sealed envelope™

Red Pill and Randomisation

Version 19

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October 3, 2018

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Chapter 1

Overview

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

Randomisation is an integral part of Red Pill, and is also offered as a standalone component. This comprehensive randomisation system allows investigators to randomise patients to clinical trials quickly and simply using their web browser and/or telephone.

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

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

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

This documentation applies to version 19, released Sep 2018. The version number is shown in the footer of every page when logged into Red Pill.

Chapter 2

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.

Chapter 3

Subjects

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

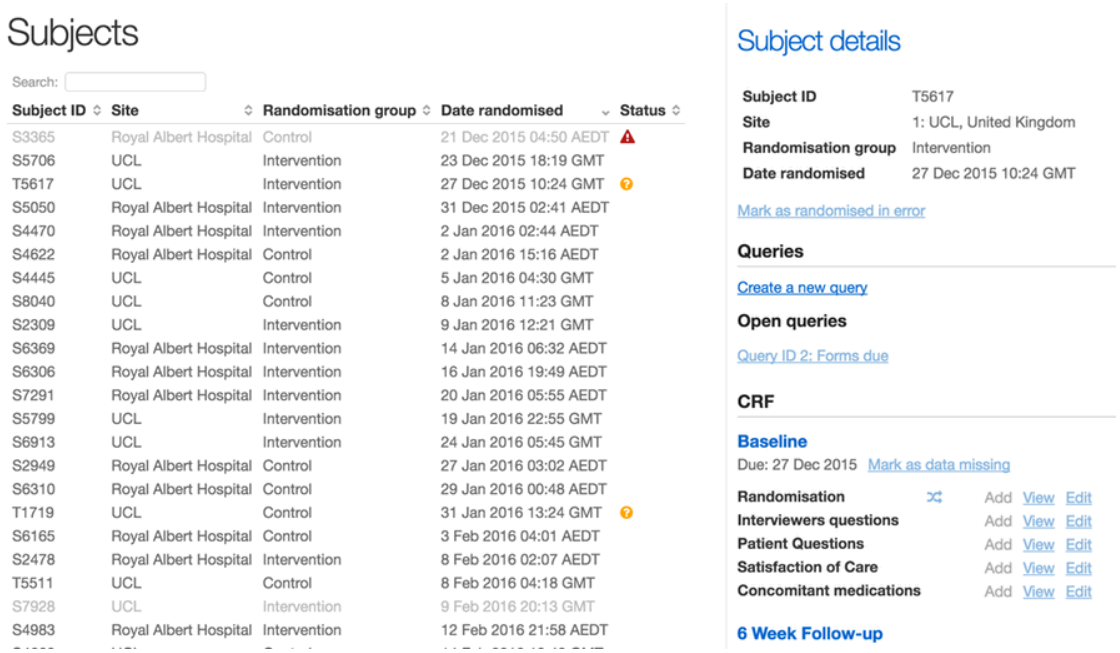


Figure 3.1: Viewing an individual subject record

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.

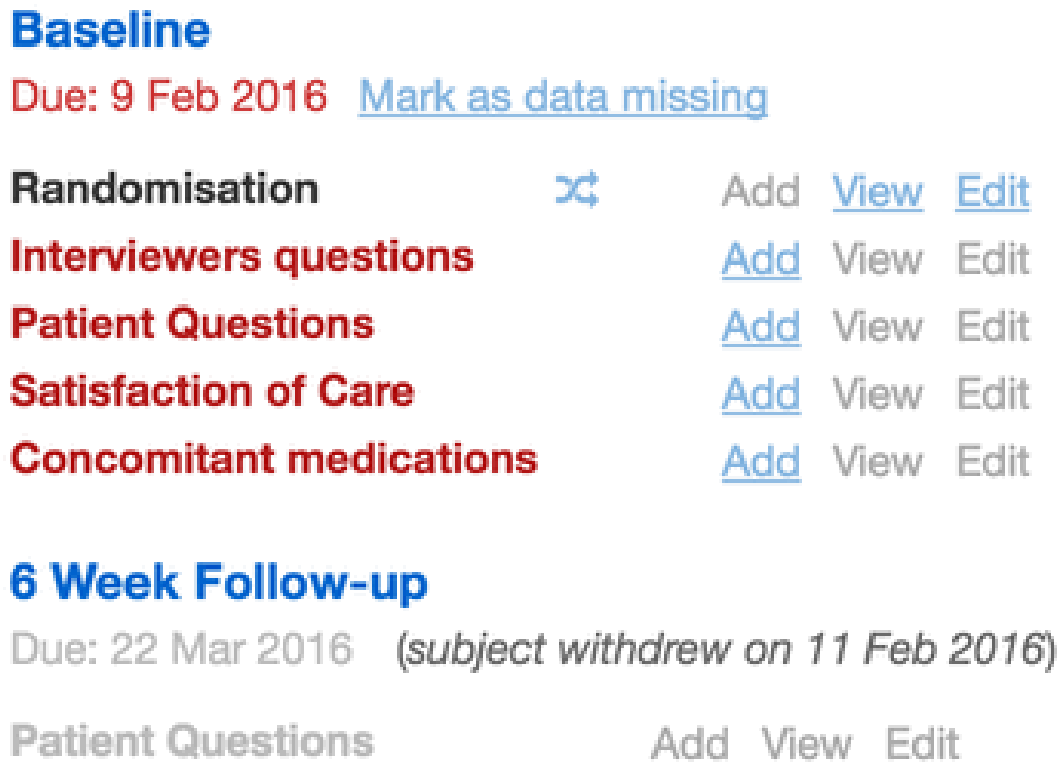


Figure 3.2: A follow-up visit due after subject withdrew

Missing forms

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

Figure 3.3: A follow-up visit marked as missing

Subject-entered forms

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

Form status

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

Chapter 4

Viewing and downloading randomisations

Viewing

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

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

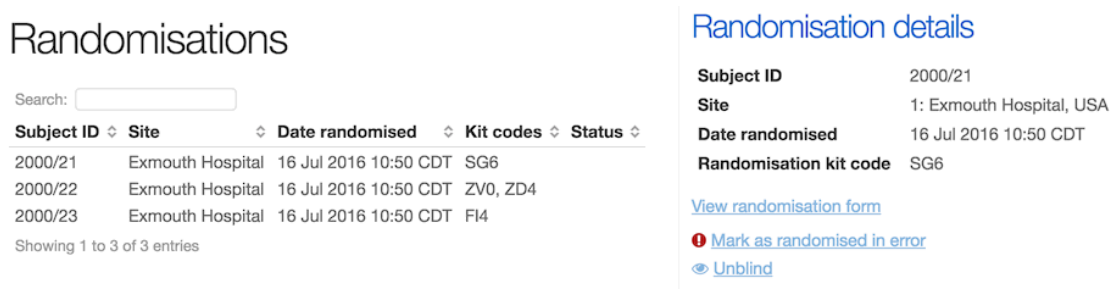


Figure 4.1: Viewing list of randomisations

The list can be restricted by typing in search terms and ordered by clicking on the row headers.

Clicking one of the randomisations or subjects in the list displays more detail for that record. A

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

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

Downloading

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

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

Chapter 5

Data entry of forms

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

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

Validation

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

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

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

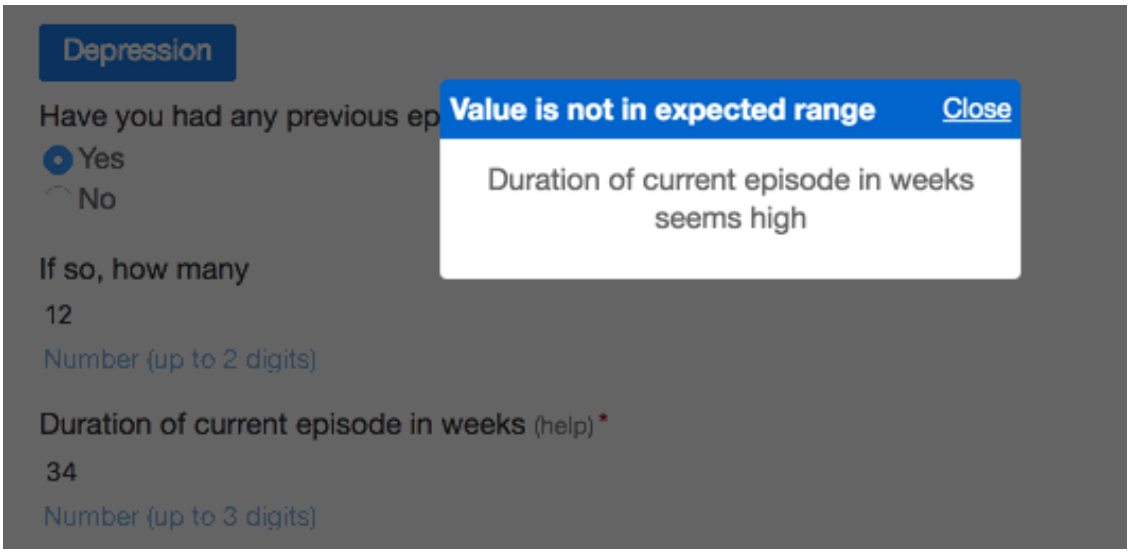


Figure 5.1: Popup warning message

fields are optional and may be left blank if desired.

Repeating sections

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

Likert scales

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

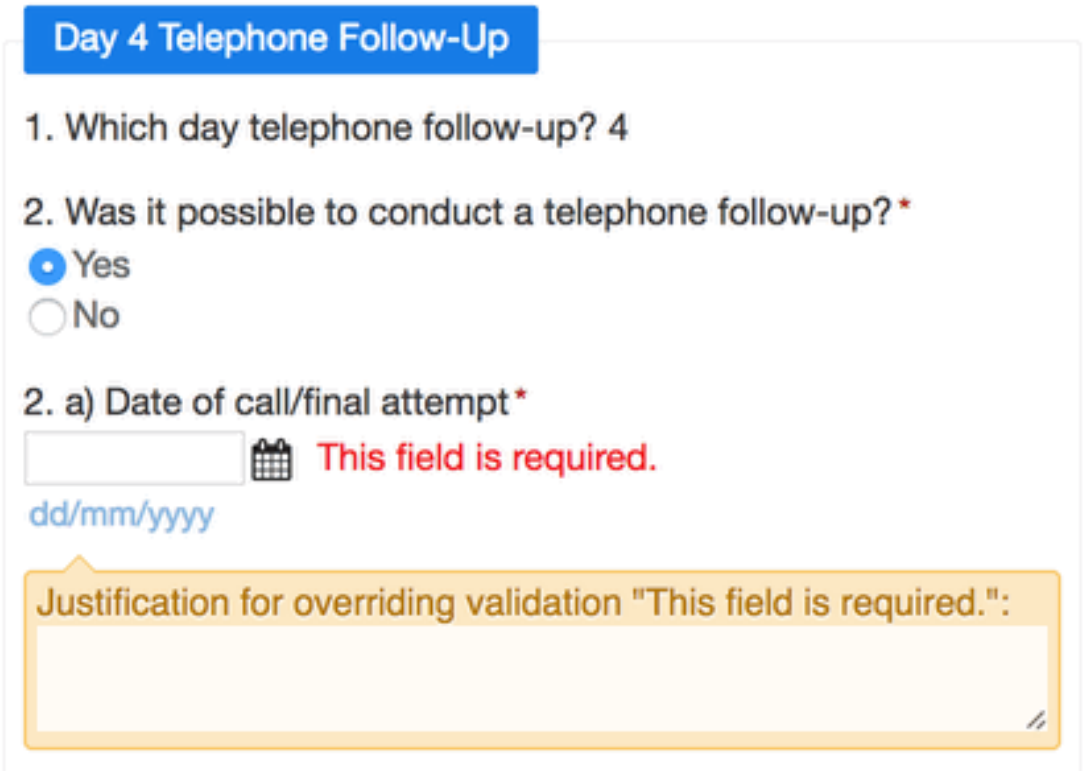


Figure 5.2: Overriding form validation

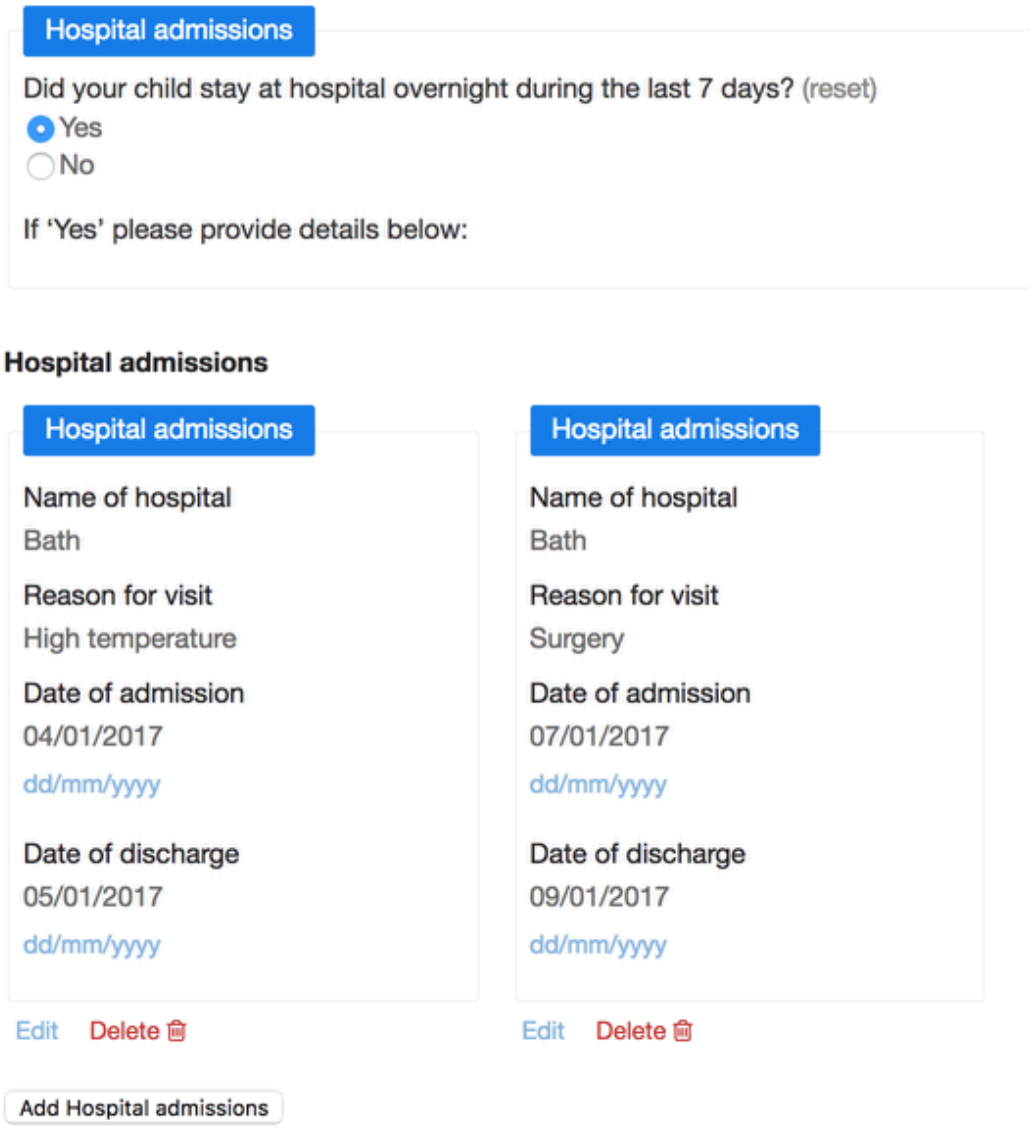


Figure 5.3: A form with subforms

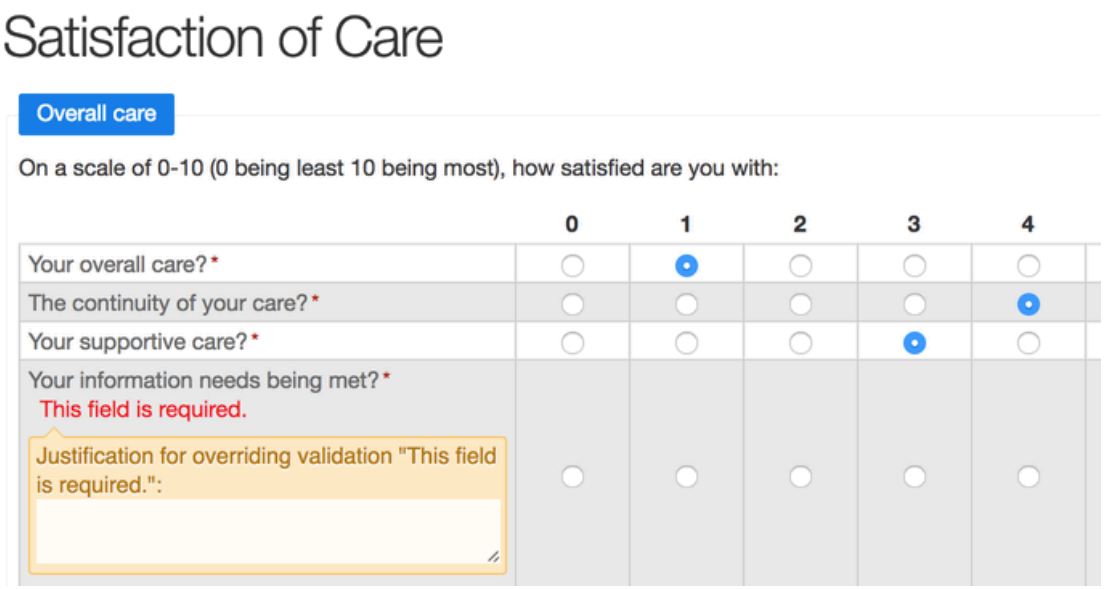


Figure 5.4: A Likert scale section

Encrypted PII fields

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

Review step

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

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

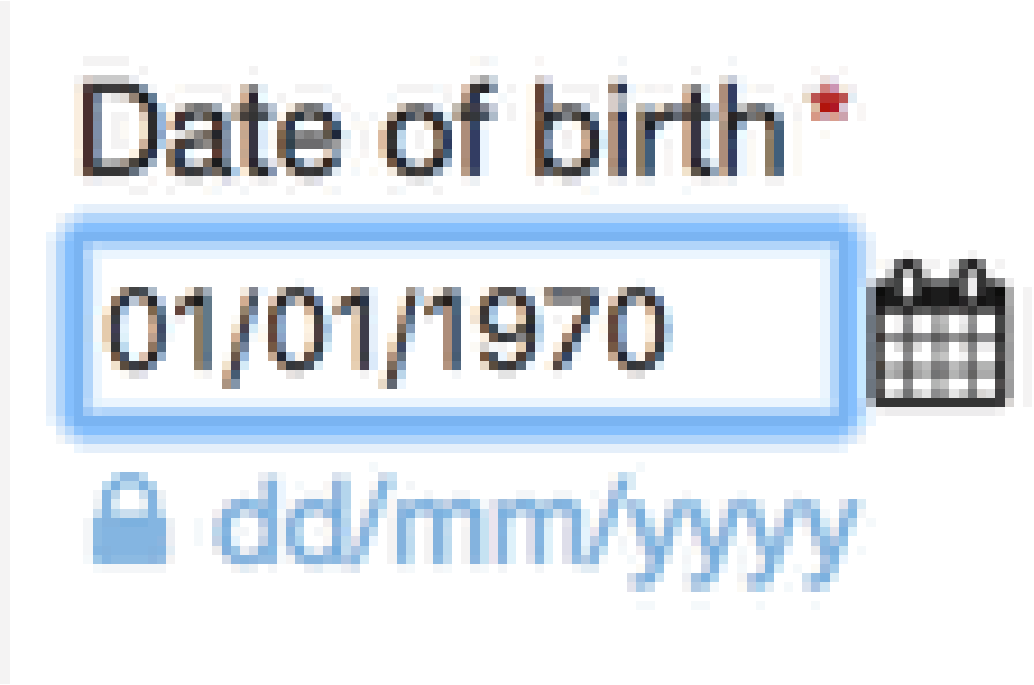


Figure 5.5: An encrypted field

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

Auto-saved drafts

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

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

> Edits to existing forms are not auto-saved.

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

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

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

Form completion messages

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

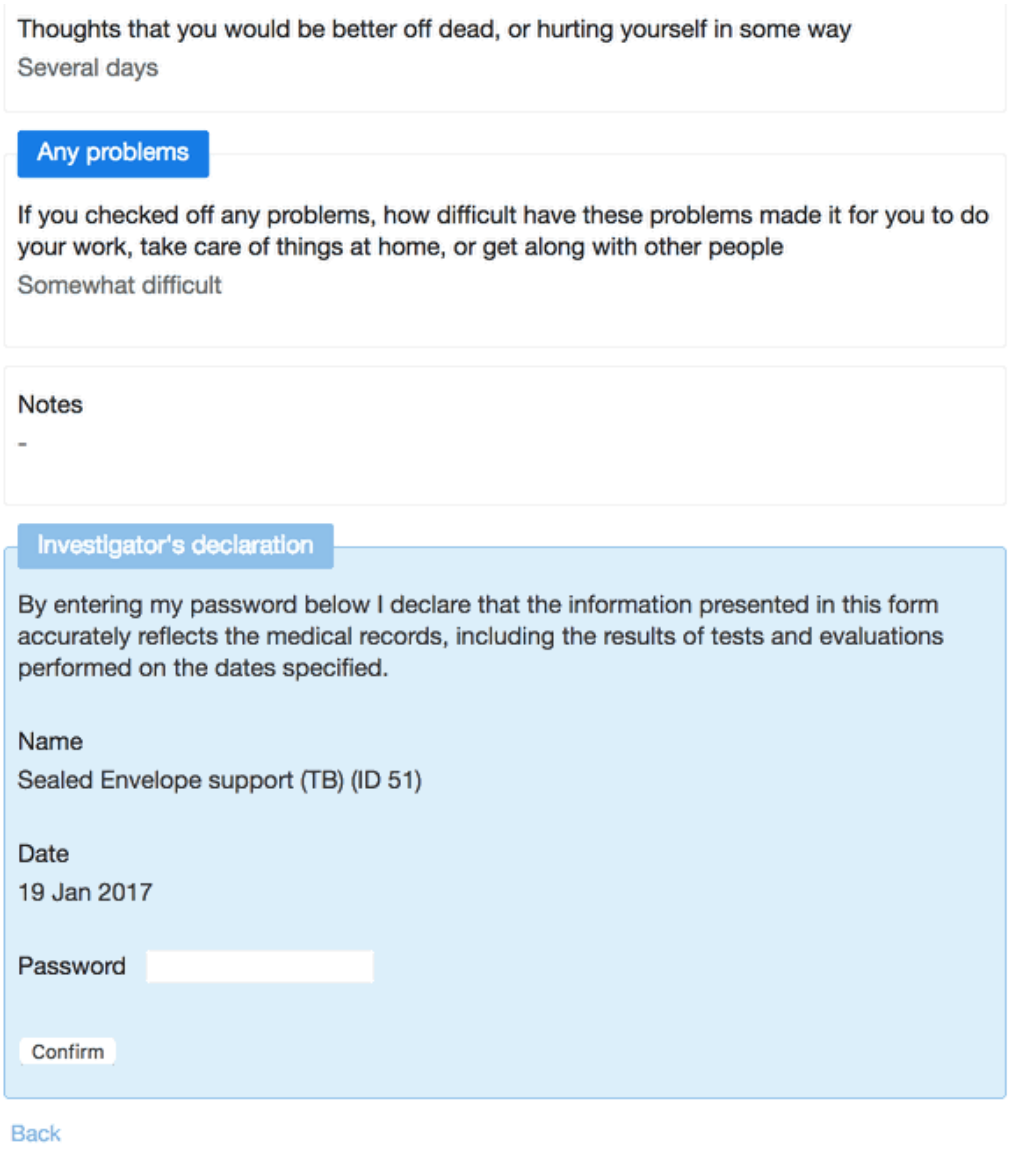


Figure 5.6: Reviewing a form before saving

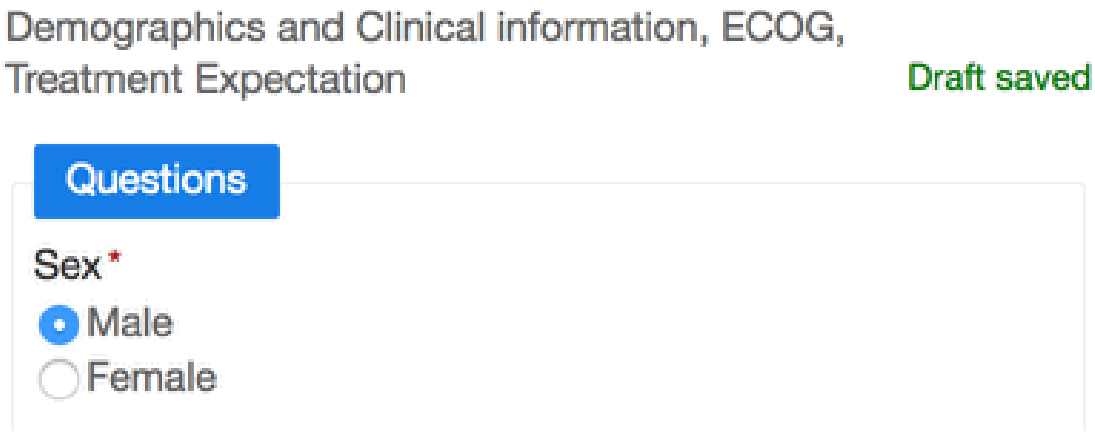


Figure 5.7: Saved draft message

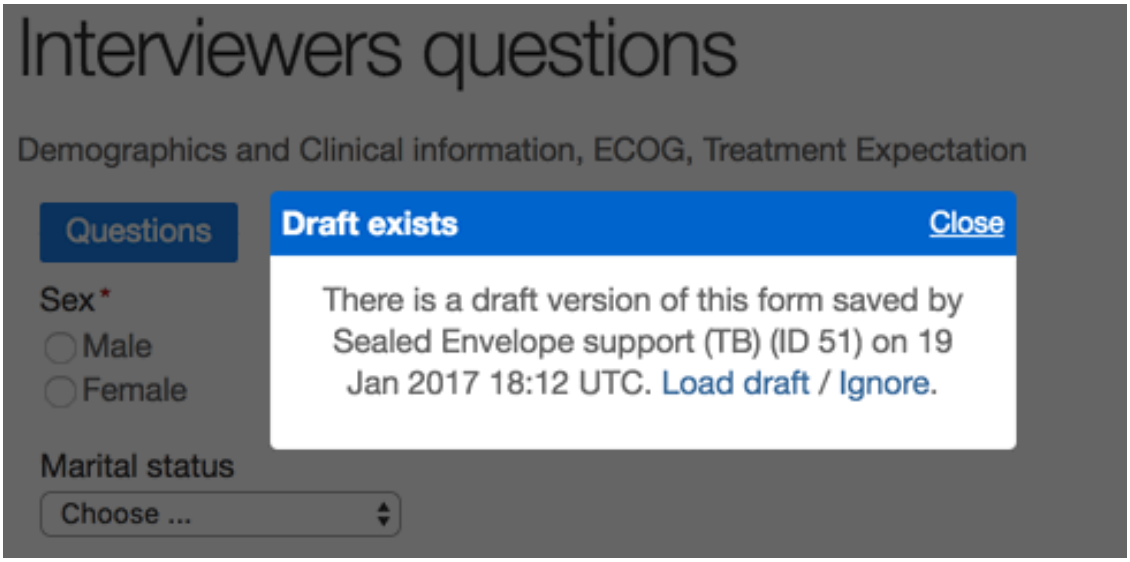


Figure 5.8: Load draft dialogue

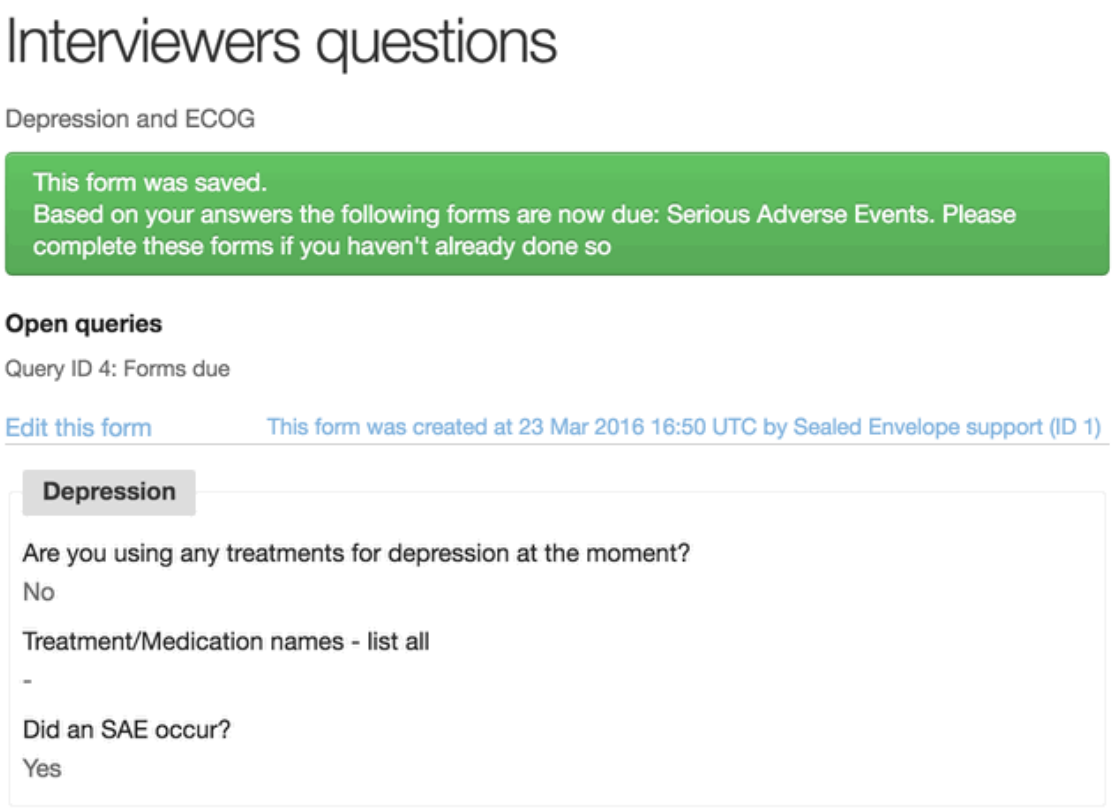


Figure 5.9: Reminder to complete related forms

Repeating forms

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

Figure 5.10: Repeat entry forms

Chapter 6

Randomising

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

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

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

Figure 6.1: Result of randomising a subject

Telephone randomisation

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

Notifications

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

Manual randomisation

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

Randomisation limit

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

Randomisation list

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

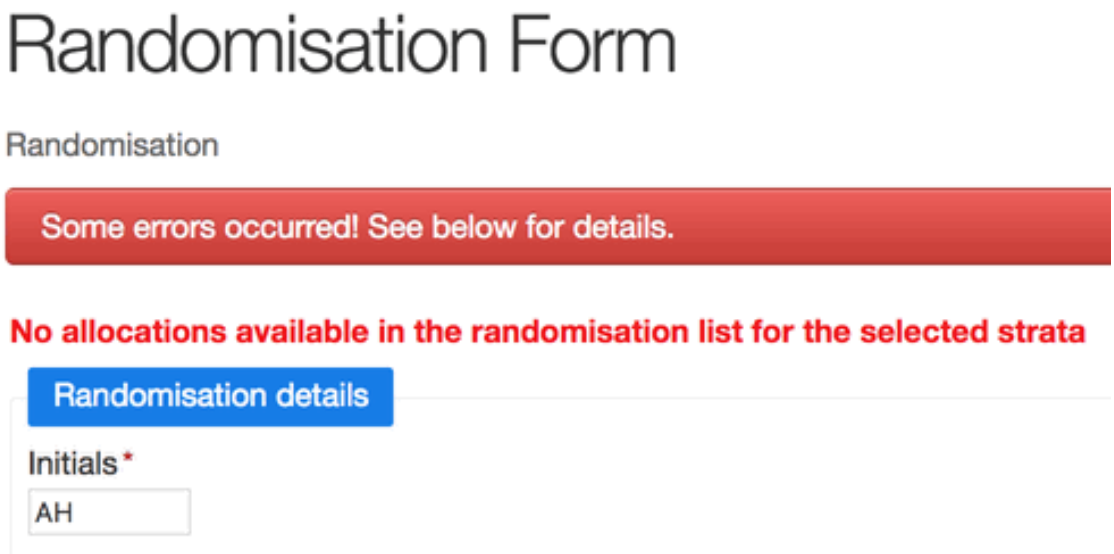


Figure 6.2: No allocations available when randomising a subject

Randomisation disabled

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

Randomisation form

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

Chapter 7

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. A useful discussion of post-randomisation exclusions can be found in this paper:

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

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

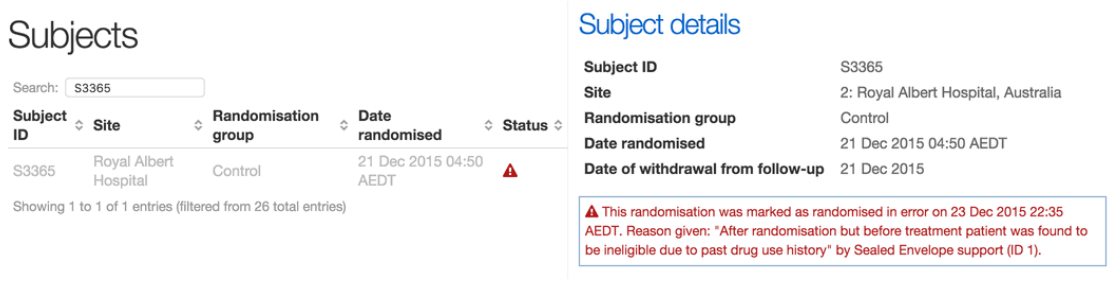
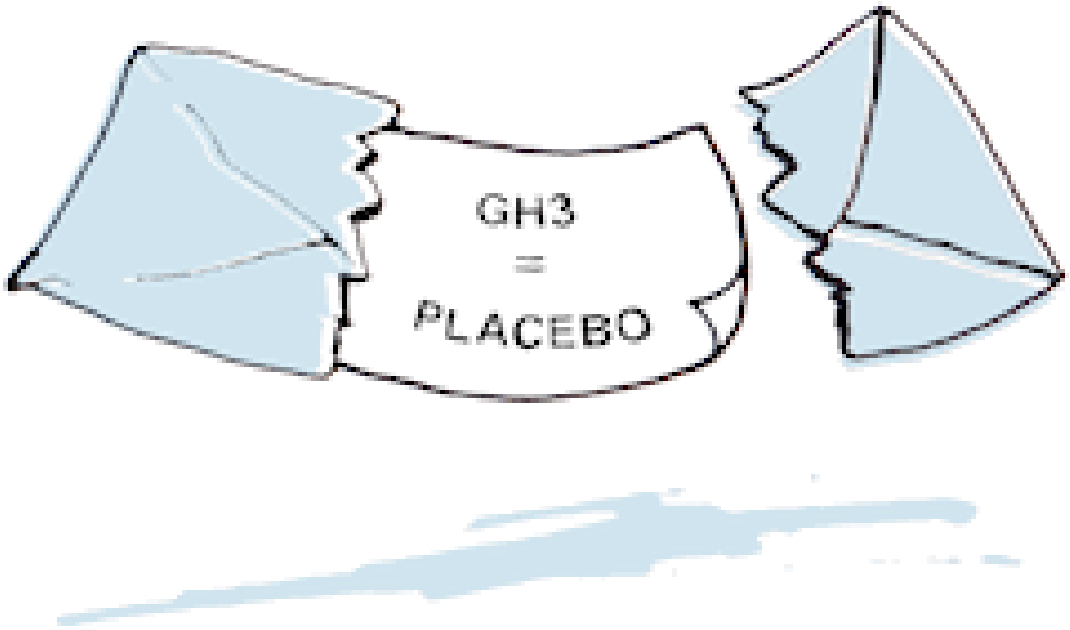


Figure 7.1: A randomisation marked in error

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.

Chapter 8

Unblinding (code-break)



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

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

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

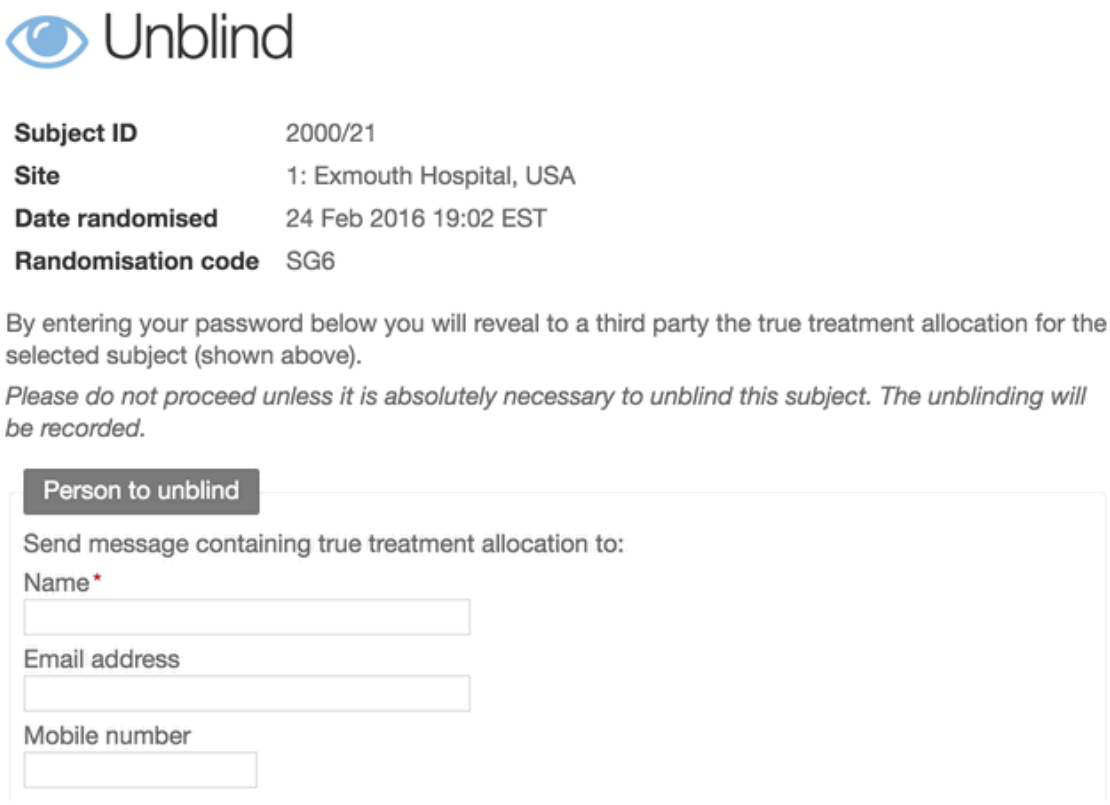


Figure 8.1: Unblinding a designated person

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

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

in the details for the randomisation concerned.

The format of blinded and unblinded notifications can be viewed on the specification page.

After unblinding

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

Figure 8.2: An unblinded subject record

Chapter 9

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 enrols 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.

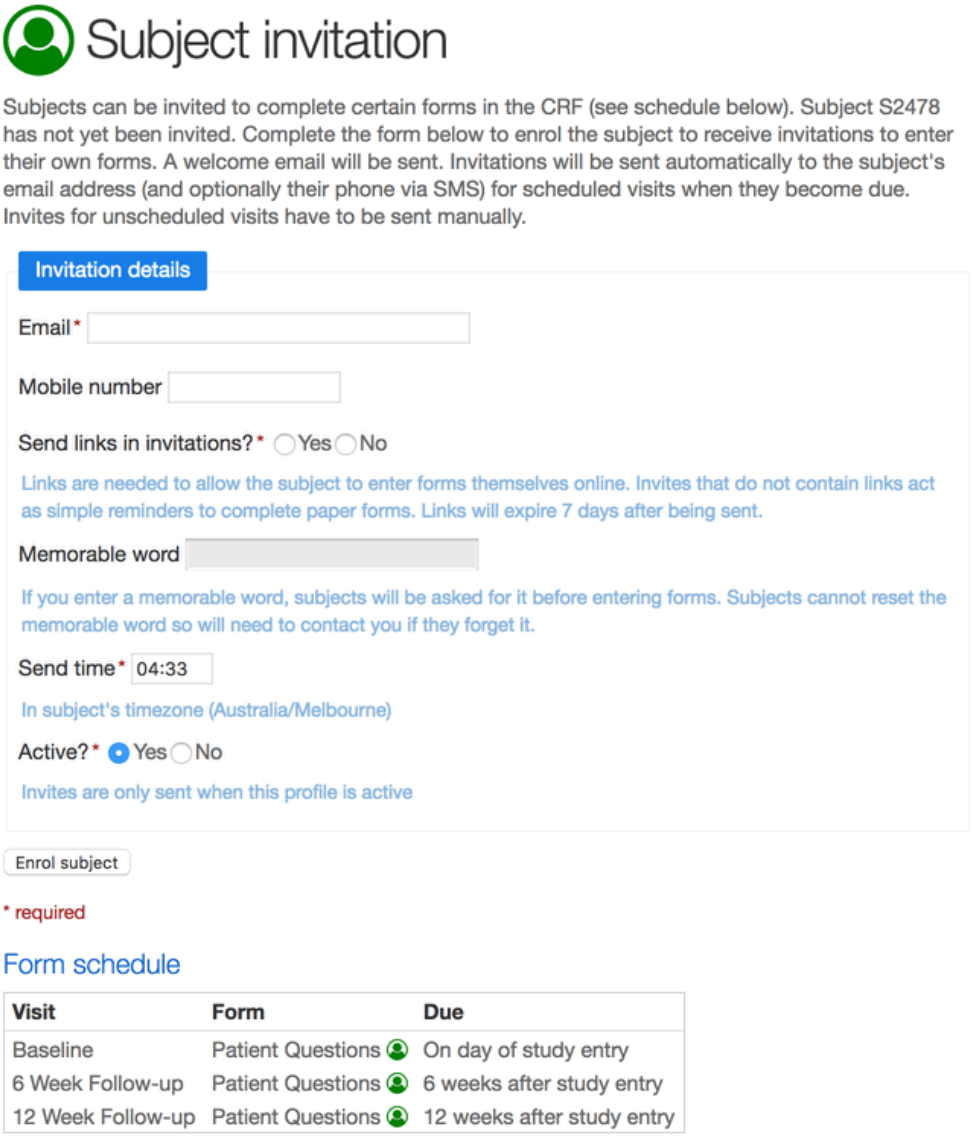


Figure 9.1: Subject invitation form

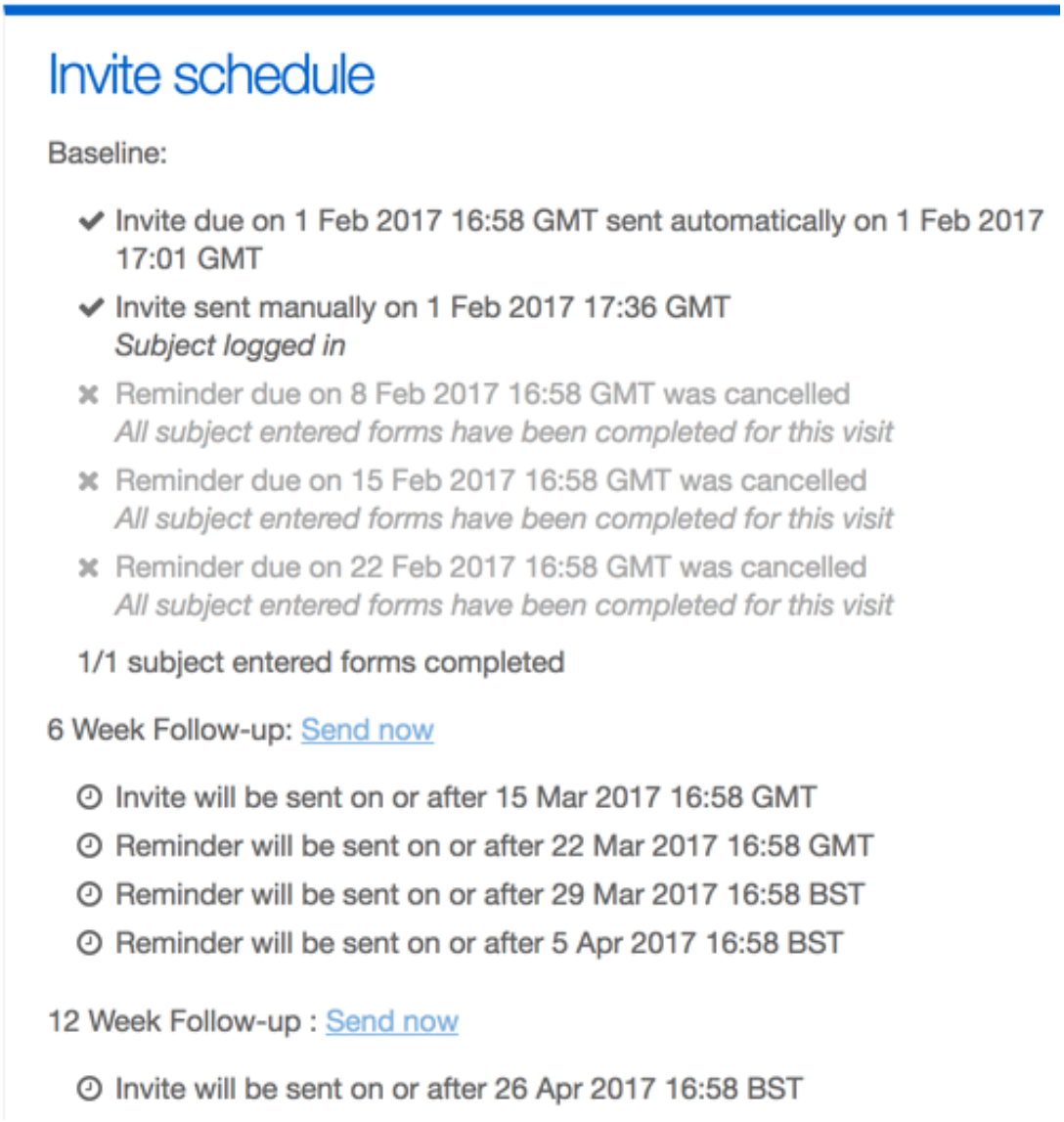


Figure 9.2: Subject invitation schedule

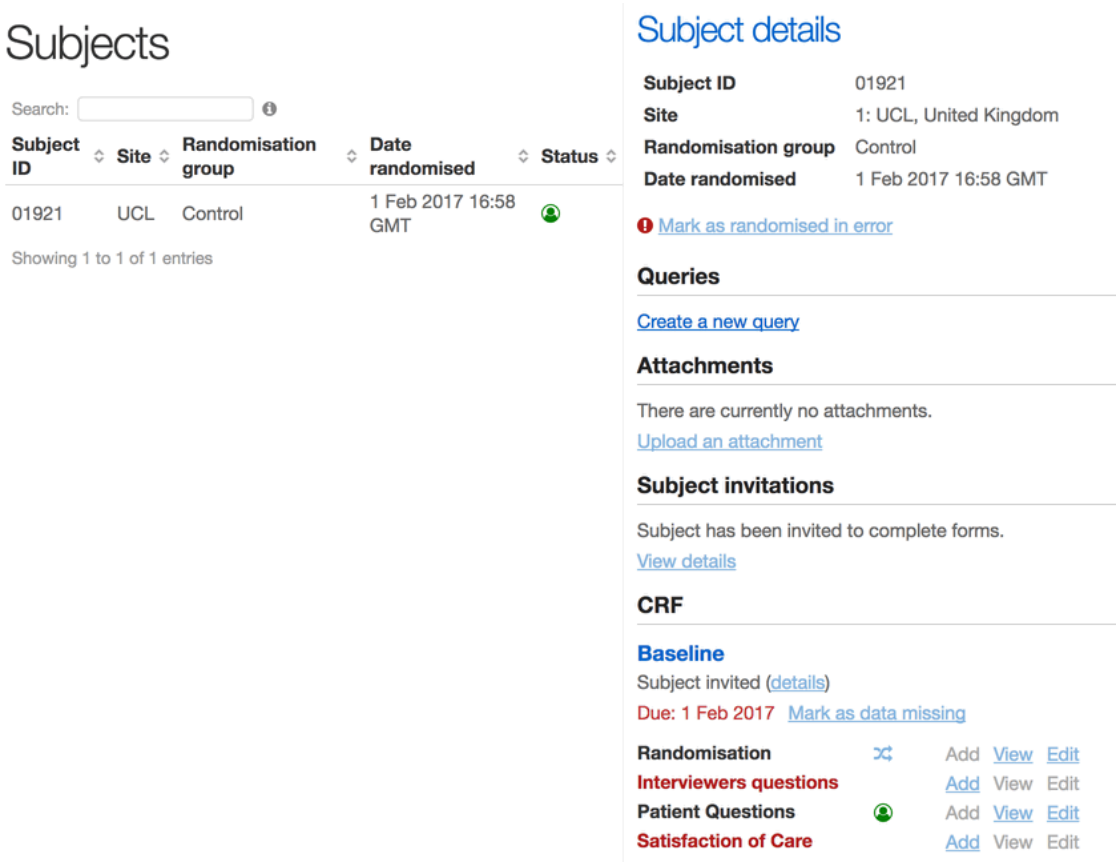


Figure 9.3: Subject list

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 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.

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:

- 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

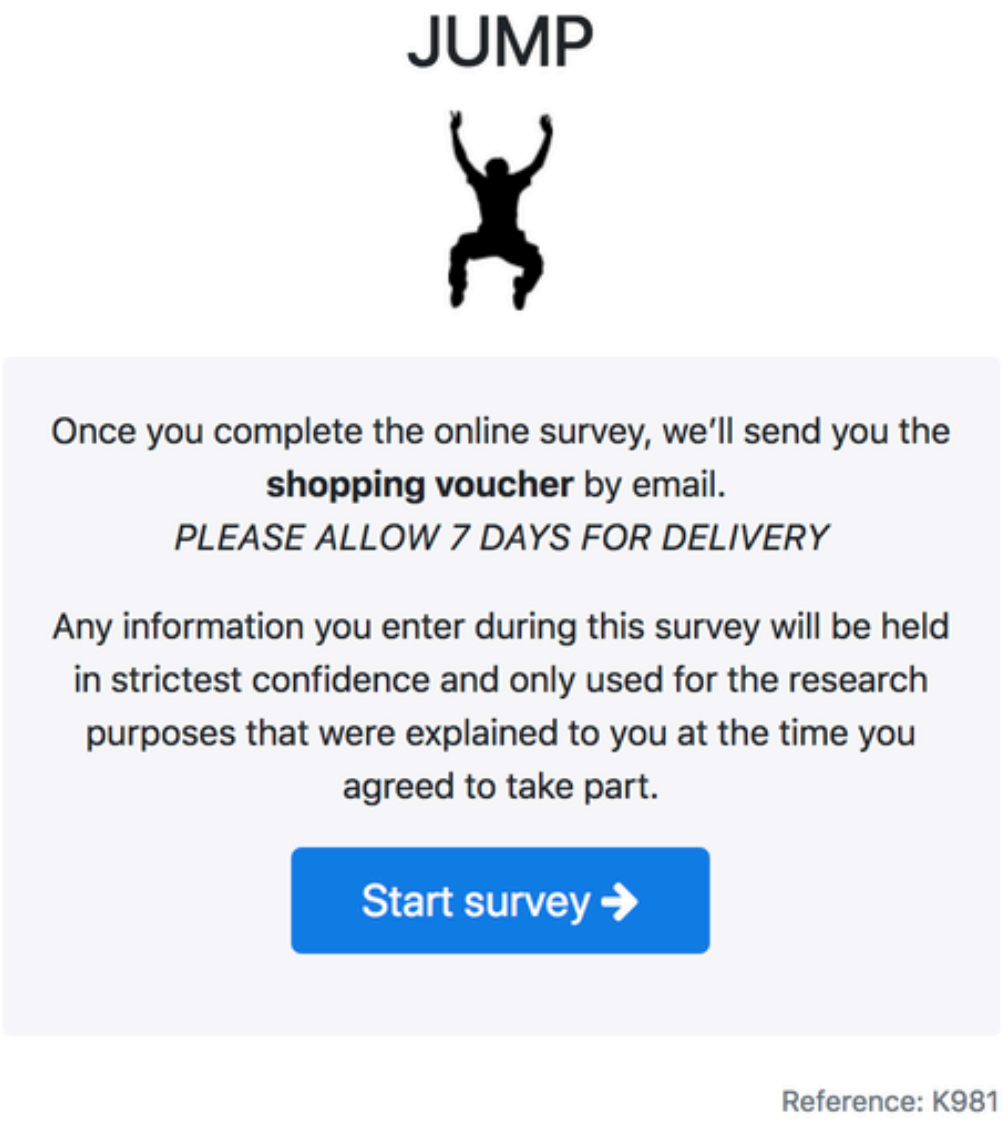


Figure 9.4: Welcome screen

JUMP

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

Please complete the following form:

1. Patient Questions

Figure 9.5: List of forms as seen by the subject

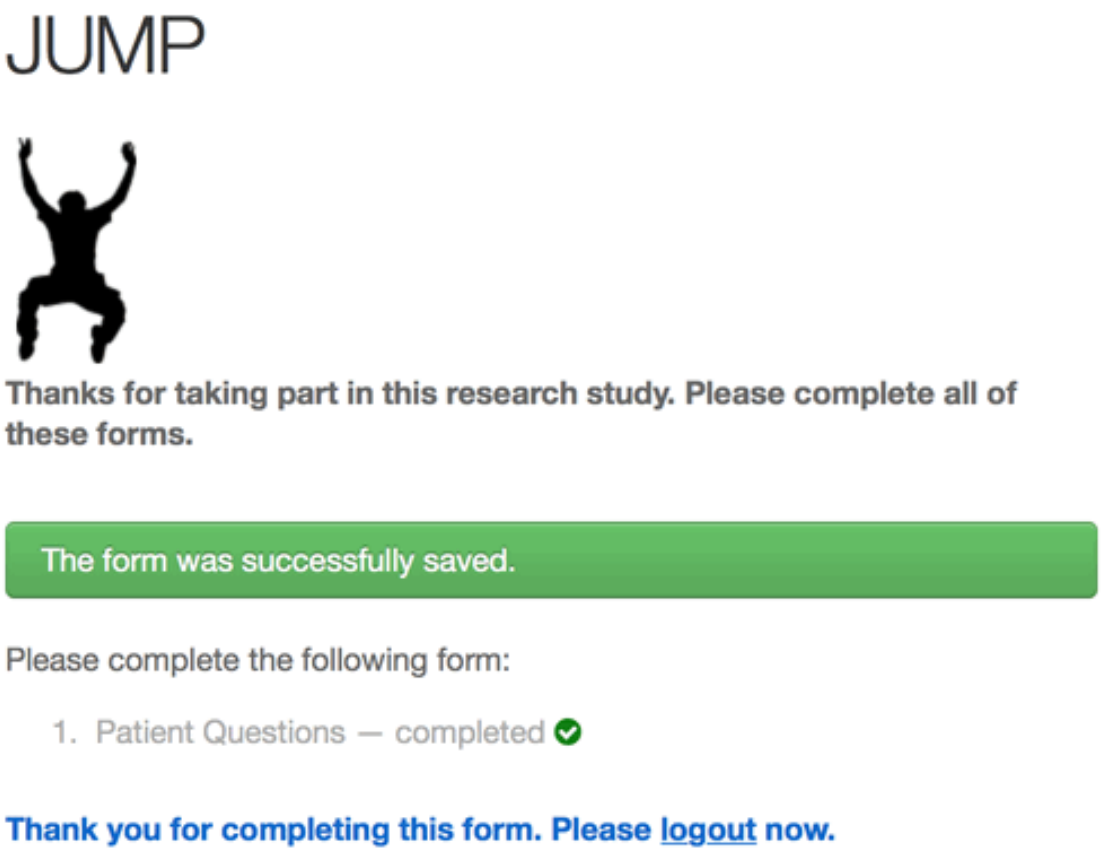


Figure 9.6: Completed forms as seen by the subject

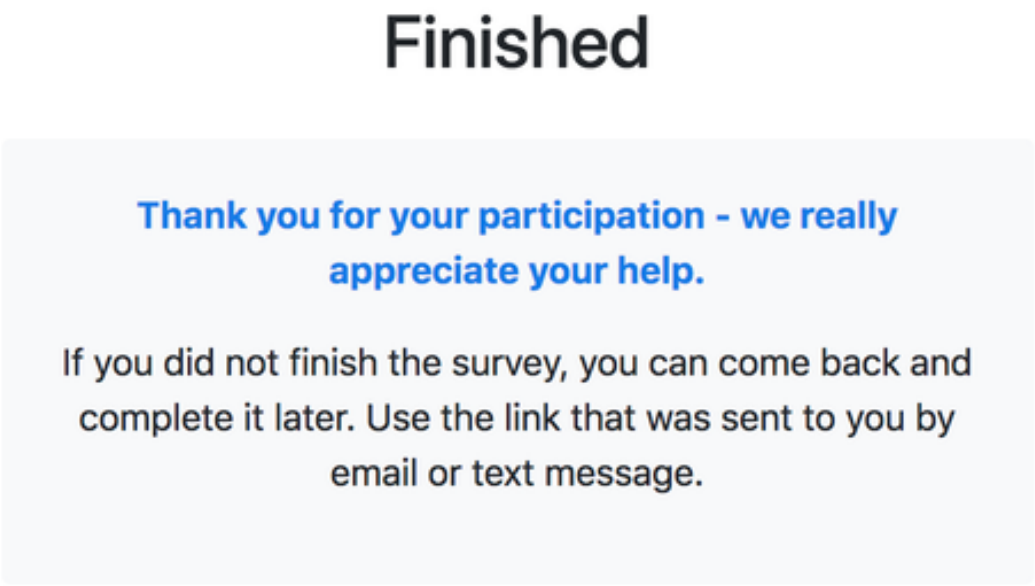


Figure 9.7: Finished screen

Chapter 10

Viewing forms

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

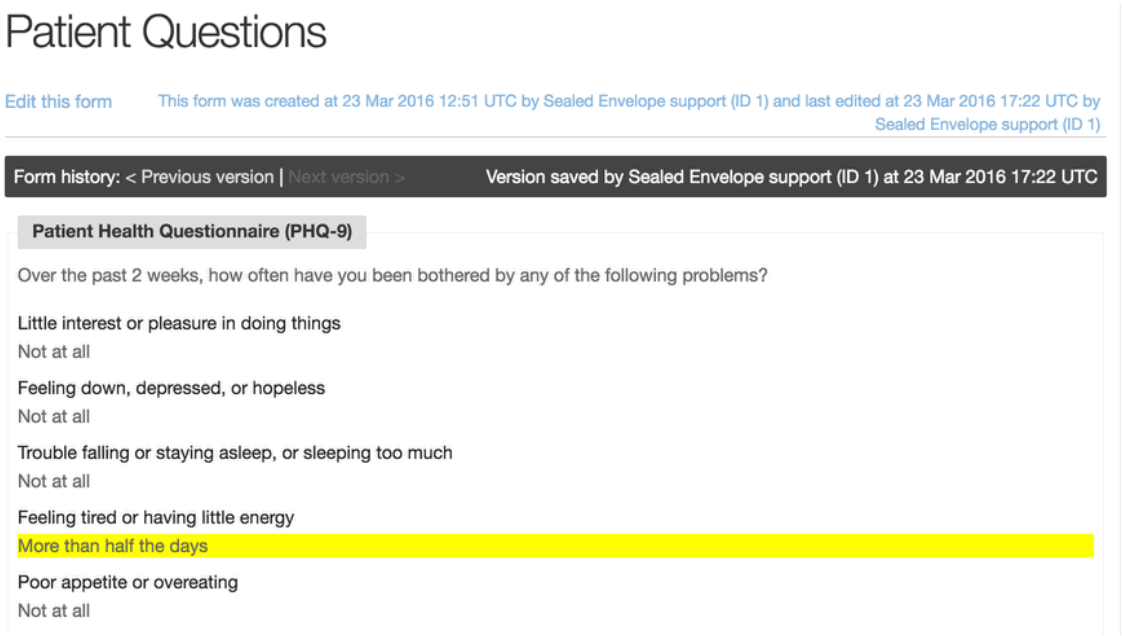


Figure 10.1: Viewing a form that has been edited

Chapter 11

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.

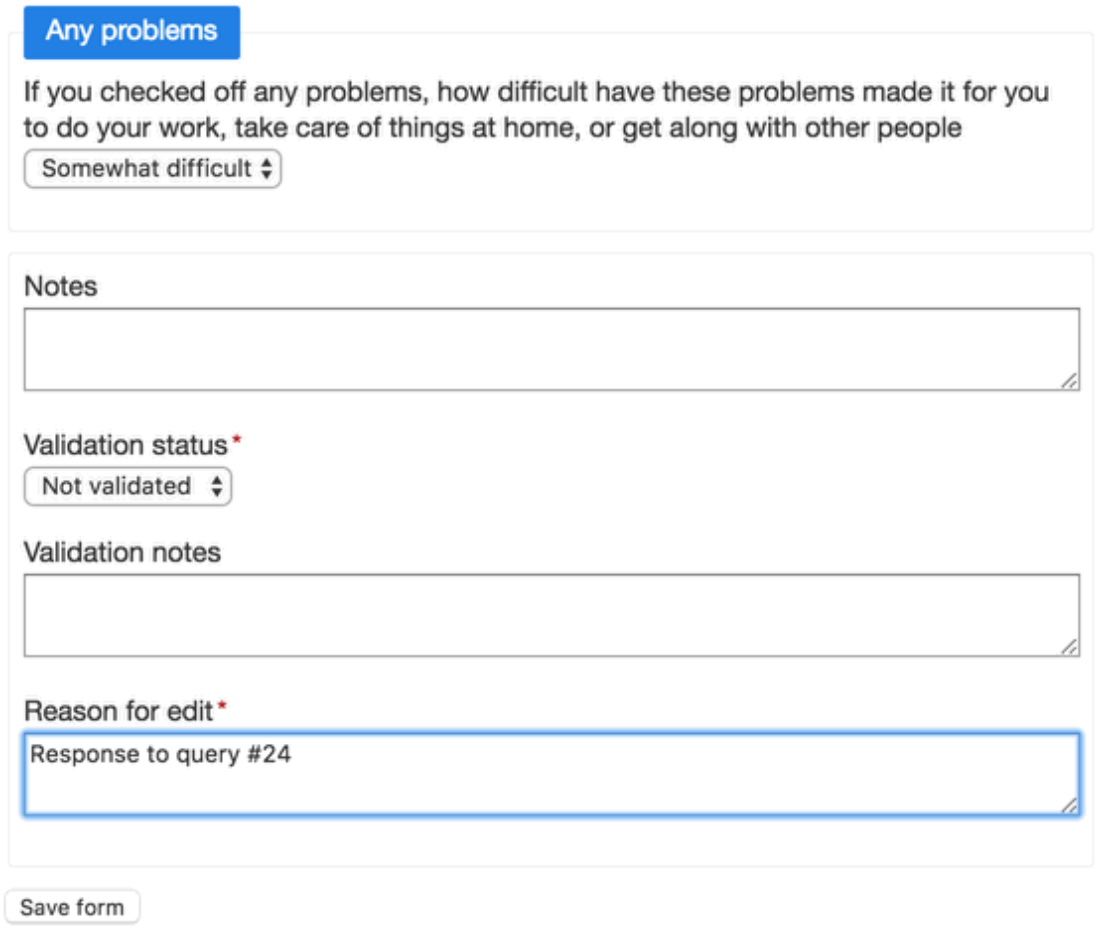


Figure 11.1: Editing a form

Chapter 12

Editing randomisations

Randomisation forms may be edited by viewing the form and clicking on the 'Edit this form' link.

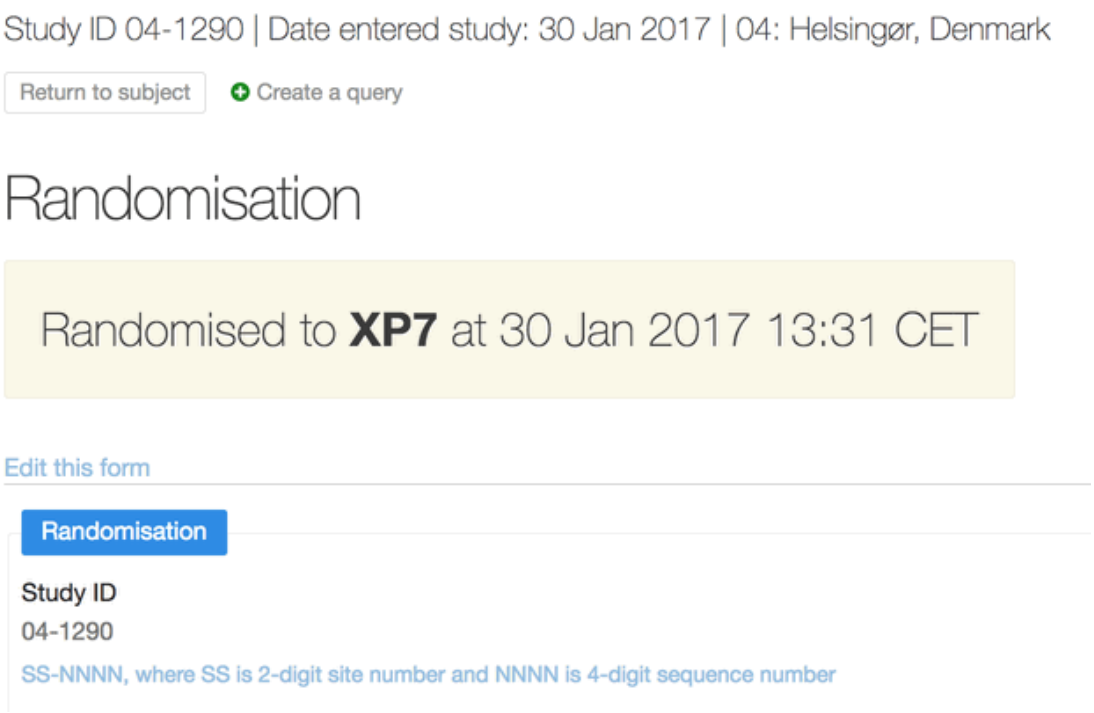


Figure 12.1: Viewing a randomisation form

Randomisation forms have the following special features:

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

Chapter 13

Obsolete forms

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

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

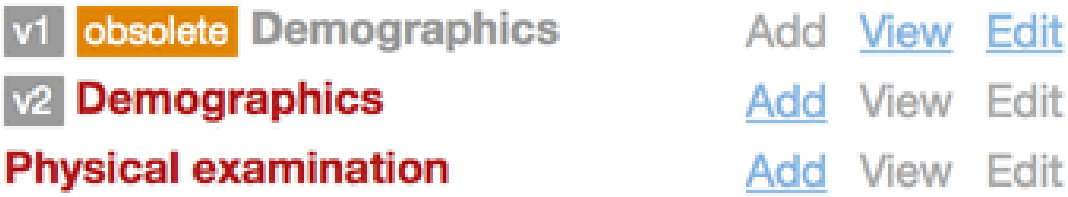


Figure 13.1: Subject with obsolete form

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

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

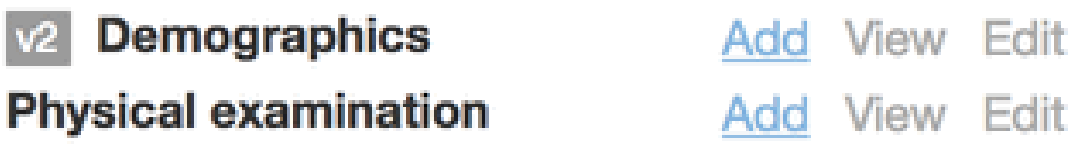


Figure 13.2: Subject without obsolete form

Downloads

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

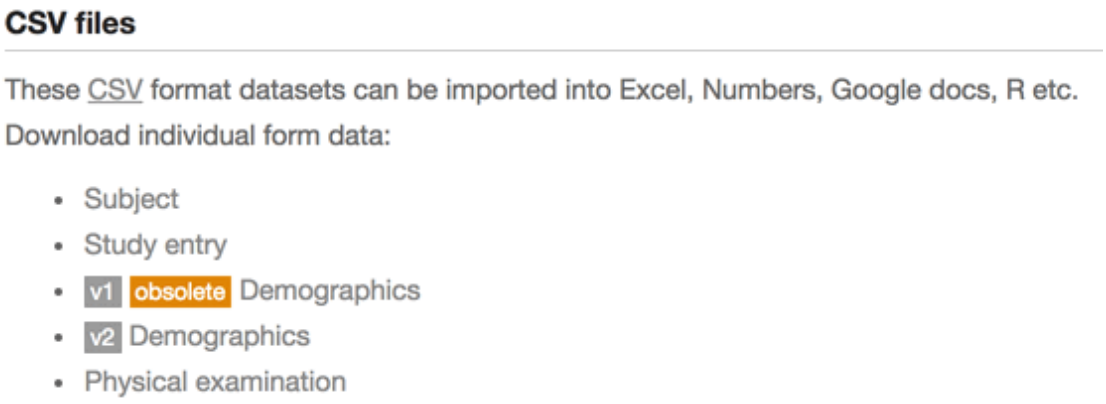


Figure 13.3: Download page showing different versions of a form

Chapter 14

Overdue forms

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

> Note that visits without time-points are not shown

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

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

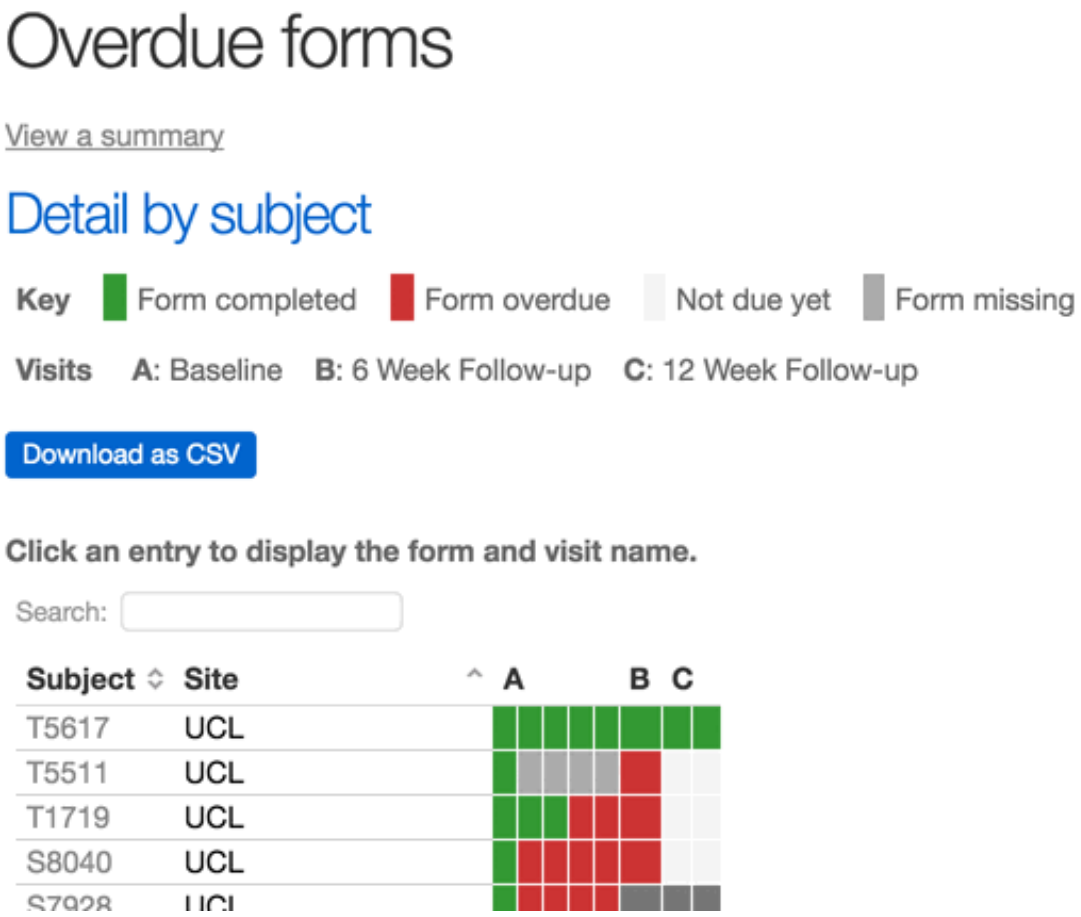


Figure 14.1: Overdue forms detail

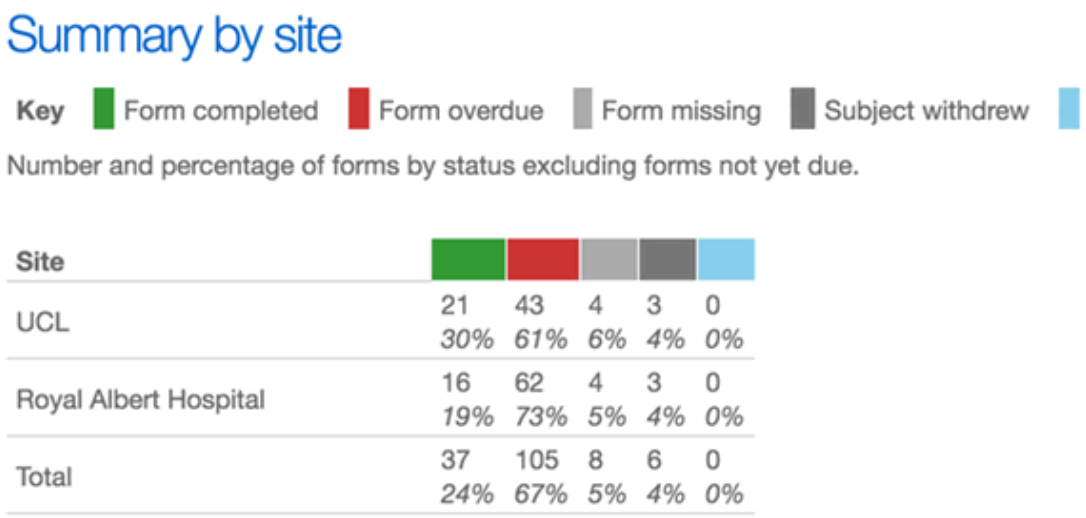


Figure 14.2: Overdue forms summary

Chapter 15

Code lists

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

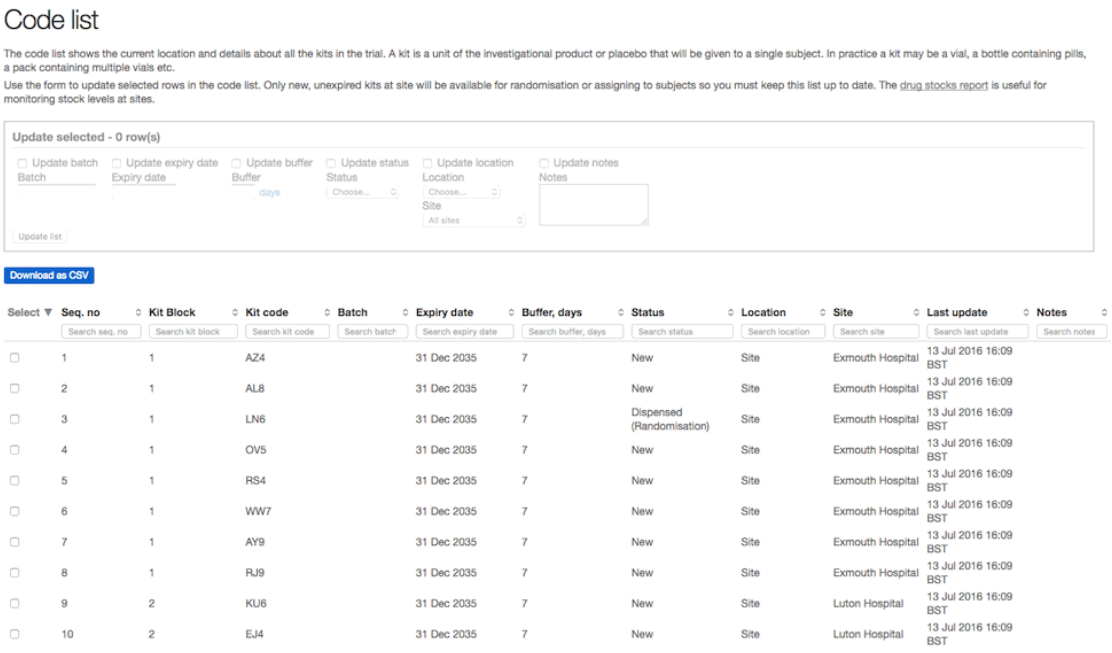
The randomisation system does not display the treatment group, but it is useful for administrators to view the other columns in the code list because it shows the location of trial treatments and whether they are available for use.

Terminology

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

Kit

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



Code list

The code list shows the current location and details about all the kits in the trial. A kit is a unit of the investigational product or placebo that will be given to a single subject. In practice a kit may be a vial, a bottle containing pills, a pack containing multiple vials etc.

Use the form to update selected rows in the code list. Only new, unexpired kits at site will be available for randomisation or assigning to subjects so you must keep this list up to date. The drug stocks report is useful for monitoring stock levels at sites.

Update selected - 0 row(s)

☐ Update batch — Batch
☐ Update expiry date — Expiry date
☐ Update buffer — Buffer — days
☐ Update status — Status — Choose...
☐ Update location — Location — Choose... — Site — All sites
☐ Update notes — Notes

Update list

Download as CSV

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

Figure 15.1: Code list page

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

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

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

Sequence number

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

Batch

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

Expiry

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

Viewing a code list

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

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

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

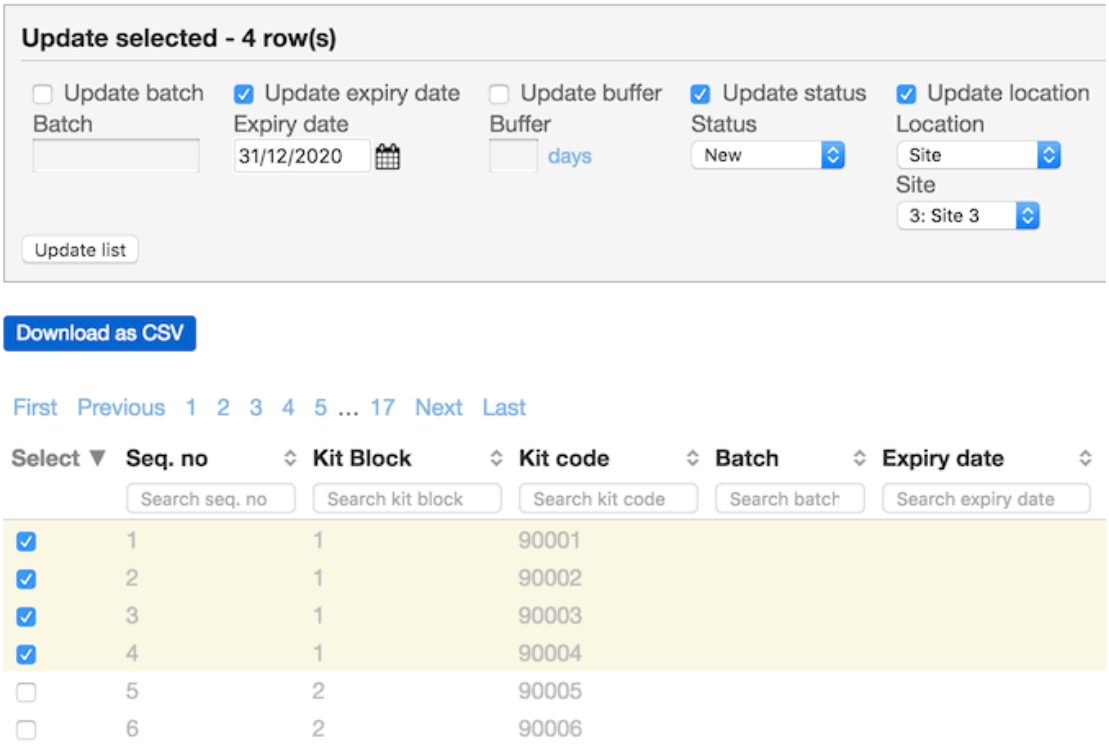


Figure 15.2: Updating a code list

- 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.

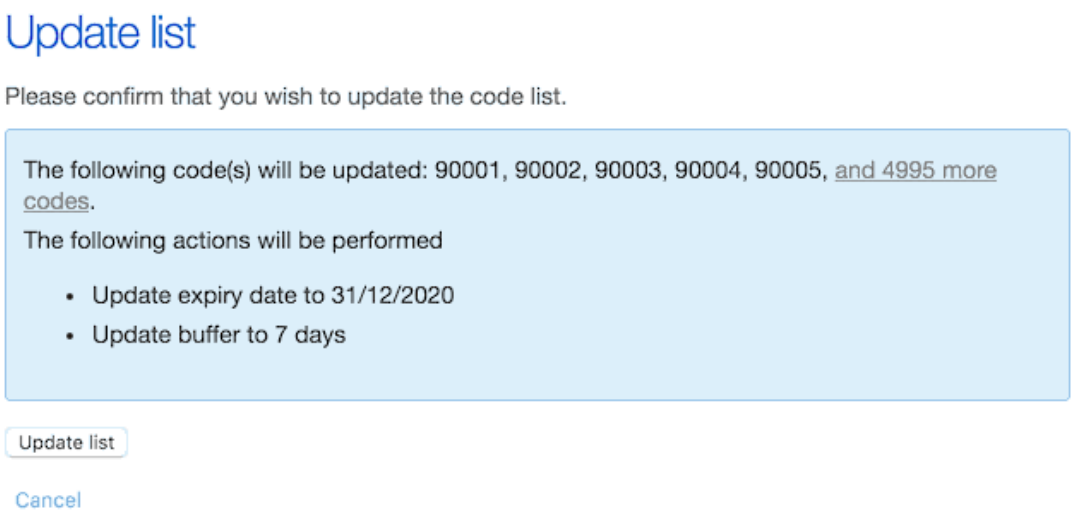


Figure 15.3: Confirmation of changes to code list

Deallocating a kit from a subject

Sometimes it may be desirable to deallocate a kit from a subject, such as when a subject was randomised in error or withdraws before the kit is used. This can be done by updating the kit in the codelist and changing the status from **Dispensed** back to **New**. This makes the kit available again for use at the site. Kits deallocated in this way are still shown when viewing the original subject along with the date of deallocation.

Dispensing policy

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

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

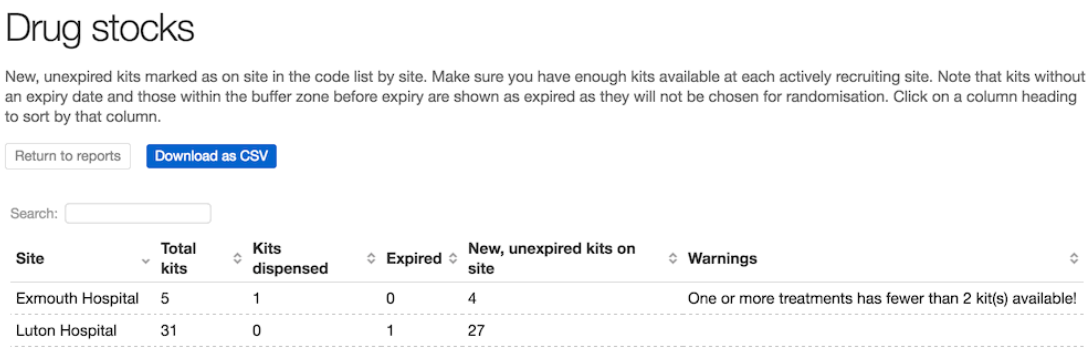
Kits are chosen at random from the pool of eligible kits (with lower numbered kit blocks preferred) to reduce the chance of treatment information being gleaned from the order in which kits are used. Note this means that kits are *not allocated in sequence number order*.

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

Stock levels

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

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



Drug stocks

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

Return to reports | Download as CSV

Search:

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

Figure 15.4: Drug stocks report

Downloading

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

```
id,patientId,code,kitBlock,kitType,batch,expiryDate,expiryBuffer,kitStatus,dispensedVisit,
    location,siteId,dateUpdate,notes,siteName
1,3,SG6,1,,,2035-12-12,0,Dispensed,Randomisation,Site,2,"2016-07-14 17:02:24",,"Luton
    Hospital"
2,2,ZV0,1,,,2035-12-12,0,Dispensed,Randomisation,Site,2,"2016-07-14 17:02:24",,"Luton
    Hospital"
3,1,FI4,1,,,2035-12-12,0,Dispensed,Randomisation,Site,2,"2016-07-14 17:02:24",,"Luton
    Hospital"
4,,ZD4,1,,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital"
5,,XB3,2,,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital"
6,,HC3,2,,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital"
7,,KG0,2,,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital"
8,,YH5,2,,,2035-12-12,0,New,,Site,2,"2016-07-15 15:55:36",,"Luton Hospital"
```

The fields present are:

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

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

Chapter 16

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.

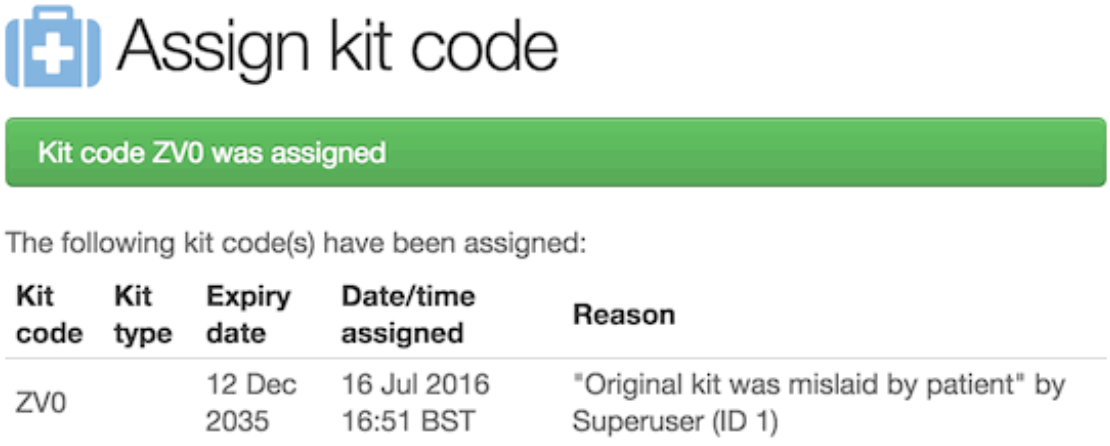


Figure 16.1: Result of assigning a kit code

Failed kit assignment at randomisation

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

Notifications

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

Viewing assigned kits

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

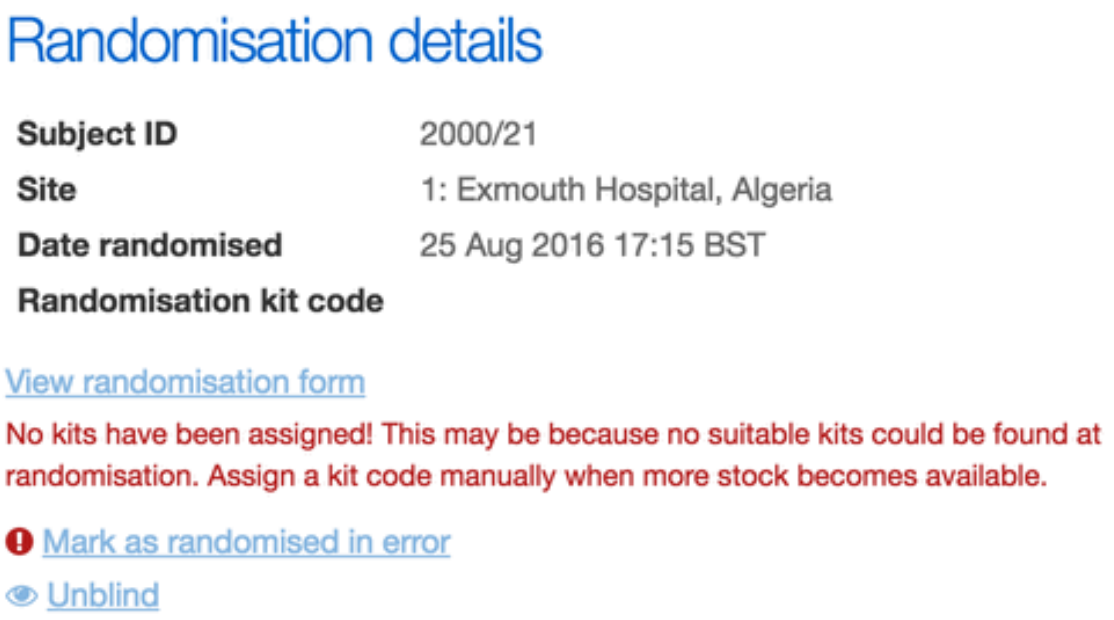
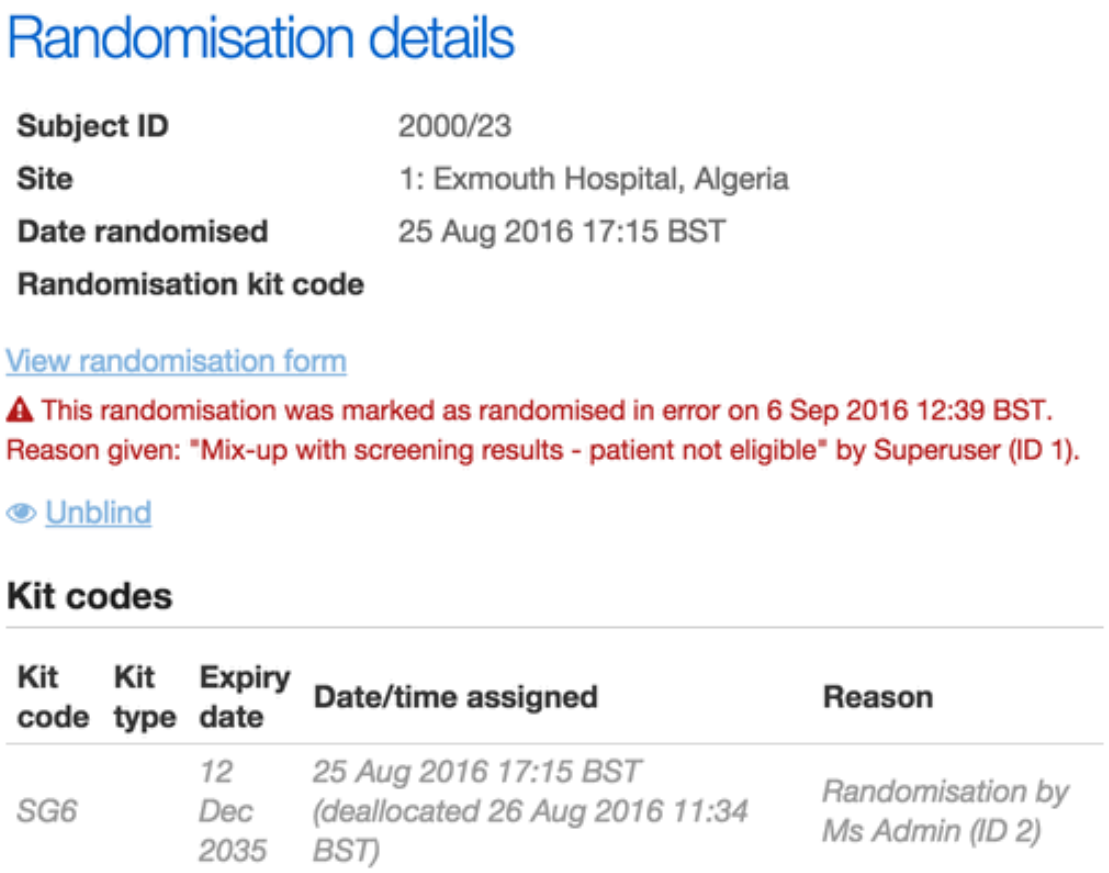


Figure 16.2: Subject without assigned kit

Figure 16.3: Randomisation with assigned kits

Deallocated kits

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



Randomisation details

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

View randomisation form

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

Unblind

Kit codes

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

Figure 16.4: Randomisation with deallocated kit

Chapter 17

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.

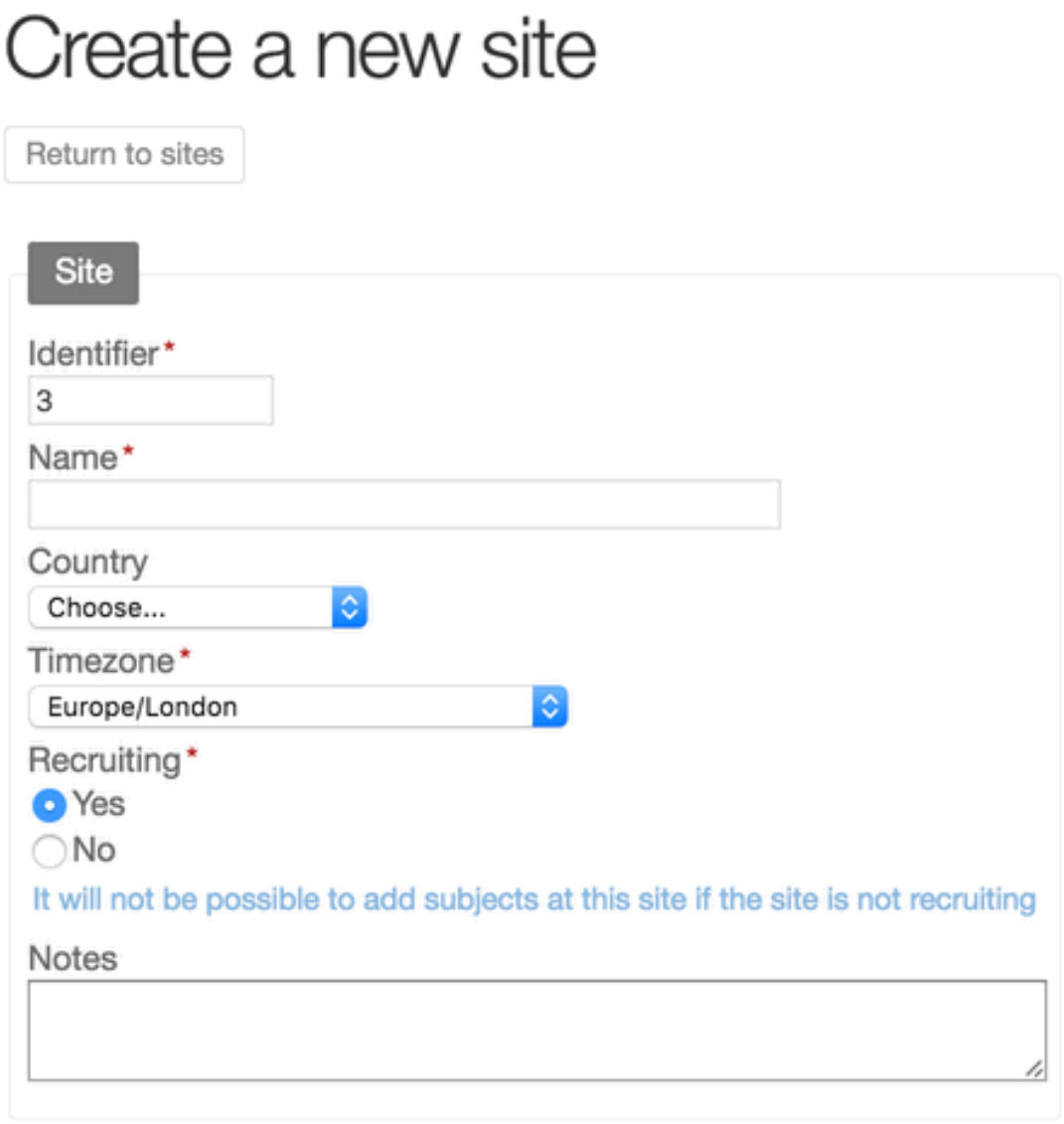


Figure 17.1: Adding a new site

Chapter 18

Queries

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

Opening queries

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

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

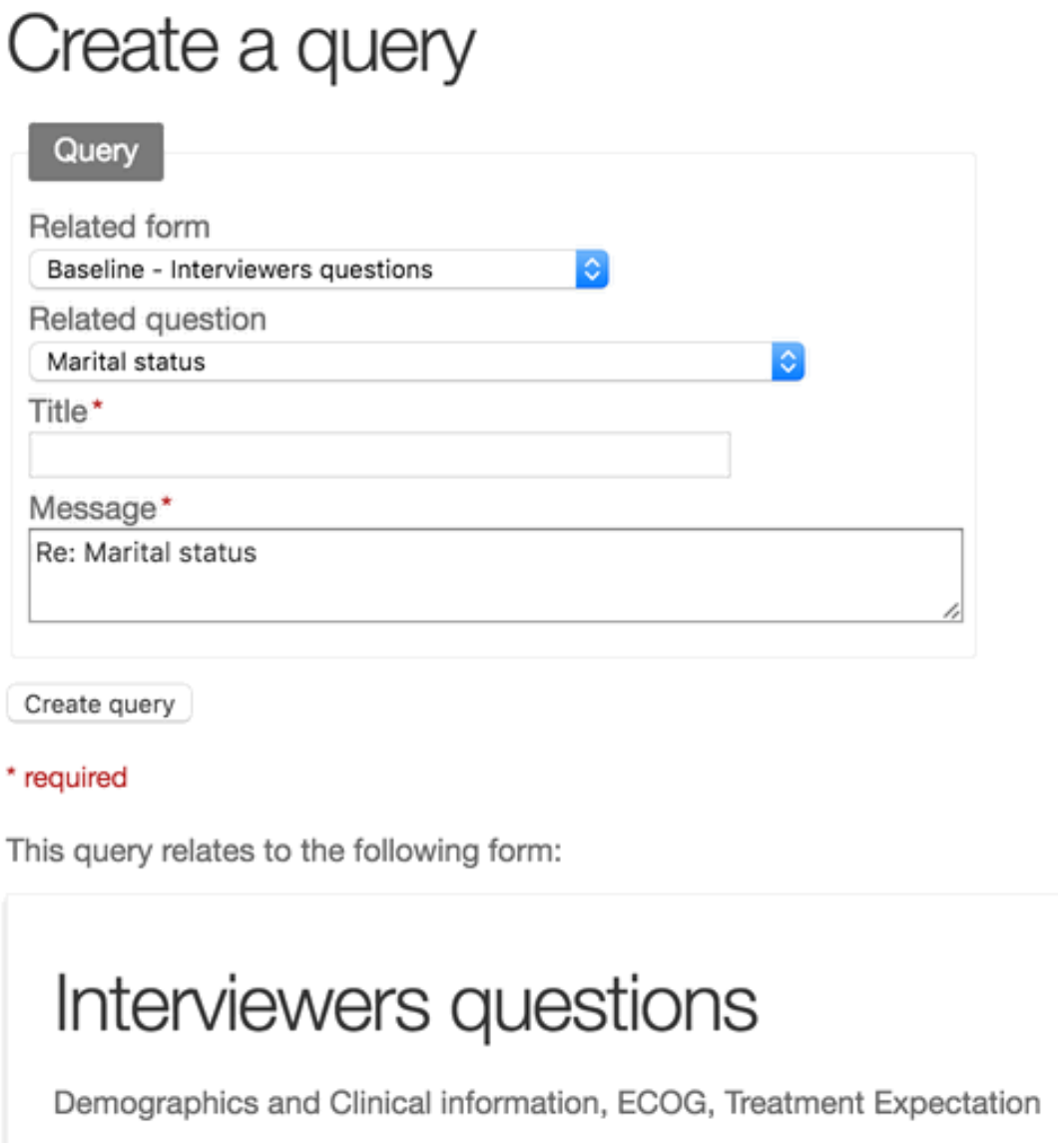


Figure 18.1: Creating a new query

Adding messages

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

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

Email notifications

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

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

The format of the notification email is:

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

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

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

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

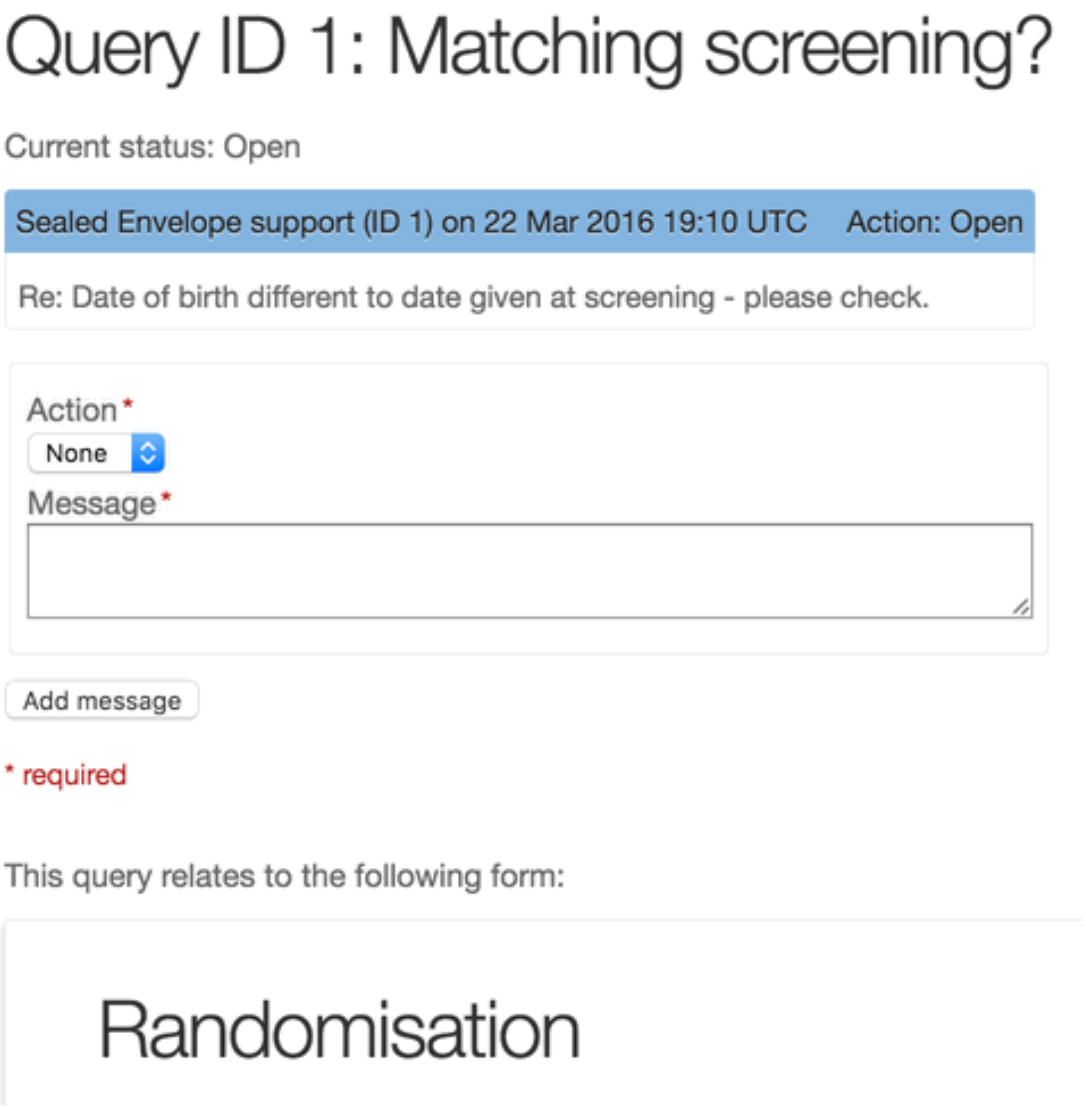


Figure 18.2: Viewing an open query

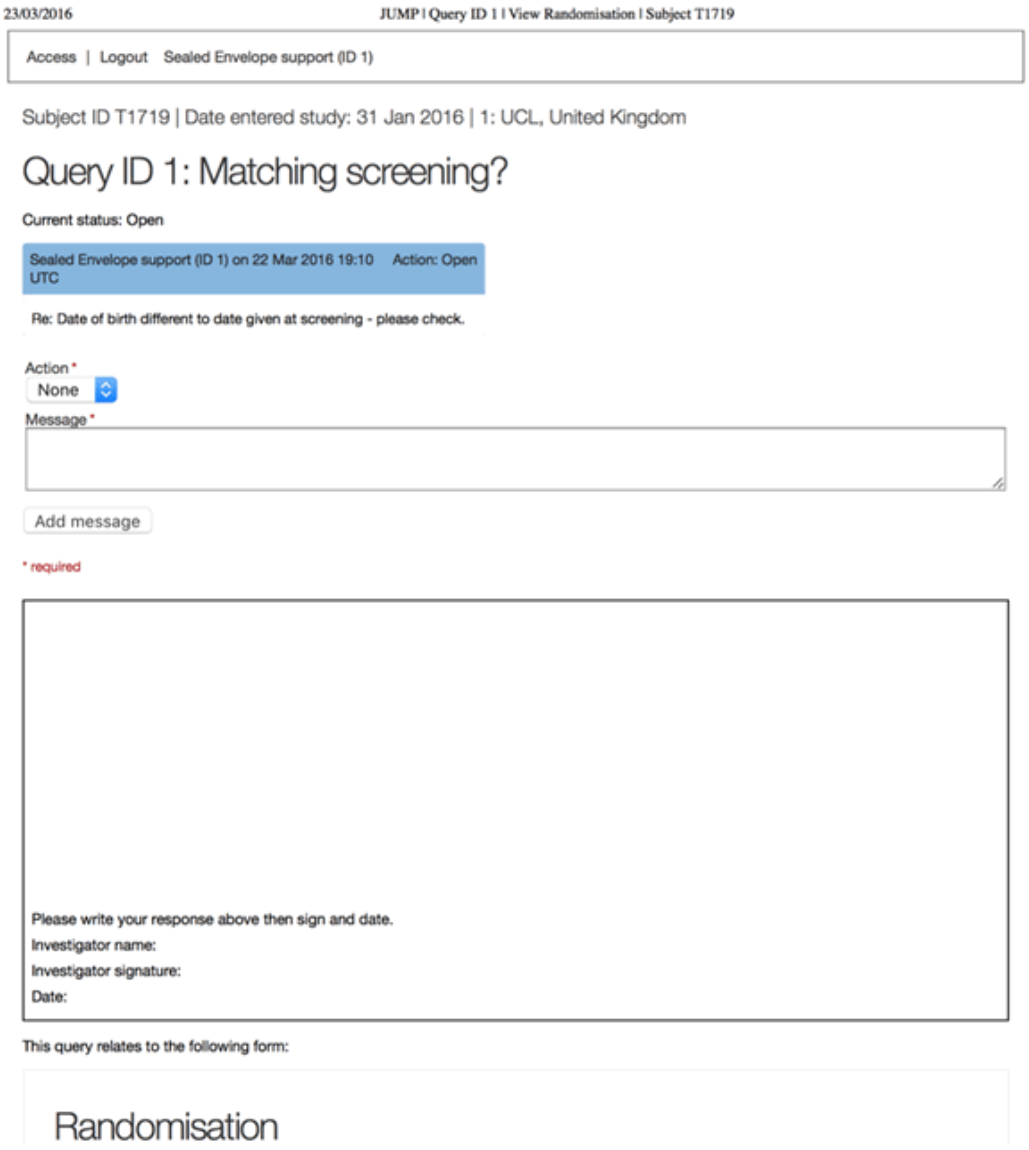


Figure 18.3: Response box shown when printing a query

Listing queries

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

Chapter 19

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.

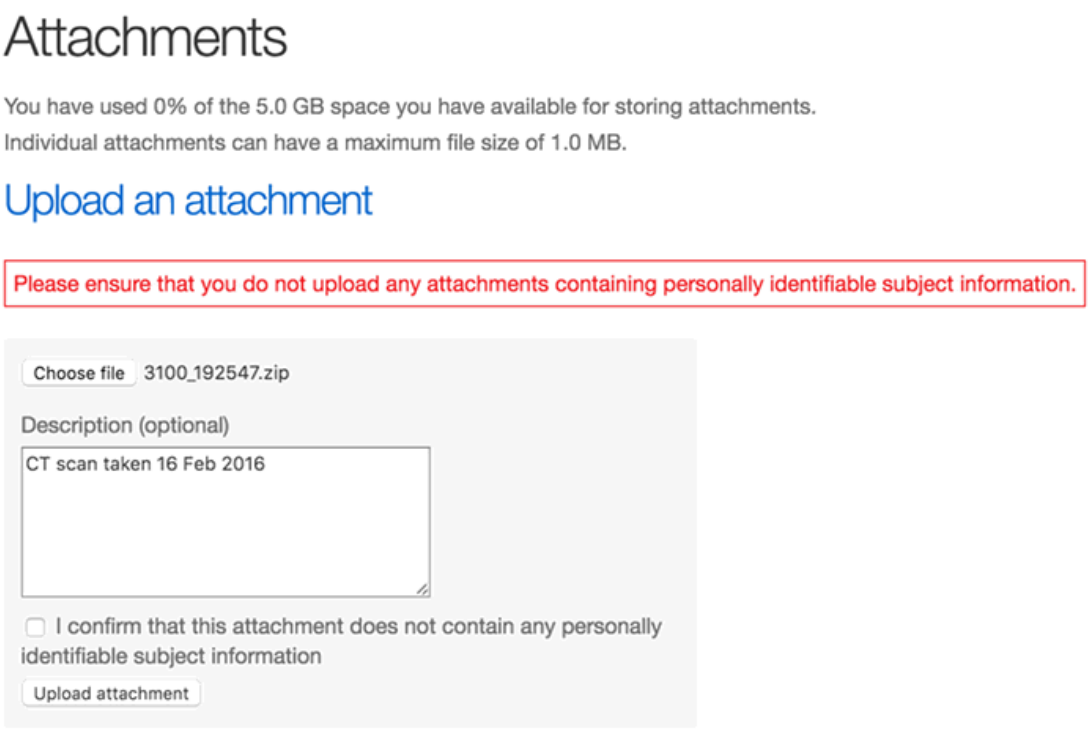


Figure 19.1: Uploading an attachment

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

Viewing and downloading existing attachments

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

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

Deleting an attachment

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

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

Running out of space

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

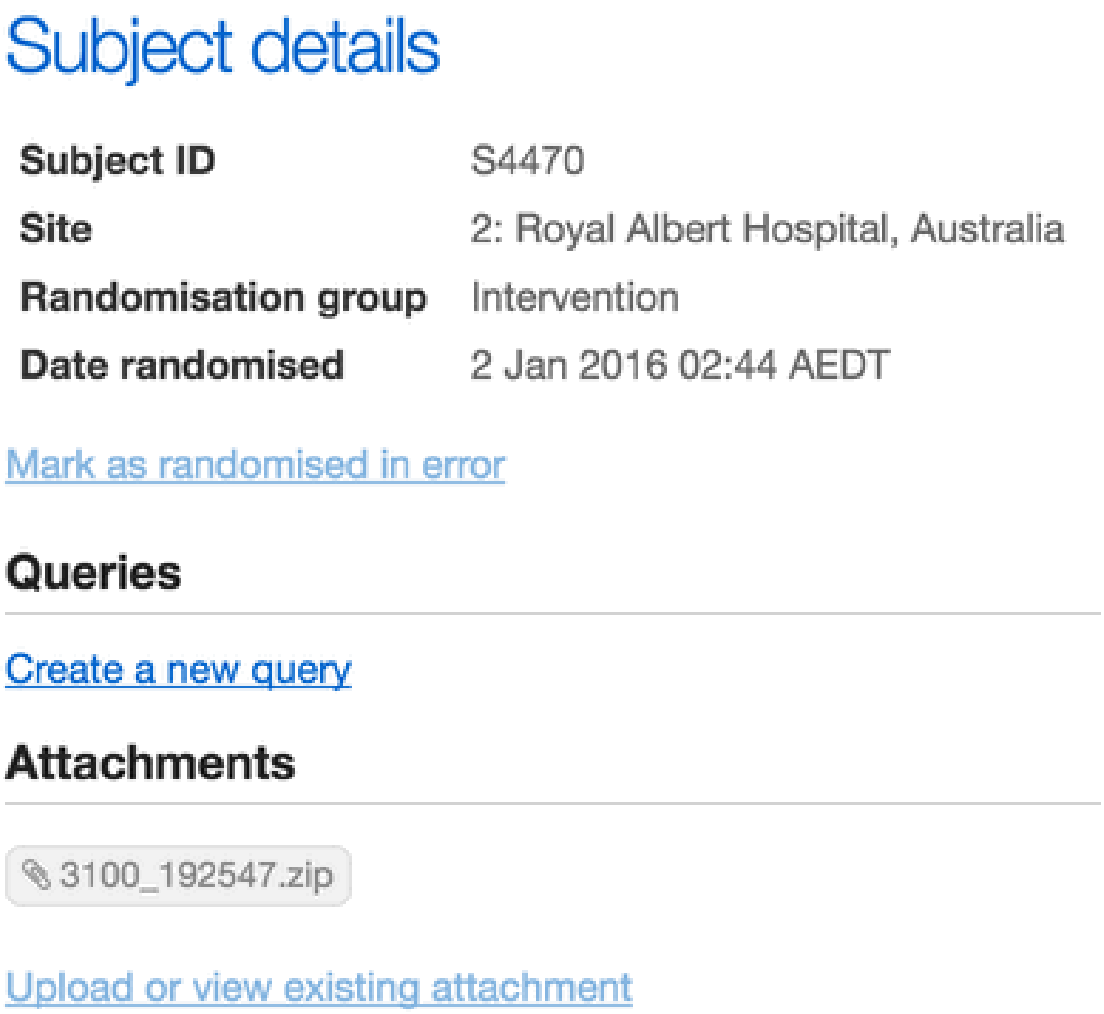


Figure 19.2: An attachment listed in the subject view

Figure 19.3: Table of attachment details

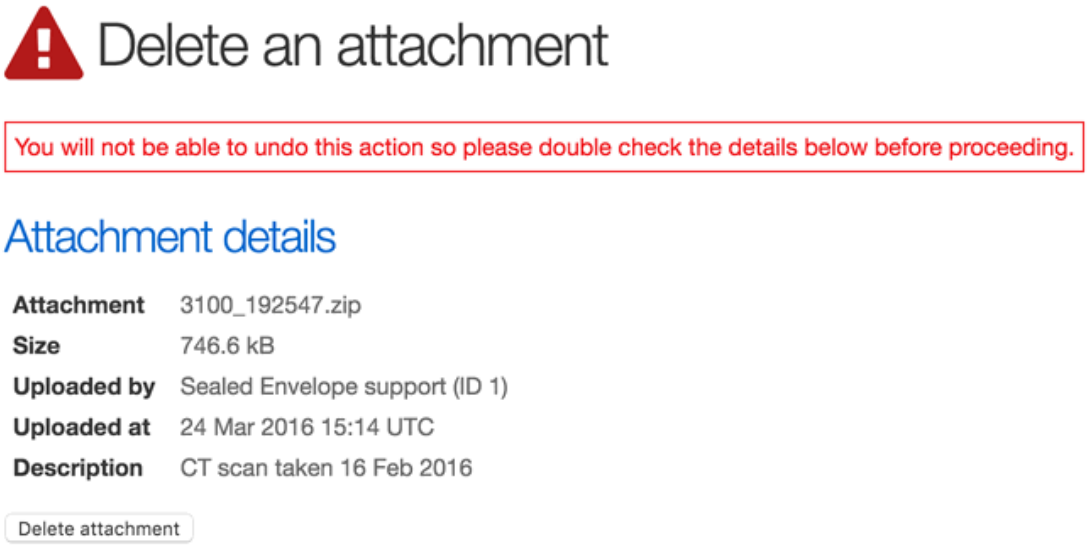


Figure 19.4: Deleting an attachment

Chapter 20

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.

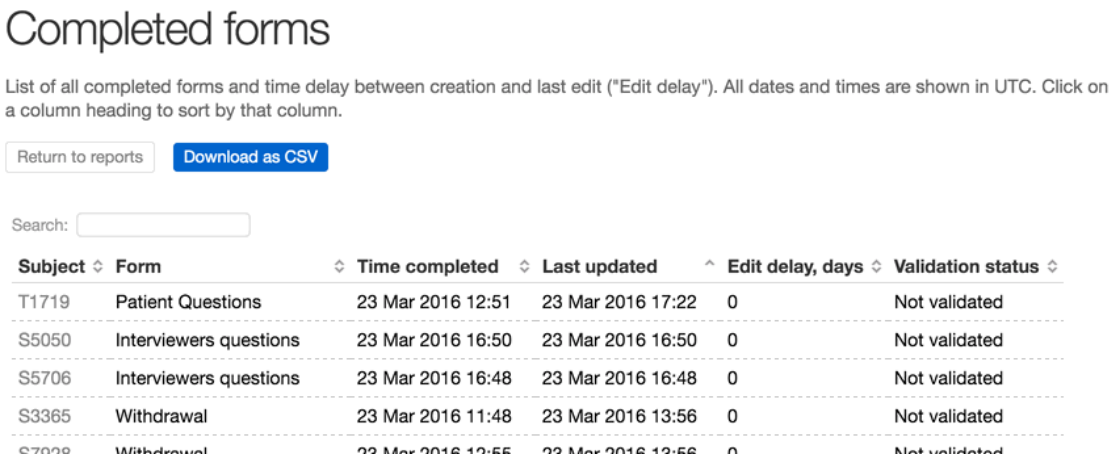


Figure 20.1: Viewing a report

Chapter 21

Downloads

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

Data dictionary

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

Encrypted PII fields

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

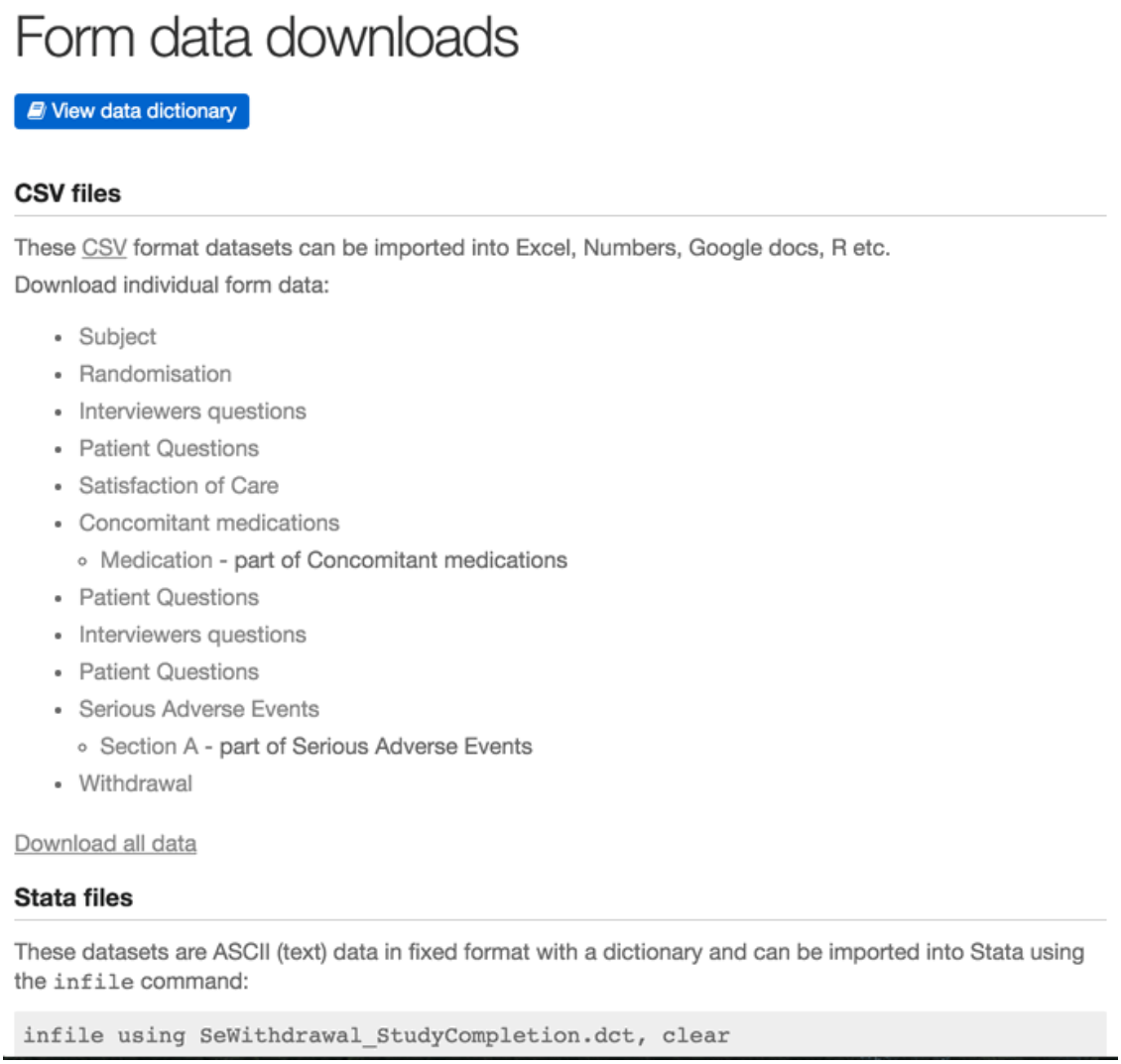


Figure 21.1: Form data download page

Form data dictionary

Download form data

Data types are specified as MySQL data types.

Subject

Database table name is **patient**.

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

Figure 21.2: Form data dictionary

CSV format

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

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

Figure 21.3: Viewing CSV file in spreadsheet

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

Subforms

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

Stata format

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

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

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

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

Example

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

```
dictionary {
  str244 identifier `"Patient identifier"'
  long id `"id"'
  long patientId `"Subject id"'
  str244 userIdentifier `"User who created row"'
  str244 lastUserIdentifier `"User who last updated row"'
  str244 created `"Timestamp for row creation (UTC)"'
  str244 updated `"Date & time of last update to row (UTC)"'
  str244 question1 `"Sex - Questions"'
  str244 question2 `"Marital status - Questions"'
  str244 question3 `"If other, please specify - Questions"'
  str244 question4 `"Have you had any previous episodes of depression? - Depression"'
  str244 question5 `"If so, how many - Depression. Number (up to 2 digits)"'
  str244 question6 `"Duration of current episode in weeks - Depression. Number (up to 3
    digits)"'
  str244 question7 `"Are you using any treatments for depression at the moment? -
    Depression"'
  str244 question8 `"Treatment/Medication Name - Depression"'
  str244 reasonForEdit `"Reason for editing row"'
  str244 notes `"Notes"'
  str244 validationOverrides `"Justifications for overriding validation"'
  str244 validationStatus `"Validation status"'
  str244 validationNotes `"Validation notes"'
  str244 _dateEntered `"Date of study entry yyyy-mm-dd"'
  str244 _dateWithdrew `"Date of withdrawal from follow-up - Withdrawal."'
  str244 _site `"Site"'
  str244 _country `"Country"'
```

```
  str244 _visit `"Visit"'
}
"T5617" 1 1 "Sealed Envelope support (ID 1)" "Sealed Envelope support (ID 1)" "2016-03-23
    11:36:19" "2016-03-23 11:36:19" "Male" "Partner - Living with" "" "Yes" "3" "3" "No"
    "" "" "" "{}" "Not validated" "" "2015-12-27" "" "1: UCL" "United Kingdom" "Baseline"
"T1719" 2 2 "Sealed Envelope support (ID 1)" "Sealed Envelope support (ID 1)" "2016-03-23
    12:51:18" "2016-03-23 12:51:18" "Female" "Married" "" "No" "" "2" "No" "" "" "" "{}" "
    Not validated" "" "2016-01-31" "" "1: UCL" "United Kingdom" "Baseline"
```

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

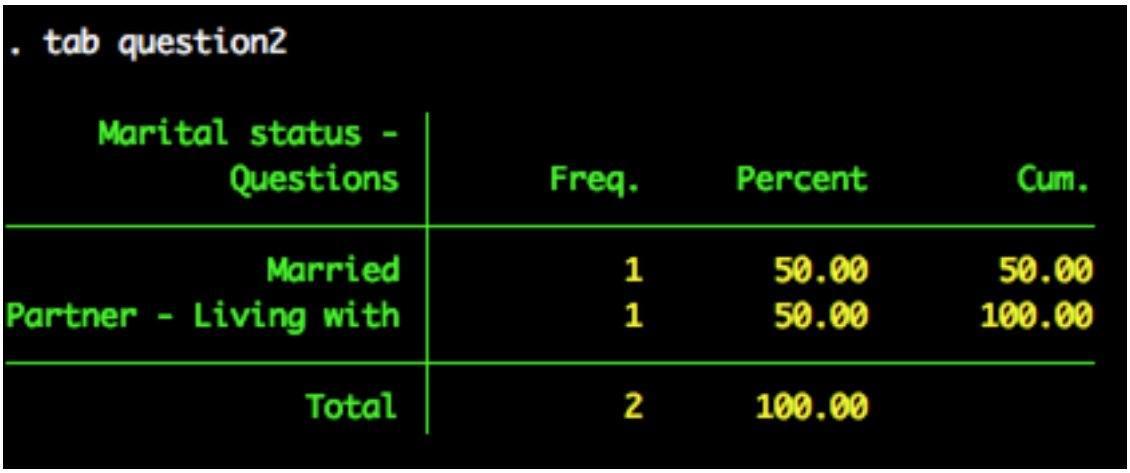
```
  obs:             2
 vars:            25
 size:           404 (99.9% of memory free)
-------------------------------------------------------------------------------
              storage  display     value
variable name   type   format      label      variable label
-------------------------------------------------------------------------------
identifier      str5   %9s                    Patient identifier
id              byte   %12.0g                 id
patientId       byte   %12.0g                 Subject id
userIdentifier  str30  %30s                   User who created row
lastUserIdent~r str30  %30s                   User who last updated row
created         str19  %19s                   Timestamp for row creation (UTC)
updated         str19  %19s                   Date & time of last update to row (UTC)
question1       str6   %9s                    Sex - Questions
question2       str21  %21s                   Marital status - Questions
question3       str1   %9s                    If other, please specify - Questions
```

Figure 21.4: Form data imported into Stata

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

Conversion notes

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



```
. 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 21.5: Tabulating imported form data

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

Stata with .do file format

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

Chapter 22

Uploads

CRF data, randomisation lists and code lists may be uploaded from CSV files. Designer and Administrator roles can access this feature via the **Upload** link in the top menu.

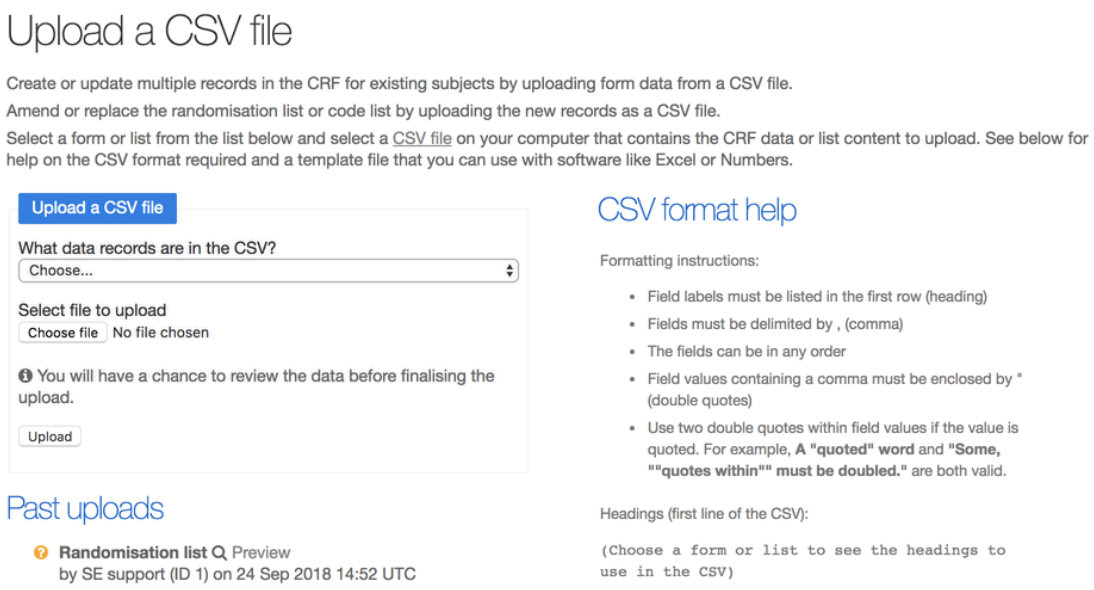


Figure 22.1: Upload page

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.

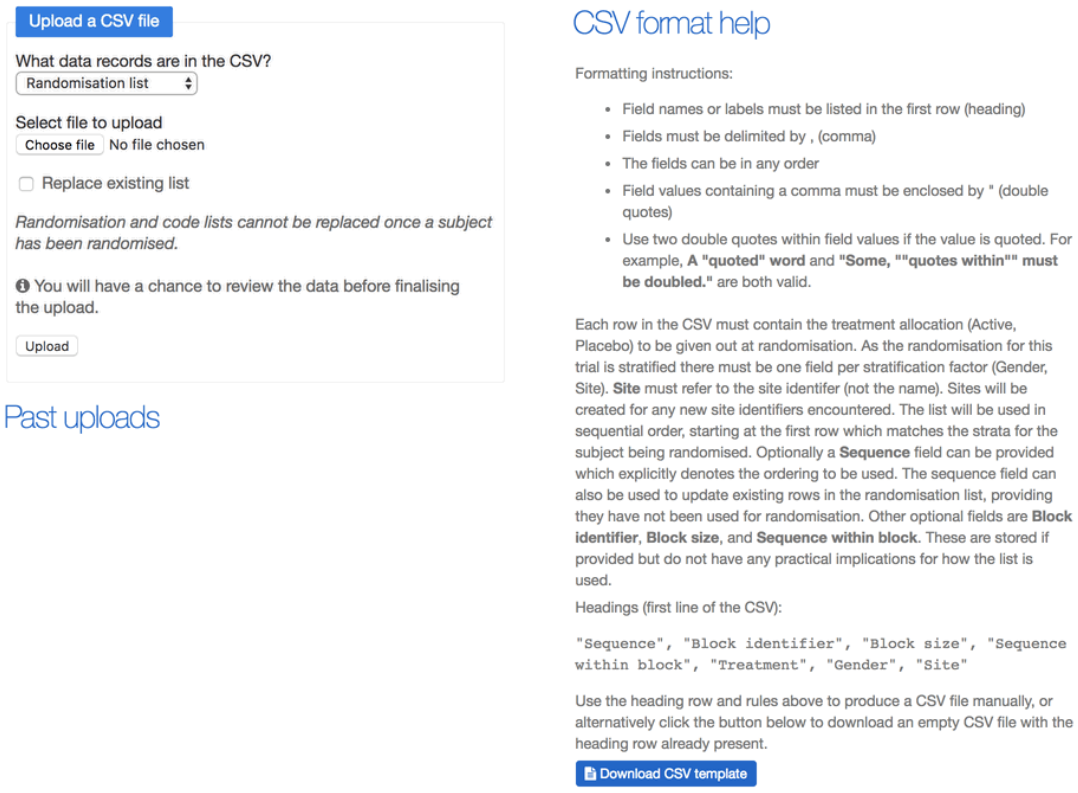


Figure 22.2: Upload randomisation list

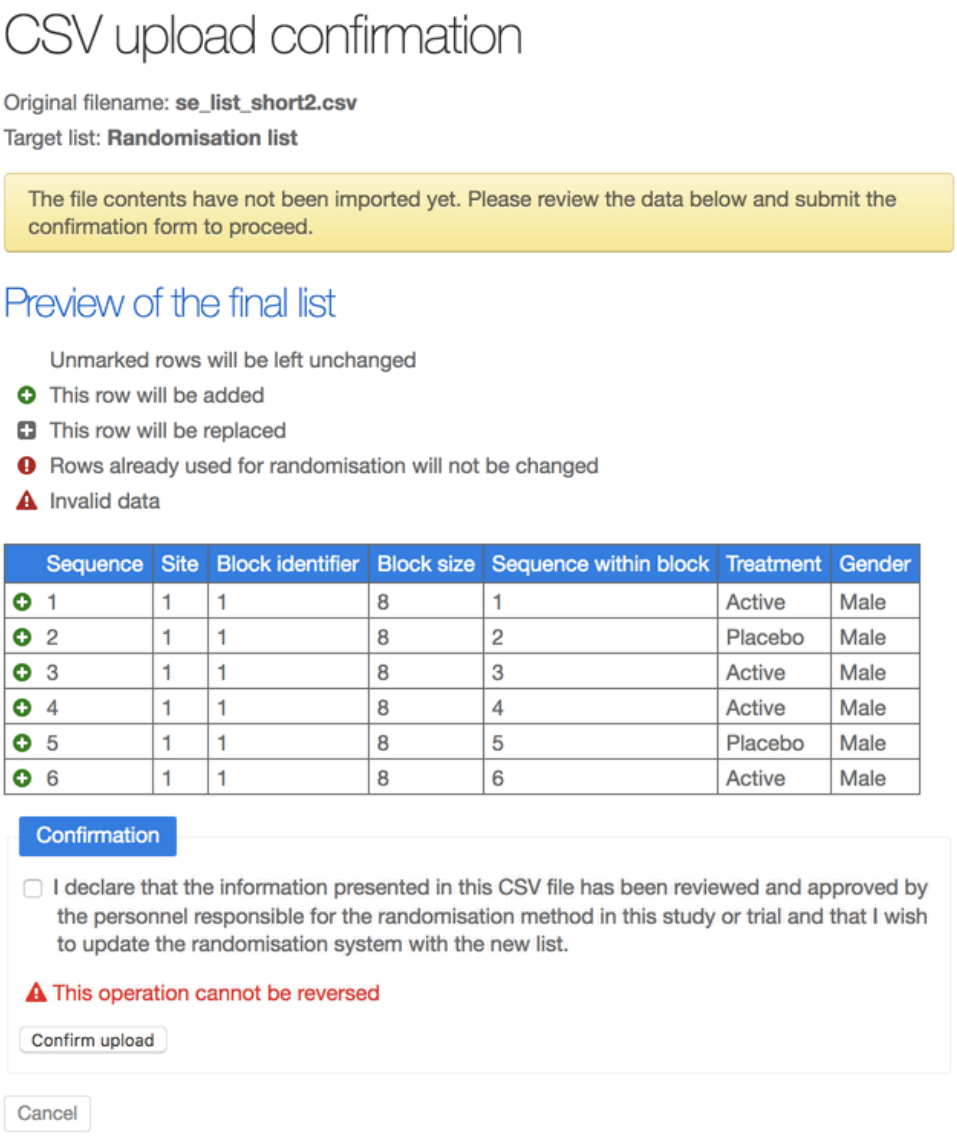


Figure 22.3: Preview randomisation list

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.

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 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

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 block, `Kit block`

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 22.4: Extend randomisation list

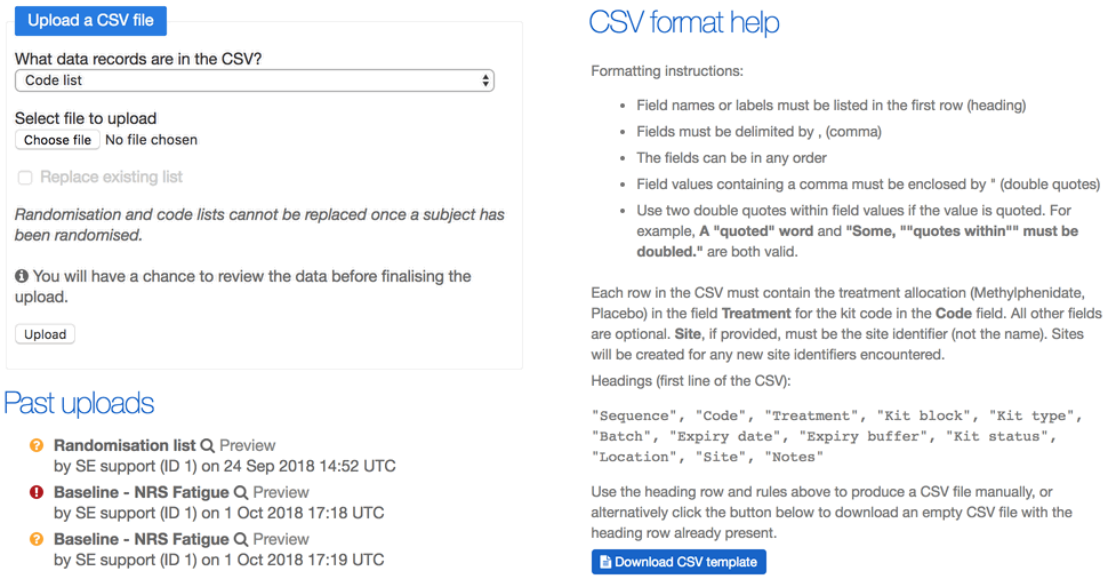


Figure 22.5: Upload code list

- 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`
- 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 instead of being entered manually. This may be useful for uploading data from laboratory results or other data collection systems for instance.

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

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

Figure 22.6: Code list warnings

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.

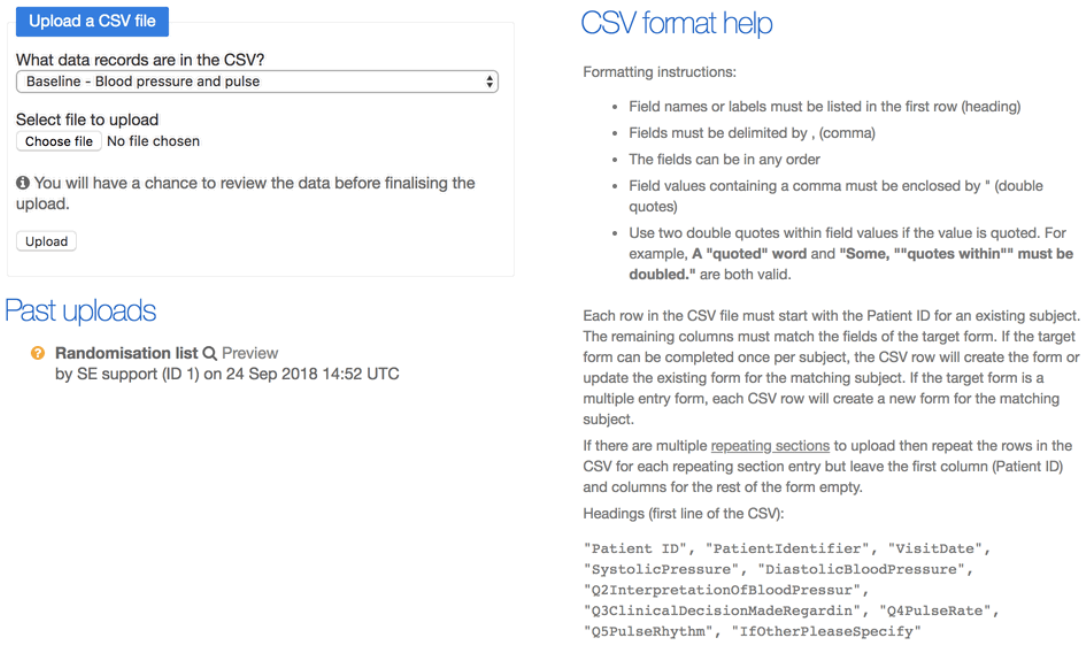


Figure 22.7: Upload form data

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.

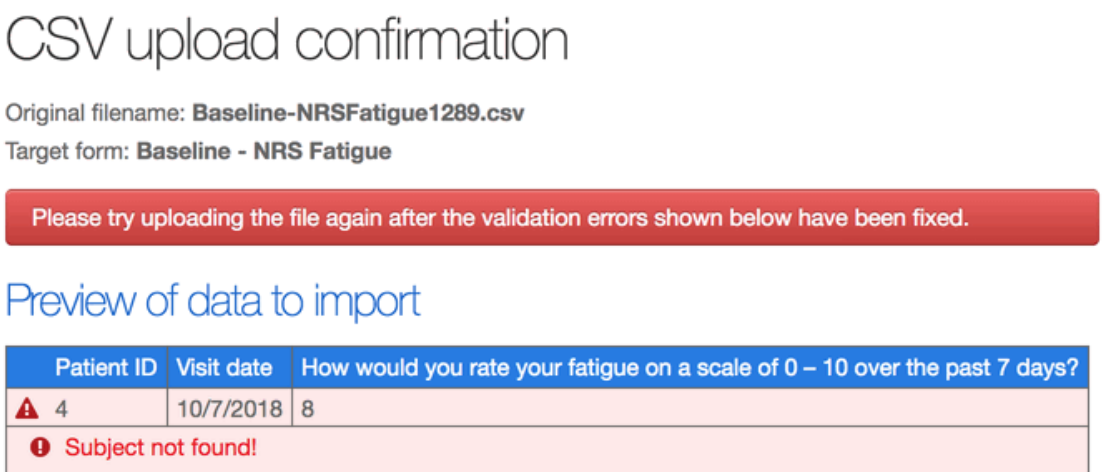


Figure 22.8: Upload form data with errors

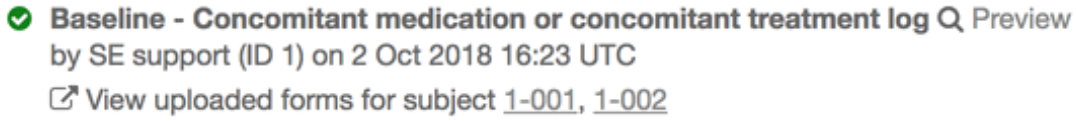


Figure 22.9: Upload links

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 22.10: 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	

Patient ID	Visit date	New medication
☑ 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 22.11: 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.

Chapter 23

Audit trail

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

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

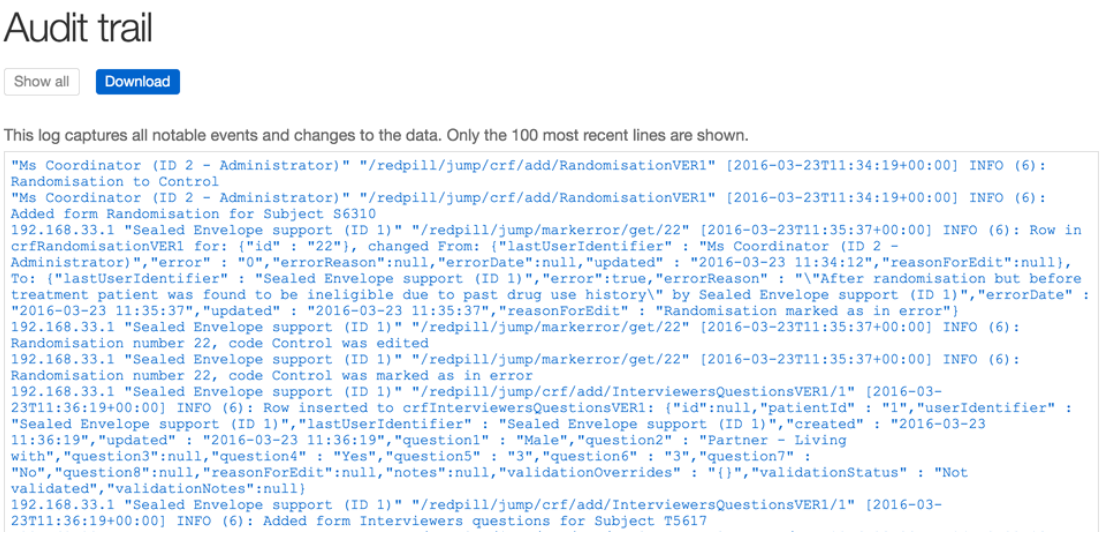


Figure 23.1: Audit trail

- Notice level - usually this will be “INFO (6)”
- Message

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

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

plus a change in the data:

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

Example extract

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

```
     : "Yes","ageRange" : "No","dateWrittenInformedConsentGiven" : "10\/08\/2008","
    validationStatus":null,"validationNotes":null}
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/crf/reviewadd/
    BaselineEligibilityCriteria/1" [2015-10-22T17:45:47+01:00] INFO (6): Added form
    Eligibility Criteria Check At Recruitment for Patient SDN01
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/crf/reviewedit/
    BaselineEligibilityCriteria/1" [2015-10-22T17:48:40+01:00] INFO (6): Row in
    crfBaselineEligibilityCriteria for: {"id" : "1"}, changed From: {"updated" :
    "2015-10-22 17:45:47","reasonForEdit":null,"unstableUnderlyingLungDisease":null,"
    anySeriousComorbidity":null,"systolicBp":null}, To: {"updated" : "2015-10-22
    17:48:40","reasonForEdit" : "Adding some more answers","unstableUnderlyingLungDisease"
     : "No","anySeriousComorbidity" : "Yes","systolicBp" : "No"}
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/crf/reviewedit/
    BaselineEligibilityCriteria/1" [2015-10-22T17:48:40+01:00] INFO (6): Edited form
    Eligibility Criteria Check At Recruitment for Patient SDN01
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/contact/add/Individual" [2015-08-13T10
    :37:45+01:00] INFO (6): Row inserted to contact: {"id":null}
1.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/contact/add/Individual" [2015-08-13T10
    :37:45+01:00] INFO (6): Row inserted to individual: {"id" : "52","title":null,"
    lastName" : "Kinnear","firstName" : "James","jobTitle" : "Layman","responsibility":
    null,"notes":null,"type" : "individual","qualifications":null,"regNo":null,"cv" :
    "0","cvDate":null,"delegationLogReceived" : "0","delegationLogReceivedDate":null}
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/contact/add/Individual" [2015-08-13T10
    :37:45+01:00] INFO (6): Added contact James Kinnear
```

Chapter 24

Settings

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

Review step

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

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

> Note the review step is always enabled for randomisation forms

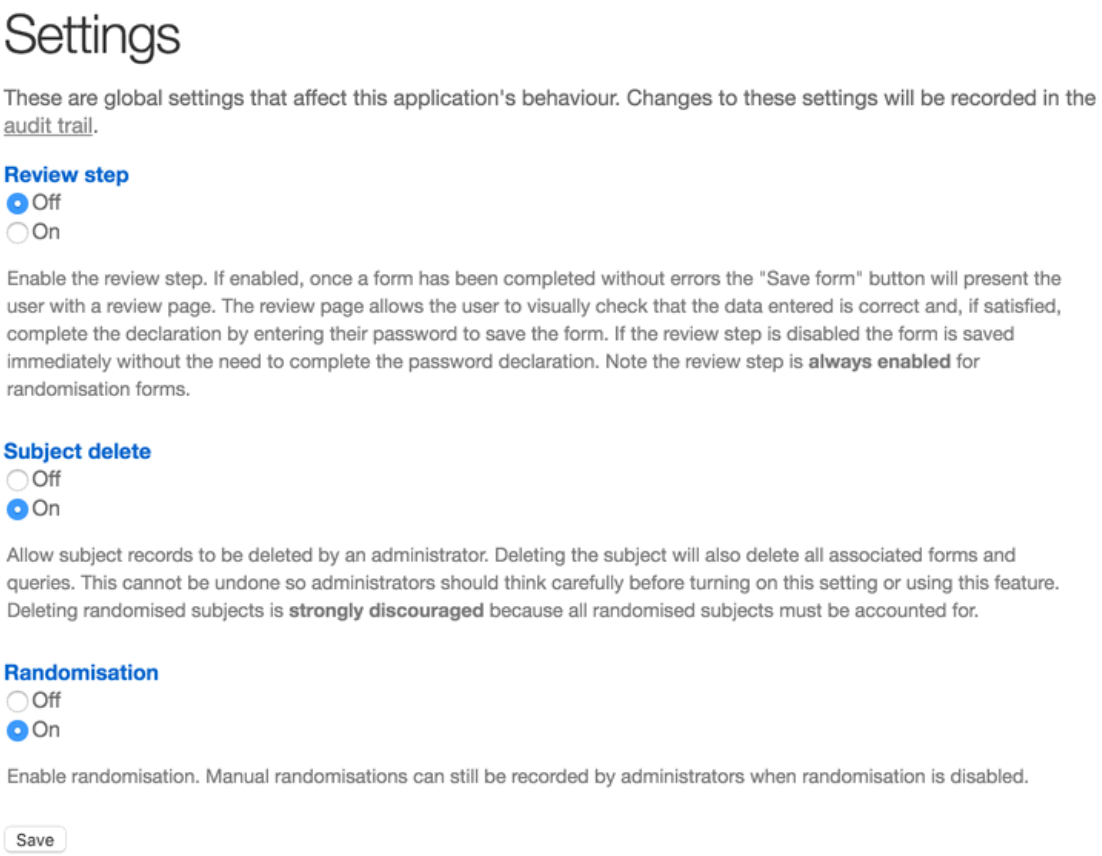


Figure 24.1: Settings page

Investigator edit

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

Subject delete

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

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

If a subject was randomised in error mark them as such rather than deleting the record.

Form delete

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

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

Randomisation

Randomisation systems and Red Pill systems with a randomisation form can turn randomisation on or off. When randomisation is disabled, administrator accounts can still record manual ran-

domisations. This may be useful, for instance, if offline randomisations have been carried out due to the Sealed Envelope website being unavailable.

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

Chapter 25

Specification

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

- Names of forms that can be completed multiple times per patient.
- The timetable used by the form scheduling feature, showing when visits are due and the forms within each visit.
- Whether any of the forms can be self-completed by subjects, and information about custom text shown to the subject in invitation emails and after logging in.
- Details on randomisation method used, treatment groups, allocation ratio, strata, blinding, code list length, randomisation limit, data collected at randomisation (where relevant).
- Format of randomisation, unblinding and kit assignment email notifications.
- If attachments are enabled, the maximum file size allowed and percent of storage allowance used.
- The 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 25.1: Specification page

Chapter 26

Making changes to the specification

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

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

Change # Sequential change number 1, 2, 3, …
Visit Name of visit, e.g. *Baseline*
Form Name of form, e.g. *ECG results*
Item / Question The question to be added or changed, eg. *1. ECG - Has a baseline ECG been taken?*
Change type One of:

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

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

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

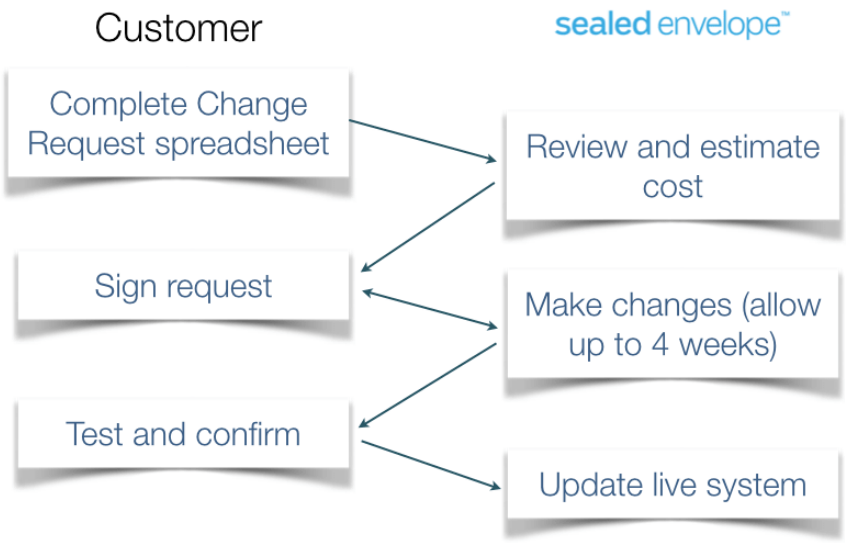


Figure 26.1: Flowchart for change request process

- Single line text
- Paragraph text - a text box allowing long text entries
- Encrypted text - a text box whose value will be stored in an encrypted format
- Number
- Date
- Yes/No
- Category - please list all categories eg, Mild; Moderate; Severe
- Clock time - the time of day in 24hr clock format (e.g. 13:15)
- Elapsed time - a duration in hours and minutes (e.g. 30:50)
- Explanation - explanatory text (e.g. The following questions are about your health)

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

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

Chapter 27

Minimisation

Minimisation[1] is a method of randomisation that allocates subjects to the treatment group that best maintains balance in stratifying factors. It is effective even at small sample sizes and with multiple stratification variables.

Example

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

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

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

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.

Stratifying 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 method[2] 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.

Stratifying 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

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

of $3 + 2 = 5$.

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

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

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 method[3] 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 Q1, Q2, and Q3, where minimisation to Q1 would result in an allocation of the placebo and minimisation to either Q2 or Q3 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.

[3] Kuznetsova 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

Chapter 28

Random permuted blocks

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

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

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

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

Stratification

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

```
___ | ____________________________________________________________________________
____________________________________________ |
Men | [A B A B], [A A B B B A], [B B A B A A], [B A A B] |
Women | [B B A A B A], [A B B A], [B B A A], [A B B A] |
```

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

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

Choice of block size

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

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

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

Chapter 29

Simulations

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

How are the simulations produced?

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

Data specification document

Here is an example of a data specification:

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

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

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

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

Analysing the simulated data

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

Example

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

First we import the simulated dataset.

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

Now lets start exploring the dataset.

```
. tab gender

     gender |      Freq.     Percent        Cum.
------------+-----------------------------------
     Female |        124       31.00       31.00
       Male |        276       69.00      100.00
------------+-----------------------------------
      Total |        400      100.00
```

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

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

     +-------------------------------------------------------------+
```

```
     | initials   gender   severity          dob            agegroup |
     |-----------------------------------------------------------------|
  1. |       QO     Male       High   08/08/2001   6.5 years or over |
  2. |       MT     Male        Low   29/09/2002   6.5 years or over |
  3. |       YZ     Male       High   06/12/2003   6.5 years or over |
  4. |       PK     Male        Low   15/11/2009          <6.5 years |
  5. |       MH   Female       High   29/09/2003   6.5 years or over |
     +-----------------------------------------------------------------+
```

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

```
. tab gender group

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


. tab severity group

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


. tab agegroup group

                  |         group
         agegroup |    Active    Control |     Total
------------------+----------------------+----------
```

```
6.5 years or over |        94         96 |       190
       <6.5 years |       106        104 |       210
------------------+----------------------+----------
            Total |       200        200 |       400
```

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

```
. tab siteid group

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

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

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

```
}
```

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

```
. tab group if Control < Active

      group |      Freq.     Percent        Cum.
------------+-----------------------------------
     Active |         20       11.70       11.70
    Control |        151       88.30      100.00
------------+-----------------------------------
      Total |        171      100.00
```

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

```
. cii 171 151

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

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

```
. tab group if Active < Control

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

. cii 156 137

                                                    -- Binomial Exact --
    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+---------------------------------------------------------------
```

```
             |        156    .8782051    .0261849        .8163508    .9250541
```

So again the confidence interval includes the expected proportion 0.875.

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

```
. tab group if Active == Control

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

. cii 73 43

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

The confidence interval includes the expected value of 0.5.

Chapter 30

Randomisation API

The randomisation API allows your server or database programme to perform randomisations using Sealed Envelope or download randomisations on demand. The API is not enabled by default - you must request access to this feature. If enabled, the API username and password will be shown on the specification page. Documentation for developers is available on request.

The API is used by the Open Clinica Randomize module to perform randomisation from within Open Clinica.