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Trial Monitor User Guide

Version 1.10

Guillemot Design Ltd

Pharma Open Source Community:

PhOSCo Clinical Trials

Trial Recorder User Guide

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Trial Monitor User Guide

Trial Monitor

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Trial Monitor is the application program within PhOSCo Clinical Trials that is used to review and designate the status of clinical data collected by Trial Recorder about the subjects of the trial according to the trial protocol. PhOSCo Clinical Trials Trial Builder will have been used to create the definition of the trial, specifying what pages appear in what order, what questions appear on each page, and the validation checks that will be made on the individual pieces of data that the user of Trial Recorder will collect and enter into the application.

Trial Monitor will be used primarily by monitoring and data management staff. The functions provided by Trial Monitor allow the manipulation of status information and annotations attached to clinical data, but do not allow the update of clinical data itself. If a Data Manager needs to amend the clinical data values themselves, this must be performed using Trial Recorder; a Data Manager may use both modules, while Monitors can only use Trial Monitor, and Recorders only Trial Recorder.

This Guide

The PhOSCo Clinical Trials Trial Monitor User Guide is intended as a brief introduction into how to use the principal elements of PhOSCo Trial Monitor. As each Trial Protocol may be significantly different, customised as they are by PhOSCo Clinical Trials Trial Builder, it is not possible in a single manual to cover all the variations and behaviour you may find in any one trial, so this Manual provides a Quick Start section introducing the major functions of the module and a Reference Manual section where significant material is described in detail. You should consult the documentation or other training materials provided for the specific customisation of your trial for guidance on the conduction of specific trials.

Bibliography

The latest version of this manual and other related documentation may be found on the public area of the website. Other manuals include:

The PhOSCo Clinical Trials Planner's Guide

The PhOSCo Clinical Trial Builder User Guide

The PhOSCo Clinical Trial Recorder User Guide

The PhOSCo Clinical Trial Browser User Guide

The PhOSCo Clinical Trial Server User Guide

Installation

Installation and start-up check may have been done for you.

If not, consult your distribution documentation to get instructions on how to install the Trial Monitor software itself, and the prerequisite Java engine.

Besides Java and Trial Monitor itself, you must provide an SQL database engine (unless you are installing a version which comes with an inbuilt database engine). Any SQL engine that provides ANSI compatible SQL and the appropriate data types via JDBC should work with Trial Recorder, but you must make sure that the SQL software provided includes a JDBC driver. Some Relational Database Management Systems (RDBMS) may require minor modifications to the database handler; see the JCTdbFactory Java Class for details.

Make sure you obtain at least a level 1.3 installation of Java.

Once your SQL engine is installed, set up the database as outlined in the manual "PhOSCo Clinical Trials Database".

Note that ODBC will almost certainly not work properly, and you should not attempt to use the JDBC-ODBC bridge. This is because ODBC cannot be guaranteed to work properly with multi-threaded applications such as Trial Recorder.

With Trial Monitor, there is an initialisation procedure provided to load the metadata from Trial Builder into an empty database. Instructions for this, and how to set up the parameter files required for Trial Monitor, are also in the distribution documentation for your particular platform.

Once that is done, you're ready to go!

Starting up

Your distribution documentation should tell you how to invoke the program on your particular platform, either using a GUI interface icon or a console command. We recommend that you use a console command for the first time, as any error messages output by the program will be sent to the console until the GUI interface of Trial Monitor starts up. If the database connection cannot be started for any reason, the GUI interface will not be started, and using a GUI icon normally only displays the console for a very short time if there are any problems, and you won't be able to read the error messages.

A file called TMPARMS.DAT is essential for the correct startup of Trial Monitor. This tells the program where the database is to be found, which Trial is to be used, and what the local site is, as well aas other operating parameters. It also contains the "User Parameters" which are the values to be substituted in certain validation checks as defined by whoever designed the Trial using Trial Builder. The format and contents of this file are presented in a later section.

If you've installed the software, and the database has been set up correctly, there should be no problems, and the initial dialogue of Trial Monitor should display.

Language

The version presented here is the distributed UK English Language version.

PhOSCo Clinical Trials software has all been written with "Internationalisation" in mind, and it should be relatively easy to produce other language versions, including languages which use non-ASCII character sets, or to use the Internationialisation functions to produced customised English versions without having to change the application code.

Java uses Unicode which supports most known languages, and PhOSCo Clinical Trials software has been written with all text strings which are displayed placed in "Resource Bundles". A "Resource Bundle" is a separate Java Class which in our case contains all the language strings displayed by the application. To produce another language version of the application it should only be necessary to translate the language strings in this resource bundle (one each for Trial Builder and Trial Recorder), to compile the bundle, and replace it in the application classes used at runtime.

At the time of writing, the Trial Builder Resource Bundle contained approximately 560 language strings and the Trial Recorder Resource Bundle contained approximately 340 language strings.

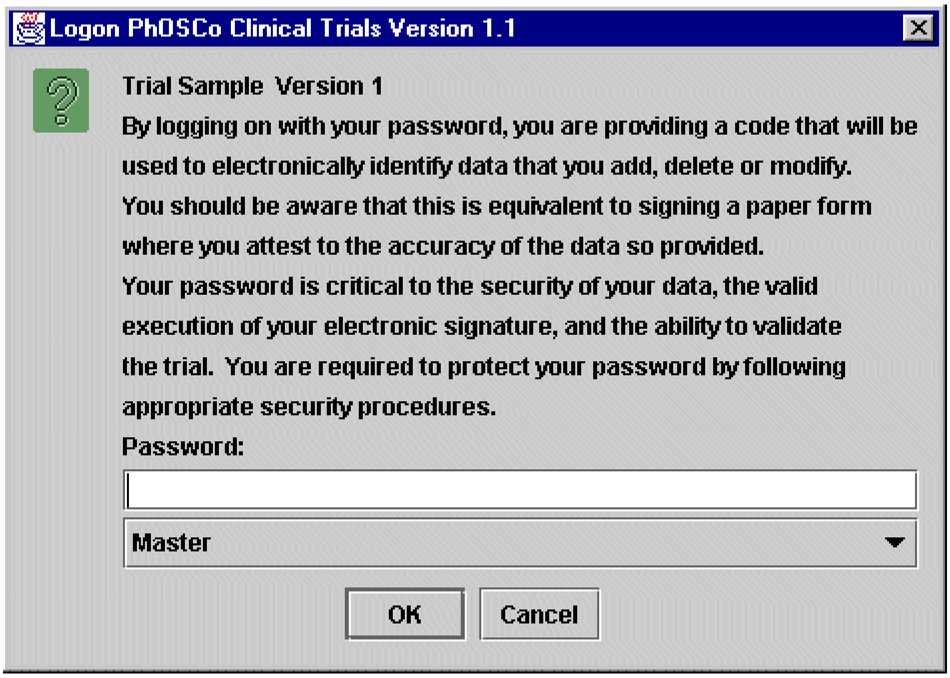
Trial Monitor uses elements from both these Resource bundles.

Depending on the language and the size of translated strings and their display requirements, it may also be necessary to make minor modifications to input dialogues and their processing.

Data Input functions are performed throughout by standard Java functions. Where there is a Java version 1.2 or better language implementation which supports your language of interest, input in that language should work without the need to amend code.

Trial Monitor Quick start

Logging On



This is the dialogue box you will see when you log on to Trial Monitor, and also if your system is inactive for a period of time determined by the person(s) customising your trial. You must select your name from the drop-down box, and type in your password, and then press the "OK" button, to proceed.

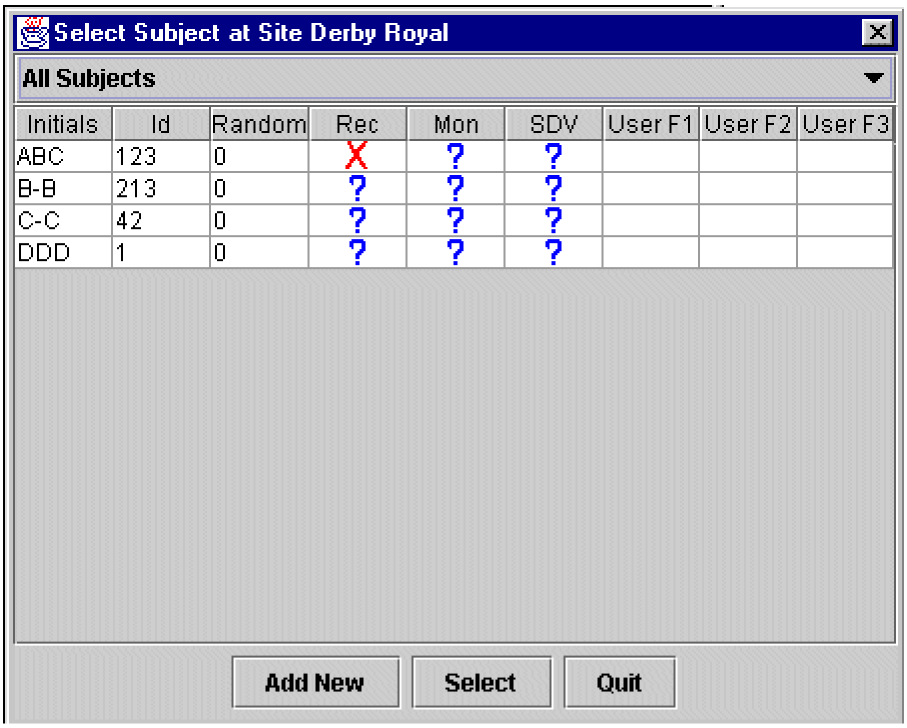
Pressing the "Cancel" button will halt the application.

You will have three chances to enter a correct user name and password combination.

Note that different regulatory frameworks may have different requirements and interpretations regarding electronic signatures, and you may have to use the "Signatures" function from the Tool bar as well as the standard data entry. You should follow the operating procedures that you will have been given by those running the trial.

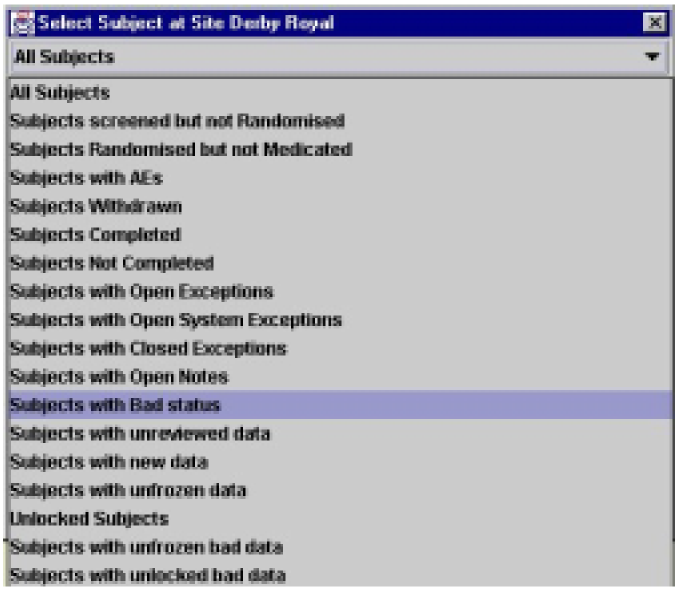
Selecting a Subject

Trial Monitor will only display the main screen when a Subject has been selected, so you must next either select a Subject or create a new one.



To select a Subject, scroll through the available ones in the list box and click on the one you want with your mouse. Then press the "Select" button.

You may change the Subjects for Selection list by selecting an option from the dropdown list at the top:



This allows you to restrict the display in the Subjects list box to those with Bad Status, Adverse Events, not Completed, and so on.

If you wish to add a new Subject, press the "Add New" button. This will present three text boxes in turn, allowing you to enter the new Subject Initials, unique system reference number, and User Number. The Subject User Number is optional, the other two are not. Subject Initials should be unique at your site (so that you can easily identify the Subject record), and may be up to five characters long. The Subject Number must be unique at your site, as it is used as the key value to identify records associated with that Subject.

The Subject User Number is a reference number for use by the organisation running the trial, and is not used by the software. Together with three customisation-dependent Subject User Fields (which may contain character data), it may be added or amended at any time and may be used for whatever purpose is required, for example as a randomisation number.

Once you have added a new Subject, the record will appear in the list box, and may be selected just like an existing Subject.

If you wish to see the subjects at the Site in an order other than their initials, click with your mouse on the column you want to see them in order of. In your trial, the three columns "User F1", "User F2", and "User F3" may have had their title customised to something else; in any case, you can use these fields as well as the others to sort the sequence of the Subjects by, as well as their initials, numbers, and status.

The Main Screen

Once a Subject has been selected, Trial Monitor will display the main screen. If a Subject is new, the Screen displayed will be the initial Table of Contents screen. If a Subject has had data added, the screen displayed will be the last CRF page that had data added or amended.

In Trial Monitor, there are just the two types of screen: Visit or Group Header screens, and CRF Page screens, which display a CRF page.

The Visit or Group Header Screen

A Header screen consists of the elements displayed here.

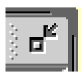
There is a title bar, common with the CRF Page screen, which displays the program name and the current context of the trial; the Trial name and number, the Site name and number, The name of the current Monitor, the Subject Initials and number, and the Trial Element name, in this example a Visit name. This title bar contains the usual iconify, enlarge/shrink, and quit buttons. We recommend the use of full screen mode for Trial Monitor.

There is no Menu bar in Trial Monitor. Instead, in the top right hand corner, there is an icon group which is used to page around the trial and display the status of various levels in the trial.

All these icons, and the screen background, are customisable, as is the entire content of the CRF pages, so what you see in your customisation may look entirely different from what you see here, but should work in the same manner.

The remainder of the Table of Contents screen displays the structure of the trial, element by element, as a Java "Tree" control, initially "collapsed", as you see here. This means that only trial level elements are displayed.

Closing Down



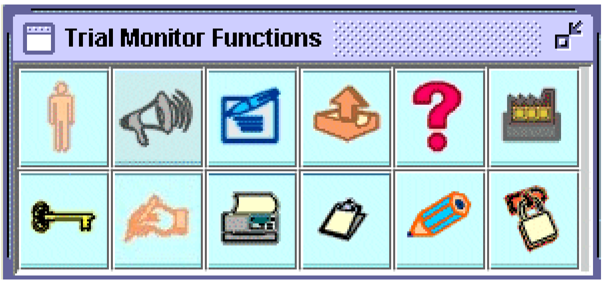
The only way to close down Trial Monitor is to use the Application Close button on the title bar of the window.

Other Functions

Trial Monitor Functions and CRF Page Navigation, and Page Monitoring functions can be performed by use of the three panels which are currently minimised at the bottom of the screen. To bring them up, click on them with your mouse.

The Monitor Functions Tool bar

Most functions are accessed from this Tool Bar.



The icon will change and the Tool bar display. To get rid of the Tool bar, click on the icon again.

Moving the mouse cursor over the icons in the Tool bar will display a "Tool Tip" or name of the function that pressing on the icon will perform. Going from left to right, the functions are, top row:

Subject dialogue	The same dialogue as is presented at opening the application, which allows you to switch between existing subjects and to add new ones.
About box	Version and copyright information
Page Note Add	Allows you to add a note to the page (to add a note to a widget, bring up the Status Dialogue by left mouse clicking on the status bitmap of the widget, and press the New Note button).
View Notes	Allows you to browse notes and exception notebooks attached to the current page and its widgets. If this is a Table of Contents Page, you may look at notes and notebooks for the whole scope of the Subject data.
Help	There are two help systems inside Trial Monitor, this one and "Protocol Assistance". This button gives you access to a series of HTML pages. Normally, these will be customised to the trial that you are running, but may also give general information. It is the responsibility of the people who customise the trial to set up this Help, though a skeleton set is provided with the application. Protocol Assistance is described later.
Batch Functions	Allows you to run Batch Validation (rerun validation checks on whole pages, visits, and subjects), and where customised, Laboratory Data Load, Translation, and Autocoding functions.

Bottom row:

Password	Update your password, and if you are a Site Administrator, other Site Administration functions.
Signatures	Sign off Subject, Visit, or Page data by competent authority.
Print	Print empty Paper CRF forms or populated data CRFs.
Locally defined	A pop-up menu of functions; this may be customised for you, but the default is:

Add user to Site	Add a new User
Lock/Freeze	A dialog to Lock or Freeze an entire Page, Visit, or Subject.

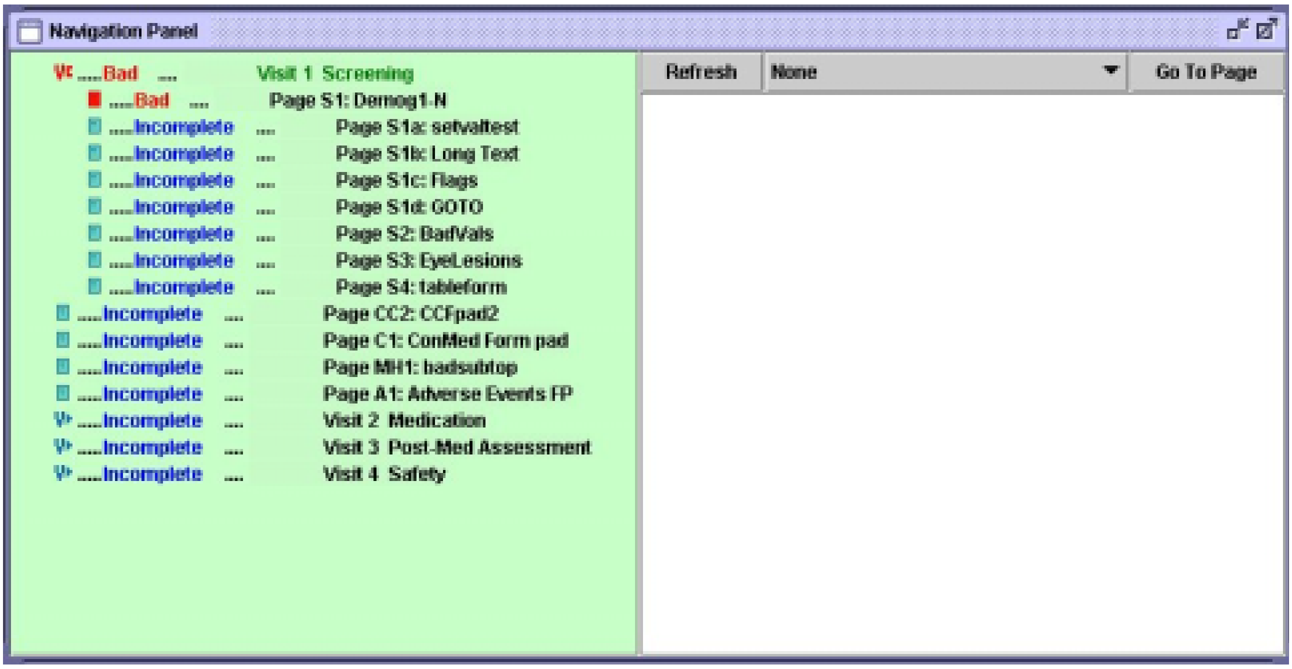
Paging: the Navigation Panel

There are two ways of going to a different page.

The first is to click on the line defining a trial element in the tree display in the Navigation Panel. This will take you directly to that element.

The second is to click on one of the three paging icons in the top right corner. The one on the left will take you to the previous element in the trial, if any; the one on the right will take you to the next element in the trial, if any, and the centre one will take you to the closest previous element that is at a higher level in the trial, if any - for example, if you were in the third CRF within a visit, this would take you back to the Visit page.

To bring up the Navigation Panel, click on it with your mouse.



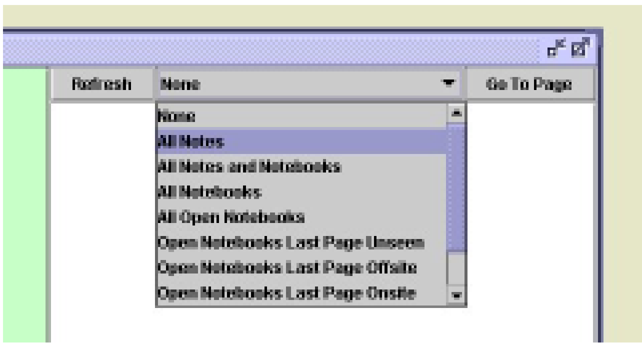
This Panel can be resized by dragging the mouse cursor from the edges of the Panel, or minimised or maximised by clicking on the icons at its top right.

The Panel is split into two halves, vertically.

The left hand side displays a tree structure of the current Trial, with the current page highlighted. As with most tree controls, elements which contain others (such as Visits containing CRF Pages) can be displayed either expanded or collapsed. To expand or collapse any element, click on its leading icon with your mouse. You can go directly to any element that is displayed by double clicking on it with your mouse; this makes for very easy navigation around the pages of the trial.

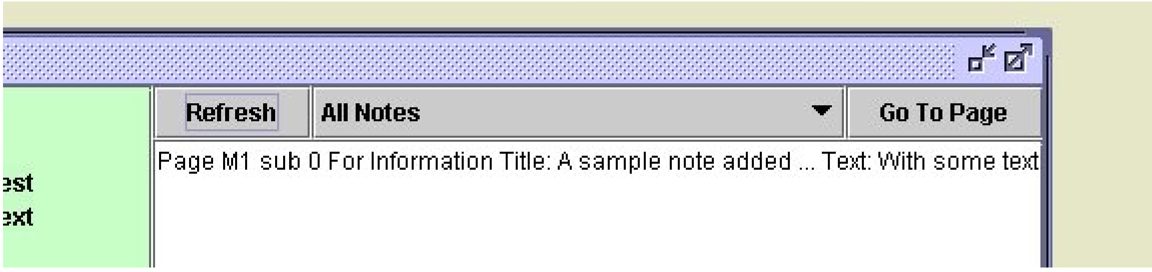
Besides the structure of the trial, this tree also display the current status of each page displayed; whether it is incomplete or contains bad or significant data, and later whether every element has been completed, reviewed, frozen, or locked, and so on. You can therefore use this panel to see where there is bad data, and go directly to it.

The right hand side displays annotation or Exception Note data if required. To populate this you make a selection from the central list:



and press the "Refresh" button.

In this case there is only one note for the Subject:

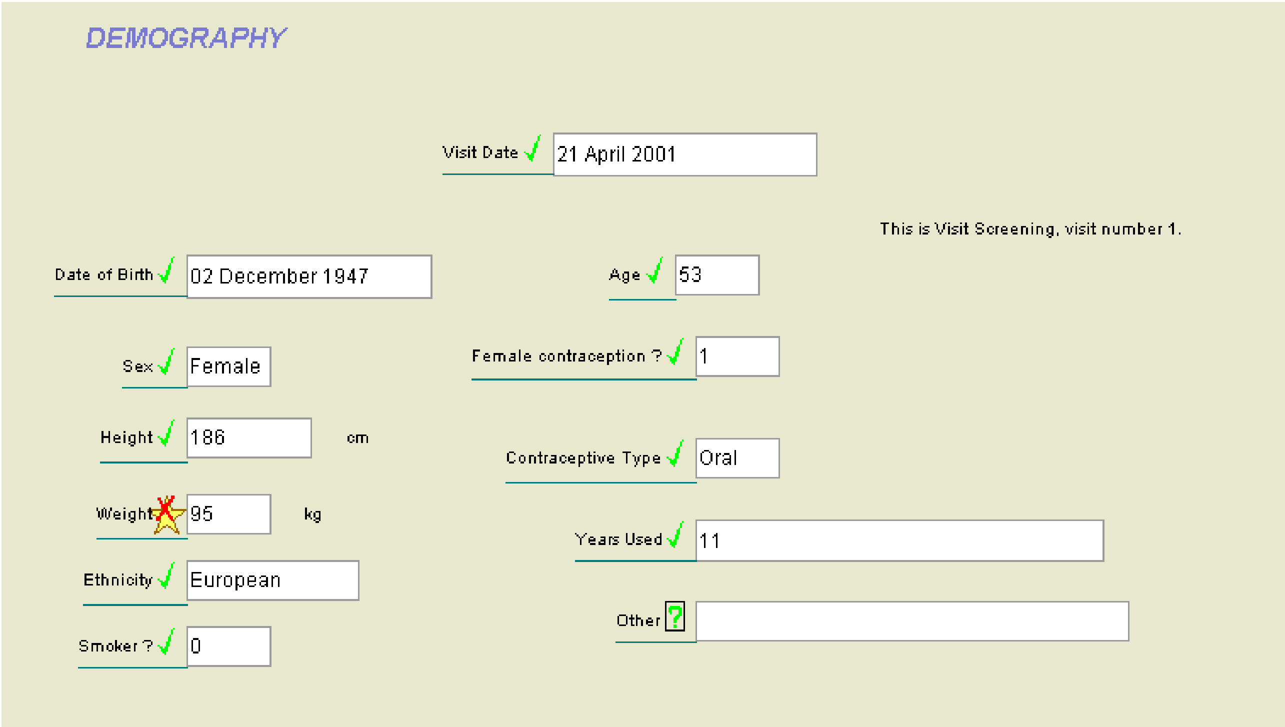


which as we can see is on Page M1 subpage 0. Besides the Page, we can see what type of Note it is, and the beginning of both the Note Title and the Note text.

If we want to see the Page and widget the Note is attached to, we highlight the note by clicking on it with the mouse and press the "Go To Page" button at the top.

These functions make it very easy to navigate around the trial, and find the data we want or exceptions we have to deal with.

The CRF Page



The layout of a Trial Monitor CRF page is identical to that of the same page in Trial Recorder, except that the individual widgets are displayed a little differently. As you can see on this page, most widgets are displayed as simple windows with the data values in text - regardless of whether the widget is a text widget, a multiple choice question, a slider, and so on. The widget labels display the same as in Trial Recorder, except that if the widgte is required to have Source Data Verification performed on it, it is underlined with a blue line.

This is because the Monitor has no need to (and in fact cannot) manipulate the data values. A Monitor just requires an unambiguous display of what the data values are.

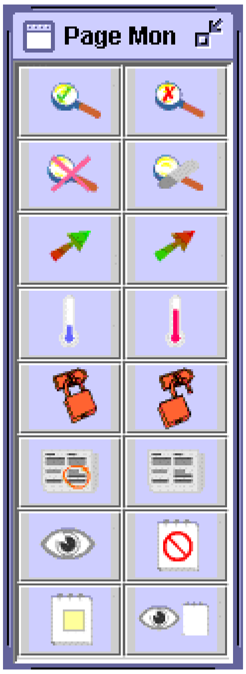
The status bitmaps at the front of the widgets are the same as in Trial Recorder. They are all listed in the section "Status Bitmaps" in the Reference section. What they look like depends mainly on the Recorder Status of the Widget. Widgets have distinct Recorder and Monitoring Status flags, many of each. These are detailed in the section "Status Codes" in the Reference Section

Trial Monitor, besides displaying data and the audit trail, can be used to modify the Monitor Status of widgets and to annotate them and their CRF pages with notes and exception notebooks.

These monitoring functions can be accessed from two places: the Widget Monitoring Toolbar and the Page Monitoring Toolbar. As stated before, the Page Monitoring Toolbar is normally displayed on every page. It can be dismissed by pressing the "iconify" icon on the toolbar header. If it is not currently being displayed because it has been iconified, it can be recalled by clicking the right-hand mouse button over any unoccupied area of the screen.

The Page Monitoring Toolbar

To bring up the Page Monitoring Toolbar, click on it with your mouse. This and the Widget Monitoring toolbar are used to perform Monitoring Functions.



The Widget Monitoring Toolbar

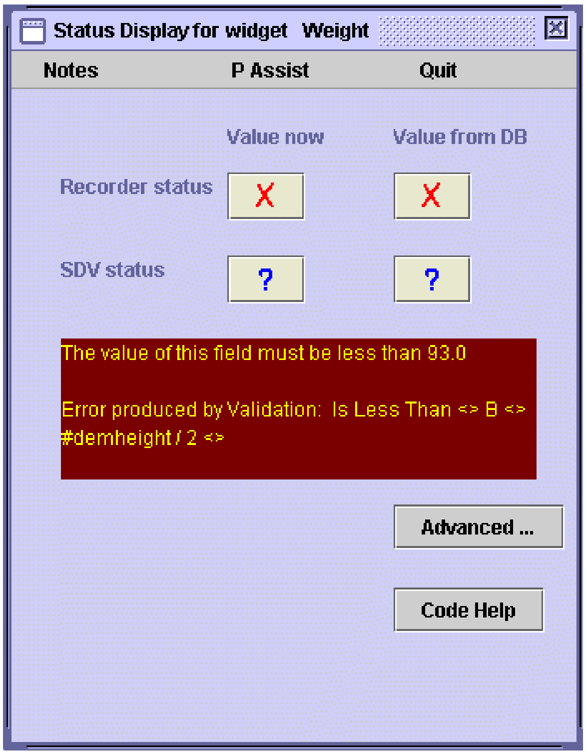
The Widget Monitoring Toolbar can be brought up by clicking the left mouse button over the display window of any widget. It looks like this:

As you see, it is remarkably similar to the Page Monitoring Toolbar, and in fact the buttons on it perform identical functions. The only difference between the Page and Widget Monitoring Toolbars is that the buttons on the Page Toolbar apply the status or annotation in question to all the widgets on the current CRF page, while the buttons on the Widget Monitoring Toolbar only apply that status or annotation to the widget on which the Toolbar was brought up. The Widget Monitoring Toolbar has a button to inspect the widget Audit Trail, and two for Notes and Notebooks.

Clicking the left mouse button on a status bitmap produces a Status Display similar to that in Trial Recorder, as shown on the next page.

The Status Display

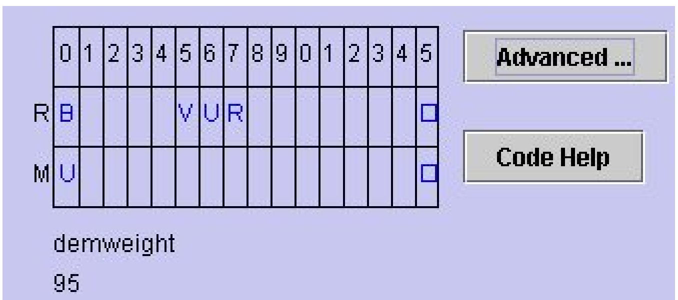
Clicking on a widget Status Bitmap with the left mouse button displays the Status Display Panel for that widget:



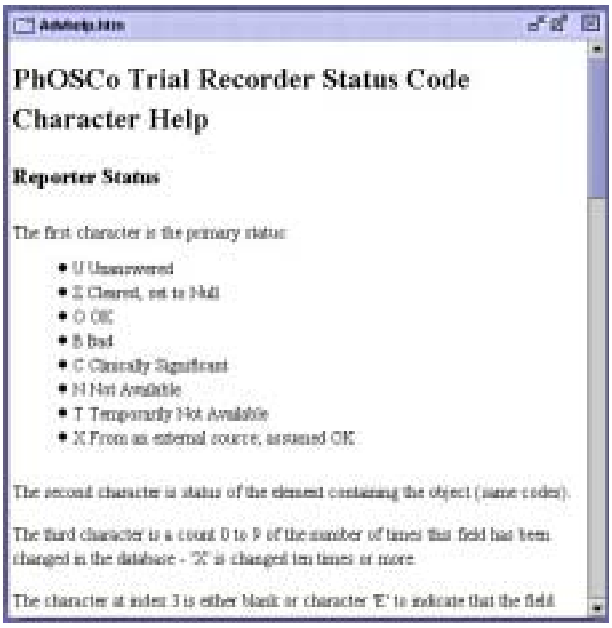
This box shows the name of the widget and its status both now and when the page was originally entered, the "Value from DB" (value from the database). You can see what any particular icon means by placing the mouse cursor over it and getting a "tip box":

When, as in this case, the widget has failed a validation, the validation error message is displayed in a central panel, together with the validation that produced the error message. Usually, it should not be necessary for users to understand the validation itself; it is put there for audit and trace reasons.

There are also two buttons on this display box, which give you more information. If you press the "Advanced" button, you get a display of all the status characters of the widget, together with the internal field name and internal value (which may be differnet rom the displayed value, for example with dates and code lists.



If you need to know what the individual code letters mean, the "Code Help" button displays a Help Panel explaining them, though again most users should not be concerned with these:

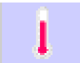
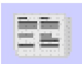
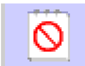
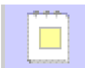
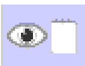
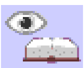


Finally, the menu bar in the Status Display panel has three options:

Notes	-	Lists the current Notes attached to the widget and lets us browse them
P Assist	-	Displays the Protocol Assistance (if any) for the widget
Quit	-	Closes the Panel.

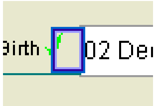
Monitoring Functions

The functions on the Monitoring Toolbars are:

	SDV OK.	Set Monitor SDV Status to OK
	SDV Bad	Set Monitor SDV Status to Bad
	SDV Not Possible.	Set Monitor SDV Status to Not Possible
	Remove SDV.	Set Monitor SDV Status off
	Apply Waiver	Set Monitor Status to Waived. Cancels Non-OK Recorder Status
	Remove Waiver	Removes Waiver from Monitor Status.
	Freeze.	Sets Monitor Status to Frozen.
	Thaw	Sets Monitor Frozen Status off
	Lock	Sets Monitor Status to Locked
	Unlock	Sets Monitor Locked status off
	Mark	Sets Monitor Status to Marked
	Unmark	Removes Mark from Monitor Status
	Set Reviewed	Sets Monitor Status to Reviewed
	New Exception Notebook	
	New Note	
	View Exception Notebooks	
	View Notes	
	Audit History	View Audit History for widget.

Some of these monitoring functions (the Waiver, Freeze and Thaw, and Mark) will have an effect on the Status Bitmap at the front of the widget or widgets to which they apply. The others cause the background of the widget to change.

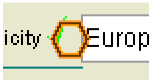
For example, any widget that has the Monitor Status of "Reviewed" will display blue Rectangle under the status bitmap of the widget. This will be displayed in Trial recorder as well as in Trial Monitor. Here's what it looks like:



If the Monitor SDV status code is set, the "Reviewed" rectangle won't appear. If the widget has passed SDV and the code is set to SDV OK, the background to the status bitmap will be a green triangle:

If, on the other hand, the SDV code is SDV bad, it will be a red circle:

Alternatively, if the Code was set to be SDV Not Possible, it will be a brown hexagon:



If the SDV code is removed by using the Remove SDV function, the status bitmap background is once more set to the blue rectangle, because it has been reviewed.

The Frozen, Waiver, and Mark status bitmaps can be seen in the Reference Manual section "Status Bitmaps".

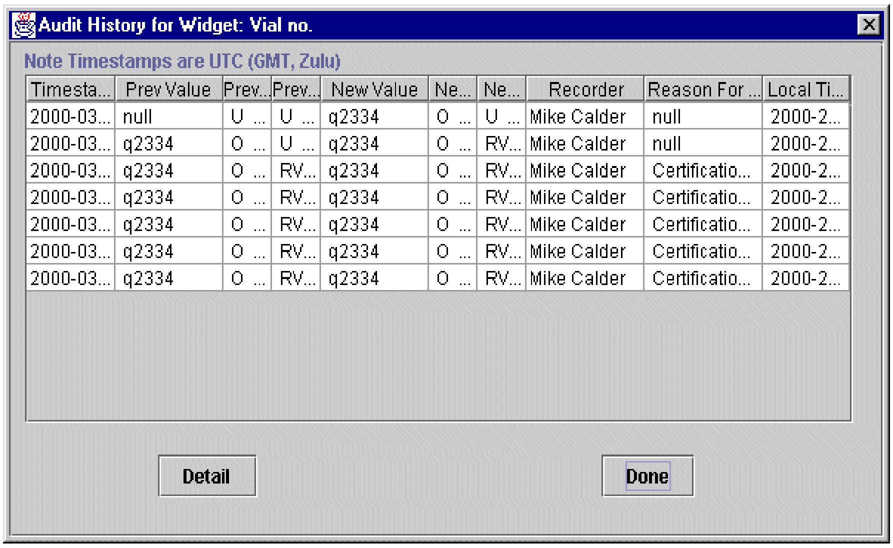
The position of these bitmaps, as well as their physical appearance, can be customised by whoever sets up the trial, so yours may vary from this.

Locked Fields appear with a blue background, in both Trial Monitor and Trial Recorder:

Notes and Exception Notebooks are dealt with in the next section.

The Audit History function causes the display of a table of the audit trail records for the widget (this button doesn't occur on the Page Monitoring Toolbar).

This picture shows an example of this table with probably more than the normal number of entries - most widgets would only have two or three audit trail records at trial close, unless there had been some confusion about data values or significant monitoring activity.

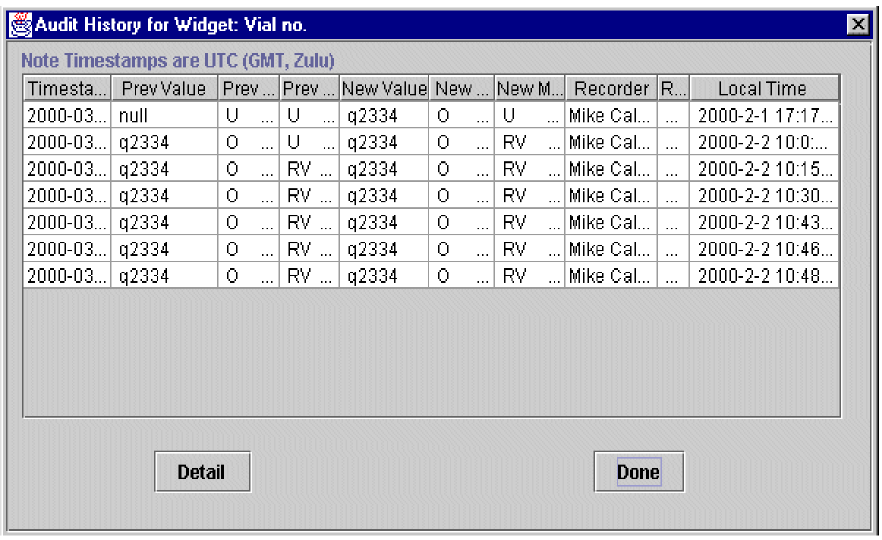


Timesta...	Prev Value	Prev...	Prev...	New Value	Ne...	Ne...	Recorder	Reason For ...	Local Ti...
2000-03...	null	U ...	U ...	q2334	O ...	U ...	Mike Calder	null	2000-2...
2000-03...	q2334	O ...	U ...	q2334	O ...	RV...	Mike Calder	null	2000-2...
2000-03...	q2334	O ...	RV...	q2334	O ...	RV...	Mike Calder	Certificatio...	2000-2...
2000-03...	q2334	O ...	RV...	q2334	O ...	RV...	Mike Calder	Certificatio...	2000-2...
2000-03...	q2334	O ...	RV...	q2334	O ...	RV...	Mike Calder	Certificatio...	2000-2...
2000-03...	q2334	O ...	RV...	q2334	O ...	RV...	Mike Calder	Certificatio...	2000-2...
2000-03...	q2334	O ...	RV...	q2334	O ...	RV...	Mike Calder	Certificatio...	2000-2...

The columns of data displayed are:

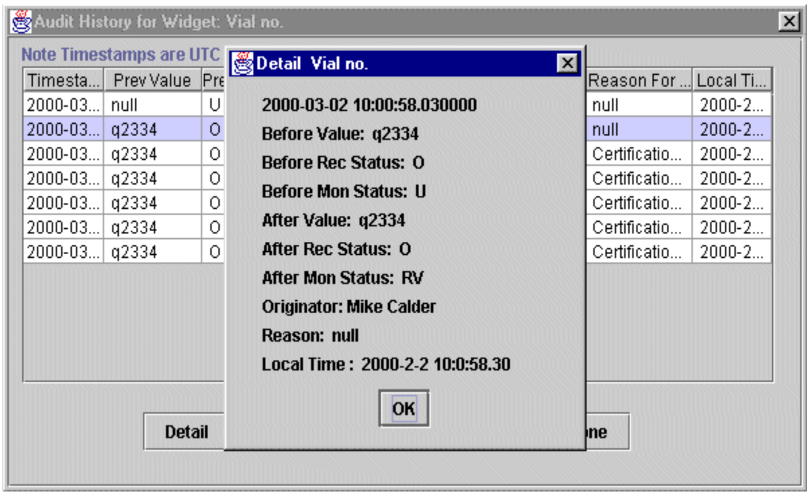
1. The system timestamp in UTC
2. The data value before the change the audit record is a record of
3. The Recorder Status before the change
4. The Monitor Status before the change
5. The data value after the change
6. The Recorder Status after the change
7. The Monitor Status after the change
8. The person who made the change
9. The Reason For Change (if a data value change) or type of Signature Certification
10. The local time at which change was made

It is a standard Java table, so the columns, which can't for reasons of space display the full data content, can be expanded by dragging with the mouse if you want to see more of the data for a column for all rows of the table, as in the following picture, where we've expanded the Local Time column:



Timesta...	Prev Value	Prev ...	Prev ...	New Value	New ...	New M...	Recorder	R...	Local Time
2000-03...	null	U ...	U ...	q2334	O ...	U ...	Mike Cal...	...	2000-2-1 17:17...
2000-03...	q2334	O ...	U ...	q2334	O ...	RV ...	Mike Cal...	...	2000-2-2 10:0:...
2000-03...	q2334	O ...	RV ...	q2334	O ...	RV ...	Mike Cal...	...	2000-2-2 10:15...
2000-03...	q2334	O ...	RV ...	q2334	O ...	RV ...	Mike Cal...	...	2000-2-2 10:30...
2000-03...	q2334	O ...	RV ...	q2334	O ...	RV ...	Mike Cal...	...	2000-2-2 10:43...
2000-03...	q2334	O ...	RV ...	q2334	O ...	RV ...	Mike Cal...	...	2000-2-2 10:46...
2000-03...	q2334	O ...	RV ...	q2334	O ...	RV ...	Mike Cal...	...	2000-2-2 10:48...

Alternatively, if what you want to see is the full detail for one row, you can press the "Detail" button after highlighting the row you want to see the details of by clicking on it with the left hand mouse button. The row will be highlighted in blue, and after pressing the "Detail" button you will get this display:



This is one of the few occasions using the PhOSCo software where you see the "raw" status codes, which are detailed in the Reference Manual section of this Guide. In this case, we have a data value which has passed validation ("O" Recorder Status = "OK") but not seen by a Monitor ("U" in Monitor status = "Uninitialised") has after the change been reviewed by a Monitor ("R" Monitor Status = "Reviewed") and has passed Source Data Verification ("V" in second position of Monitor Status = "SDV OK").

You'll notice that in this case Reason (For Change) is "null"; Reason For Change is only required when a data value is changed; not on initial entry, or on normal Monitoring activities.

Note Functions

Notes can be attached to the CRF page as a whole, or to individual widgets on the page. The dialogues used to add and display them are virtually identical in format and use, so we'll just look at the widget examples.

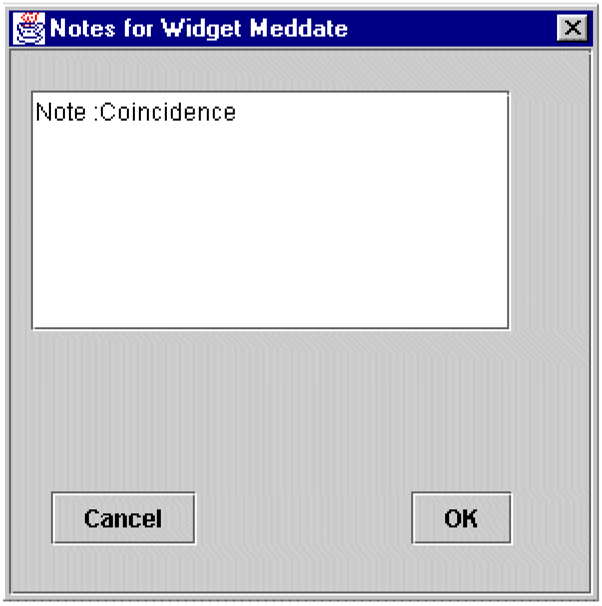
You can tell if a page has notes of any type attached, because the Notes status icon will be present in the top right hand corner (see "Status Icons" in the Reference Manual section), and you can look at them using the "View Notes" button of the Page Monitoring Toolbar or the main Toolbar (the one popped up by the Toolbar icon at top right).

You can tell if a widget on a page has any notes attached to it by the fact that it is has a yellow star in front of it:

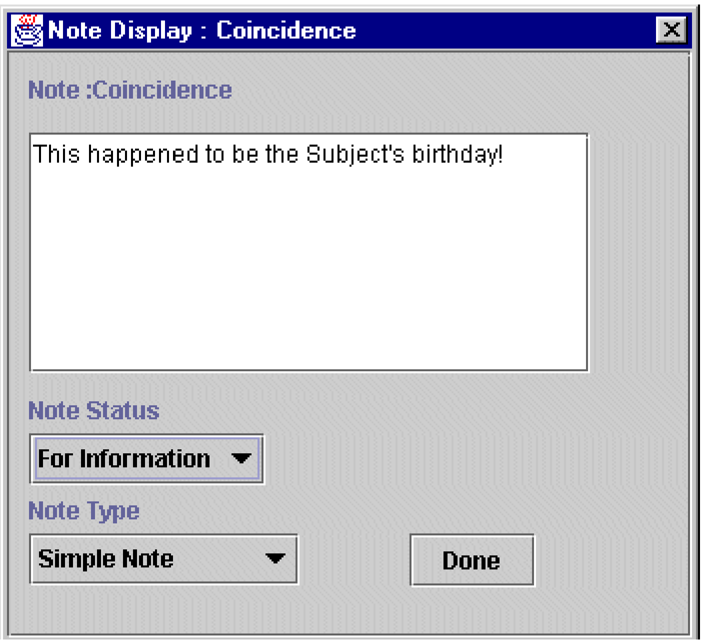
Viewing Notes

In Trial Monitor, there are two ways of getting to look at the notes for a widget. The first is the same way as in Trial Recorder, by popping up the Status Display for the widget by left mouse clicking on the status bitmap of the widget, and pressing the "Notes" button in the Status Display panel. The second is by left mouse clicking over the body of the widget to get the Widget Monitoring Toolbar, and pressing one of the two buttons "View Notes" or "View Exception Notebooks". All of these will give you the same dialogue, but the "View Exception Notebooks" button will only display the titles of Exception Notebooks for the widget, while the others will display the titles of all notes and notebooks that you are authorised to see.

This is the Notes List Display:



In this example, there is just one note. To see the contents of a note, highlight the title of the note you wish to see by left mouse clicking on it, and press the "OK" button.



The Note Display dialogue shows the title and text of the note, and always has the "Done" button to dismiss the panel. If you are the author of a note, there are two additional features on the dialogue, because you are allowed to change the Status and Type of notes that you add.

Note Type

A note (but not a notebook) can be of three basic types:

1. A simple note,
2. A note restricted by security level, or
3. A note restricted to reviewers.

A Simple note is one that can be seen by everybody, regardless of their security level or type.

A note restricted by security level is a note that can only be seen by those users whose security level is equal to or greater than the security level assigned to the note.

A note restricted to reviewers is one that can only be seen by Monitors, Data Managers, and Browsers. It cannot be seen by Recorders.

The note type is assigned by the note author when it is added, and can be changed by the author at any later time.

Note Status

Note status can be one of three values:

1. for Information,
2. Open Query, or
3. Closed Query.

These should be self explanatory, and again can be changed at any time by the note's author.

Adding Notes

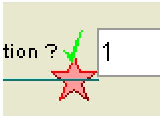
You can add a note to a widget from the Widget Monitoring Tool bar, or to the page from the Page Monitoring Toolbar. In either case the dialogue is the same:

Type in the title and text of the note, select the Notes Status and Type, press the "OK" button, and the note is added. Remember that once added, a note's title or text cannot be changed; only the type or status can be modified.

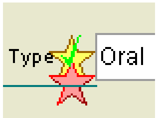
Adding and viewing Exception Notebooks

Adding an Exception Notebook is very similar, using the appropriate button on the Monitoring toolbar for the page or widget, and the dialogue is similar to that for a note, with the exception that the Note Status and Type selections are absent, because a Notebook has no additional Type (Exception Notebook *is* a note type) and the status of a new Exception Notebook is always Open.

An Exception Notebook attached to a widget causes a red star to be displayed under the status bitmap of the widget:

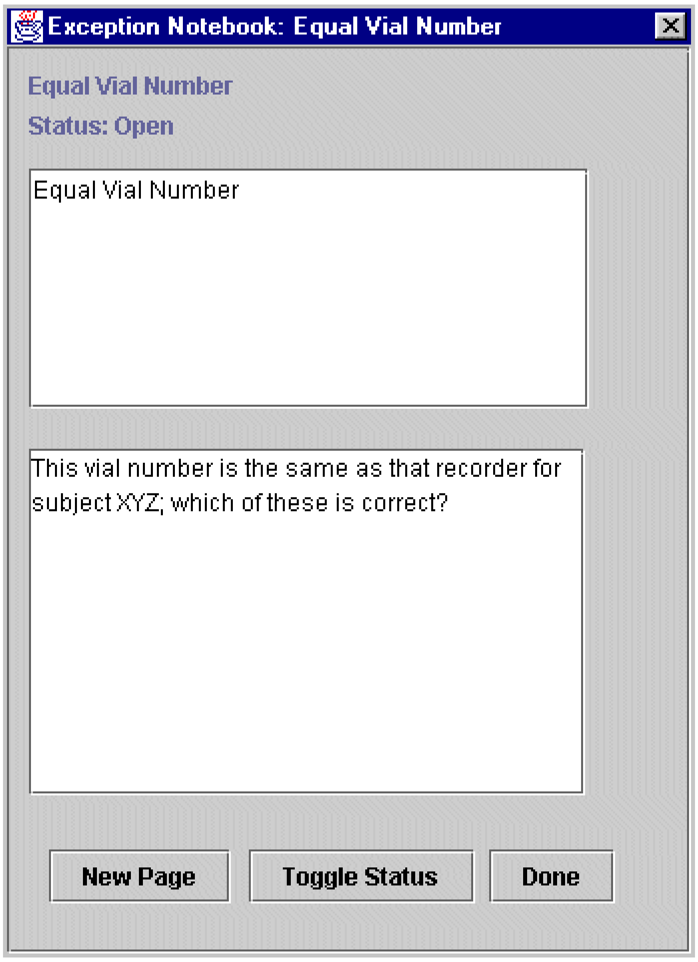


If both notes and notebooks are present, the two colours of stars both appear:



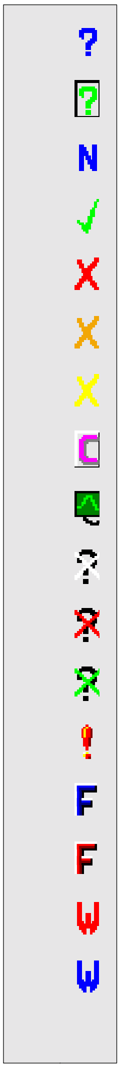
Exception Notebooks can be viewed in a similar manner to Notes, the only significant difference appearing once a particular notebook has been selected and display requested:The top list box shows the title of each page in the notebook, and the lower area is the text of that particular page. If there are multiple pages in the notebook, selecting the title line in the top list box causes the text for that page to be displayed in the lower area; it is thus easy to flip through the whole content of the notebook from this single display. This dialogue can also be used to add new pages to the end of the notebook - press the "New Page" button and you will get the page add dialogue already seen above.

If you are the author of the notebook, you will see the "Toggle Status" button. This allows you to change the status of the notebook, closing an open one or opening a closed one. If you are not the author of the first page of the notebook, you will not see this button.



Exception Notebooks, capable as they are of recording a "conversation" between Recorders and Reviewers, are a simple mechanism for exploring, resolving, and at the same time documenting the progress of resolution of data discrepancies and other exceptional conditions.

Status Bitmaps



Unanswered - Required

Unanswered - Optional

Cleared

OK

Bad

Amber Warning

Yellow Warning

Clinically Significant

Imported from an external source - not validated.

Temporarily Not Available

Not Available - Not Available NOT OK

Not Available - Not Available OK

Monitor Marked

Monitor Frozen

Monitor Frozen Bad Recorder

Monitor Waived

Monitor Waived and Frozen

Status Codes

There are two separate sets of status codes stored against each widget, the Recorder Status, and the Monitor Status. Each set of codes is 15 characters long. Some of these are used for internal system purposes, some can be set by user actions. In both cases, the main status code is the first.

Recorder Main Status (1st character)

U	Not initialised
Z	Cleared to null from previously entered data
O	OK
B	Bad Data
A	Amber Warning Level
Y	Yellow Warning Level
C	Clinically Significant
N	Not Available
T	Temporarily Unavailable
X	Obtained from an external source

Recorder Visibility Code (5th Character)

V	Visible
I	Invisible

Recorder Updatability Code (6th Character)

R	Read-Only
U	Updateable

Recorder Requirement Status (7th Character)

R	Required
O	Optional

Monitor Main Status

U	Uninitialised
R	Reviewed
M	Marked (implies Reviewed)
W	Waiver (implies Reviewed)
F	Frozen (implies Reviewed)
Q	Frozen Waiver (implies Reviewed)

Monitor SDV Code (2nd Character)

V	Passed Source Data Verification
X	Failed Source Data Verification

Status Icons

The Status Icons are the lower row of three smaller icons in the top right hand corner of the screen.

The first on the left, which may not be present on many pages (and will not be present on Table of Contents pages) indicates that there are Notes or Exception Notebooks attached to the page. (As opposed to attached to widgets on the page, which will be shown by rectangles drawn around the widgets concerned.)

The central icon shows the overall Subject status.

The right hand of the three shows the status of the current CRF page - again, this is not present on Table of Contents pages.

These icons are customisable, so the ones you see may differ, but we recommend that where these are customised, the colour scheme should remain the same, to avoid confusion.

Notes Icon

This should appear either as a yellow letter N, denoting that there are only informatory notes on the page, or a red or blue letter N. Red indicates that open Exception Notebooks are present, blue that Exception notebooks re present on the page but are all closed.

Subject Icon

The colour of the letter S indicates the Recorder Status; gray means incomplete, green good, red that there is bad data somewhere in the Subject's data. Magenta indicates Clinical Significance.

The background to the letter indicates the reviewed status. Gray means not reviewed, a blue background means that review is complete for the Subject.

Page Icon

The colour of the letter P indicates the Recorder Status; gray means incomplete, green good, red that there is bad data on the page. Magenta indicates Clinical Significance.

The background to the letter indicates the reviewed status. Gray means not reviewed, a blue background means that review is complete for the Page.

Passwords

You can change your password at any time by using the dialogue provided when you click on the Password icon (the key) in the Toolbar. You will have to change it periodically. Those who customise trials can set a period of time after a password change after which it must be changed again.

Your id and password is used to generate a hash code, a unique digital signature, which is applied to all the data that you key in, and the audit trail carries this electronic signature, which cannot be separated from the data without it being obvious that tampering has occurred. It is therefore critical that you protect your password so that others cannot use it and thereby "forge" your electronic signature.

You must follow the password operating procedures that you will be given as part of the materials with this trial or your part in it may not be capable of passing the appropriate validation procedures.

As well as providing your id and password at logon time, if you leave this application running for a period of time without entering data or moving the mouse, it may "time out" and you will have to log in again. This time period can be set by those customising your trial.

Any password failures will be logged as violations to the audit trail and transmitted to the monitoring site. Occasional failures and miskeyings are expected, but extended repetitions may well be investigated.

Electronic Signatures

We believe that the PhOSCo Electronic Signatures are sufficiently general and comprehensive so as to meet any reasonable regulatory framework. Where this proves not to be the case, it is our attention to attempt to correct any deficiency or apparent deficiency in as short a time as possible.

It should be noted, however, that ultimate security is possible only with ultimate effort. Paper signatures may be forged; with sufficient ingenuity, trouble, and expense of effort, so may any electronic signatures. It is possible to detect both types of forgery with appropriate quality control procedures; it is possible to reduce the probability of both types of forgery by ensuring that appropriate security procedures, particularly regarding the care of passwords, are in place and followed. No technical solution can replace the care and vigilance of those responsible.

Briefly, the principles involved are:

1. An identifiable person is one whose identity is made known to the application by a predetermined userid who logs onto the application by selecting a userid and providing a password associated with that id. To ensure a reasonable degree of security the plaintext of the password is nowhere stored in any electronic form; on originally defining, or subsequently changing, a password the system calculates a hash code from both the password and userid by means of a one way function, and it is this hashcode which is stored in a secure location. (A "one way function" is a function where the result can be determined from the input, but it is both computationally difficult in the mathematical sense to perform the reverse function and the mapping may not be one to one; so practically speaking neither the password nor the userid can be recovered from the hashcode.) At logon or other times where a password is entered, the userid and password provided are again used to calculate the hashcode, and this is compared with the stored version.
2. The primary record must be marked as being sourced by an identifiable person.
3. The primary record must be marked with the date and time of entry of the data.
4. The primary record must be marked with the place of entry of the data.
5. Unless the password has been compromised it must be impossible or at least computationally difficult to make a change to a data record whilst concealing the fact of such a change.
6. It must be made clear to the person entering the data that the act of logging on and entering data identifies them as the author of the data and that this is procedurally equivalent to them signing a paper record to that effect.
7. It must be made clear to the owner of the userid and password pair that the security and validity of the scope of the data they are responsible for is dependent on their following defined and adequate procedures to retain the security of their passwords. These should include the normal standards of not writing passwords down in accessible or obvious places, not using trivial or obvious passwords, periodically changing passwords, not allowing any other person to know or use their ids or passwords, not leaving running applications unattended, and so on. Some or all of these may be aided by application function (password ageing, password triviality checking, activity period checking) but it is ultimately the responsibility of the trial sponsor to provide adequate guidance, the user to act with sufficient care, and the trial sponsor again to perform data validation at trial close to ensure that procedures have been followed and that data is within defined quality levels.
8. A copy of the electronic form of the data must capable of being be provided to the regulatory authority together with the software necessary to display the originator, time, and place of entry of the data in conjunction with the data itself, and software sufficient to demonstrate to the regulatory authority that in these records the person defined was the originator of the data at the time and place specified, and that there has been no tampering with the records.

PhOSCo Clinical Trial Software can be demonstrated to satisfy all these requirements, and where the person who enters the data is a person with sufficient authority and who is competent to declare the record true and accurate, or where in conjunction with a monitoring procedure by a competent monitor, whose review and update of monitoring status of the data is subject to the same procedures as the original data entry, the act of entry and review can be held jointly to be of sufficient merit, this may be sufficient to satisfy regulatory authorities.

Where the person entering the data is for any reason not competent or lacks the authority to make such a declaration, and this cannot be rectified by the monitoring process for whatever reason, it may be necessary to add additional certification. This may performed in PhOSCo Clinical Trials by electronic signature certification.

Data record electronic signatures

To log on to the application, a user must have been previously defined to the system by the person customising the trial protocol, and an initial password assigned to that person. The password is not stored electronically; as with all password entry in PhOSCo software, the plain text password is used in combination with the plain text user name to form a one-way hashcode, which is stored.

During log on, the user must supply a password which together with his user name forms an acceptable hashcode. The password must be one which has been changed within a configurable period of time, otherwise the user must at that point provide an updated password. New passwords are subject to password triviality checking.

This password dialog also ensures that the user is aware that data is logged with his electronic signature, and that password protection is important.

During the period when the application is running, if no input is received for a configurable period of time, the user will be prompted to re-select his user name and re-enter his password before being permitted to continue.

All data entered in Trial Recorder, and all status update by Trial Monitor, is logged at the point in time of entry to one of several audit trail tables, one for each type of data (clinical data points, subject data, notes, events, and so on). It is these audit trail tables which comprise the primary electronic record; the data point table merely provides a convenient extract from the primary record for computational and presentational purposes.

The audit trail records record, for every transaction, the place, time, and originator of the data or status change, and each record is numbered sequentially.

So that it may be discovered if any tampering with the audit tables occurs, the key information, including place, time, originator, and sequential number, is encoded using a process that involves as input the password hashcode of the originator of the data or status change at the point in time when the data or status was entered or modified. At any future time, in order to decode a record, it is necessary to know who entered the data or status, at what time, and what their user name and password were at that point in time. A utility program can be used to scan through the table records performing a check of this and to ensure that the encoded version matches the plain text version. Use of this utility must be one of the checks performed at trial close to ensure that data integrity has not been compromised.

The PhOSCo General Licence provides that a copy or copies of Trial Browser may be made freely available to regulatory authorities together with a copy of the trial database. This ensures that the regulatory authority may inspect a certified copy of the primary record, and, by means of the software so provided, satisfy themselves as to the origination and electronic signature of each and every data record. The source code of the application, test cases, test harness, and the test data necessary to validate application function is available to the regulatory authority so that they can satisfy themselves as to the adequacy of any algorithms, routines, or programs involved.

It is clear that this process is entirely dependent on the security of the users' passwords, the security of the storage of the password hashcodes in the trial database, and of course the integrity of the users themselves. This last is a topic not of our concern, and the first is one that can only be aided by the application as detailed above but is otherwise the responsibility of the users and those running the trial. Hashcode security can be addressed by ensuring that the only table which stores these is stored in a database with sufficient security; it is recommended in any case that the database engine used to store data is one that provides adequate security and either true encryption or at the least some means of obfuscation.

We believe that where sufficient care is taken over passwords and database security, the implementation described above is sufficient to satisfy any person or authority that the person recorded as being responsible for the entry of data or status is the person who actually performed that entry. Further assurance as to quality levels can only be achieved by a system of Source Data Verification, either complete or partial based on statistical quality control techniques.

That only leaves the case where the persons responsible for entry do not have appropriate authority or are otherwise not competent to certify the data as being true and accurate. Here there may be a need to use Electronic Signature Certification.

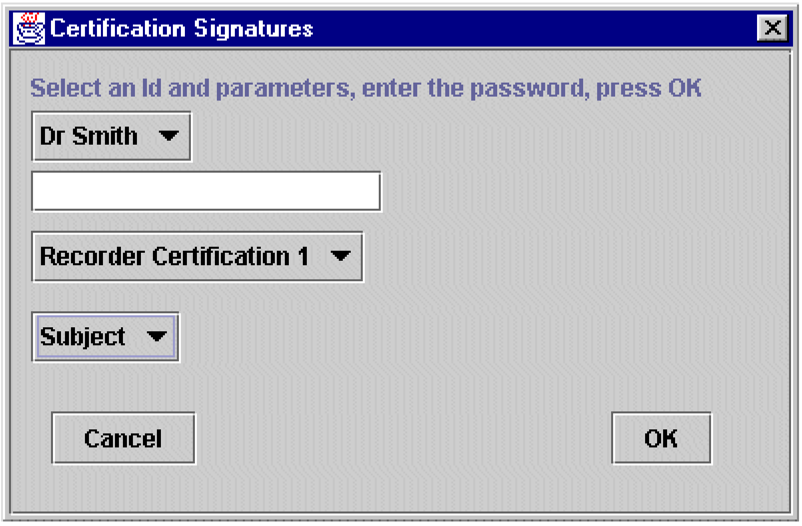
Electronic Signature Certification

Each Data Point (corresponding to a single question on a CRF page) in the PhOSCo clinical database contains two separate sets of status bytes: one for Recorder status, the other for Monitor status.

The ninth, tenth, and eleventh of each of these two sets of status bytes are reserved to identify whether that data point has received a particular level of electronic signature certification.

Trial Builder allows the definition of six Trial Customisation Parameter strings to describe the different categories of certification defined by each of these status bytes.

When any competent person wishes to certify the status of the data for a Subject, this can be done by invoking the signatures dialogue from the Trial Recorder or Trial Monitor Toolbar.



This dialogue allows the user to select which of these certification categories is to be applied. If the user is a Recorder, only Recorder categories may be applied, if a Monitor, only Monitor categories; both may be applied in either application by a Data Manager.

The dialogue allows the user to select whether the certification is to be applied to all the data current for the current Subject, all the data current for the current Visit, or all the data current for the current page. It is the responsibility of the person making the certification to have ensured that the data and status information being certified meets the appropriate requirements.

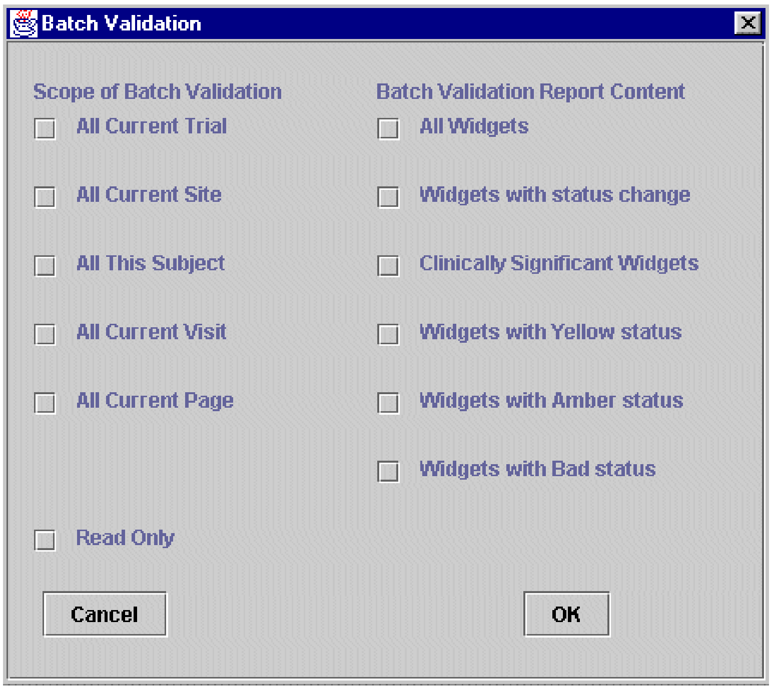
On entry of this information, and being confirmed by the appropriate password, the status byte corresponding to the certification category is set on for every data point within the scope of the certification. A record of the nature and scope of the certification, together with the place, date and time, and originator of the certification is stored in the event audit trail table, and a record of the certification is added to the data point audit trail table.

If at any future time the data or Recorder status of any data point with a certification status byte set is altered or amended in any way other than by the addition of further certification, all certification status bytes on that data point will be set off, and that fact noted in the data point audit trail table.

It is therefore possible at all times to determine whether any individual data point has received any particular category of certification, and by who and when.

Batch Validation

Clicking on the Batch Validation icon from the Toolbar will bring up the Batch Validation dialogue.



Batch Validation is the process whereby all the elements that you select will have their validation checks re-performed. As you can imagine, this may take a little time if you have a lot of data, but will only be a few seconds on a reasonable machine for a single subject with only a dozen or so pages.

This should only need to be done rarely; for example when a validation has had to be changed changed half-way through the scope of a trial.

Running it is simple. The check boxes on the left determine which elements in your database will be revalidated, and those on the left will determine which widgets will appear on the Batch Validation report.

The "Read Only" check box is important. If this is checked, then the Batch Validation exercise will not update the status values in the database; it will be a "what-if" exercise. If it is not checked, the status values in the database will be amended.

The "report" produced by Batch validation is actually a CSV (Comma Separated Value) file which can be imported into most spreadsheets or report generator software, to produce a nicely printed report or analysis. The Information that each record contains is:

Trial Site
Subject
CRF Page
Subpage
Widget Name
Data Value
Status
Previous Value
Previous Status

Appendix I: User Parameter File

The TMPARMS.DAT file is essential for the correct running of Trial Monitor, and must be in the current directory when the program is invoked. It is an ASCII file, with individual lines specifying individual parameters or comments.

A line beginning with the characters // is considered a comment and is ignored.

Other lines define parameters and parameter values. The first non-whitespace token on a line is considered to be a parameter, and the remainder of the line is considered to be the parameter value, ignoring any leading or trailing whitespace characters.

User Parameters can have any name required, as long as they do not contain whitespace characters.

The following sample file presents and explains the mandatory and optional parameters.

```
// User Parameter File for testing
//
// Mandatory Parameters for Trial Monitor
//
// Number of Trial that will be started
//
trialno 101
//
// Name of Site whose data is to be updated
//
sitename Derby Royal
//
// Name of site at which function is being performed
//
actsite Trial HQ
//
//  Don't Stop two instances of TM running on same machine
//
//allowmultipleinstances yes
//
//
// If the monitor is to spawn a Communications Thread for comms to a
// Server, the parameter "communicator" should be "yes".
//
//    Note that this functionality has not yet been activated
//
communicator yes
//
// Port number the Communications Thread will look for the Server on.
//
//    Note that this functionality has not yet been activated
//
ServerPort 9989
//
//
// Backup and Restore:
//
// Full path of database file to be backed up
//
srcdbfile e:\jctprod\ctj\jctmeta.db
//
// Full path of this User Parameter file to be backed up
//
srcusrfile e:\jctprod\run\usrparms.dat
//
// Full path of database file backup
//
bakdbfile G:\TRDB.BAK
//
// Full path of User Parameter file backup
//
bakusrfile G:\TRUSR.BAK
//
//
//
```

```
//
// Parameters for Trial xxxxxx (override defaults)
//
// Database type:
//                   1 = No longer used
//                   2 = Sybase JDBC
//                   3 = Interbase JDBC
//                   4 = McKoi JDBC
//                   5 = Oracle JDBC
//
dbtype 4
//
// Database connection parameters.  Note that some databases may need
//                                  other parameters. See specific
//                                  database documentation.
//
//  Sybase JDBCDriver com.Sybase.jdbc.SybDriver
//  Sybase URL        jdbc:sybase:Tds:localhost:2638?ServiceName= + dbname
//
//
//  McKoi  JDBCDriver   com.mckoi.JDBCDriver
//  McKoi  DBURL        :jdbc:mckoi:localhost/
//
//
JDBCDriver   com.mckoi.JDBCDriver
DBURL        :jdbc:mckoi:localhost/
dbname JCTSRV7
userid dba
userpw sql
//
locking no
trace yes
//
//
// Optional trial Parameters: "User" parameters
//
minbadbpsys 80
maxbadbpsys 180
minambdbpsys 90
maxambbpsys 160
```