sealed envelope™

Randomisation

Version 10

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Contents

Chapter 1

Overview

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

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

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

This documentation applies to version 10, released 25th September 2015.

Chapter 2

Getting started

Investigator and randomisation accounts

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

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

Once you access a trial you will be able to see previous randomisations at your site and perform randomisations yourself.

Administrator accounts

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

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

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

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

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

Chapter 3

Randomising

For trials set-up for internet randomisation a **Randomise** link will be shown in the left-hand menu or a **Randomisation** form will be present in the CRF. Either route takes the user to the randomisation form that requests relevant patient 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 patient 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 patient 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 patient with the same details has previously been randomised (duplicate).

Telephone randomisation

For trials set-up for telephone randomisation the user may randomise a patient 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

Figure 3.1: Result of randomising a patient

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

Randomisation limit

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

Randomisation disabled

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

Randomisation form

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

Chapter 4

Viewing and downloading randomisations

Viewing

For trials set-up for internet randomisation only, clicking the **Randomisations** link in the left-hand sidebar 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 **Patients** link in the left-hand sidebar will display a list of patients. Randomised patients can be identified from the **Date randomised** column.

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

Clicking one of the randomisations or patients in the list displays more detail for that record. A link will be displayed to mark as randomised in error if the patient has been randomised. Some trials may also have a link to unblind the randomisation.

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

Downloading

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

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

- id: primary key, unique id
- Parent patient. Foreign key: patient table.id. In Red Pill applications this is the id of the patient that the randomisation belongs to
- Patient identifier: unique patient identifier, may be user entered or generated
- User who created row: the name and user id of the randomiser
- User who last updated row: the name and user id of the person who last edited the randomisation
- Date & time of randomisation
- Randomisation code: this will be the treatment group for unblinded trials
- Unblinded?: has the patient been unblinded? 0=no, 1=yes
- Reason for unblinding: the reason entered when the randomisation was unblinded
- Date unblinded
- Manual randomisation?: was this a manual randomisation?
- Randomised in error?: was the patient randomised in error? 0=no, 1=yes
- Reason marked in error
- Date marked error: the date the randomisation was marked as in error
- Timestamp for row creation
- Date & time of last update to row
- Reason for editing row
- Notes
- Justifications for overriding validation: reasons for overriding validation errors
- Validation status: forms may be marked as 'Not validated', 'Validated', or 'Data unusable'
- Validation notes: notes recorded when changing the form validation status
- Date entered study
- Date withdrew
- Site: name of site
- Country
- Visit: the visit that the form is associated with

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

Chapter 5

Editing randomisations

Randomisation forms may be edited but note the following:

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

Chapter 6

Randomised in error

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

Randomisations should only be marked as in error when a mistake has been made, such as randomising ineligible patients or randomising the same patient 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. Marking in error cannot be undone, so care should be taken to ensure the correct record is chosen by double checking the patient identifier shown in the heading. The user will be asked to enter a reason and their password to confirm the need for marking as in error.

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

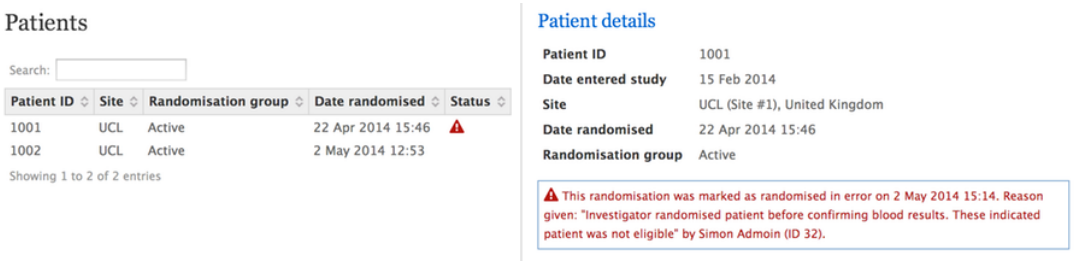


Figure 6.1: A randomisation marked in error

Chapter 7

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 patient 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 patients/randomisations list, then the **Unblind** link in the patient 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.

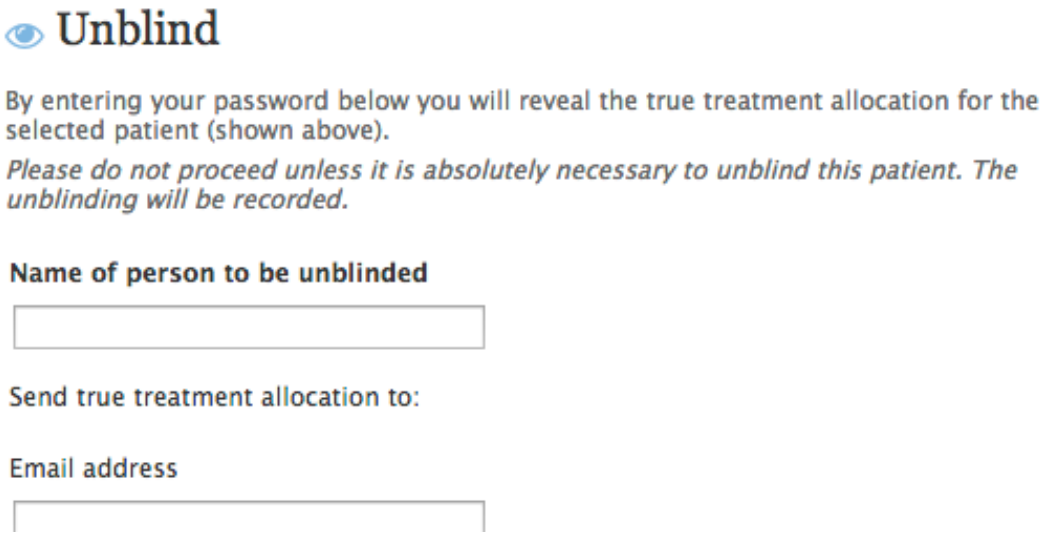


Figure 7.1: Unblinding a designated person

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

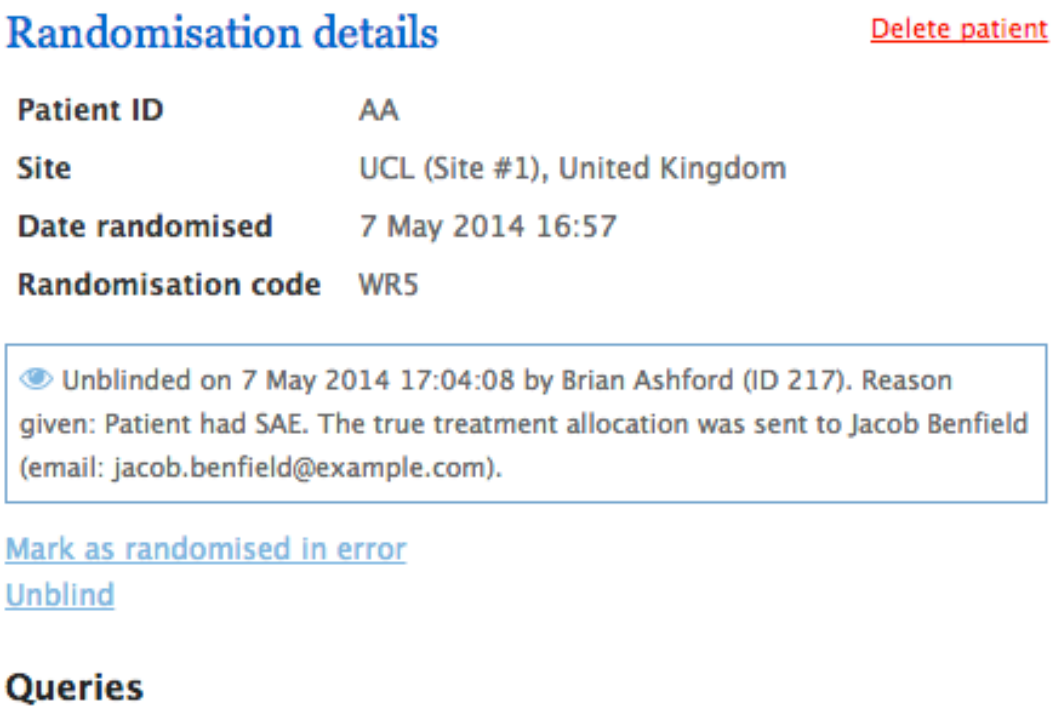


Figure 7.2: An unblinded patient record

Chapter 8

Code lists

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

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

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

Viewing a code list

For trials that have a code list, a **Code list** link will be shown in the left-hand sidebar to administrators. The list can be searched in the same way as the randomisations. Some trials have expiry dates on codes - these are shown in the list if this option is enabled.

Updating

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

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

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

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

Downloading

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

```
id,randomId,siteId,block,expiryDate,code,onSite,used,dateUsed,siteName
1,7,23,2000,2012-11-29,2000/21,1,1,"2007-04-18 12:45:43",Bath
2,6,23,2000,2012-11-29,2000/22,1,1,"2007-04-14 22:12:17",Bath
3,,23,2000,2012-11-29,2000/23,1,0,,Bath
4,,23,2000,2012-11-29,2000/24,1,0,,Bath
5,8,23,2000,2012-11-29,2000/25,1,1,"2007-04-23 20:37:12",Bath
6,,23,2000,2012-11-29,2000/26,1,0,,Bath
7,13,23,2000,2012-11-29,2000/27,1,1,"2007-04-28 22:59:45",Bath
8,,23,2000,2012-11-29,2000/28,1,0,,Bath
9,,,2001,2011-12-30,2001/21,0,0,,
10,,,2001,2011-12-30,2001/22,0,0,,
```

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

id Unique index number (primary key)
randomId If used, the id of the randomisation record the code was assigned to

block Block id
code Randomisation code
notes Notes
onSite Is randomisation code on site and available for randomisation? 0=No, 1=Yes
siteId Site number - location or intended location of treatment linked to randomisation code
siteName Name of site
used Has randomisation code been used? 0=No, 1=Yes
dateUsed If used, Date and time randomisation code used

Chapter 9

Sites

Trial sites (centres) must be added to the system before adding a patient or randomising, completing forms, updating a code list, or creating investigator accounts. Sites must also have their status set to either *Authorised to recruit patients* or *Recruiting patients* before patients can be added. The site number may be used in some trials to create a patient identifier of the form `SSNNN` where `SS` is the site number and `NNN` is a sequential number (either within or across sites).

Administrators can add sites by clicking on the **Contacts** link in the left-hand sidebar, followed by the **New site** link.

Note that sites **may not be deleted** once they are referenced by another record in the database (e.g. when a patient form has been completed for a patient at that site).

The contacts help contains some more information on managing contacts.

Figure 9.1: Adding a new site

Chapter 10

Contacts

Clicking on the **Contacts** link in the the left-hand sidebar takes the user to the trial contact pages. The user can click on the **A-Z** links to restrict contacts by name.

In addition a search facility is available in the top right hand corner of the page. This can be used for a general search through the contacts by typing in a name or address into the search box. Alternatively the associated drop down bar may be used to find contacts of a chosen type, such as investigators, sites or other organisations. Exact matches are generated by enclosing search terms in double quotes. Exact match searches are case sensitive whereas normal searches are not.

Clicking on a contact or submitting a search that returns just one contact will cause more detailed information about that contact to be displayed on the right hand side of the screen.

Adding contacts

Contacts can be added by clicking on the **New person**, **New organisation**, or **New site** links that appear near the top of the page. A form will be displayed appropriate to the type of contact. Completing the form and clicking the submit button will create the new contact.

Once the contact is created additional information such as addresses, phone numbers and email addresses may be added to the contact. This is achieved by first viewing the contact, then clicking on the **Address**, **Number**, or **Email** links shown above the contact details.

Contact events can be added with the **Event** link. Contact events are useful for recording notes of conversations, meetings or other events. Records of monitoring visits can also be added to site contacts.

Links are used to create relationships between different contacts. Related people or organisations are shown when viewing the details of a contact. At least one side of the link must

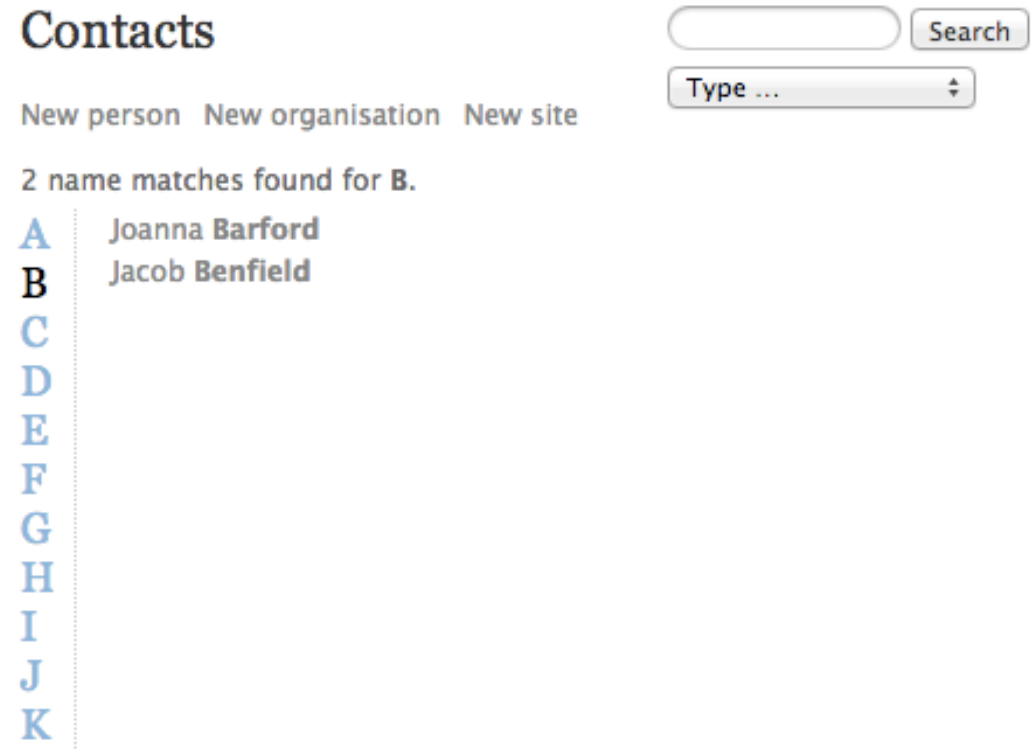


Figure 10.1: List of contacts starting with B

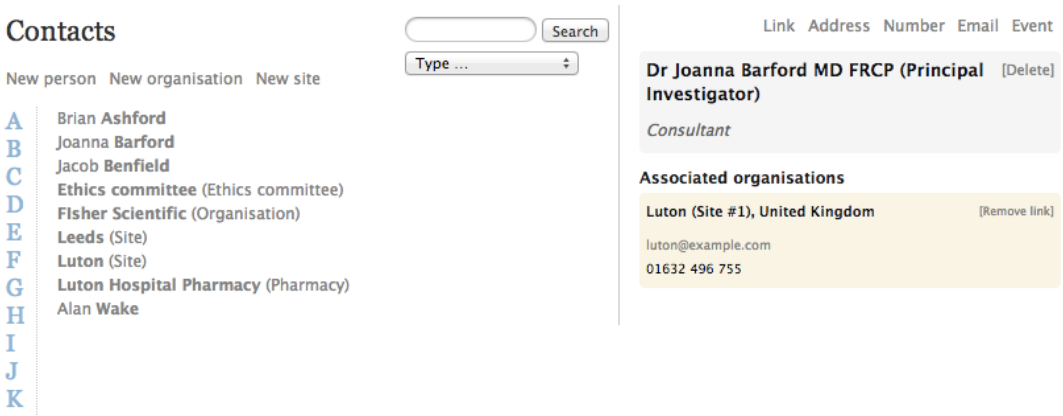


Figure 10.2: Viewing details of a contact

Figure 10.3: Creating a new person contact

involve an organisation - two people may not be linked. To add a link view a contact and use the **Link** link to pick the related contact.

Editing contacts

To edit a contact it must first be viewed. The contact may then be edited by clicking on its name in the right-hand panel. Similarly, additional information may be edited by simply clicking on it. Use the contact's **[Delete]** link to delete the record from the database.

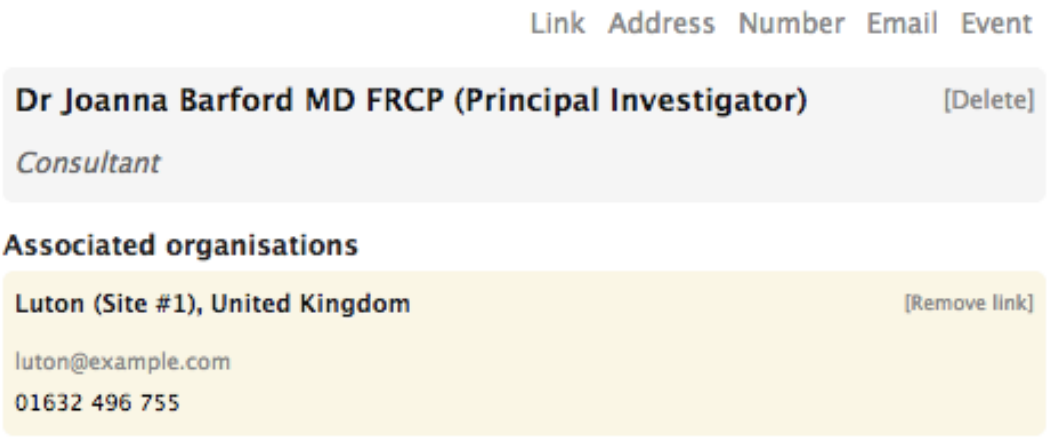


Figure 10.4: Adding additional information to an existing contact

Chapter 11

Queries

Queries are intended to be used by administrators to raise questions about the form data for investigators to answer and for investigators to notify administrators of any issues they are aware of in completed forms. Queries can be linked generally to a patient, or more specifically to a particular form for a patient. 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 patient details panel or when viewing a form, by clicking on the **Create a query** link. The query must be given a title and an initial message. To link the query to a specific Form, choose the appropriate form from the related form drop-down control. Once it has been created, the query will be shown on the patient 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 patient details panel.

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

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

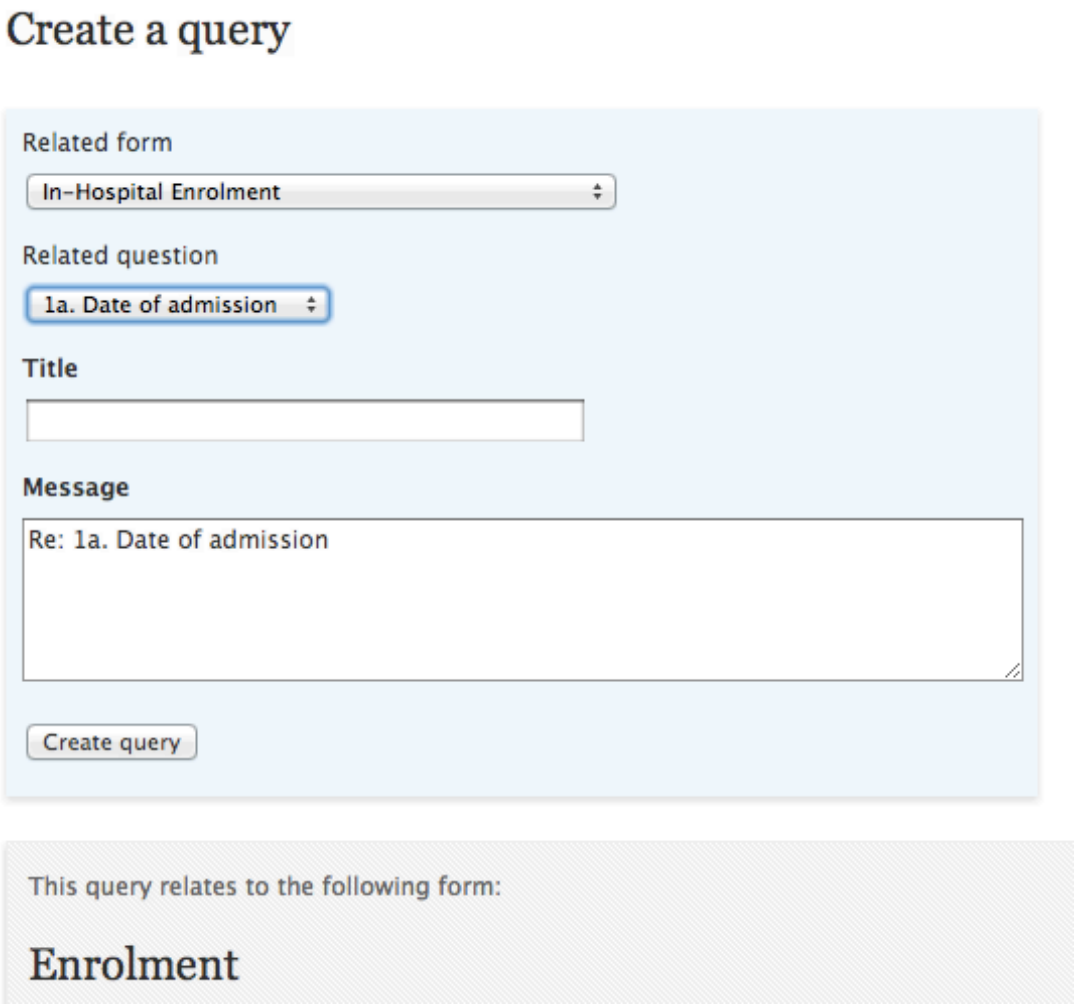


Figure 11.1: Creating a new query

may also re-open a closed query by setting the action to 'Reopen' when adding a new message to it.

Figure 11.2: Viewing an open query

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:

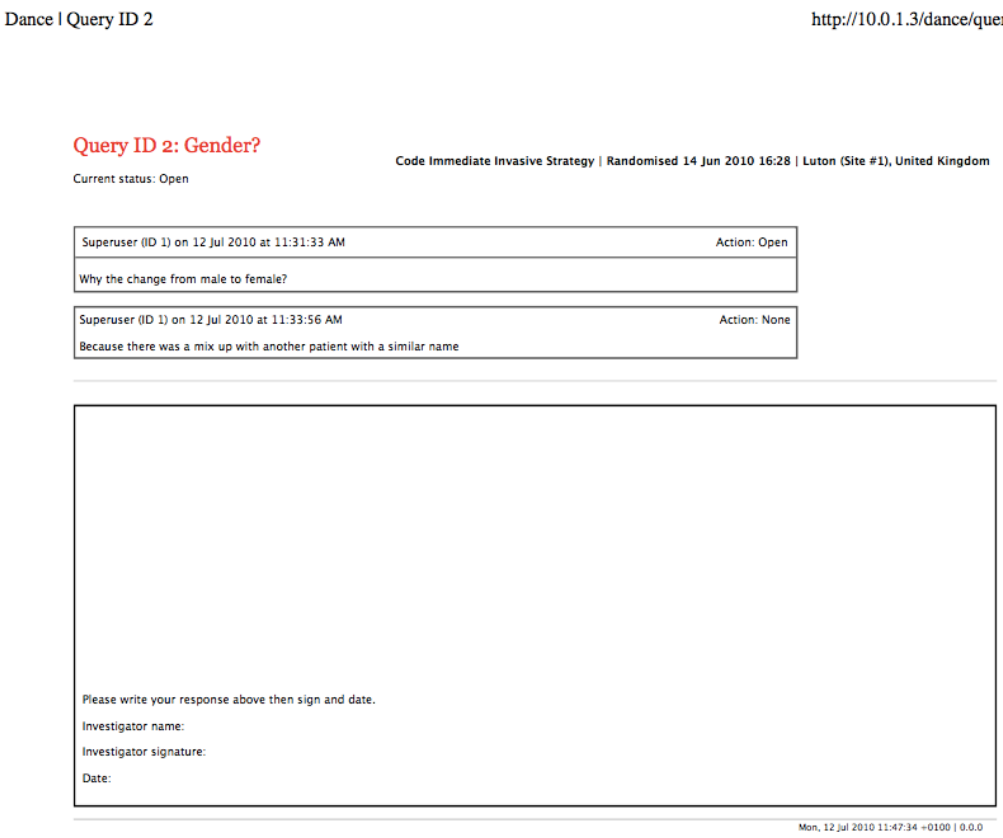


Figure 11.3: Response box shown when printing a query

- On creation: all administrators, and all investigators at the same site as the patient 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 <automated@sealedenvelope.com>
Subject: [Trialname] Query updated
Date: Thu, 22 Oct 2009 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 2009 15:43 Europe/London (GMT
    +0100).
```

Listing queries

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

Chapter 12

Reports

Various reports summarising data-entry and randomisation activity and site status are available by clicking on the **Reports** link in the left-hand sidebar. 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.

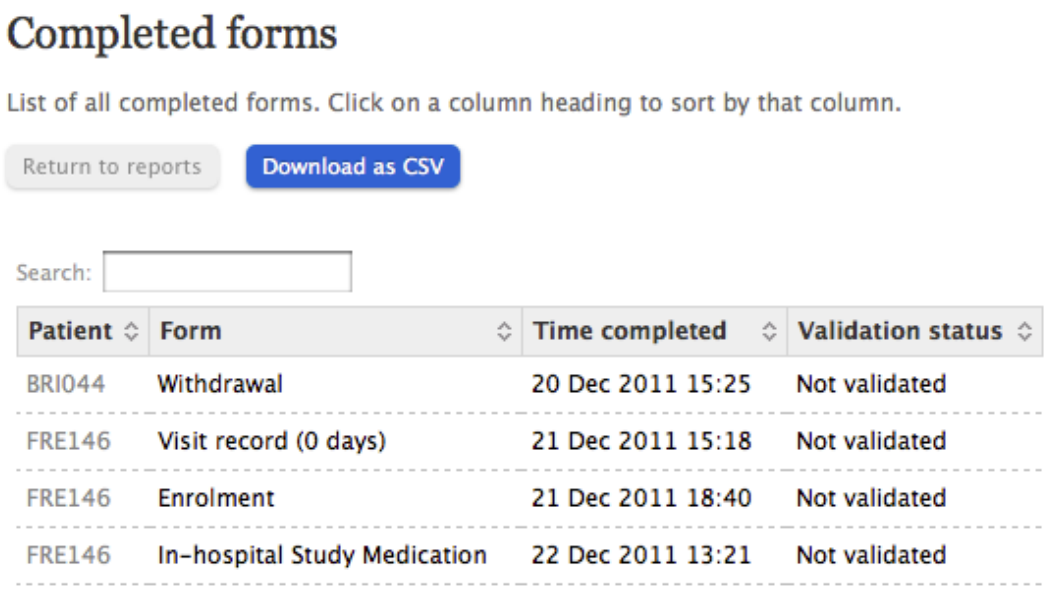


Figure 12.1: Viewing a report

Chapter 13

Downloads

CRF data may be downloaded in either CSV or Stata fixed format via the **Download** link in the left-hand sidebar. 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).

CSV format

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

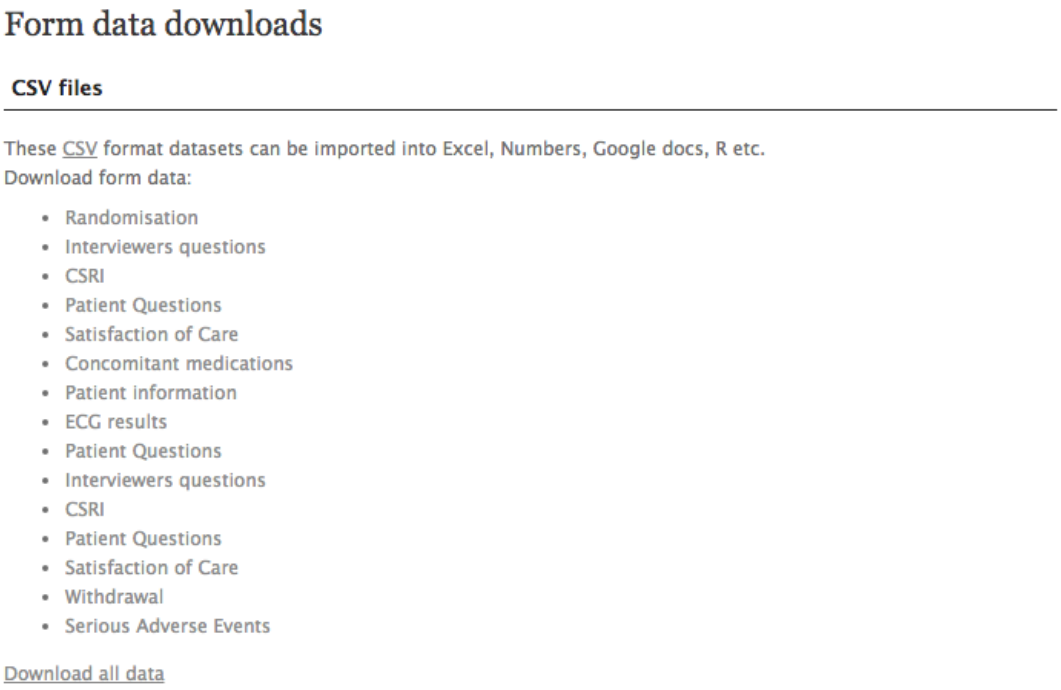
Every file contains a patient identifier field so that data stored in different forms can be linked together.

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 patient identifier field to identify the patient record it belongs to. The data can be easily imported into Stata using the infile command.

For example, to import the withdrawal data the following infile command would be used in Stata:

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



Form data downloads

CSV files

These CSV format datasets can be imported into Excel, Numbers, Google docs, R etc.
Download form data:

- Randomisation
- Interviewers questions
- CSRI
- Patient Questions
- Satisfaction of Care
- Concomitant medications
- Patient information
- ECG results
- Patient Questions
- Interviewers questions
- CSRI
- Patient Questions
- Satisfaction of Care
- Withdrawal
- Serious Adverse Events

Download all data

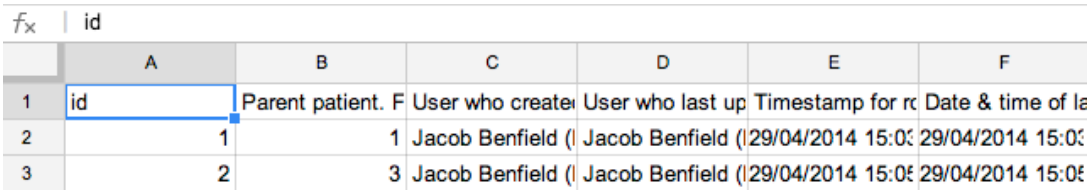
Stata files

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

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

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

Figure 13.1: Form data download page



fx | id

	A	B	C	D	E	F
1	id	Parent patient. F	User who create	User who last up	Timestamp for rc	Date & time of la
2	1	1	Jacob Benfield (I	Jacob Benfield (I	29/04/2014 15:03	29/04/2014 15:03
3	2	3	Jacob Benfield (I	Jacob Benfield (I	29/04/2014 15:05	29/04/2014 15:05

Figure 13.2: Viewing CSV file in spreadsheet

where `SeWithdrawal.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 patients have been entered so far:

```
dictionary {
  long id
  long patientId `"Parent patient. Foreign key: patient table.id"'
  str244 userIdentifier `"User who created row"'
  str244 lastUserIdentifier `"User who last updated row"'
  str244 created `"Timestamp for row creation"'
  str244 updated `"Date & time of last update to row"'
  str244 reasonForEdit `"Reason for editing row"'
  str244 notes `"Notes"'
  str244 validationOverrides `"Justifications for overriding validation"'
  str244 validationStatus `"Validation status"'
  str244 validationNotes `"Validation notes"'
  str244 question1 `"Form details - Site number. Number (up to 3 digits)"'
  str244 question2 `"Form details - Participant number. Number (up to 3 digits)"'
  str244 question3 `"Form details - Date CRF completed. dd/mm/yyyy"'
  str244 question4 `"Questions - Sex"'
  str244 question5 `"Questions - Marital status"'
  str244 question6 `"Questions - If other, please specify"'
  str244 question7 `"Questions - Ethnicity"'
  str244 question8 `"Questions - Employment status"'
  str244 question9 `"Questions - Current or most recent job"'
  str244 question10 `"Questions - Highest level of education completed"'
  str244 question11 `"Depression - Have you had any previous episodes of depression?"'
  str244 question12 `"Depression - If so, how many. Number (up to 5 digits)"'
  str244 question13 `"Depression - Duration of current episode in weeks. Number (up to
     5 digits)"'
  str244 question14 `"Depression - Are you using any treatments for depression at the
    moment?"'
  str244 question15 `"Depression - Treatment/Medication Name"'
  str244 question16 `"Depression - Treatment/Medication Name [additional fields as
    needed]"'
  str244 question17 `"AUDIT - How often do you have a drink containing alcohol?"'
  str244 question18 `"AUDIT - How many drinks containing alcohol do you have on a
    typical day when you are drinking?"'
```

```
  str244 question19 `"AUDIT - How often do you have six or more drinks on one occasion
    ?"'
  str244 question20 `"AUDIT - How often during the last year have you found the you
    were not able to stop drinking once you had started?"'
  str244 question21 `"AUDIT - How often during the last year have you failed to do
    what was normally expected from you because of drinking?"'
  str244 question22 `"AUDIT - How often during the last year have you needed a first
    drink in the morning to get yourself going after a heavy drinking session?"'
  str244 question23 `"AUDIT - How often during the last year have you had a feeling of
     guilt or remorse after drinking?"'
  str244 question24 `"AUDIT - How often during the last year have you been unable to
    remember what happened the night before because you had been drinking?"'
  str244 question25 `"AUDIT - Have you or someone else been injured as a result of
    your drinking?"'
  str244 question26 `"AUDIT - Has a relative or friend or a doctor or another health
    worker been concerned about your drinking or suggested you cut down?"'
  str244 question27 `"ECOG - ECOG performance status"'
  str244 question28 `"Treatment Expectation - Name of treatment"'
  str244 question29 `"Treatment Expectation - To what extent do you think you will
    improve if you receive this treatment?. Number (up to 5 digits)"'
  str244 question30 `"Treatment Expectation - Have you ever received this treatment
    before?"'
  str244 question31 `"Treatment Expectation - If yes, please provide further detail
    about the effect of the treatment on yourself"'
  str244 dateEntered "Date entered study"
  str244 dateWithdrew "Date withdrew"
  str244 siteName "Site"
  str244 countryName "Country"
  str244 identifier "Patient identifier"
  str244 visit "Visit"
}
1 1 "Jacob Benfield (ID 813)" "Jacob Benfield (ID 813)" "2014-04-29 15:03:09"
    "2014-04-29 15:03:09" "" "" "{}" "Not validated" "" "010" "100" "28/4/2014" "Male"
    "Married" "" "White" "Employed" "Landscape gardener" "A level (or equivalent)" "Yes
    " "2" "15" "No" "" "" "1.  Monthly or less" "2.  5 or 6" "0 - Never" "0 - Never" "0
     - Never" "0 - Never" "0 - Never" "0 - Never" "0 - No" "0 - No" "0 = Fully Active,
    able to carry on all pre-disease performance without restriction" "Paracetamol"
    "34" "No" "" "2014-04-10" "" "Luton" "United Kingdom" "RV10001" "Baseline"
2 3 "Jacob Benfield (ID 813)" "Jacob Benfield (ID 813)" "2014-04-29 15:05:08"
    "2014-04-29 15:05:08" "" "" "{}" "Not validated" "" "010" "180" "29/4/2014" "Female
    " "Partner - Living with" "" "Indian" "Self employed" "Vet" "Degree" "No" "" "19" "
    No" "" "" "0.  Never" "0. 1 or 2" "0 - Never" "" "" "" "" "" "0 - No" "0 - No" "1 =
      Restricted in physically strenuous activity but ambulatory and able to carry out
```

```
    work of a light or sedentary nature, e.g., light house work, office work" "
    Paracetamol" "0" "No" "" "2014-04-10" "" "Luton" "United Kingdom" "RV18001" "
    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:            48
 size:         1,078 (99.9% of memory free)

              storage  display     value
variable name   type   format      label      variable label

id              byte   %12.0g
patientId       byte   %12.0g                 Parent patient. Foreign key: patient table.id
userIdentifier  str19  %19s                   User who created row
lastUserIdent~r str19  %19s                   User who last updated row
created         str19  %19s                   Timestamp for row creation
updated         str19  %19s                   Date & time of last update to row
reasonForEdit   str1   %9s                    Reason for editing row
notes           str1   %9s                    Notes
validationOve~s str2   %9s                    Justifications for overriding validation
validationSta~s str13  %13s                   Validation status
validationNotes str1   %9s                    Validation notes
question1       str3   %9s                    Form details - Site number. Number (up to 3 digits)
question2       str3   %9s                    Form details - Participant number. Number (up to 3 digits)
question3       str9   %9s                    Form details - Date CRF completed. dd/mm/yyyy
question4       str6   %9s                    Questions - Sex
question5       str21  %21s                   Questions - Marital status
question6       str1   %9s                    Questions - If other, please specify
question7       str6   %9s                    Questions - Ethnicity
question8       str13  %13s                   Questions - Employment status
question9       str18  %18s                   Questions - Current or most recent job
question10      str23  %23s                   Questions - Highest level of education completed
question11      str3   %9s                    Depression - Have you had any previous episodes of depression?
question12      str1   %9s                    Depression - If so, how many. Number (up to 5 digits)
question13      str2   %9s                    Depression - Duration of current episode in weeks. Number (up to 5
                                                digits)
```

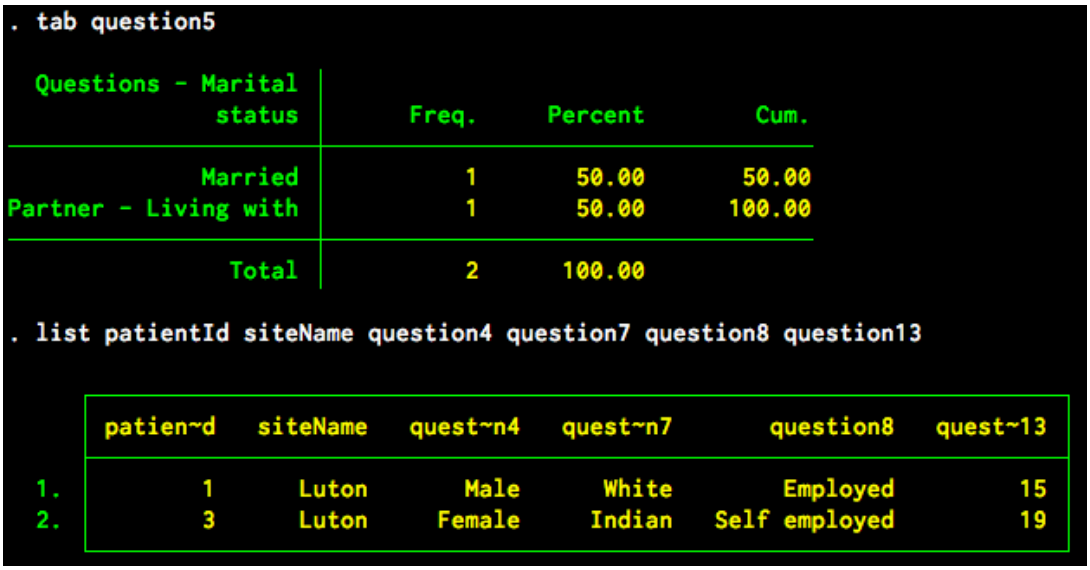
Figure 13.3: Interview data imported into Stata

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

Conversion notes

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

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



```
. tab question5

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

. list patientId siteName question4 question7 question8 question13

     +-------------------------------------------------------------------+
     | patien~d   siteName   quest~n4   quest~n7      question8   quest~13 |
     |-------------------------------------------------------------------|
  1. |        1      Luton       Male      White       Employed         15 |
  2. |        3      Luton     Female     Indian   Self employed         19 |
     +-------------------------------------------------------------------+
```

Figure 13.4: Interview data imported into Stata

- Dates and times are imported as strings in Stata. Stata's data conversion functions can be used as required to convert the strings to Stata's native datetime format.

Chapter 14

Audit trail

Clicking the **Log** link in the left-hand sidebar 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 copied and pasted into a local text file if required (click 'Show all' first). From version 9.6 onwards there is also a button to download the audit trail. This 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 contacts
- Randomisations
- Movement of blocks within code lists
- Unblinding
- Downloads from the system such as reports in CSV format, CRF data, code list and the audit trail itself

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

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

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

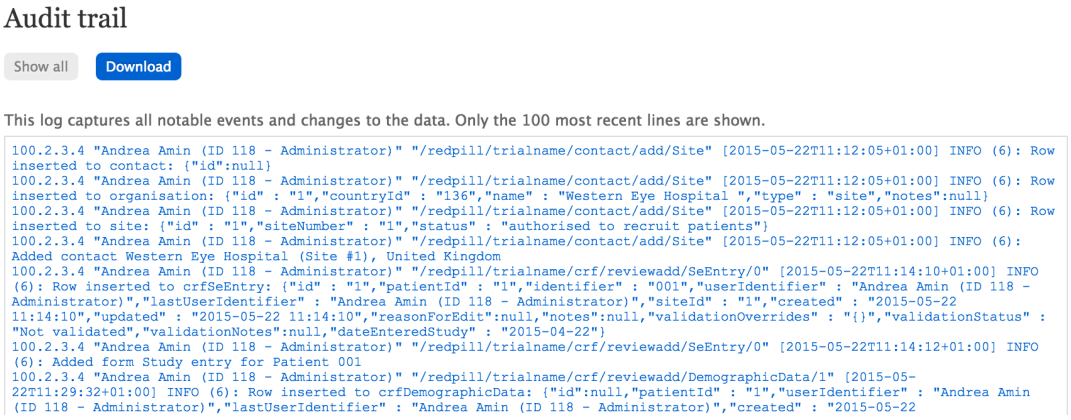


Figure 14.1: Audit trail

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

plus a change in the data:

```
"Row in crfBaselineEligibilityCriteria for: {"id" : "1"}, changed From: {"updated" :
    "2014-10-22 17:45:47","reasonForEdit":null ..."
```

Example extract

```
100.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/crf/reviewadd/
    BaselineEligibilityCriteria/1" [2014-10-22T17:45:47+01:00] INFO (6): Row inserted
    to crfBaselineEligibilityCriteria: {"id":null,"patientId" : "1","userId" : "1","
    lastUserId" : "1","created" : "2014-10-22 17:45:47","updated" : "2014-10-22
    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" [2014-10-22T17:45:47+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" [2014-10-22T17:48:40+01:00] INFO (6): Row in
    crfBaselineEligibilityCriteria for: {"id" : "1"}, changed From: {"updated" :
    "2014-10-22 17:45:47","reasonForEdit":null,"unstableUnderlyingLungDisease":null,"
    anySeriousComorbidity":null,"systolicBp":null}, To: {"updated" : "2014-10-22
    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" [2014-10-22T17:48:40+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" [2014-08-13
    T10:37:45+01:00] INFO (6): Row inserted to contact: {"id":null}
1.2.3.4 "Simon Admin (ID 2)" "/redpill/trialname/contact/add/Individual" [2014-08-13
    T10:37:45+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" [2014-08-13
    T10:37:45+01:00] INFO (6): Added contact James Kinnear
```

Chapter 15

Settings

A settings page is available to administrators that allows some features to be turned on or off to suit the requirements of your trial. Changes to settings are recorded in the audit trail. There are some common settings (see below) and you may also have some trial specific settings. The settings page was introduced in Red Pill 9.6.0.

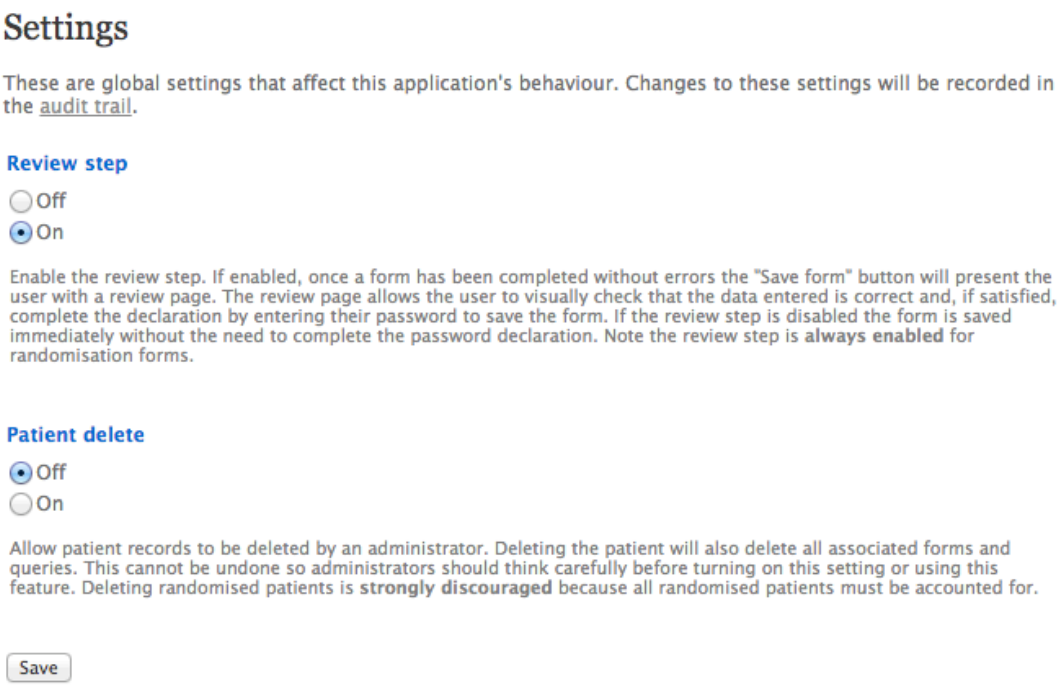


Figure 15.1: Settings page

Review step

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

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

> Note the review step is always enabled for randomisation forms

Patient delete

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

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

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

Randomisation

Randomisation systems and Red Pill systems with a randomisation form can turn randomisation on or off (). 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 contact and set the status to something other than *Authorised to recruit patients* or *Recruiting patients*.

Chapter 16

Specification

The specification for a Red Pill application can be viewed by clicking the **Specification** link on the left-hand sidebar. The specification is only accessible to administrator users. It shows the following information where relevant:

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

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

Chapter 17

Making changes to the specification

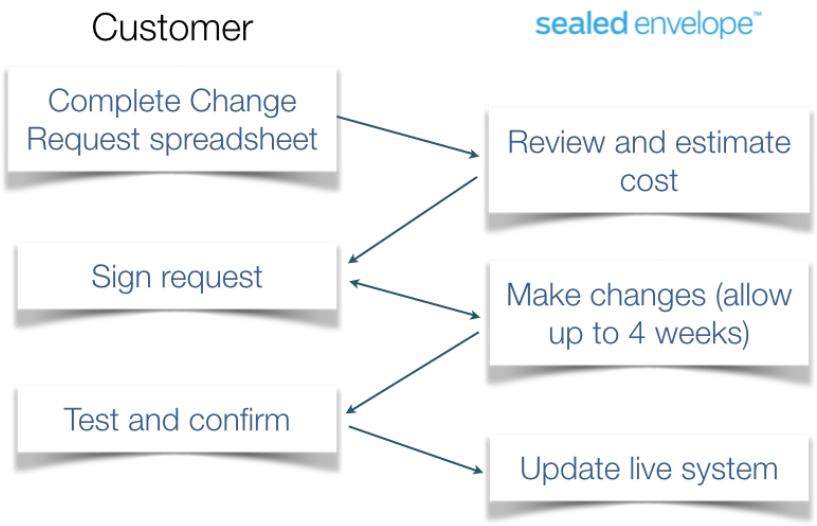


Figure 17.1: Flowchart for change request process

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

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

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

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

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

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

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

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

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

Chapter 18

Minimisation

Minimisation is a method of randomisation that allocates patients 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 patient 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 patient age, so that younger patients, who are expected to have a better outcome, are evenly distributed to the placebo and drug groups.

The randomisations to the trial so far look like this:

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

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

To decide which treatment to allocate the patient to, the balance of treatments in the trial is

compared for patients with the same characteristics as the patient to be randomised. There are various ways of calculating the imbalance, but the most popular method[1] (and the one Sealed Envelope uses) is to simply sum the frequencies across the strata for each treatment. In this example the frequencies are:

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

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

Incorporating a random element

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

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

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

ICH Topic E9 Statistical Principles for Clinical Trials

The Sealed Envelope randomisation system defines a probability that a purely random allocation will be made, instead of using minimisation. So for each randomisation there is a chance (usually around 30%) that the treatment will be chosen at random. This is equivalent to using a biased coin to determine the next treatment, with the bias in favour of the treatment that would make the treatment groups more balanced[2]. If there are two treatments allocated in a 1:1 ratio, and a 30% chance of choosing the treatment at random, then the probability that the under-represented treatment will be chosen is 0.85 ($0.3 \times 0.5 + 0.7$). This probability can be viewed for your trial on the specification page.

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

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

Factorial trials

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

	Placebo	Aspirin
Placebo	x	x
β-carotene	x	x

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

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

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

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

To calculate the minimisation scores for each treatment group, the frequency in the relevant cell plus the marginal totals are used:

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

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

Chapter 19

Random permuted blocks

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

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

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

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

Stratification

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

```
——— | ——————————————————————————————————————————————————————————————————
————————————————————————————————————————————————————— |
Men   | [A B A B], [A A B B B A], [B B A B A A], [B A A B] |
Women | [B B A A B A], [A B B A], [B B A A], [A B B A] |
```

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

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

Choice of block size

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

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

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

Chapter 20

Simulations

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

How are the simulations produced?

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

Data specification document

Here is an example of a data specification:

```
{
  "sample_size": 400,
  "fields": {
    "siteId": {
      "min": 1,
      "max": 10,
      "type": "int"
    },
    "dob": {
      "format": "d/m/Y",
```

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

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

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

Analysing the simulated data

You can download the simulated data and import into a spreadsheet or statistics package for analysis. You can check, for instance, that the randomisation protocol is balancing the treat-

ment 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 age-group 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 21

API

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

Request

Access to the list of randomisations for your trial is provided by HTTP GET request to the url:

`https://{PATH TO YOUR TRIAL}/api/csv`

where the path to your trial is the url you would normally use to view the trial home page, e.g.

`https://www.sealedenvelope.com/redpill/mytrial`

Please note:

- the API must be accessed via HTTPS, it will not work via HTTP.
- You should connect to the url using HTTP basic authorisation using the username and password that we have supplied.
- Access to the API is limited by IP address. Please supply us with a list of IP addresses that you expect to be connecting from.

Response

The response will be a CSV dump of all randomisations to date, sent with a content type of "text/plain", e.g.

```
id,"Parent patient. Foreign key: patient table.id","Patient identifier","User who
    created row","User who last updated row","Date & time of randomisation","
    Randomisation code",Unblinded?,"Reason for unblinding","Date unblinded","Manual
    randomisation?","Randomised in error?","Reason marked in error","Date marked error
    ","Timestamp for row creation","Date & time of last update to row","Reason for
    editing row",Notes,"Justifications for overriding validation","Validation status","
    Validation notes","Randomisation - Patient Initials","Randomisation - Patient's
    Date of Birth. dd/mm/yyyy","Randomisation - Currently taking antidepressant?","
    Randomisation - PHQ 2 Score. Number (up to 2 digits)","Randomisation - MINI
    indicated current major depressive episode?","Randomisation - AUDIT Score. Number (
    up to 2 digits)","Randomisation - Does the patient meet all other eligibility
    criteria?","Randomisation - Has the patient given written informed consent?","Date
    entered study","Date withdrew",Site,Country,Visit
1,1,AA001,"Jacob Benfield (ID 813)","Jacob Benfield (ID 813)","2014-05-01 10:05:25",
    OE9,0,,,No,0,,,"2014-05-01 10:05:25","2014-05-01 10:05:25",,,,"Not validated",,AA
    ,10/08/1957,Yes,6,Yes,16,Yes,Yes,"2014-05-01 10:05:25",,UCL,"United Kingdom",
    Registration
2,2,BB002,"Jacob Benfield (ID 813)","Jacob Benfield (ID 813)","2014-05-01 14:58:40",
    WS4,0,,,No,0,,,"2014-05-01 14:58:40","2014-05-01 14:58:40",,,,"Not validated",,BB
    ,17/02/1980,Yes,4,Yes,10,Yes,Yes,"2014-05-01 14:58:40",,UCL,"United Kingdom",
    Registration
3,3,CC003,"Jacob Benfield (ID 813)","Jacob Benfield (ID 813)","2014-05-01 17:11:13",
    QB2,0,,,No,0,,,"2014-05-01 17:11:13","2014-05-01 17:11:13",,,,"Not validated",,CC
    ,5/5/1968,Yes,3,Yes,9,Yes,Yes,"2014-05-01 17:11:13",,UCL,"United Kingdom",
    Registration
```

The first line is a header. The data will vary by trial, but all trials will contain the following standard fields:

- id: primary key, unique id
- Parent patient. Foreign key: patient table.id. In Red Pill applications this is the id of the patient that the randomisation belongs to
- Patient identifier: unique patient identifier, may be user entered or generated
- User who created row: the name and user id of the randomiser
- User who last updated row: the name and user id of the person who last edited the randomisation
- Date & time of randomisation
- Randomisation group or code: this will be the treatment group for unblinded trials or code for blinded trials
- Unblinded?: has the patient been unblinded? 0=no, 1=yes
- Reason for unblinding: the reason entered when the randomisation was unblinded

- Date unblinded
- Manual randomisation?: was this a manual randomisation?
- Randomised in error?: was the patient randomised in error? 0=no, 1=yes
- Reason marked in error
- Date marked error: the date the randomisation was marked as in error
- Timestamp for row creation
- Date & time of last update to row
- Reason for editing row
- Notes
- Justifications for overriding validation: reasons for overriding validation errors
- Validation status: forms may be marked as 'Not validated', 'Validated', or 'Data unusable'
- Validation notes: notes recorded when changing the form validation status
- Date entered study
- Date withdrew
- Site: name of site
- Country
- Visit: the visit that the form is associated with

For blinded trials the data will *not* contain the treatment group.

Testing

You can test the request by visiting the API URL in your browser. You should see a dialog box requesting the username and password. Enter the details we supplied and you should then see the response. If you are connecting from an unauthorised IP address you will instead see the message *Authorization required over https*.

Or using curl:

```
$ curl -u <username>:<password> https://www.sealedenvelope.com/redpill/mytrial/api/csv
```