

Handling CRF Design Changes in a Live Environment

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1. ABSTRACT

Building an EDC database is based on the study protocol which should contain all required information for the eCRF. Precision, consistency, and completeness are highly important for that. In many situations these criteria are not met. In other scenarios the protocol demands a high level of complexity from the EDC design. For example, study procedures can be country or site specific, or a combination of paper and electronic diaries is used. These aspects and challenges should be taken into account when reviewing the protocol.

Even when the protocol fulfills these criteria, and the protocol is not overly complex, change requests in the production phase cannot be avoided but are often time consuming and error prone.

This paper provides a number of examples of change requests to the eCRF and the database and describes how these were implemented. In addition, lessons learned about smart design changes will be shared and discussed.

2. INTRODUCTION

The eCRF is the main tool for collecting and structuring data in a clinical trial. At database go live, the study eCRF is released to the production (also called 'live') environment. It is then ready to be used to collect study data. Before release, an extensive validation is performed to ensure the eCRF meets all requirements and needs. This includes testing of the screen design, edit checks and calculations.

Unfortunately, a design change may be required during the study. Updates to a live database should be handled with care. Before requesting the database modification, a risk analysis should be performed to determine possible issues that may occur due to the changes to the initial eCRF design. Then a change request should be created that provides a clear description of the required updates and the process to be followed to implement the changes. The change request should be reviewed and approved by different functions within the study team.

All changes should be tested thoroughly in a testing environment before the design changes are implemented in the live database. Furthermore, additional actions from the study team are often required after the changes are released to the live environment. For example, site staff may need to approve the revised eCRF, study monitors may need to re-verify the data and statistical programmers may need to adapt their programs that create data listings.

Some guidance is given in this document on how to deal with change requests, how to prevent design changes and how to minimize the time spent on implementing the changes.

3. DESIGN CHANGES IN VIEDOC™

The process to update a clinical trial database usually depends on the functionalities available in the electronic data capture (EDC) system that is used for the trial. For example, in the Viedoc EDC system, there are two ways to implement a change to the eCRF design: Fully customizable design and Revised design.

Fully customizable design is generally used to implement design changes due to a protocol amendment and revised design is used to update the study eCRF to resolve issues or to add a question to the form.

3.1. FULLY CUSTOMIZABLE DESIGN

With this option, a complete new version of the eCRF (i.e. full eCRF version) is created. The new version exists next to the already existing full version(s). Changes made to the design will only affect forms which are created after the new eCRF version is made effective. This means that a site and/or a subject can have more than one eCRF version.

For example, data of the first three visits is collected in the eCRF version 1.0. Due to protocol amendment, a new version of the eCRF (i.e. version 2.0) is published with effective date January 10, 2017. Data of the remaining visits which occurred after January 10, 2017 are captured in the eCRF version 2.0. Data of the first three visits remains in eCRF version 1.0.

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3.2. REVISED DESIGN

A revised design is used to upgrade forms that were already submitted. When there is more than one full eCRF version available, the design change must be implemented (if required) for each form in the different full versions.

For example, if a form is available in both eCRF version 1.0 and 2.0 and update is required in both versions, then two revisions are needed to update the form to version 1.1 and 2.1. Furthermore, approval from each site is required to apply the revised form to the sites in the clinical trial database. The old form remains applicable in the site until the revised form is approved.

4. WHY DESIGN CHANGES CAN BE REQUIRED IN A LIVE STUDY

Common causes of design changes in live studies are given in this chapter, illustrated with real-life examples from different clinical trials.

4.1. PROTOCOL AMENDMENT

The trial protocol can be amended in the clinical conduct phase for various reasons. For example, due to new insights coming from an interim analysis or lessons learned during study conduct. An update of the study eCRF is sometimes required to align with the amended protocol.

Examples

In a clinical study, a protocol amendment was issued that included an additional assessment to be performed. A full customizable design was used to create a new full version of the eCRF. New items required for the protocol amendment were added with edit checks. Before release, the form design and the edit checks were thoroughly tested in a test environment to ensure everything works properly. The effective date of the new full eCRF version was set to the effective date of the protocol amendment. Thus visits with a visit date before the protocol amendment were not affected.

In another clinical study, the definition of an inclusion criterion provided by the protocol is not clear. A request was made to update the inclusion criterion in the eCRF, to make it more clear for the sites. However, as the study eCRF should reflect the protocol, it was not allowed to modify the eCRF text without amending the protocol. A design change could only be performed after the protocol was amended.

4.2. COLLECTION OF ADDITIONAL SOURCE DATA

Some information is only collected on the source documents and not entered in the study eCRF. During the study, it may be decided to submit additional source data if determined required for analysis.

Example

In a clinical study, information regarding backup kits was collected on the source documentation. As the backup kits were used more often than anticipated, the study team decided to collect information about the use of backup kits in the eCRF. Therefore 2 questions were added to the CRF form: 'Was backup study product dispensed during this visit?' and 'Product number of backup study product'. See figure 1 below.

The image shows a screenshot of an eCRF form with two questions. The first question is 'Was assigned study product dispensed during this visit?' with radio buttons for 'Yes' and 'No', and a text input field for 'Product number of dispensed study product'. The second question, 'Was backup study product dispensed during this visit?', is highlighted with a red rectangular box. It also has radio buttons for 'Yes' and 'No', and a text input field for 'Product number of backup study product'. A black box with the text 'NEW data' in red is overlaid on the 'Yes' radio button of the second question.

Figure 1

As this additional data was to be collected for all subjects in the study, a revised design was used to add the two new questions to all existing forms and to any new forms that will be created. Approval from the site was required to apply the

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revised form to the site in the clinical trial database. Furthermore, source verification was needed to be performed by the study monitor.

4.3. DATA ENTRY ISSUES

Sometimes a design change is required to resolve issues experienced by the sites when entering data into the EDC system. Although the eCRF was tested thoroughly before release, an unexpected issue may occur during the study.

Example

In the Adverse Event (AE) form, an edit check is present that checks the AE end date against the end date of the related Serious Adverse Event (SAE). During study conduct it was noted that the edit check did not work properly when one of the end dates is a partial date. An error message appeared indicating that the SAE End date was not on or before the AE end date. See figure 2.

The screenshot displays a 'Serious Adverse Event section' with the following elements:

- Is the Adverse Event serious?** Radio buttons for 'Yes' (selected) and 'No'.
- Start Date:** A date picker showing 'dd MMM yyyy'.
- End Date:** A date picker showing '14 Feb 2018'.
- Category of SAE:** Radio buttons for 'Results in death', 'Life threatening situation', 'Requires hospitalisation', 'Prolongation of existing hospitalisation', 'Persistent or significant disability or incapacity', and 'Other medically significant event'.
- Error Message:** A red-bordered box at the bottom contains a red exclamation mark icon, the label 'End Date', and the text 'SAE End date is not on or before the AE End date. Please correct.'

Figure 2

Additionally, the form could not be saved because of the presence of the error message. See figure 3 below.

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Figure 3 shows a screenshot of a clinical trial form and its settings. The form displays the 'End Date' as '14-Feb-2018'. The settings panel on the right, titled 'SAESPDAT Settings', shows validation rules. Three callouts explain the form's behavior:

- Allows form save is ticked:** A checkbox labeled 'Allows form save' is checked in the settings panel.
- AE End date Feb 2018 SAE End date 14 Feb 2018. Message SAE End date is not on or before the AE End date. Please correct.** An error message is displayed in the settings panel: 'SAE End date is not on or before the SAE Start date. Please correct.'
- Allows form save not ticked, so CRF cannot be saved when error AE_3 is shown.** A checkbox labeled 'Allows form save' is unchecked in the settings panel.

Figure 3

As the site could not retrieve the full AE end date and the form could not be saved because of the form setting, a design change was implemented to allow the site to respond to the error message and to allow the form to be saved despite of the error. It was decided not to update the edit check itself as the study conduct was already completed and this issue only occurred once.

4.4. CRF SETUP ISSUES

A design change may also be required to resolve eCRF setup issues.

Examples

In a clinical study with infants, feeding formula names should be selected from a codelist in the eCRF. The option 'Other' is to be selected if the used product is not present on the list. However, during clinical conduct it was noted that the 'Other specify' field did not appear when the option 'Other' was selected. As this information was required for analysis, a revised design change was implemented to correct the issue.

In another clinical study, a regurgitation codelist was incorrectly updated in a design change. A tabulation was added at the end of an 'output export value' by mistake. See figure 4 below.

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Items with format name					
#	Format name	Format type	Code list display text	Code list value	Output export value
35	_REGUR	string	0 - 2 episodes per day	0	0 - 2 episodes per day
			3 - 5 episodes per day of small volume	1	3 - 5 episodes per day of small volume
			>5 episodes/day of >1 coffee spoon	2	>5 episodes/day of >1 coffee spoon
			>5 episodes/day of about half of the feeding in < half of the feedings	3	>5 episodes/day of about half of the feeding in < half of the feedings
			Continuous regurgitations of small volume > 30 minutes after each feeding	4	Continuous regurgitations of small volume > 30 minutes after each feeding
			Regurgitation of half to complete volume of a feeding in at least half of the feedings	5	Regurgitation of half to complete volume of a feeding in at least half of the feedings
			Regurgitation of the "complete feeding" after each feeding	6	Regurgitation of the "complete feeding" after each feeding

The text '0-2 episodes per day' was changed to '0-2 episodes per day ' .

Figure 4

This extra character was not spotted during the User Acceptance Test (UAT) and the design change was released to production. As this revision required approval from each site before it can be applied, there was a period of time where the old and the revised versions existed simultaneously in the clinical trial database. This led to an issue with the data export because the old and the revised codelists could not be merged in SAS. Therefore, a new revised design change was needed to remove the tabulation in the value.

In a questionnaire form, the score for each question was populated by the system based on the response provided by the subject. One of the questions on the form was linked to another item on a different CRF form. A condition was programmed on the question field to populate the score with '0' in case the related item was empty. Therefore, when opening this questionnaire form without completing the related CRF form first, the score was already filled in with '0' for the question. This was confusing for the site staff and could cause misinterpretation of the data. See figure 5.

Figure 5

To solve this issue, an update has been done to delete the link between the answer to the question and the item in the other form, from where it was populated. The answer should now be entered manually, and the score and status will not already appear by opening the form.

In a study with vulnerable adults, some questions on the questionnaire were found to be too difficult to answer and therefore often left empty by the subjects. The empty fields could be confirmed as 'missing' in the EDC system and a reason could be provided. However, the form also contained scores which were populated by the system based on the responses provided by the subject. If the answer is missing, then the score is empty. Unfortunately, a populated field does not have the option to be confirmed as missing in the EDC system. Furthermore, the populated item was set as a 'required' item in the eCRF. That means that even though the question could be left empty and confirmed as missing, the score was required and marked red by the system. See figure 6 below.

Figure 6

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Because of this, the form could not be submitted. A revised design change was implemented to disable the 'required' option that allows the form to be saved with empty fields.

In a clinical study where a questionnaire was used, it was discovered by the study monitor that the order of the questions on the English version of the questionnaire (as used in the eCRF) was different than the order on the German version of the questionnaire (which was used at the site). This led to confusion of the site staff when entering data in the eCRF. To prevent data entry errors, a revised design change was created to align the order of the questions in the eCRF with the source document.

These kind of issues could be prevented by performing a check at study start to ensure the questionnaires used at the sites are aligned with the questionnaires used in the CRF. Furthermore, the order of the questions should also be checked when a questionnaire is translated to other languages.

After site initiation visit for another clinical study, the site staff noted that an incorrect site number was assigned to their site in the clinical trial database. The site numbers in the EDC system had to be updated. Also the lab reference ranges which were linked to the sites needed to be corrected. Fortunately, no subjects were enrolled yet and therefore no additional action was required for the randomisation.

4.5. SITE OR COUNTRY SPECIFIC PROCEDURES

When a new site or country is added to the trial that follows site- or country specific procedures, a design change may be required to accommodate the new site/country.

Examples

Stool samples were collected in a multi-country clinical trial with infants. For all subjects, the stool samples were collected at the site. Data of these stool samples were entered in the eCRF by the site personnel, who is responsible to enter all CRF data. During study conduct, a new country was added that followed a different procedure for collecting stool samples. A dedicated Study Nurse collected the stool samples at parent's home. The Study Nurse was also responsible to enter all data, that is collected at home, in the eCRF (i.e. stool samples, paper diaries and questionnaires). She was specially trained for these combined tasks and a separate role for the Study Nurse needed to be created in the EDC system, with access to the relevant CRF forms. See figure 7 below.

The screenshot shows the user profile configuration for 'Study Nurse Lab'. The 'Name' field is highlighted with a red box. The 'Status' is set to 'ON'. The 'Description' field contains the text 'Study Nurse for Austria who collects and handles stool samples'. The 'Avatar' section shows a grid of icons. The 'Special' section includes checkboxes for 'User can only view form data (this overrides all edit permissions)', 'Export o...', 'Medical coding', and 'View reference data'. The 'CRF Rights' section is highlighted with a red box and includes checkboxes for 'Add/update subject/event/form data and query answers', 'Reset/Delete eve...', 'Add/change queries', 'Add pre-queries', and 'Promote pre-queries'. The 'eLearning' section includes checkboxes for 'Site User Training (SUTV4)' and 'Monitoring Training (MTPV4)'.

Figure 7

Furthermore, the study monitor was not able to perform source data verification (SDV) for the stool sample data because the information was not stored at the site. So it was decided to disable the SDV requirement for these data and to verify the stool sample data in the eCRF with the stool sample data from the lab instead. At Go-live this different procedure was not known so a fully customizable design change was implemented to create a country specific design for the new country.

In another clinical study, infant formula names should be selected from a codelist in the eCRF. Because of this design, addition of a new country to the study requires a design change to extend the codelist, to include the formula names available in the country. See figure 8 below.

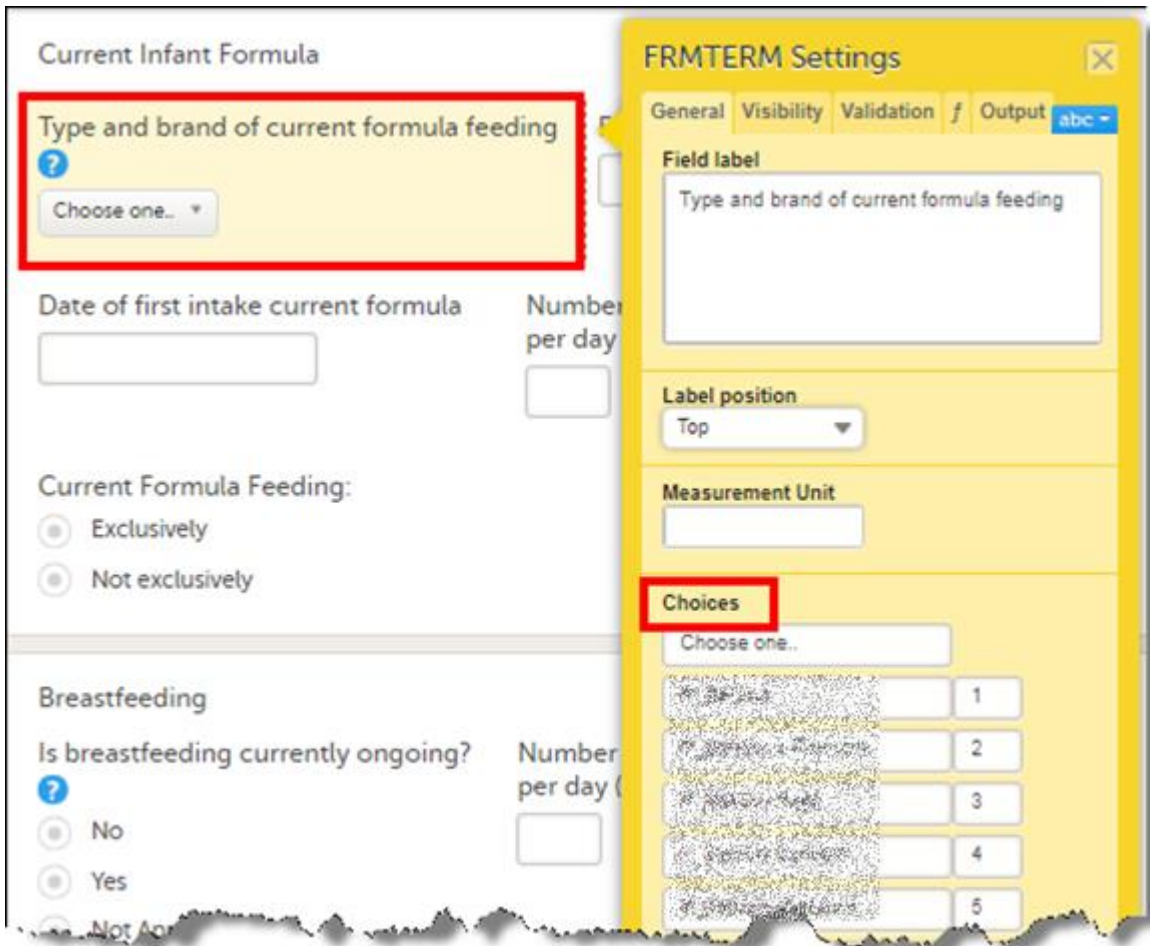


Figure 8

Because the codelist contained the formula names from all countries, the codelist was very long and an additional check was required to be performed by Data Management to ensure the sites did not select a formula name from another country. A smarter design for the use of codelists is presented below in section 5.2.

5. SMART WAYS FOR SETTING UP A CLINICAL TRIAL DATABASE

An efficient eCRF design allows the collection of data required for analysis in an appropriate format for export and further processing. In this chapter, smart ways for setting up a clinical trial database that is stable and resistant to future changes are shared.

5.1. LIBRARY OF STANDARDISED CRFS AND EDIT CHECKS

Everybody will agree that a big library of validated CRFs with edit checks and formats is a perfect starting point to create a new clinical trial database. The library should be maintained by an independent Library Manager, that keeps track of the versions of the standard CRFs. Requests to update a standard CRF so it can be used in a study should be submitted to the Library Manager and (s)he will decide which updates are allowed to be implemented.

When creating a clinical trial database, standard forms are to be used whenever possible. As the standard CRFs are already validated, this also means less validation for the study. Minor changes to the standard forms, which do not have any impact on the edit checks and do not leave out vital items are allowed without the need for revalidation. Other changes to the standard forms require full testing in the UAT.

Study specific CRF forms can also be created if needed. These forms should be properly tested in a testing environment to ensure all aspects of the eCRF meet the study requirements and needs (e.g. form design, edit checks, calculations, formats, coding).

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5.2. USE HIDDEN MARKERS FOR SITE- AND COUNTRY SPECIFIC ITEMS

Make use of the functionalities available in the EDC system. In the Viedoc EDC system, hidden labels can be created for items and edit checks. When certain questions and/or edit checks are only applicable for a specific site/country, a hidden site/country label can be added in the eCRF that is linked to the site/country item. When site/country is selected, the label is populated by the system with the site/country code. This allows the use of site/country specific codelist or creation of site/country specific form. For example, when a hidden country label is used on a form and the country is completed with 'NL' (for Netherlands), an additional item is visible on the form that displays a codelist containing Dutch flavor names.

Figure 9 shows a condition programmed on a form to populate the hidden country label with 'NL'. When this condition is met, a specific codelist for 'NL' is displayed on the form. See figure 11 below.

Figure 9 shows a configuration screen for a form item. At the top, there is a 'Show' dropdown menu. Below it are three radio button options: 'always', 'on simple condition evaluates true', and 'on advanced condition evaluates true'. The 'on advanced condition evaluates true' option is selected. Below the radio buttons is a text box containing the following condition code: `!D1SERV1NR.contains('1') && START.DM.COUNTRY == 'NL'`. A blue question mark icon is visible to the left of the code box.

Figure 9

Figure 10 shows a condition programmed on a form to populate the hidden country label with 'PL'. When this condition is met, a specific codelist for 'PL' is displayed on the form. See figure 12 below.

Figure 10 shows a configuration screen for a form item, similar to Figure 9. The 'Show' dropdown menu is set to 'on advanced condition evaluates true'. The condition code in the text box is: `!D1SERV1NR.contains('1') && START.DM.COUNTRY == 'PL'`. A blue question mark icon is visible to the left of the code box.

Figure 10

Figure 11 shows a 'Choices' dropdown menu. The dropdown is open, showing a list of 9 items. Each item is displayed in a greyed-out font and is followed by a white box containing a number from 1 to 9. The items are: 1, 2, 3, 4, 5, 6, 7, 8, and 9.

Figure 11

Figure 12 shows a 'Choices' dropdown menu, similar to Figure 11. The dropdown is open, showing a list of 9 items. Each item is displayed in a greyed-out font and is followed by a white box containing a number from 2 to 9. The items are: 2, 3, 5, 7, 8, and 9.

Figure 12

Use of country specific codelists is preferred above the design described in section 4.5, where one long codelist is used for the study. When a new country is added to the study, instead of extending the codelist, a new item with a country specific codelist can be created for the new country. This will prevent issues in SAS that may occur when merging two codelists from different design versions.

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5.3. ALIGN THE CRF DESIGN WITH THE STUDY PROCEDURES

When setting up the clinical trial database, ensure the forms and visits are set-up consistently with the study flow. Take into account the procedures for sample handling, the use of electronic or paper diary, the early termination process, visit windows defined in the protocol, etc. Add instructions in the eCRF when needed.

Furthermore, it is important to understand the study procedures to ensure the eCRF is setup according to study needs. Keep the following in mind when setting up a clinical trial database: Procedures for the planned assessments, the in- and exclusion criteria, protocol deviations, site- and country specific procedures that may affect the CRF design, etc.

5.4. KEEP TRACK OF DESIGN CHANGES

Keep track of the design change requests and the design changes implemented in the trial. See table 1 below for an example of a design changes tracker. This tracker can also be used for lesson learned; it can be referred to when creating a new clinical trial database, in order to avoid similar issues in the new study.

Old version	New version	Assignment date	Changes made	Reason changes	Change #	Assigned to (sites)
3.0	3.1	30/01/2018	Backup kits recording in Check questions.	Backup kits are used more often and now the team wants to have the backup kit numbers recorded in Viedoc.	MSC_005	All sites

Table 1

5.5. PROPER TESTING OF THE CRF

Proper testing is very important to ensure the quality of the study eCRF. Every aspect of the clinical trial database should be tested, from the data entry screens until the SAS datasets which are generated. Create a detailed test plan and ensure the following aspects are also included in the testing:

- All possible data can be entered (for example partial dates, missing data, extreme values)
- Reference ranges are defined correctly
- Visit windows are set as per protocol
- Edit checks are working properly in all scenarios
- Visit and CRF flow are setup according to the protocol
- Different roles are setup as per study requirement (e.g. each role can only see the forms they are allowed to see)
- Data export to SAS is as expected

5.6. TEST ALL THINKABLE SCENARIOS THAT MAY OCCUR IN THE STUDY

Different subject flows are possible in the study. Ensure all scenarios that may occur in the study are included in the testing. Create at least one test subject for each of the following categories:

- Subjects dropping out before or directly after randomisation (if applicable)
- Subjects dropping out after each visit for withdrawal consent
- Subjects dropping out after each visit for adverse event
- Subjects dropping out after each visit as lost to follow up
- Data collected without proper informed consent
- Subjects completed the study

6. SMART WAYS FOR SETTING UP DESIGN CHANGES IN A TRIAL

As the process to implement design changes can be very time consuming, updates to a live database should be kept to a minimum. There are several ways to minimize the number of design changes in a trial.

6.1. TIMING OF DESIGN CHANGES

It may be a good idea to make a design change after an Interim Analysis and not before, because a design change may have an impact on the programming of data listings and to prevent delays in providing data as clean as possible for the Interim Analysis.

6.2. IMPLEMENT MULTIPLE UPDATES IN ONE DESIGN CHANGE

Keep track of the design change requests and try to implement as much requests as possible in one design change, without making the update too complex. For example, it should be taken into account whether a change should affect already entered data or if it is only applicable for new events. Combining multiple requests into one design change minimizes the time required for testing and documentation.

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6.3. USE CRF INSTRUCTIONS AND TRAINING TO CLARIFY ISSUES

When it is noted that a site experiences some difficulties in understanding a CRF question, do not immediately consider a design change to update the CRF question. Instead, provide a CRF training or release revised CRF instructions on how to interpret and complete the question.

6.4. AVOID MAKING ESTHETICAL CHANGES

Only implement design changes which are really required. Esthetical changes may sometimes be proposed, but if the update does not have any impact on the data collection (i.e. sites are able to complete the CRF properly, without any issues) then it should be considered not to implement the change. By tracking all design change requests, it can always be decided to include the update in case another design change is required.

6.5. CREATE AWARENESS OF THE RISKS OF DESIGN CHANGE

Implementation of a design change in a live eCRF can have impact on other activities and deliverables. For example, issues may occur in the data listing programs due to a new variable in the study data. As these issues may not be spotted during the UAT, it is important to perform an impact assessment together with the study team, before the design change is implemented.

6.6. ENSURE HIGH QUALITY OF THE CRF AT STUDY START

To avoid the need of a design change during the study, ensure the eCRF is properly validated before releasing it to production. All aspects of the eCRF design should be tested, including the codelists that are used and the SAS datasets which are generated from the EDC system. All scenarios that may occur in the trial should be included in the testing, for both data values and data flow. Perform a QC check on the SAS datasets and provide a test transfer to the statistical programmer to ensure data are in an appropriate format for further processing.

6.7. PARTICIPATE IN PROTOCOL REVIEW

Ensure a representative from Data Management is involved in the protocol review. Collaboration between medical writer, medical monitor, data manager and statistician at the protocol development stage may lower the need for a protocol amendment during the trial. Think of practical issues when reviewing the protocol and its supporting documentation. For example, discourage the use of site- or country specific procedures in the protocol.

7. CONCLUSION

Updates to a live clinical trial database could be minimized, for example by implementing the following:

- Adequate review of the study protocol by different functions
- Use of standardized CRFs
- Proper testing of the eCRF which includes all scenarios that may occur in the study

However, design changes during a study cannot entirely be avoided. In case an update of a live database is required, it should be handled efficiently and smartly as described in this paper.

8. ACKNOWLEDGMENTS

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