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# Scientific and Practical Substantiation of Ways of Developing and Introducing Electronic Case Report Forms to Ensure the Quality of Bioequivalence Studies

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## Research Article

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## INTRODUCTION

Nowadays, in Ukraine the number of clinical trials conducted with the purpose of establishing bioequivalence of domestic drugs to their foreign analogues has increased dramatically. The key establishment which is responsible for collecting data regarding the bioequivalence parameters of drug is the place of study (PS). Source data verification (SDV) is the most common method of quality control at PS, so the higher requirements from the Sponsor to the quality of the research are, the more often the monitor tries to carry out visits to PS to perform SDV. However, contemporary literary sources indicate that the increase in the number of monitoring visits and 100% SDV is unreasonably expensive and doubtfully improve the quality of research. In this article there have been 1050 CRFs of bioequivalence studies, performed in Clinical and Diagnostics Center of National University of Pharmacy, analyzed for corrected errors. Although the results have satisfied us and confirmed the high level of quality control at PS, we would give preference for computer control of technical mistakes especially at a time when several studies are simultaneously carried out at the clinical site and saving time is very important for Investigators. Considering all the aspects of disadvantages of paper CRF usage, an algorithm for the development of e-CRF has been proposed. Implementing the developed e-CRF in the system of Clinical and Diagnostics Center of National University of Pharmacy will obviously help to improve data entry while reducing the number of monitoring visits to the clinical site and save time for Investigators who are involved in the study of bioequivalence of drugs.

Over the last decade in Ukraine the number of clinical trials conducted with the purpose of establishing bioequivalence of domestic drugs to their foreign analogues has increased dramatically. The drug manufacturer pays special attention both to the quality of the product itself and to the quality of the conditions in which it is studied.

The key establishment which is responsible for collecting data regarding the bioequivalence parameters of drugs, is the place of study (PS). For instance, it is the PS where study subjects get enrolled, the effects of the generic and the original drugs are clinically evaluated, and which is especially important, study subjects' biological samples are collected, the latter being foundation on the bio analytical laboratory conducts assessment of pharmacokinetic parameters of the effects of drugs, drawing its conclusion on bioequivalence. Data received by researchers during the study of bioequivalence are sent to the Sponsor (the Manufacturer)/ the Contract Research Organization (CRO), thus forming the basis for the formation of the registration file for the generic drug at its final stage of implementation – registration phase. Therefore, during each clinical study, PS and its personnel directly involved in the study must strictly comply with the requirements of Good Clinical Practice (GCP). From the Sponsor's/ CRO perspective these requirements are interpreted as the increase of visits to the site (on-site monitoring) before, during and at the end of the study to obtain data that would meet the highest standards [1].

The Guidance of the International Conference on Harmonization emphasizes that data obtained during the clinical studies should be actively monitored to ensure data quality [2]. The quality of data in clinical research is regarded as the absence of errors and their compliance with the objectives of the study [3]. The absence of errors is checked during on-site visits by study monitor (Monitor or Clinical Research Associate) – a key figure in the detection of inconsistencies, errors and validity in data collection of clinical research [1]. According to the GCP requirements of paragraph 4.9.2 "Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained" [2], so the verification process of the source data becomes the one of the main monitor tasks (Source data verification – SDV). SDV is the most common method of quality control at PS, so the higher requirements from the Sponsor to the quality of the research are, the more often the monitor tries to carry out visits to PS to perform SDV. However, contemporary literary sources indicate that the increase in the number of monitoring visits for the purpose of improving the quality of research greatly increases the cost, and at the same time, has " questionable benefits" [1,3,4]. The point is that it is not necessary to develop a quality system for every possible error or to perform 100% manual review of all the data, because "there will always be errors that slip through the quality check process" [5]. Therefore, the key objective doesn't exclusively seem to be increasing on-site monitor visits and 100% SDV, but minimizing the effect of data errors on the final result of clinical study [3]. The use of electronic case report form (eCRF) in the practice of clinical trials helps to timely remove possible errors, conduct ongoing remote monitoring by Sponsor/CRO and responsible persons of the PS. According to some sources, this method of quality control of work with the data obtained in a clinical trial and bioequivalence studies is 15 times as effective as manual SDV [3,6,7].

Despite the significant advantages of eCRF usage in clinical trials and bioequivalence studies, in particular, the Sponsor/CRO, monitors, and staff of the PS have a caution attitude toward introduction of eCRF in everyday practice. This may be due to additional expenses for training, development, verification and validation of eCRF that should be borne by the Sponsor/CRO, in case of carrying out such a process. In addition, the staff of PS has to pass specific training on dealing with such eCRF and get appropriate skills to ensure quality data entry.

In the process of creating quality management system of the PS the development and implementation of eCRF may be initiated by the clinical site itself. The PS personnel who will be involved in the development, validation and practical application of such eCRF, should be provided with an appropriate methodological base for executing the above. Thus, the aim of our work is to substantiate the ways of developing eCRF in order to ensure quality control of bioequivalence studies of drugs and to offer practical approaches to its implementation at PR from the scientific and practical point of view.

## MATERIALS AND METHOD

In this research, we have studied the materials of 21 clinical bioequivalence studies of drugs with the participation of healthy volunteers which used paper CRFs. For 3 clinical trials (CT) with the participation of volunteers with different diseases, there have been the electronic CRFs applied and in the course of the study there have been electronic databases on the subject of patterns, the nature of the interaction during the work analyzed. All the above studies were conducted in Clinical and Diagnostics Center of the National University of Pharmacy (NUPh CDC) during the period from 2006–2014. In the process of our work there were analyzed approximately 1050 case report forms. All selected bioequivalence studies have similar research protocols, schemes of drug administration and the duration of study.

In the course of the study the methods of systematic analysis, generalization, and formalization are used.

## RESULTS and DISCUSSION

PS is a responsible link in the quality assurance framework of conducting bioequivalence studies. Co-investigators of PS have to ensure proper implementation of GCP and all the requirements of the study Protocol; to monitor AE/AR timely, to clearly define the extent of the need and the use of concomitant therapy in accordance with the study protocol, etc. [8]. In case of determining non-equivalence of the researched drugs by the bioanalytical laboratory the first check of the quality of data acquisition, the possibility of fabrication and falsification conducted at PS. **Figure 1** shows the relationship between key participants in the process of clinical bioequivalence studies of drugs. As you can see in this picture, the process of working with data involves a large number of participants that have different structural subordination, various functions in the study of bioequivalence of drugs, as well as different scope of knowledge and skills at working with data and ensuring an adequate quality. All this complicates the work in the quality assurance system of data management and requires additional methodological and organizational support.

It is also worth emphasizing that when the equivalence of the generic medicinal product to the original one isn't established, then the reasons for this may be due to either errors in study performing at PS and errors in the technological development or manufacture of the investigational drug. Thus, the task of the PS investigator is to make the study process maximally monitored and efficiently performed, in order not to take responsibility for the drug development, which doesn't concern PS (in particular technological shortcomings).

In accordance with the modern requirements of GCP and quality assurance system for this matter at PS a video surveillance system can be implemented, as well as standard operating procedures (SOPs), the procedure for archiving and storage of study

data and the implementation of the requirements of the quality management system according to international standards ISO 9000. For example, at NUPh CDC they introduced a system of video surveillance and recording of the process of a clinical trial, which is archived and stored for the following 15 years with all the study documents regarding this research. The video records capture time and date of the given study as well as samples handling, their processing and storage prior to their transfer to the bioanalytical laboratory, the state of volunteers during their hospitalization, the course of all the research procedures and so on. In addition, the NUPh CDC has implemented a quality management system based on integrating of the principles of ISO 9000 standards system and the requirements of the guidelines ICH Q8, ICH Q9 and ICH Q10 in traditional procedures of clinical studies management that are performed according to the GCP requirements.

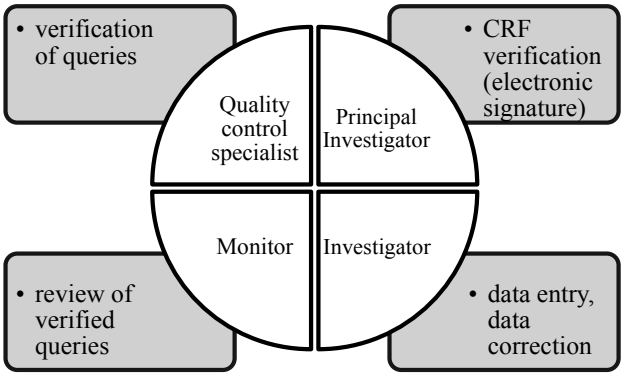


**Figure 1.** Allocation of responsibilities of participants involved in bioequivalence study of drugs.

The presence of an archive at NUPh CDC has allowed us to realize a retrospective analysis of 1050 CRFs as they are left in a way of self-copied pages and are stored on the clinical site after the end of the study. These paper CRFs were reviewed for the presence of the mistakes that were made during data entry, identified when carrying out the monitoring visits and identified during the quality control (QC) **(Figure 2).**

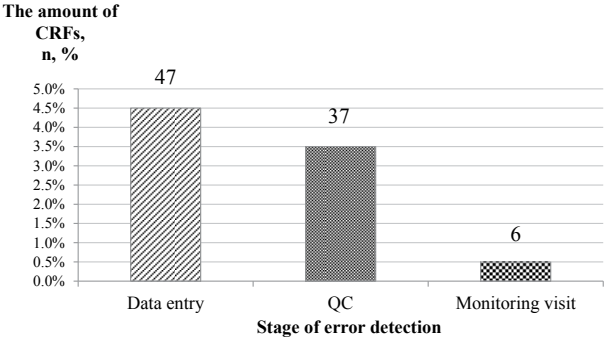


**Figure 2.** The number of CRFs with corrected errors at various stages of their detection.

In **Figure 2** the phase of error detection implies that the Investigator who is responsible for data entry, makes a mistake and corrects it independently, which forms 4.5% at 1050 CRFs. Then after the Investigator a Quality Control Specialist reviews the CRFs for the presence of discrepancies in the source documentation. In our case he finds 37 errors, corrected by the Investigator. This type of cooperation between the Quality Control Specialist and the Investigator allows to minimize the number of errors, which confirms 0.5% of the errors during the visits of the monitor. This means that in most studies the monitor in general doesn't find any error in the CRFs. Indeed, in 1050 CRFs for 21 studies, the monitor finds only 6 CRFs in which there are errors that "slipped" through a multi-stage inspection of the site staff.

We have checked the nature of these errors and determined that in general they were technical and non-systemic ones, seen only on one page of the entire CRF (error in randomization/screening number; no date, wrong number of analysis/ECG, etc.). It should be noted that they were insignificant, their absence/incorrect indicators were not an endpoint of research, so such errors cannot affect the final results of the study [9].

Although these results have satisfied us and confirmed the high level of QC at PS, we would give preference for computer control of technical mistakes especially at a time when several studies are simultaneously carried out at the clinical site and saving time is very important for Investigators.

According to the analysis of our experience with paper and electronic CRFs and theoretical sources [3], the assessment criteria of data entry method with the possibility of protection from errors have been identified and a comparative analysis of the advantages and disadvantages of using electronic and paper CRFs has been carried out **(Table 1).**

**Table 1.** Comparative analysis of the advantages and disadvantages of using electronic and paper CRF.

| Assessment criteria of data entry | If the criteria are met during the work with the corresponding type of CRF | |
|---|---|---|
| | Paper CRFs | Electronic CRFs |
| 1. Data can be entered within the limited time interval, if the filling is not timely made, pages are blocked | | yes |
| 2. Possibility of the simultaneous SDV | | yes |
| 3. Possibility of the simultaneous QC | | yes |
| 4. Automatic control of the data entry quality (date control, completion of the missing area, protection of data entry history) | | yes |
| 5. Possibility of filter use (duplicate vital signs records, constant results of laboratory parameters, similar birth dates, use of concomitant therapy) | | yes |
| 6. Monitoring study procedures | yes | yes |
| 7. Entry of inadequate parameters | | yes |
| 8. Control of data corrections (correction history) | yes | yes |
| 9. Chronological control of data entry | | yes |
| 10. Data entry in the real period of time | | yes |
| 11. Automatic completion of unnecessary pages/ items (for example in case of volunteer's withdrawal) | | yes |
| 12. Presence of the back-up copy in case of data loss | | yes |
| 13. Necessity of the special technical requirements at the PS | | yes |
| 14. Necessity of the special training for the monitor and PS personnale at the PS | | yes |

The analysis demonstrates a clear advantage of the electronic CRF as compared to paper analogues in almost all evaluation criteria in the area of data entry method. For those criteria that have been established for the both types of CRFs such as the monitoring of study research procedures and the control of data corrections, it is obvious that the use of electronic version of CRF will enhance these functions because they will be performed within the real period of time with simultaneous quality control.

Thus, we can conclude that using electronic case report forms will simultaneously solves several important problems associated with the data entry in a CRF, namely automatic control of data entry enables reducing the number of technical errors that necessarily occur during work with a large amount of data (the system will check it); it also becomes possible to perform simultaneous SDV and QC both at the place of study and remotely, which further decreases the number of monitoring visits to the site.

Automatic completion of unnecessary pages or items saves time not only for the Investigator who is responsible for data entry, but for the whole research team. The monitor, who is located outside of PS, will be able to observe the data entry process on-line and remotely ask questions in the real period of time, not retrospectively during monitoring visits as it used to be. This, in its turn also encourages investigators to enter data in a timely manner and simultaneously to respond to current queries, so that in advance to be prepared for the monitor visits to the study site.

Considering all these aspects of e-CRF, we propose the algorithm for the development of e-CRF which we have come up with in **Figure 3.** This algorithm must provide limited access, namely: a special list of persons, who will have individual opportunities to work with the electronic system, is essential, as the Investigator who has the right to enter data, mustn't verify it. The monitor, on the contrary, verifies the data but doesn't enter it into an electronic form, except for queries creation. Absolute authority is delegated to the Principal Investigator who should be able to enter data, and verify, to respond to the queries and to sign the CRF.

In this connection, each participant will have a separate password and access that will allow to authorize and to fix the date of entries, corrections, comments, queries, etc.

We assume that the use of e-CRF at the PS will improve the quality of data entry while reducing the number of monitoring visits to the clinical site and save time for Investigators who are involved in the study of bioequivalence of drugs. We believe that the development of e-CRF by the clinical site and its further usage will compensate for the costs that will be incurred by the PS in connection with the development and maintenance of this computer system because with the help of this system the clinical site does not only increase the level of quality control at PS, but also reaches an international level of work with the data obtained during clinical studies of drugs, therefore becoming more appealing for Sponsors/pharmaceutical manufacturers.

The proposed ways of e-CRF development in order to ensure quality control of bioequivalence studies of drugs, as well as practical approaches and developed algorithm of the process implementing at the PS, prove to be universal and beneficial for being used by PS in their practice.

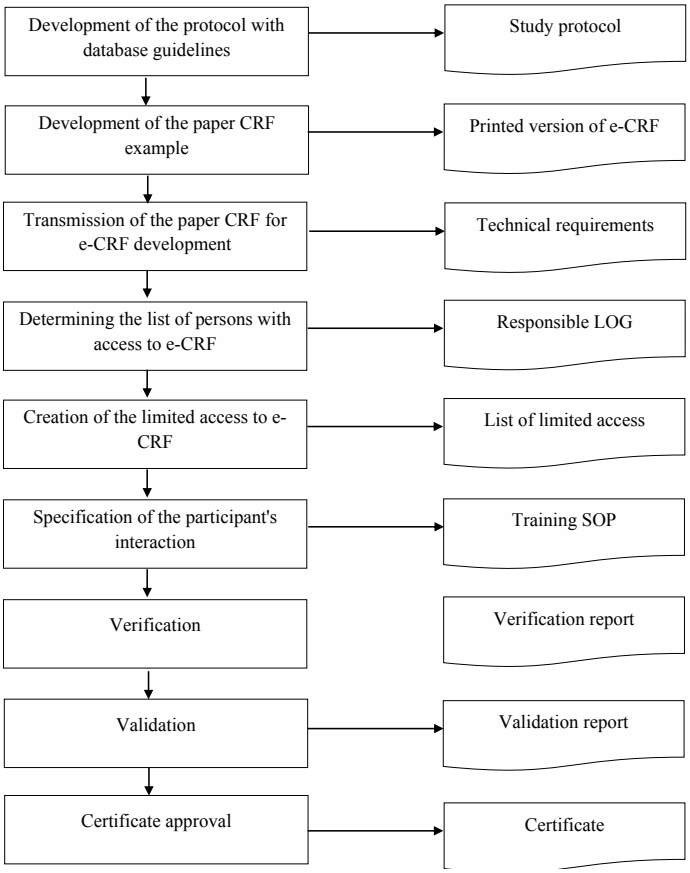


**Figure 3.** Algorithm of e-CRF development.

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