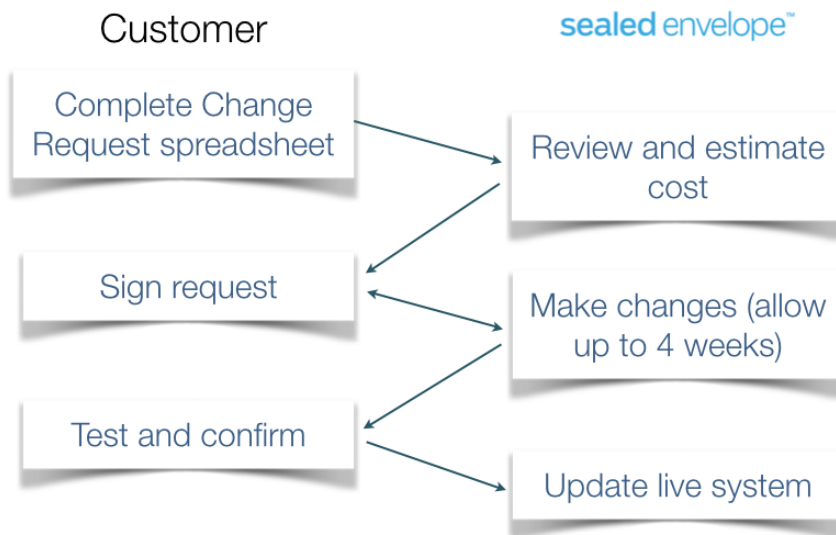


Figure 26.1: Flowchart for change request process

- 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
- 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 27

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

Number	Sex	Age	Treatment group
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:

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

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 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

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

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 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 28

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 29

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
```

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

```
. tab severity group
```

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

```
. tab agegroup group
```

agegroup	group		Total
	Active	Control	

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 30

Randomisation 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. If enabled, the API username and password will be shown on the [specification page](#). Documentation for developers is available on request.

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