

sealed envelope™

Red Pill and Randomisation

Version 24

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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.

Choose the version of the documentation that applies to your trial. The version number is shown in the footer of every page when logged into a Red Pill application.

Getting started

Accessing the system

The [Access](#) application is the gateway for Red Pill and randomisation systems. The web address 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.

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

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

Next you should add some investigator accounts for each site so that 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.

Subjects

Subject records can be viewed by clicking on the **Subjects** link in the top menu (this may be labelled **Randomisations**, **Participants** or similar depending on your system). 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.

Subjects

Search:

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 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 2: A follow-up visit due after subject withdrew

Forms not available

Forms may not be available until certain conditions are met. For instance, the randomisation form may not be available until the screening visit is completed and the eligibility criteria met. You can see which forms are not available both on the [overdue forms](#) page (if the visit has a time-point), and in the **Forms not available report**.

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

Forms not available

List of forms that are not available based on answers given to questions in other forms. Click on a column heading to sort by that column.

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

Search:

Subject	Visit	Form not available	Reason	Based on answers in form(s)
FH127P	[Vr] Informed Consent & Randomisation	eConsent: Carer	Carers only	Study Entry
FH127P	[Vr] Informed Consent & Randomisation	Carer Informed Consent	Carers only	Study Entry
FH127P	[Vr] Informed Consent & Randomisation	Randomisation	No Carer found for this Participant	
FH127P	[V0] Baseline	Socio-Demographic Information: Carer	Carers only	Study Entry
FH127P	[V0] Baseline	Zarit Carer Burden Interview	Carers only	Study Entry
FH127P	[V0] Baseline	Carer Quality of Life Questionnaire for Parkinsonism	Carers only	Study Entry

Figure 3: Forms not available report

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: A follow-up visit marked as missing

Subject-entered forms (ePRO)

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](#).

Viewing and downloading randomisations

Viewing

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

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

The screenshot shows a web interface for viewing randomisations. On the left, there is a search bar and a table with columns: Subject ID, Site, Date randomised, Kit codes, and Status. The table contains three entries for subject IDs 2000/21, 2000/22, and 2000/23, all from Exmouth Hospital, dated 16 Jul 2016 10:50 CDT, with kit codes SG6, ZV0, ZD4, and FI4. Below the table, it says 'Showing 1 to 3 of 3 entries'. On the right, a sidebar titled 'Randomisation details' shows information for subject ID 2000/21: Site (1: Exmouth Hospital, USA), Date randomised (16 Jul 2016 10:50 CDT), and Randomisation kit code (SG6). Below this, there are links for 'View randomisation form', 'Mark as randomised in error' (with a red error icon), and 'Unblind' (with an eye icon).

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	FI4	

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: 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).

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.

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.

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 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.

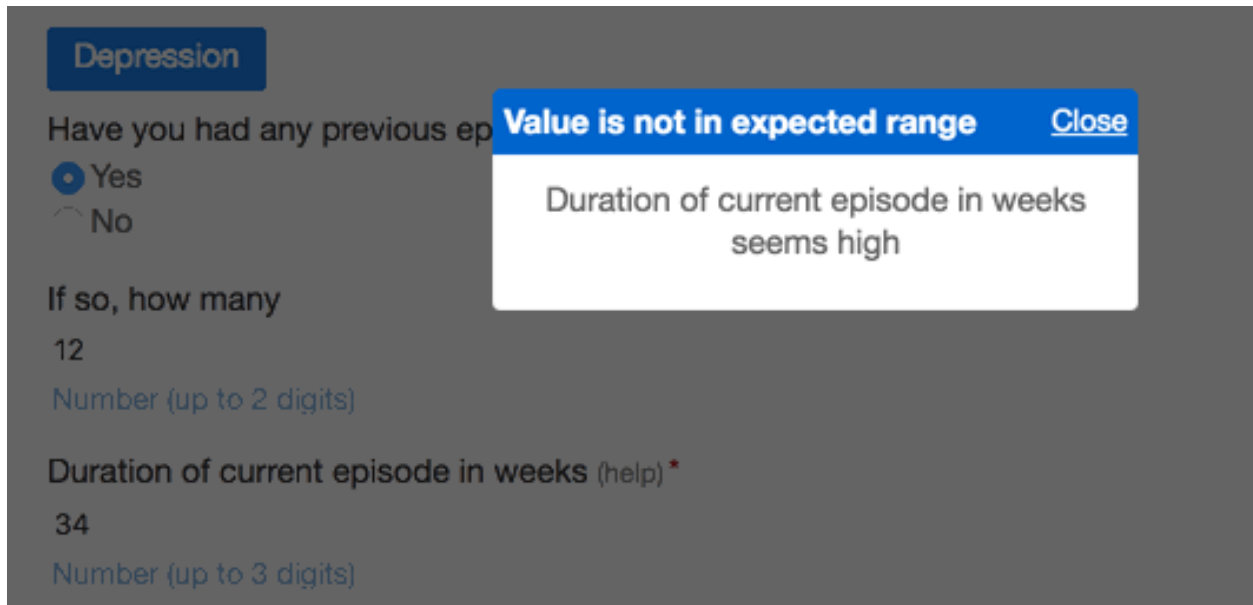


Figure 6: Popup warning message

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. On devices with small screens the options will be displayed as regular radio buttons as the grid can make the responses too compressed and hard to use.


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, as long as the user's role has the **View Personally Identifiable Information** permission. Role permissions can be seen on the [specification page](#).


PII fields will be in encrypted format when [downloaded](#). Read [more about how to decrypt this data after download](#).

Biological samples - Dried Blood Spot

Dried Blood Spot card received?

Date sample received
  **Must be after 04/02/2021**
dd/mm/yyyy

Justification for overriding validation "Must be after 04/02/2021":

Date sample provided
 
dd/mm/yyyy

Time sample provided

hh:mm

Figure 7: 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 8: 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="text"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Figure 9: A Likert scale section

Date of birth *




 dd/mm/yyyy

Figure 10: An encrypted field

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.

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).

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

Confirm

[Back](#)

Figure 11: Reviewing a form before saving

Demographics and Clinical information, ECOG,
Treatment Expectation

Draft saved

Questions

Sex *

Male

Female

Figure 12: 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 13: Load draft dialogue

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.

Visit: [V0] Baseline [+ Create a query](#)

The following forms are now due based on answers in this form:

[Vn] Any Time - Adverse Event Log (CheckQ4 was answered Yes)

[Vn] Any Time - Serious Adverse Events (Please complete the Serious Adverse Events form)

Follow-Up Checklist

This form was saved.

Figure 14: Reminder to complete related forms

The **Forms conditionally required report** shows which forms are due based on rules that are triggered when saving a form. The report shows whether the related forms have been completed or not.

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 15: Repeat entry forms

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 will 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).

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,

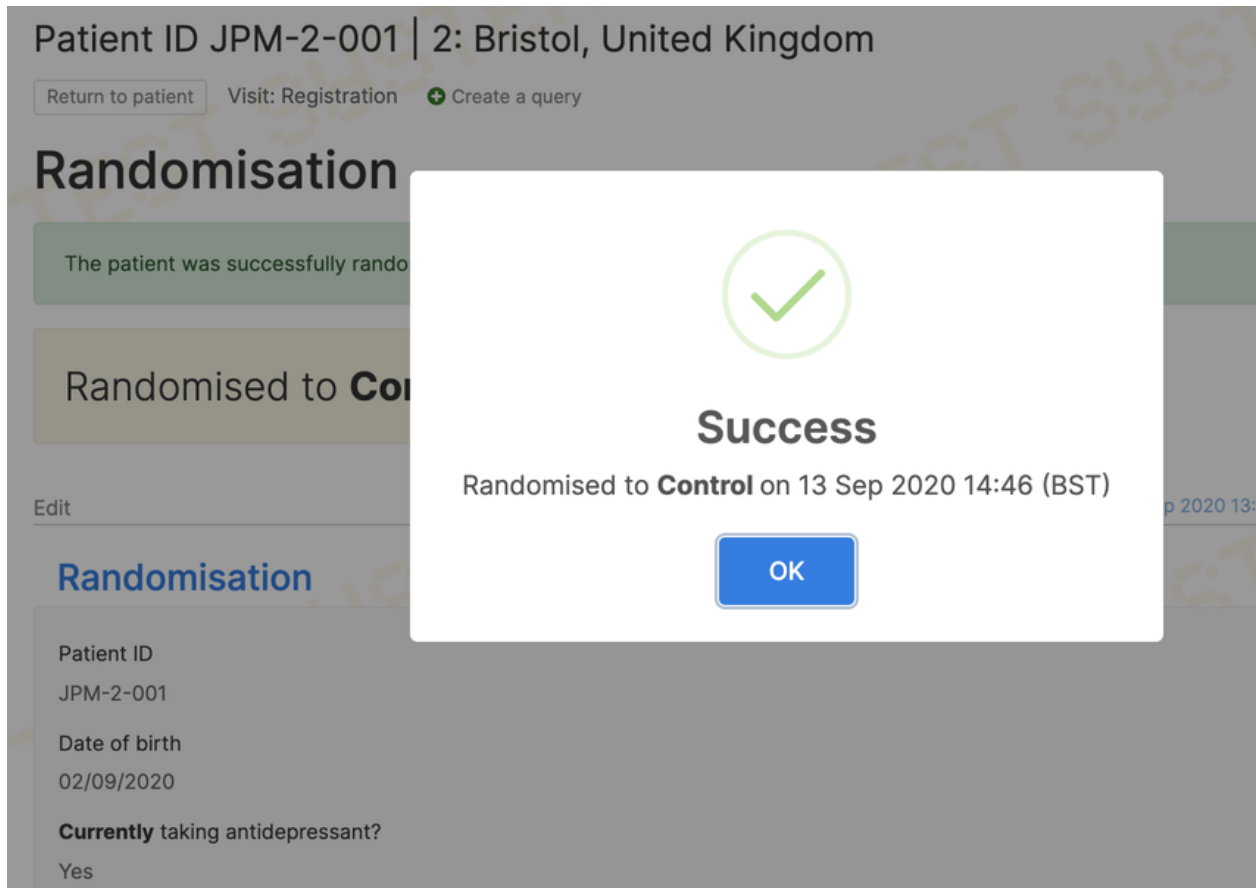


Figure 16: Result of randomising a subject

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 group or code will be automatically sent out to all relevant users that have [notifications enabled](#). Relevant users are those with permission to view the randomisation form for the subject. Randomisation notifications are also sent to all [notification accounts](#).

We advise you **not to rely solely** on email notifications for critical tasks like prescribing, because email is inherently unreliable. For instance, if investigators print out the randomisation email to take to the trial pharmacy, allow an alternative such as printing the completed randomisation form.

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 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.

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 17: No allocations available when randomising a subject

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.

For trials using **permuted blocks** marking in error does not affect the block that the allocation was taken from. Once an allocation is used in a block, it cannot be undone. This means you should try to minimise mistakes to avoid unduly affecting the treatment balance.

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. Some useful discussions of post-randomisation exclusions can be found in these papers:

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.

Yelland LN, Sullivan TR, Voysey M et al. [Applying the intention-to-treat principle in practice: Guidance on handling randomisation errors](#) *Clinical Trials*. 2015; **12(4)**:418-423.

The Yelland paper makes the following recommendations for handling common randomisation errors:

Randomisation error

Recommendations

How to handle in Red Pill

Participant randomised using incorrect baseline information

Accept the randomisation but record the correct baseline information

Edit the randomisation form

Ineligible participant randomised

Keep the participant in the trial and collect all relevant data, unless an unbiased process for excluding ineligible participants has been pre-specified. Seek clinical input to determine their appropriate management.

-

Participant randomised multiple times:

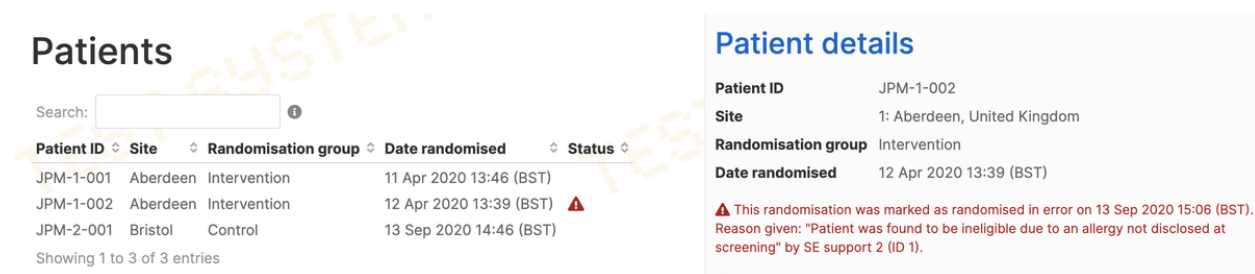
(a) Only one set of baseline and outcome data will be obtained.

<p><p>(b) Multiple sets of baseline and outcome data will be obtained.</p> </td> <td> <p>(a) Retain the initial randomisation and disregard the second randomisation.</p> <p>(b) Retain both randomisations, unless an unbiased process for excluding the second randomisation has been pre-specified.</p> </td> <td>(a) Mark the second randomisation as in error. If a withdrawal form is present complete it to prevent other forms in the CRF being completed .</td> </tr> <tr> <td>Participant received incorrect treatment</td> <td>Record the treatment the participant received and seek clinical input regarding their ongoing treatment.</td> <td>Open a query documenting what happened.</td> > </tr></p>
--

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Mark in error

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.



The screenshot displays a 'Patients' table and a 'Patient details' panel. The table lists three patients, with the second one (JPM-1-002) marked with a red warning triangle. The details panel for JPM-1-002 shows the randomisation was marked as in error on 13 Sep 2020 15:06 (BST) with the reason: "Patient was found to be ineligible due to an allergy not disclosed at screening" by SE support 2 (ID 1).

Patient ID	Site	Randomisation group	Date randomised	Status
JPM-1-001	Aberdeen	Intervention	11 Apr 2020 13:46 (BST)	
JPM-1-002	Aberdeen	Intervention	12 Apr 2020 13:39 (BST)	⚠
JPM-2-001	Bristol	Control	13 Sep 2020 14:46 (BST)	

Showing 1 to 3 of 3 entries

Patient details

Patient ID JPM-1-002
Site 1: Aberdeen, United Kingdom
Randomisation group Intervention
Date randomised 12 Apr 2020 13:39 (BST)

⚠ This randomisation was marked as randomised in error on 13 Sep 2020 15:06 (BST). Reason given: "Patient was found to be ineligible due to an allergy not disclosed at screening" by SE support 2 (ID 1).

Figure 18: A randomisation marked in error

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

Unblinding (code-break)



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

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

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

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

After entering these details and clicking the 'unblind' button the user will **not** be shown the true treatment allocation on-screen. Instead an unblinded email, text message or fax will be sent to the designated person. An email stating that an unblinding has taken place



Participant ID US-001-0001
Site US-001: Chicago General, United States of America
Date verified 26 Aug 2020 13:18 (CDT)
Date randomised 26 Aug 2020 13:49 (CDT)

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

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

Person to unblind

Send message containing true treatment allocation to:

Name *

Email address

Mobile number

Figure 19: Unblinding a designated person

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.

Participant details

Participant ID	US-001-0001
Site	US-001: Chicago General, United States of America
Date verified	26 Aug 2020 13:18 (CDT)
Date randomised	26 Aug 2020 13:49 (CDT)

Unblinding history

Unblinded on 13 Sep 2020 09:12 (CDT) by SE support 2 (ID 1). Reason given: Patient SAE. The true treatment allocation was sent to Desmond Sleet (email: di.sleet@example.com).

Figure 20: An unblinded subject record

Subject entered forms (ePRO)

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.

What the subject sees

Once a subject goes to the URL in their email or SMS invitation they will see a welcome screen. This will include a field to enter their memorable word if one has been set. The welcome message shown is configurable to show trial specific information to participants.

After the welcome screen, subjects 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

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 21: 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 22: 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 23: Subject list

JUMP



Once you complete the online survey, we'll send you the **shopping voucher** by email.

PLEASE ALLOW 7 DAYS FOR DELIVERY

Any information you enter during this survey will be held in strictest confidence and only used for the research purposes that were explained to you at the time you agreed to take part.

[Start survey →](#)

Reference: K981

Figure 24: Welcome screen

[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 25: 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.

If the subject logs out they will see a finished message.

Security

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

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 26: Completed forms as seen by the subject

Finished

Thank you for your participation - we really appreciate your help.

If you did not finish the survey, you can come back and complete it later. Use the link that was sent to you by email or text message.

Figure 27: Finished screen

- 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

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.

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 28: Viewing a form that has been edited

Encrypted PII fields

Fields containing personally identifiable information (PII) that have been configured in the CRF builder to be stored in an encrypted format have restricted visibility. PII fields are not visible unless the user role has the PII permission. By default this permission is given to Investigator and Randomisation roles. Permissions can be checked on the [specification page](#).

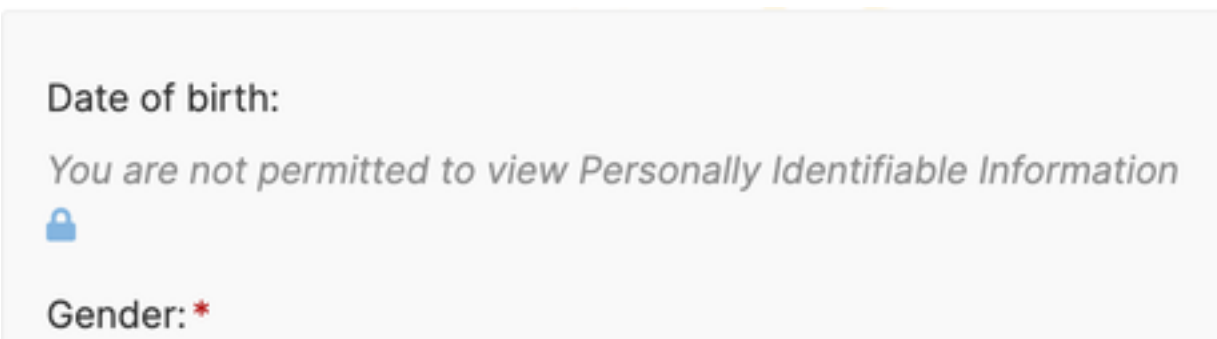


Figure 29: Viewing a PII field

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](#) unless the [form delete setting](#) is turned on. As an alternative, the validation status may be set to 'Data unusable' to indicate that the whole form should be disregarded at the analysis stage.

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 30: Editing a form

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 31: 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.

Deleting forms

Completed forms may be deleted when the [form delete setting](#) is turned on. Usually only users with an administrator role can delete forms, but you can check permissions on the [specification page](#).

To delete a form first [view it](#), then click the red *Delete* link. This will show the **Delete a form** page where a reason for deletion must be provided. The user must enter their password to sign the declaration to delete the form. The deletion is recorded in the [audit trail](#), including the data that was in the form. However, it is not possible to undelete a form directly (it must be re-entered manually).

Study entry form

The form used to add subjects to the database cannot be deleted. Use the subject delete feature instead.

Randomisation form

It is not possible to delete a randomisation form. Use the [mark randomisation in error](#) feature instead.

Withdrawal form

Deleting the withdrawal form reverses the withdrawal of the subject, and any forms that were due for completion after the date of withdrawal will become accessible again.



Delete a form

Form: 1. SDQ

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

All queries related to this form will be deleted.

The deleted form will be shown in the [audit log](#).

Reason

Reason for deletion *

Declaration

By entering my password below, I confirm I wish to permanently delete this form and all associated queries.

Name

SE support (ID 1)

Date

2 Jul 2019

Password *

Delete this form

Figure 32: Deleting a form

Form versions

If changes are made to the CRF after data collection has started, Red Pill keeps track of the different versions of the same forms.

- When adding a form in the CRF the most recent version is always used
- If the *Allow obsolete forms* [setting](#) is on, users can select an older form version when adding a form
- When editing an existing form the version is the same as when the form was added
- If the *Allow form upgrade* [setting](#) is on, it is possible to upgrade an existing form to the latest version
- The [overdue forms](#) display shows an orange tile on the green indicator (form complete) to indicate a newer version of the form exists
- A form version column is present in downloads

Where a newer version of an existing form is available, an icon of a duplicate form will be shown next to the form name in the list of forms.

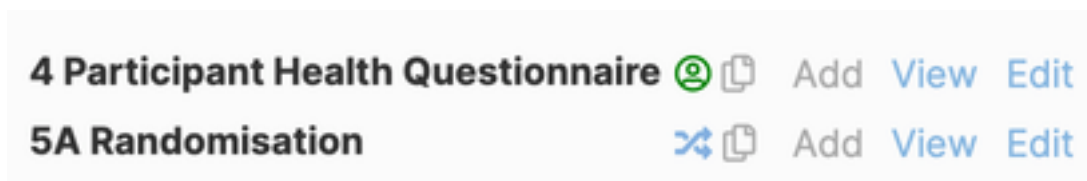


Figure 33: Forms with newer version available

4 Participant Health Questionnaire

This is version 1 of this form. A newer version exists. Change form version to

Choose...
Version 4: 4 Participant Health Questionnaire
Version 3: 4 Participant Health Questionnaire
Version 2: 4 Participant Health Questionnaire

Height

Please enter your height *

cm

feet & inches

[reset]

feet

ft. Number (up to 2 digits)

inches

in. Number (up to 3 digits)

Figure 34: Upgrading a form

Overdue forms

The **Overdue forms** page displays each subject as a row in a 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 are shown in dark grey. Empty forms in visits marked as missing are mid grey. Blue cells indicate that the form is not applicable to that subject – such as a pregnancy form to a male subject. 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 participant

Key ■ Form completed ■ Form completed (new version available) ■ Subject withdrew ■ Missing data ■ Form overdue ■ Form not applicable ■ Not due yet

Visits A: Registration B: Post-verification to Randomisation C: Pharmacy Dispensing D: Participant Contact Details E: Alternative Contact
 F: Treatment Start Date G: Online Questionnaire - Day 30 H: Online Questionnaire - Day 60 I: Online Questionnaire - Day 90
 J: Online Questionnaire - Day 120 K: Online Questionnaire - Day 150 L: Outcomes M: Exit From Trial

[Download as CSV](#)

Click an entry to display the form and visit name.

Search:

Participant	Site	A	B	C	D	E	F	G	H	I	J	K	L	M
ZA-040-0001	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0002	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0003	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0004	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0006	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0007	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0008	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0009	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0010	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0011	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0012	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0013	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0014	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■
ZA-040-0015	CHRU	■	■	■	■	■	■	■	■	■	■	■	■	■

Figure 35: Overdue forms detail

Overdue forms

[View a detailed list](#)

Summary by site

Key ■ Form completed ■ Form completed (new version available) ■ Subject withdrew ■ Missing data ■ Form overdue ■ Form not applicable

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

Site	Form completed	Form completed (new version available)	Subject withdrew	Missing data	Form overdue	Form not applicable
Barnes-Jewish Hospital Downtown	254 6%	1654 37%	7 0%	21 0%	102 2%	2467 55%
St. Louis Children's Hospital	36 6%	259 45%	0 0%	4 1%	14 2%	268 46%
Other	21 4%	129 27%	0 0%	0 0%	13 3%	308 65%
Mercy Hospital St. Louis (Creve Coeur)	2 2%	22 22%	0 0%	0 0%	4 4%	73 72%
Missouri Baptist Medical Center	8 8%	35 35%	0 0%	0 0%	2 2%	55 55%

Figure 36: Overdue forms summary

Code (kit) lists

Code lists (also known as kit or medication 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:

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 days Status Location Site 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"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<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 37: Code list page

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.

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. Text or date columns can be filtered using statements like:

- A - rows matching A
- A B or A,B - rows matching A and B
- (A B) or (A,B) - rows matching A or B
- (A B) C or (A,B) C - rows matching A or B and C

Numeric columns (displayed with a lighter font color and aligned to the right) behave slightly differently:

- 1 - rows with value 1
- (1 2) or (1,2) - rows with value 1 or 2
- 1-3 - rows with value within the range of 1 to 3
- (1-3 7-8) or (1-3,7-8) - rows with value within the range of 1 to 3 or 7 to 8.

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.

You can also select kits by using filters on the list (see above). Once your list is filtered to the subset of the list that you want to update, all matching rows can be selected by using **Select** > **All [n] matching rows**. This operation can be repeated to add rows matching different criteria to the selection.

Update selected - 4 row(s)

Update batch
 Update expiry date
 Update buffer
 Update status
 Update location

Batch:
 Expiry date: 31/12/2020
 Buffer: days
 Status: New
 Location: 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 38: 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 39: 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

Eligible kits are sorted by expiry date and block number, so that kits that expire earlier will be chosen in preference to kits that expire later. For kits with the same expiry date, lower kit block numbers are preferred.

Kits are chosen at random from the pool of eligible kits (with earlier expiry and 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

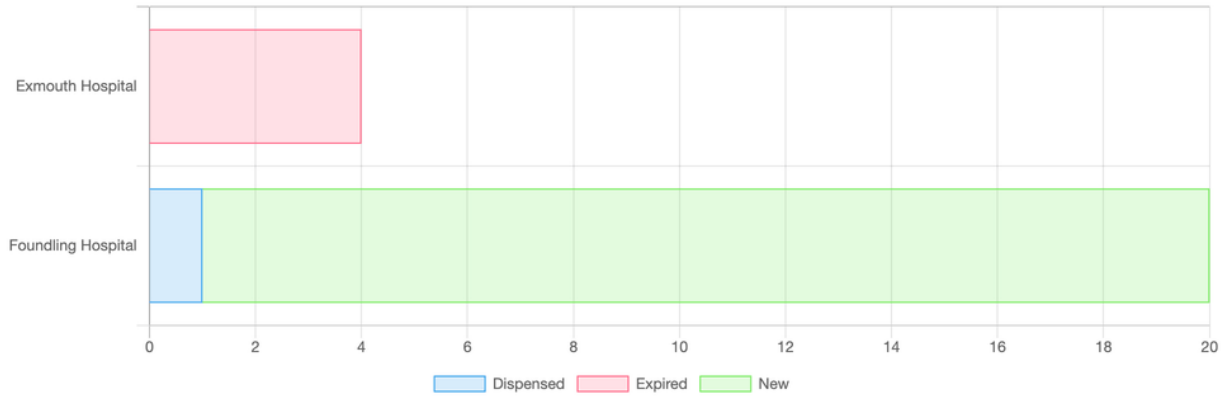
It is the administrators responsibility to update the code list to reflect the real world location of kits and make sure sites have enough stock available for randomisation and follow-up visits as appropriate. The drug stocks report shows the number of new, unexpired kits available at each site. It will also show warnings for sites where there are no kits available for any treatment group. Randomisation may fail if there are insufficient kits available at site.

The code list can be updated directly, or via the [site restocking feature](#), which enables low stock emails and automatic restocking of sites to be configured.

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	Kit type	Total kits	Kits dispensed	Expired	New, unexpired kits on site	Warnings
Exmouth Hospital	Standard	4	0	4	0	One or more treatments has NO kits available!
Foundling Hospital	Standard	20	1	0	19	

Figure 40: 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,Standard,,2035-12-12,0,Dispensed,Randomisation,Site,2,"2016-07-14
17:02:24",,"Luton Hospital"
2,2,ZV0,1,Standard,,2035-12-12,0,Dispensed,Randomisation,Site,2,"2016-07-14
17:02:24",,"Luton Hospital"
3,1,FI4,1,Standard,,2035-12-12,0,Dispensed,Randomisation,Site,2,"2016-07-14
17:02:24",,"Luton Hospital"
4,,ZD4,1,Standard,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital
"
5,,XB3,2,Standard,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital
"
6,,HC3,2,Standard,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital
"
7,,KG0,2,Standard,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital
"
8,,YH5,2,Standard,,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
- 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

Site restocking

Automatic site restocking only applies to trials using a code list and with [pre-labelled kits](#). Its use is optional, as the code list can be [edited directly](#). However, the site restocking feature is useful for multi-centre trials where sites are restocked continuously throughout the trial.

Getting started

First you need to create a distributor. Use the *Create a new distributor* button on the sites page, and add the distributor details as required, including the distributor email address. When automatic restocking is turned on, shipping notifications will be sent to this address indicating which kits need to be shipped to which site.

Next, you need to allocate kits to the distributor using the [code list](#) to make sure that it has kits available to be shipped. Note that only new, unexpired kits will be shipped to sites.

Go to the site you want to restock and choose the distributor for this site. Enter the shipping address for the site, days that kits take to be delivered and expiry buffer. Expiry buffer is a site specific buffer similar to the code list expiry buffer. It prevents kits that are near their expiry date being shipped to a site.


You can then enable automatic restocking and set the target and restock levels.

Target and restock levels

The target stock level is the desired maximum stock level (number of kits) to hold at a site, and the restock level defines the threshold that triggers automatic restocking. You can define these levels for each site and by kit type (if a site holds different types of kits).

Automatic restocking

Automatic restocking of kits is **Off**

 When the stock level falls to the re-stock level, a low kit stock email will be sent to warn that the site is running low.

Kit levels

The current stock levels at this site are shown below. Make sure there are enough kits for future randomisations and kit assignments.

Kit type	Target stock level	Current level*	Re-stock level
Standard	10	9	4
	Active: 5 Placebo: 5		Active: ≤2 Placebo: ≤2

* New, unexpired kits at site (including those available to all sites)

Figure 41: Restock levels

Things to consider when defining the restock level are the number of participants recruited at the site, how fast they are recruiting, how long it takes the stock to get there, the shelf-life of the drug, and storage capacity at the site.

Both the target and restock levels are automatically divided by the system according to the allocation ratio, e.g. a level of 10 means a level of 5 for active and 5 for placebo (in a 1:1 trial). In this way, automatic restocking is triggered when either active or placebo kits fall to the restock level. Restocking always happens for **all** treatment groups and kit types below the target level regardless of the type of kit that triggered it.

Low stock emails

Low stock emails can be turned on if automatic restocking is off. In this case, you will receive a warning email when the stock gets low, but this does not generate a shipment, and you will need to create a manual shipment to restock the site.

How does it work?

If automatic restocking is turned on, the stock is monitored by the system, and when the restock level at a site is reached, it triggers restocking. This is only done once per day, so you may not get an email immediately when setting up new sites.

A shipment is then created from kits available at the distributor. Kits for each treatment group and kit type will be chosen to restore the stock back to the target level.

The system sends a dispatch email to the distributor containing a dispatch note. This is a PDF with details of the site and kits to be sent there.

A pharmacy account at the site can be used to mark shipments received and download shipment dispatch notes. Administrators can also mark shipments received at any site.

When a shipment is marked as received, the code list is automatically updated. Details about the shipment are recorded, namely temperature excursions and kit status on arrival. Only kits marked as 'intact' will be available for randomisation.

Email notifications

The following emails are sent:

- *New shipment* Sent when automatic restocking is turned on and the number of new, unexpired kits available at a site drops to the restock level at that site.
- *Cancel shipment* Sent when a shipment is cancelled.
- *Late shipment* Sent when a shipment has not been marked received at the site within the expected number of days.
- *Low kit stock* Sent when the number of new, unexpired kits available at a site falls to the restock level at that site. Low kit stock emails can only be turned on when automatic restocking is off.
- *Failed restock* Sent when an automatic shipment could not be created because of insufficient stock at the distributor.

These emails are sent to administrators and other roles that can view the code list, as well as notification accounts. The *new shipment* and *cancel shipment* emails are also sent to the distributor if the distributor email has been set.

Shipments

Distributor 1: [Distributor 1, United Kingdom](#)

This distributor is **in use**.


4

Total kits at this distributor

4

New, unexpired kits available for shipping

Standard: 4

 Allocate more kits to this distributor in the **code list** to avoid disruption to shipments.

Shipments are expected to be delivered within **1** day(s).

[Create manual shipment](#)

Shipment number SE-BUMP-3

Cancelled

Manual shipment by Jane Ploug (ID 1955)

Created 11 Jun 2021 15:03 (BST). Last updated 11 Jun 2021 15:04 (BST)

Kits: JE8, WY4

 [Dispatch note](#)

Reason cancelled:

mistake

Shipment number SE-BUMP-2

Delivered

Automatic re-supply (re-stock level Standard: 5)

Created 27 May 2021 15:32 (BST). Last updated 11 Jun 2021 14:41 (BST)

Kits: GNO, IY3, RI6, SZ2, SZ4, VU2

 [Dispatch note](#)

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.

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

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 43: Result of assigning a kit code

assigned as soon as the site is re-supplied. This situation can be prevented by turning on the *Ensure all groups available at site* [setting](#).

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.

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 2000/21
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 44: 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 45: Randomisation with assigned kits

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 46: Randomisation with deallocated kit

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.

Site

Identifier *

This site identifier will be used when generating a Patient ID. Please ensure that the site identifier is formatted correctly (e.g. include leading zeros if required) as it will not be possible to change this identifier once a patient has been added at this site

Name *

Country



Timezone *



Recruiting *

Yes

No

It will not be possible to add patients at this site if the site is not recruiting

Notes

Target recruitment

The target recruitment can be specified for sites by entering the target number of participants to be recruited at each site and the target date (by which the target recruitment is expected to be reached).

When the target recruitment is set, a fill bar will appear next to the site name on the sites list, indicating the progression of recruitment at the site. On the site page, a box will also appear showing the target recruitment.

An estimate of the average (mean) number recruited per month will be shown once two or more participants have been added to a site. A message is shown indicating whether the target is likely to be met by the target date given the average recruitment rate. For blinded trials, the average recruitment estimate can be useful for predicting how fast stock gets used at the site, and so help pick the target and restock levels for [automatic site restocking](#).

Once the target is met a message is displayed, but **recruitment can still continue at the site past the target**. To prevent recruitment at a site you must change the *Recruiting* setting to *No*.

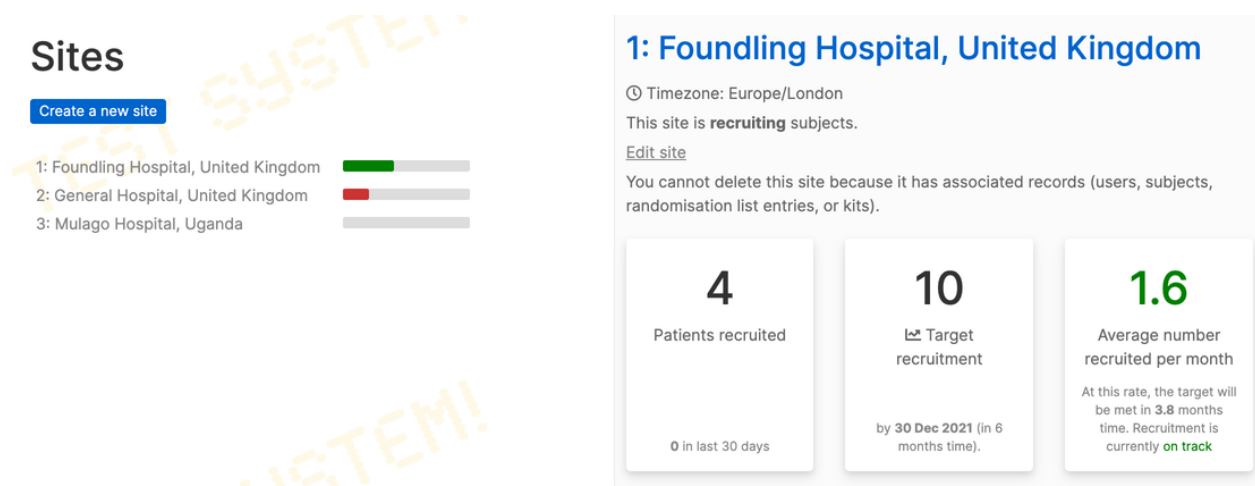


Figure 48: Viewing sites

Automatic restocking and shipments

For trials with a [code list](#) you may see automatic restocking and shipments sections. See [site restocking](#) for help on these features.

Queries

Queries are intended to be used by administrators and monitors to raise questions about the form data for investigators to answer and for investigators to notify administrators and monitors 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. Check permissions for query viewing and creation on the [specification page](#).

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 49: Creating a new query

Adding messages

Messages may be added to queries by users, 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 users who can view queries at the same site as the subject the query relates to (providing they have permission to view the form 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.

Query notifications are NOT sent to [notification accounts](#)!

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 50: Viewing an open query

Access | Logout | Sealed Envelope support (ID 1)

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

Query ID 1: Matching screening?

Current status: Open

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

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

Action *

None

Message *

Add 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 51: 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.

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.

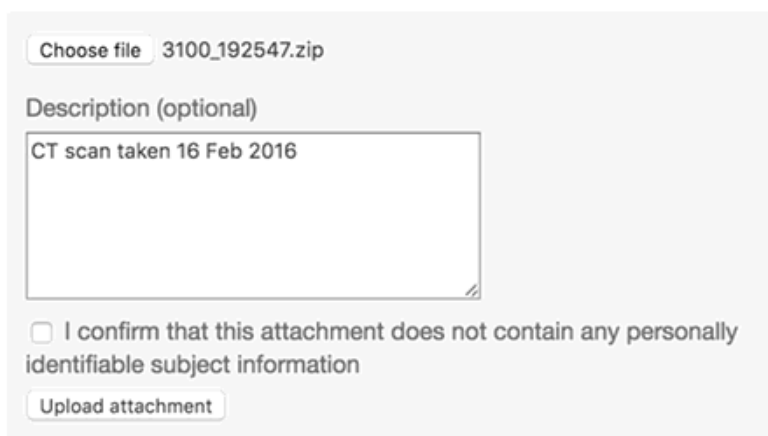
Submitting the form will store the attachment in the subject's CRF.

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 form 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 for "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 52: Uploading an attachment

Viewing and downloading existing attachments

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

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 53: An attachment listed in the subject view

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

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 54: Table of attachment details

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.

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 55: Deleting an attachment

Running out of space

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

Reports

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

Completed forms

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

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

Search:

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

Figure 56: Viewing a report

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](#). [Decryption of downloaded data](#) provides detailed instructions.

CSV format

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

Every file contains a 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

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 57: 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 58: Form data dictionary

Patient identifier	id	Subject id	User who cre	Timestamp for row creation (UTC)	Sex - Questions	Marital status - Questions	If
T5617	1	1	Sealed 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 59: Viewing CSV file in spreadsheet

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
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 60: 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.

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.

```
. 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 61: Tabulating imported form data

Decryption of downloaded data

You can now use our [decryption page](#) to easily decrypt downloads.

If a form has encrypted fields the download will contain the values of these fields in an encrypted format. An example of a CSV file where the date of birth has been encrypted is shown below.

Date & time of last update to row (UTC)	Date of birth - Randomisation. dd/mm/yyyy	Does the patient meet all inclusion criteria?
2016-08-11 18:30:25	U2FsdGVkX18BH/rs5o6X635KFSi26/5epe+hdFD0gH8=	Yes
2016-08-18 17:05:18	U2FsdGVkX1+rbukCo7HxKWb/Vdv/1uLJDaQY4RW4lCM=	Yes
2017-01-13 16:49:37	U2FsdGVkX1+vKpmwQVOrDDViSSQFMHJ+wOAKJB4PEg=	Yes
2017-01-13 17:22:12	U2FsdGVkX1/NChF1M5hl297WVjM7nrhqHOXdUwIA4nE=	Yes
2017-01-26 15:11:18	U2FsdGVkX18DYFOIOvZsuJHraQMzDzyoWbrTpT8rcO0=	Yes

Figure 62: Viewing CSV file with encrypted field in spreadsheet

To decrypt this data you will need the password (from Sealed Envelope support) and a decryption tool such as OpenSSL that can decrypt AES-256. You will also need to extract the encrypted field column into a new file so that the only data on each line is the contents of the encrypted field. You can do this by, for instance, copying and pasting the encrypted column into a text file:

```
U2FsdGVkX18BH/rs5o6X635KFSi26/5epe+hdFD0gH8=
U2FsdGVkX1+rbukCo7HxKWb/Vdv/1uLJDaQY4RW4lCM=
U2FsdGVkX1+vKpmwQVOrDDViSSQFMHJ+wOAKJB4PEg=
U2FsdGVkX1/NChF1M5hl297WVjM7nrhqHOXdUwIA4nE=
U2FsdGVkX18DYFOIOvZsuJHraQMzDzyoWbrTpT8rcO0=
```

Encrypted column pasted into file dob-encrypted.txt

Once you have obtained the decrypted data you will probably want to paste it into a new column in the CSV file to allow it to be associated again with the other subject data.

Windows

On Windows, we recommend installing [OpenSSL for Windows](#). It's easiest to create a new folder and copy the `openssl.exe` file from the download into this new folder. Next create a batch file by copying and pasting the following code into a text document using Notepad or similar and save it as `se-decrypt.cmd` in the same directory as the `openssl.exe` file. Alternatively download a copy.

```
@echo off

REM Sealed Envelope batch file to decrypt data using openssl AES 256
REM Input file is assumed to contain one encrypted item per line

set filepath=%~f1

if not exist "%filepath%" (
    echo %~n0: file not found - %filepath% >&2
    exit /B 1
)

set /P passwd="Password: "
echo Decryption of %filepath% at %DATE% > decrypted.txt
for /F "tokens=*" %i in (%filepath%) do @echo %i | openssl enc -aes-256-cbc -d -
a -md sha512 -pbkdf2 -iter 100000 -pass pass:%passwd% >> decrypted.txt
```

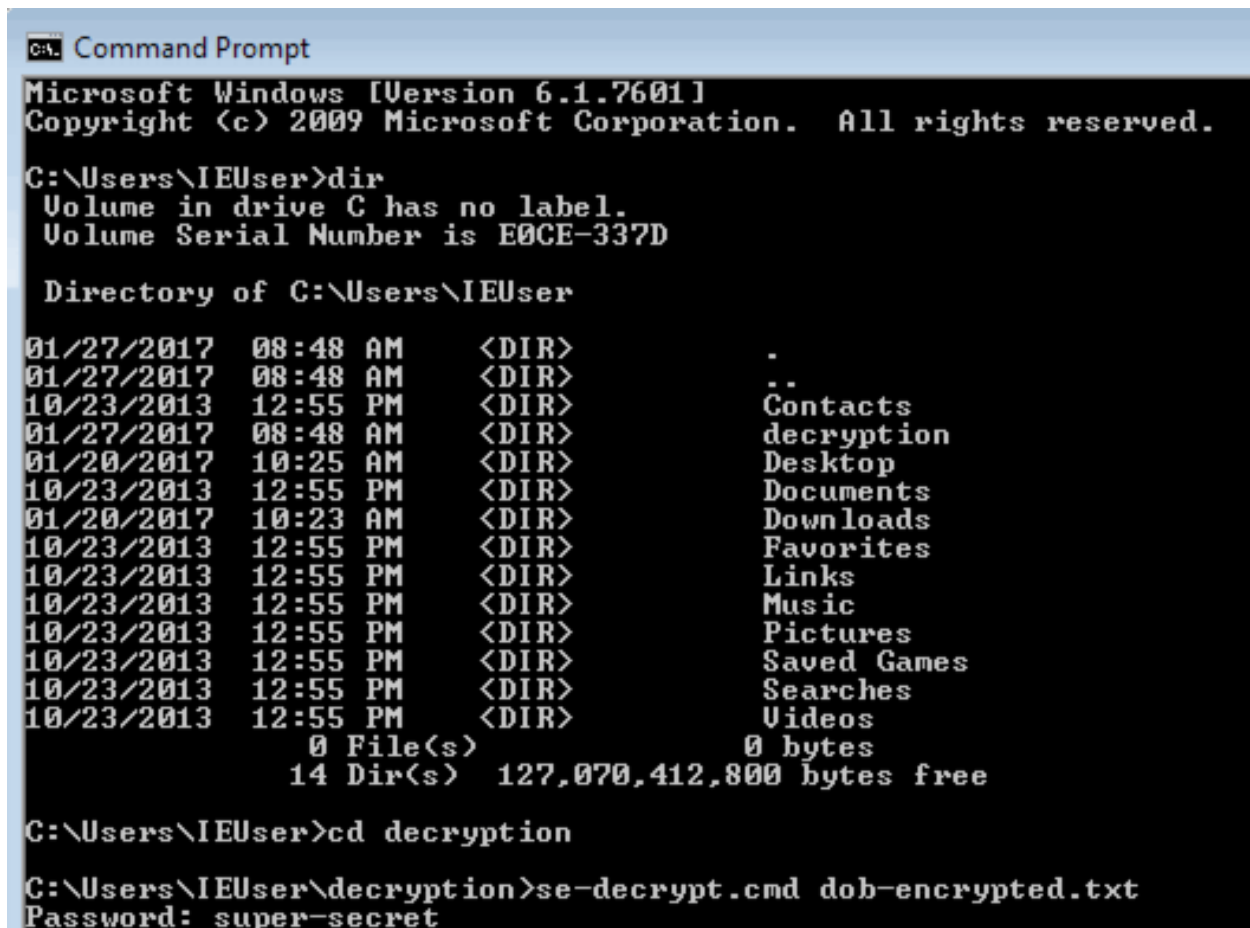
se-decrypt.cmd

You must run the batch file from the Command Prompt - you should find this somewhere in your Start menu. You need to use the `cd` command to move into the folder that contains the `openssl.exe` file and your encrypted data file. You can use the `dir` command to see the contents of the current folder. Once you are in the correct folder type the command:

```
se-decrypt.cmd dob-encrypted.txt
```

where `dob-encrypted.txt` is the name of the file containing the encrypted data. Running this command will ask for the password and create (or overwrite) the file `decrypted.txt`.

Screenshots for doing this are shown below.



```
Command Prompt
Microsoft Windows [Version 6.1.7601]
Copyright (c) 2009 Microsoft Corporation. All rights reserved.

C:\Users\IEUser>dir
Volume in drive C has no label.
Volume Serial Number is E0CE-337D

Directory of C:\Users\IEUser

01/27/2017  08:48 AM    <DIR>          .
01/27/2017  08:48 AM    <DIR>          ..
10/23/2013  12:55 PM    <DIR>          Contacts
01/27/2017  08:48 AM    <DIR>          decryption
01/20/2017  10:25 AM    <DIR>          Desktop
10/23/2013  12:55 PM    <DIR>          Documents
01/20/2017  10:23 AM    <DIR>          Downloads
10/23/2013  12:55 PM    <DIR>          Favorites
10/23/2013  12:55 PM    <DIR>          Links
10/23/2013  12:55 PM    <DIR>          Music
10/23/2013  12:55 PM    <DIR>          Pictures
10/23/2013  12:55 PM    <DIR>          Saved Games
10/23/2013  12:55 PM    <DIR>          Searches
10/23/2013  12:55 PM    <DIR>          Videos
           0 File(s)                0 bytes
          14 Dir(s) 127,070,412,800 bytes free

C:\Users\IEUser>cd decryption
C:\Users\IEUser\decryption>se-decrypt.cmd dob-encrypted.txt
Password: super-secret
```

Figure 63: Command prompt

Mac

On macOS you can use the built in OpenSSL or install it using [Homebrew](#). You will need to open [the Terminal](#) to type the relevant commands. In the example below the encrypted data is assumed to be in a file called *dob-encrypted.txt* on the Desktop. A decrypted file is created called *dob-decrypted.txt* using the password *super-secret*. Obviously you should change these parts to reflect your file names and password.

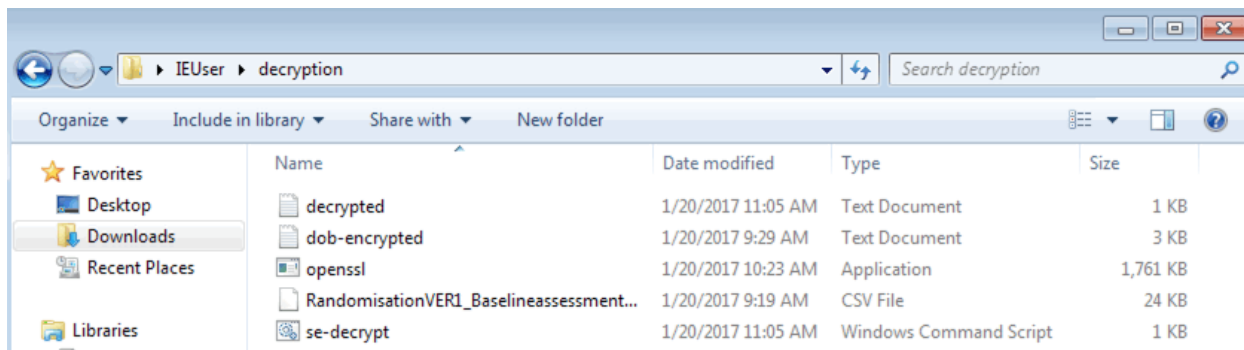


Figure 64: Folder contents

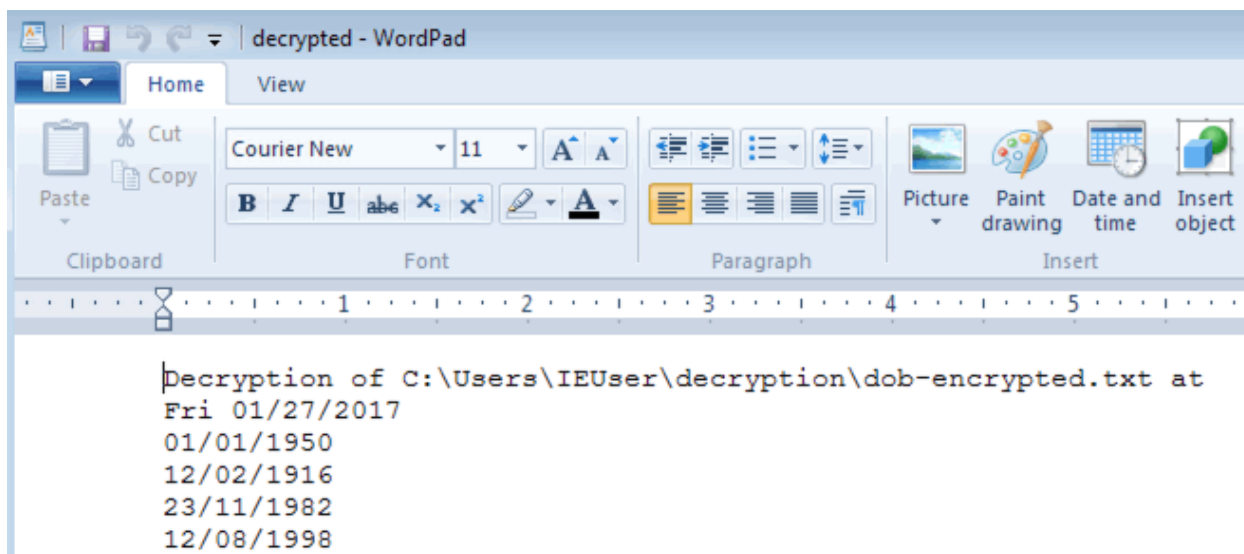


Figure 65: Decrypted file

```
$ cd Desktop
$ cat dob-encrypted.txt
U2FsdGVkX18BH/rs5o6X635KFSi26/5epe+hdfD0gH8=
U2FsdGVkX1+rbukCo7HxKwb/Vdv/1uLJDaQY4RW4lCM=
U2FsdGVkX1+vKpmwQV0rDDDViSSQFMHJ+w0AkJB4PEg=
U2FsdGVkX1/NChFlM5hl297WVjm7nrhqH0XdUwLA4nE=
U2FsdGVkX18DYF0IOvZsuJHraQMzDzyowbrTpT8rc00=
$ while read in; do echo "$in" | openssl enc -aes-256-cbc -d -a -md sha512 -pbkdf2
  -iter 100000 -pass pass:super-secret; done < dob-encrypted.txt > dob-decrypted
.txt
$ cat dob-decrypted.txt
04/08/1997
11/08/1920
19/02/1987
10/10/1980
10/10/1980
$
```

The `cd` command is used to move to the folder where the encrypted file is held. You can use the list command `ls` to view files in the current folder. The `cat` command shows the contents of a file. The decryption is carried out with the command:

```
while read in; do echo "$in" | openssl enc -aes-256-cbc -d -a -md sha512 -pbkdf2 -
  iter 100000 -pass pass:super-secret; done < dob-encrypted.txt > dob-decrypted.
txt
```

which you should adapt to use your own password and file names.

Uploads

CRF data, randomisation lists and code lists may be uploaded from CSV files. Roles with permission to upload can access this feature via the **Upload** link in the top menu.

Upload a CSV file

Create or update multiple records in the CRF for existing subjects by uploading form data from a CSV file.

Amend or replace the randomisation list or code list by uploading the new records as a CSV file.

Select a form or list from the list below and select a [CSV file](#) on your computer that contains the CRF data or list content to upload. See below for help on the CSV format required and a template file that you can use with software like Excel or Numbers.

Upload a CSV file

What data records are in the CSV?
Choose...

Select file to upload
Choose file No file chosen

i You will have a chance to review the data before finalising the upload.

Upload

CSV format help

Formatting instructions:

- Field labels must be listed in the first row (heading)
- Fields must be delimited by , (comma)
- The fields can be in any order
- Field values containing a comma must be enclosed by " (double quotes)
- Use two double quotes within field values if the value is quoted. For example, A "quoted" word and "Some, "quotes within" must be doubled."

Headings (first line of the CSV):

(Choose a form or list to see the headings to use in the CSV)

Past uploads

- Randomisation list** **Q** Preview
by SE support (ID 1) on 24 Sep 2018 14:52 UTC

Figure 66: Upload page

What are CSV files?

Comma separated value (CSV) files are plain text spreadsheet type files consisting of columns (fields) and rows (data). Columns are separated by , (comma). For example this CSV file:

```
Block identifier, Block size, Sequence within block, Treatment, Gender, Site
1,8,1,Active,Male,1
1,8,2,Placebo,Male,1
1,8,3,Active,Male,1
1,8,4,Active,Male,1
1,8,5,Placebo,Male,1
1,8,6,Active,Male,1
1,8,7,Placebo,Male,1
1,8,8,Placebo,Male,1
```

represents this dataset:

Block identifier	Block size	Sequence within block	Treatment	Gender	Site
1	8	1	Active	Male	1
1	8	2	Placebo	Male	1
1	8	3	Active	Male	1
1	8	4	Active	Male	1
1	8	5	Placebo	Male	1
1	8	6	Active	Male	1
1	8	7	Placebo	Male	1
1	8	8	Placebo	Male	1

Spreadsheet programs (like Excel or Numbers) can save sheets or tables as CSV files – look for this option in the *Save as...* or *Export to...* facility.

Requirements for CSV files

All uploaded CSV files **must**:

- Have a header in the first row consisting of field names or labels
- Enclose field values containing a comma with " (double quotes)

- Convert double quotes to two double quotes if a field value contains both commas and double quotes. For instance, the value Penicillin, brand name "Amoxycillin" must be converted to "Penicillin, brand name ""Amoxycillin"" in the CSV file. If the field value does not contain a comma there is no need to convert double quotes. For instance Penicillin (brand name "Amoxycillin") is valid.

Randomisation lists

If the randomisation method for the trial uses a list, the Designer role will see a **Randomisation list** option in the responses for the *What data records are in the CSV?* question. When this option is chosen additional help is shown on the page and a template CSV file becomes available for download.

Randomisation lists **must contain** columns for:

- Treatment group, Treatment
- Each stratification factor (if any)

and the values must **exactly match** the treatment groups and stratification groups listed on the [specification page](#). If the list is stratified by site, the CSV file must contain a **Site** column containing [site identifiers](#) (not the site names). Sites will be created for any new site identifiers encountered in the uploaded list.

Optionally randomisation lists may contain columns for:

- Sequence (1, 2, 3...) to explicitly denote the list order. If not provided a sequence number is generated from the natural order of the uploaded list.
- Block information – Block identifier, Block size and Sequence within block. Blocked lists usually contain these columns and they will be stored if uploaded for record keeping purposes. Note that they are not used in any way by the randomisation system, and there is no requirement to upload a blocked list.

Upload and preview

Once a valid list is uploaded, a preview is shown of the rows to be imported. To complete the upload the declaration must be agreed to and the *Confirm upload* button pressed.

If the upload is not completed the preview will remain available in the past uploads section. It can be completed at a later date via the preview screen.

Upload a CSV file

What data records are in the CSV?
 Randomisation list

Select file to upload
 Choose file No file chosen

Replace existing list

Randomisation and code lists cannot be replaced once a subject has been randomised.

i You will have a chance to review the data before finalising the upload.

Upload

Past uploads

CSV format help

Formatting instructions:

- Field names or labels must be listed in the first row (heading)
- Fields must be delimited by , (comma)
- The fields can be in any order
- Field values containing a comma must be enclosed by " (double quotes)
- Use two double quotes within field values if the value is quoted. For example, A "quoted" word and "Some, ""quotes within"" must be doubled." are both valid.

Each row in the CSV must contain the treatment allocation (Active, Placebo) to be given out at randomisation. As the randomisation for this trial is stratified there must be one field per stratification factor (Gender, Site). **Site** must refer to the site identifier (not the name). Sites will be created for any new site identifiers encountered. The list will be used in sequential order, starting at the first row which matches the strata for the subject being randomised. Optionally a **Sequence** field can be provided which explicitly denotes the ordering to be used. The sequence field can also be used to update existing rows in the randomisation list, providing they have not been used for randomisation. Other optional fields are **Block identifier**, **Block size**, and **Sequence within block**. These are stored if provided but do not have any practical implications for how the list is used.

Headings (first line of the CSV):

"Sequence", "Block identifier", "Block size", "Sequence within block", "Treatment", "Gender", "Site"

Use the heading row and rules above to produce a CSV file manually, or alternatively click the button below to download an empty CSV file with the heading row already present.

[Download CSV template](#)

Figure 67: Upload randomisation list

CSV upload confirmation





Original filename: **se_list_short2.csv**







Target list: **Randomisation list**

The file contents have not been imported yet. Please review the data below and submit the confirmation form to proceed.

Preview of the final list

Unmarked rows will be left unchanged

-  This row will be added
-  This row will be replaced
-  Rows already used for randomisation will not be changed
-  Invalid data

	Sequence	Site	Block identifier	Block size	Sequence within block	Treatment	Gender
	1	1	1	8	1	Active	Male
	2	1	1	8	2	Placebo	Male
	3	1	1	8	3	Active	Male
	4	1	1	8	4	Active	Male
	5	1	1	8	5	Placebo	Male
	6	1	1	8	6	Active	Male

Confirmation

- I declare that the information presented in this CSV file has been reviewed and approved by the personnel responsible for the randomisation method in this study or trial and that I wish to update the randomisation system with the new list.

 **This operation cannot be reversed**

Confirm upload

Cancel

Figure 68: Preview randomisation list

Replacing the randomisation list

Provided no randomisations have taken place yet, the uploaded list can replace any existing randomisation list held by the system. Tick the *Replace existing list* option to do this.

Once randomisation has started, only unused rows in the existing list can be replaced. This is achieved by uploading a new list with sequence numbers that match unused rows in the existing list. It is highly unusual to replace a randomisation list once a trial has started and it is recommended that statistical advice is taken before doing so.

Extending the randomisation list

The randomisation list can be extended by uploading a new list at any time. Sequence numbers (if provided) must not match any existing rows. The new list will be appended to the end of the current list. A preview of the entire list is shown before confirmation of upload.

Code (kit) lists

If the randomisation system is blinded, the Designer role will see a **Code list** option in the responses for the *What data records are in the CSV?* question. When this option is chosen additional help is shown on the page and a template CSV file becomes available for download.

Code lists **must contain** columns for:

- Treatment group, Treatment
- Kit code, Code. Must be unique
- Kit block, Kit block

and the treatment group values must **exactly match** those listed on the [specification page](#).

Optionally code lists may contain columns for:

- Sequence (1, 2, 3...) to explicitly denote the list order. If not provided a sequence number is generated from the natural order of the uploaded list.
- [Kit type](#), Kit type. Not all trials have kit types enabled. If your trial does not have different kit types you won't see kit types in the code list.
- Batch, Batch
- Expiry date in *dd/mm/yyyy* format, Expiry date

Sites to be added





The following new sites will be added when the CSV is imported:

- 2: Site 2

You will be able to change the sites' names after confirming the import.

Preview of the final list

Unmarked rows will be left unchanged

-  This row will be added
-  This row will be replaced
-  Rows already used for randomisation will not be changed
-  Invalid data







Sequence	Block identifier	Block size	Sequence within block	Treatment	Gender	Site
1	1	8	1	Active	Male	1
2	1	8	2	Placebo	Male	1
3	1	8	3	Active	Male	1
4	1	8	4	Active	Male	1
5	1	8	5	Placebo	Male	1
6	1	8	6	Active	Male	1
7	1	8	7	Placebo	Male	1
8	1	8	8	Placebo	Male	1
 9	4	8	1	Placebo	Male	2
 10	4	8	2	Active	Male	2
 11	4	8	3	Active	Male	2
 12	4	8	4	Active	Male	2
 13	4	8	5	Placebo	Male	2
 14	4	8	6	Placebo	Male	2

Figure 69: Extend randomisation list

Upload a CSV file

What data records are in the CSV?

Select file to upload
 No file chosen

Replace existing list

Randomisation and code lists cannot be replaced once a subject has been randomised.

i You will have a chance to review the data before finalising the upload.

Past uploads

- 🔍 **Randomisation list Q** [Preview](#)
by SE support (ID 1) on 24 Sep 2018 14:52 UTC
- ❗ **Baseline - NRS Fatigue Q** [Preview](#)
by SE support (ID 1) on 1 Oct 2018 17:18 UTC
- 🔍 **Baseline - NRS Fatigue Q** [Preview](#)
by SE support (ID 1) on 1 Oct 2018 17:19 UTC

CSV format help

Formatting instructions:

- Field names or labels must be listed in the first row (heading)
- Fields must be delimited by , (comma)
- The fields can be in any order
- Field values containing a comma must be enclosed by " (double quotes)
- Use two double quotes within field values if the value is quoted. For example, A "quoted" word and "Some, ""quotes within"" must be **doubled.**" are both valid.

Each row in the CSV must contain the treatment allocation (Methylphenidate, Placebo) in the field **Treatment** for the kit code in the **Code** field. All other fields are optional. **Site**, if provided, must be the site identifier (not the name). Sites will be created for any new site identifiers encountered.

Headings (first line of the CSV):

"Sequence", "Code", "Treatment", "Kit block", "Kit type",
 "Batch", "Expiry date", "Expiry buffer", "Kit status",
 "Location", "Site", "Notes"

Use the heading row and rules above to produce a CSV file manually, or alternatively click the button below to download an empty CSV file with the heading row already present.

Figure 70: Upload code list

- Expiry buffer in days, Expiry buffer
- Kit status. Must be one of 'Unmade', 'New', 'Quarantined', 'Lost', 'Damaged', or 'Destroyed'
- Location. Must be one of 'Manufacturer', 'Distributor', 'Site', or 'Other'
- Site containing [site identifiers](#) (not the site names). Sites will be created for any new site identifiers encountered in the uploaded list.
- Notes

Upload and preview

Once a valid list is uploaded, a preview is shown of the rows to be imported. To complete the upload the declaration must be agreed to and the *Confirm upload* button pressed.

Replacing the code list

Provided no randomisations have taken place yet, the uploaded list can replace any existing code list held by the system. Tick the *Replace existing list* option to do this.

Once randomisation has started, only unused rows in the existing list can be replaced. This is achieved by uploading a new list with sequence numbers that match unused rows in the existing list. It is not recommended that the treatment group or kit codes are changed when doing this, and warnings will be shown if the new list would affect them. It may be useful, however, to bulk update batch numbers, expiry dates and site locations with an uploaded list.

Extending the code list

The code list can be extended by uploading a new list at any time. Sequence numbers (if provided) must not match any existing rows. The new list will be appended to the end of the current list. A preview of the entire list is shown before confirmation of upload.

CRF data

Data for existing forms in the CRF may be bulk uploaded by Administrators instead of being [entered manually](#). This may be useful for uploading data from laboratory results or other data collection systems for instance.

Preview of the final list

Unmarked rows will be left unchanged

- + This row will be added
- + This row will be replaced
- ! There is a warning message for this row
- ! Rows already used for randomisation will not be changed
- ! Invalid data

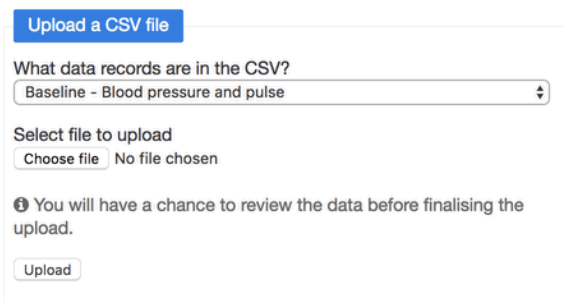
	Sequence	Kit block	Code	Treatment
+	1	1	DO8	Placebo
!	2	1	MI6	Methylphenidate
!	3	1	CR8	Methylphenidate
! Unexpected change: the Code will change if this list is imported.				
+	4	1	LW3	Placebo
+	5	2	YE2	Placebo
!	6	2	FP3	Methylphenidate
! Unexpected change: the Treatment will change if this list is imported.				
!	7	2	GB8	Placebo
! Unexpected change: the Treatment will change if this list is imported.				
+	8	2	TM5	Methylphenidate
+	9	3	HE5	Placebo
+	10	3	FZ0	Methylphenidate
	11	3	XX0	Methylphenidate
	12	3	XM1	Placebo

Providing at least one subject has been created, the Administrator role will see a list of forms in the responses for the *What data records are in the CSV?* question.

Note that it is not possible to upload data to subject entry, withdrawal or randomisation forms.

Prepare the CSV file for upload

First choose the form to upload data to under the *What data records are in the CSV?* question. The expected field (column) headings will then be shown in the 'CSV format help' section. The CSV file to be uploaded must have these column headings in the first row of the file. A template file can be downloaded by clicking the *Download CSV template* button. The type of data allowed in each column follows the same rules as for data entry. Values for categories must exactly match the value shown on the form. To see category values ("enum" types) and the type of data expected for each column view the data dictionary for the form concerned.



Past uploads

- 🔔 **Randomisation list Q** Preview
by SE support (ID 1) on 24 Sep 2018 14:52 UTC

CSV format help

Formatting instructions:

- Field names or labels must be listed in the first row (heading)
- Fields must be delimited by , (comma)
- The fields can be in any order
- Field values containing a comma must be enclosed by " (double quotes)
- Use two double quotes within field values if the value is quoted. For example, A "quoted" word and "Some, ""quotes within"" must be doubled." are both valid.

Each row in the CSV file must start with the Patient ID for an existing subject. The remaining columns must match the fields of the target form. If the target form can be completed once per subject, the CSV row will create the form or update the existing form for the matching subject. If the target form is a multiple entry form, each CSV row will create a new form for the matching subject.

If there are multiple repeating sections to upload then repeat the rows in the CSV for each repeating section entry but leave the first column (Patient ID) and columns for the rest of the form empty.

Headings (first line of the CSV):

```
"Patient ID", "PatientIdentifier", "VisitDate",  
"SystolicPressure", "DiastolicBloodPressure",  
"Q2InterpretationOfBloodPressur",  
"Q3ClinicalDecisionMadeRegardin", "Q4PulseRate",  
"Q5PulseRhythm", "IfOtherPleaseSpecify"
```

Figure 72: Upload form data

Each row in the CSV must start with the subject identifier for an existing [subject](#). If the target form can be completed once per subject, the CSV row will create the form or update the existing form for the matching subject. If the target form is a multiple entry form, each CSV row will create a new form for the matching subject.

Upload the CSV file

Select the CSV file from your computer and click the *Upload* button. The file will be validated using the same rules as apply when performing [data entry manually](#), with the following differences:

- Validation overrides are not supported
- Soft range checks (usually shown as popup warning messages) are not displayed
- Form completion messages are not shown

Any errors will be shown on the preview page and a file with errors may not be uploaded. You must fix the errors in your CSV file and re-upload. Once the file has been uploaded the forms created by the upload can be viewed at any time from the preview page of the uploaded file. In addition, a link is shown when [viewing the form](#) to the related upload.

CSV upload confirmation

Original filename: **Baseline-NRSFatigue1289.csv**

Target form: **Baseline - NRS Fatigue**

Please try uploading the file again after the validation errors shown below have been fixed.

Preview of data to import



Patient ID	Visit date	How would you rate your fatigue on a scale of 0 – 10 over the past 7 days?
 4	10/7/2018	8
 Subject not found!		

Figure 73: Upload form data with errors



- ✓ **Baseline - Concomitant medication or concomitant treatment log**  Preview by SE support (ID 1) on 2 Oct 2018 16:23 UTC
-  View uploaded forms for subject [1-001](#), [1-002](#)

Figure 74: Upload links

Repeating sections

If a form has a repeating section, the CSV file may also repeat rows as many times as necessary to record all data. Repeat the rows in the CSV for each repeating section entry but leave the first column (Patient ID) and columns for the rest of the form empty.

Patient ID	VisitDate	MedicationNameOrTreatment	StartDate	Ongoing	StopDate	ReasonForUse	Dose	Unit	Frequency	OtherFrequency	Route	Specify
S1045	23/09/2018	Aspirin	19/09/2018	No	19/09/2018	Headache	600	mg	Once daily (OD)		Oral	
		Simvastatin	01/03/2009	Yes		High cholesterol	10	mg	Once daily (OD)		Oral	
S2056	25/09/2018	Doxazosin	01/01/2007	Yes		Hypertension	4	mg	Twice daily (BD)		Oral	
S2058	29/09/2018	Buprenorphine	15/05/2018	Yes		Pain	10	mcg/hr	Other (please specify)	weekly	Other, please specify	Transdermal patch

Figure 75: CSV file for repeating section

Preview of data to import

Patient ID	Visit date	New medication										
✓ S1045	23/09/2018	Medication name or treatment	Start date	Ongoing	Stop date	Reason for use	Dose	Unit	Frequency	Other frequency	Route	specify
		✓ Aspirin	19/09/2018	No	19/09/2018	Headache	600	mg	Once daily (OD)		Oral	
		✓ Simvastatin	01/03/2009	Yes		High cholesterol	10	mg	Once daily (OD)		Oral	
✓ S2056	25/09/2018	Medication name or treatment	Start date	Ongoing	Stop date	Reason for use	Dose	Unit	Frequency	Other frequency	Route	specify
		✓ Doxazosin	01/01/2007	Yes		Hypertension	4	mg	Twice daily (BD)		Oral	

Figure 76: Preview of uploaded repeating section

File limits and storage

All uploaded CSV files that pass initial checks and can be previewed are stored in the system. They are encrypted using AES-256 at rest. There are limits on the size of individual CSV files that may be uploaded and the total storage space available. The limits for your system may be viewed on the [specification page](#). Contact Sealed Envelope support if you need to raise these limits.

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, archives, code list and the audit trail itself

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

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

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

Audit trail

Show all

Download

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

```
"Ms Coordinator (ID 2 - Administrator)" "/redpill/jump/crf/add/RandomisationVER1" [2016-03-23T11:34:19+00:00] INFO (6):
Randomisation to Control
"Ms Coordinator (ID 2 - Administrator)" "/redpill/jump/crf/add/RandomisationVER1" [2016-03-23T11:34:19+00:00] INFO (6):
Added form Randomisation for Subject S6310
192.168.33.1 "Sealed Envelope support (ID 1)" "/redpill/jump/markerror/get/22" [2016-03-23T11:35:37+00:00] INFO (6): Row in
crfRandomisationVER1 for: {"id": "22"}, changed From: {"lastUserIdentifier": "Ms Coordinator (ID 2 -
Administrator)", "error": "0", "errorReason": null, "errorDate": null, "updated": "2016-03-23 11:34:12", "reasonForEdit": null},
To: {"lastUserIdentifier": "Sealed Envelope support (ID 1)", "error": true, "errorReason": "\After randomisation but before
treatment patient was found to be ineligible due to past drug use history\" by Sealed Envelope support (ID 1)", "errorDate":
"2016-03-23 11:35:37", "updated": "2016-03-23 11:35:37", "reasonForEdit": "Randomisation marked as in error"}
192.168.33.1 "Sealed Envelope support (ID 1)" "/redpill/jump/markerror/get/22" [2016-03-23T11:35:37+00:00] INFO (6):
Randomisation number 22, code Control was edited
192.168.33.1 "Sealed Envelope support (ID 1)" "/redpill/jump/markerror/get/22" [2016-03-23T11:35:37+00:00] INFO (6):
Randomisation number 22, code Control was marked as in error
192.168.33.1 "Sealed Envelope support (ID 1)" "/redpill/jump/crf/add/InterviewersQuestionsVER1/1" [2016-03-
23T11:36:19+00:00] INFO (6): Row inserted to crfInterviewersQuestionsVER1: {"id": null, "patientId": "1", "userId": "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 77: Audit trail

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

plus a change in the data:

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

Example extract

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

```

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

```

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

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.

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.

Figure 78: Settings page

Subject delete

The ability to delete subjects is turned off by default. Deleting a subject will also remove all their CRF data, randomisation data and queries. The deleted data is shown in the [audit trail](#) but the action cannot be undone. 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 randomisations. This may be useful, for instance, if offline randomisations have been carried out due to the Sealed Envelope website being unavailable.

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

Ensure all groups available at site

Randomisation is allowed only if kits for all treatment groups are available at a subject's site. This setting only applies to double blind trials. If the setting is off, then the subject may be randomised without a kit code.

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 maximum file size allowed and percent of storage allowance used for [uploads](#).
- 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 79: Specification page

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](#).

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

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

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

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

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

Change type One of:

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

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

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

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

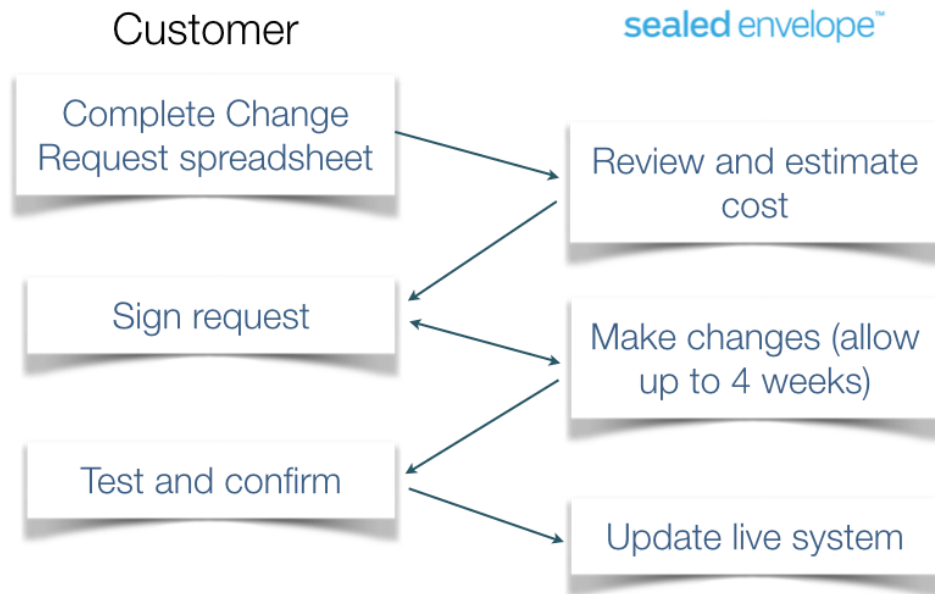


Figure 80: Flowchart for change request process

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

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

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

Minimisation

Minimisation¹ is a method of randomisation that allocates subjects to the treatment group that best maintains balance in prognostic factors. It is effective even at small sample sizes and with multiple prognostic 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. Here sex and age are prognostic factors for the trial.

The randomisations to the trial so far look like this:

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

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

To decide which treatment to allocate to the subject the balance of treatments in the trial is compared for subjects with the same characteristics as the subject to be randomised. The treatment choice that would result in the smallest treatment imbalance for that combination of characteristics is then the preferred treatment for that subject.

The next subject to be randomised is a man age 23, so before randomisation we have the following treatment counts for the strata.

Prognostic factor	Placebo	New drug
Male	3	1
<30	2	1

Clearly in males and those under 30 there is an imbalance in favour of placebo so far.

The method² that Sealed Envelope uses proceeds by first calculating for each treatment the resulting counts for each prognostic factor assuming that that treatment was allocated next. Then we calculate the absolute difference of the treatment counts for each factor, and sum those differences to give the imbalance for that treatment.

If the next treatment allocation is to the **placebo** we would have the following counts.

Prognostic factor	Placebo	New drug
Male	4	1
<30	3	1

So for sex with level Male we have absolute difference $|4 - 1| = 3$, and for age with level <30 we have difference $|3 - 1| = 2$. Summing the differences gives a treatment imbalance for the **placebo** of $3 + 2 = 5$.

If the next allocation is to the **new drug** we would instead have the following counts.

Prognostic factor	Placebo	New drug
Male	3	2
<30	2	2

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

Here for sex with level Male we have absolute difference $|3 - 2| = 1$, and for age with level <30 we have difference $|2 - 2| = 0$. Hence the sum of differences gives a treatment imbalance for the **new drug** of $1 + 0 = 1$.

Now we rank the treatment imbalances in order of increasing treatment imbalance and choose the treatment with the lowest score. Since $1 < 5$, we see that allocating the new drug treatment to the subject would best decrease the total imbalance. So the **new drug** is the preferred treatment.

Note that if there is a tie in the lowest treatment imbalance scores the preferred treatment is chosen at random from those with the tied score.

Incorporating a random element

The procedure above is deterministic unless there is a tie in the lowest treatment imbalance scores. Given the characteristics of subjects already randomised in the trial and the subject to be randomised, the preferred treatment is almost entirely predictable.

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

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

ICH Topic E9 Statistical Principles for Clinical Trials

Instead of immediately allocating the preferred treatment we specify a probability for choosing the preferred treatment. The remaining probability is split equally between the other treatments, and the treatment to be allocated is then chosen randomly based on those probabilities. So for each randomisation there is a chance that the preferred treatment will not be chosen. 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 balanced.

The probability of choosing the preferred treatment is specified when we set up a trial and can be viewed on the [specification page](#).

Each step of the calculation for every minimisation is recorded in the trial database.

Preserving the allocation ratio in trials with unequal allocation

Research published in the last decade has highlighted some issues when using this minimisation method in trials with unbalanced allocation ratios.

To address these issues we use a modified minimisation method³ that preserves the allocation ratio at every step.

This method works similarly to our standard minimisation method with the important difference that it is carried out on a set of fake treatments which are then mapped back to the real treatments for allocation.

Say that for our example above we had an allocation ratio of 1:2 for placebo to new drug. Then the minimisation would be carried out on fake treatments F1, F2, and F3, where minimisation to F1 would result in an allocation of the placebo and minimisation to either F2 or F3 would result in an allocation to the new drug.

The allocations to the fake treatments are stored separately from the real allocations in the trial database so that we can minimise their imbalance at randomisation.

We carried out simulations on our implementation of this new method to compare it to an alternative method for dealing with unequal allocation ratios. You can read about how we did this and view the results by [downloading the report](#) [pdf].

³Kuznetsova OM, Tymofyeyev Y. Preserving the allocation ratio at every allocation with biased coin randomization and minimization in studies with unequal allocation. *Statist. Med.* 2012;31:701–723

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.

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.

What's new

December 2021 - version 24.0.0

- Completed forms that become not applicable due to a form rule are now shown and still accessible to users.
- Future ePRO invites are not cancelled when they become not applicable. Instead they're cancelled at the time of processing in case they become applicable again.
- The shuffle operations used during minimisation are now recorded to the `minimisationLog` table.
- Category responses in Likert sections are displayed as normal radio inputs on small screens (like mobile devices). Previously they could be hard to use if the grid was too compressed.
- Email notifications are no longer sent on updates to manual randomisations.
- The late shipment email now correctly reports the names of all sites.
- The subject listing for apps with long code lists is now faster.

[Validation certificate 24.0.0](#)