Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(3):182-186

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Concomitant therapy in clinical trials of drugs: Its role, problems and approaches to its consideration

V. Ye. Dobrova, K. O. Zupanets and K. L. Ratushna

Department of Clinical Pharmacology and Clinical Pharmacy, National University of Pharmacy, Kharkiv, Ukraine

---

ABSTRACT

Different interpretations of concomitant therapy in various types of clinical trials and non-systemic approach to revealing its nature have pre-determined the systematization and generalization approaches to its assessment. In clinical trials concomitant therapy assessment gets the most important meaning in cases when it is necessary to precisely justify, determine and closely assess its influence because such information may become the basis for further stages of clinical trial, as well as future directions of pharmacovigilance. There have been protocols and case report forms of clinical trials with different designs, performed in Clinical and Diagnostics Center of National University of Pharmacy, analyzed. Consequently, on completion of analysis there have been various approaches to understanding and using concomitant therapy at a place of study determined. The developed algorithm of the Investigator's (or the Monitor's) assessment of registration and clinically significant abnormality assessment helps to conduct a comprehensive analysis of clinically significant abnormality, to minimize data entry mistakes, to standardize the process of fixation and assessment of concomitant therapy according to the ICH GCP requirements developed. Implementing the developed algorithm in the system of place of study will obviously help to facilitate the Monitor's work, as well as the work of investigators who are responsible for data capturing, data monitoring and data entry processing while conducting clinical trials.

Key words: clinical trials, new drugs, concomitant therapy, algorithm,

---

INTRODUCTION

An appropriate management of clinical trials (CT) of new drugs, a monitoring, assessment of quality of its realization and ensuring proper data registration is a guarantee of scientific reliability of obtained information regarding the efficacy and tolerability/safety of a certain drug [10]. Only if data of a clinical trial is exact and reliable, all drawbacks and discrepancies clarified, it is possible to conduct a statistical data processing and an analysis by medical experts [8].

Organizing CT of drugs is a complex and multistage process where groups of professionals from different branches of pharmacy, medicine, and biostatistics are involved [4]. It is a long way from the trial design and the enrollment of the first study object to the point the first results are entered into the corresponding documents. That's why even in case of planning the study accurately there may be issues that can emerge during the study and that require mobilizing all the parties / participants of CT of a given drug in order to discuss, approve and solve possible problems. Such problems can include assessing abnormal ranges, registering and processing a data entry, verifying source data, interpreting study data concerning an adverse event/ adverse reaction (AE/AR), as well as using concomitant therapy (or concomitant medications) during the study [9]. Among all problems of an appropriate organization, realization and monitoring of CT it is essential in our opinion, to draw attention to the formation of approaches to ensuring an exact and definite estimation, interpretation and registration of the use of concomitant medications in CT of drugs.

The necessity of this task is also determined by the fact that, according to the requirements of GCP, the main document of each CT, the Investigator must pay attention to cases of concomitant medications during CT. According to the protocol requirements, the monitor, as the Sponsor's representative, must check the accuracy of data entered into case report forms (CRFs) regarding "adverse events, concomitant medications and intercurrent diseases" [6]. While analyzing protocols, a study course and reports of CT of drugs health authorities, in their turn, pay attention to the administration of concomitant medications and its possible influence on the study results [7]. Notably, the issue of concomitant therapy, as well as the assessment of its influence is one of the key points in the system of quality assurance during CT of drugs.

At present, novel pediatric trial designs, including opportunistic pharmacokinetic (PK) studies of off-label therapeutics used as part of clinical care, provide a stepping stone for further pediatric research which will include enrollment of children with many concomitant medications that might affect PK parameters vs healthy volunteers [7].

According to the dictionary for clinical trials "concomitant medications are the drugs that are not being studied but which a patient is taking through all or part of a study. These may be other drugs for the same indication as the study or for other indications"[3]. The same situation is observed when the study is run on patients who need compulsory therapy in addition to the investigational product. For example, the Phase 1b/IIa study of the biologically active compound which was conducted on patients with active and moderate rheumatoid arthritis (RA) when the study protocol allowed a stable concomitant treatment with low doses of oral corticosteroids, NSAIDs or non-biological disease – modifying antirheumatic drugs (DMARDs): Methotrexatum, Leflunomide, Chloroquine, Sulfasalazine [5]. According to the requirements of inclusion criteria the concomitant therapy, which is meant as prior RA treatment, is limited by the highest dose of the above-mentioned drugs and the regimen of their use, specifically the patients must receive concomitant DMARD treatment for at least 3 months with stable dosage prior to randomization; NSAIDs with a stable dosage for at least 2 weeks prior to randomization; Oral corticosteroids maximum of 10 mg of prednisolone or equivalent per day with a stable dosage for at least 4 weeks prior to randomization.

Concomitant therapy acquires another meaning in trials on healthy volunteers: Phase I and bioequivalence studies. Moreover, the studies which are united into one group due to the regulations and statements have differences in concomitant therapy during CT. Thus, in the bioequivalence studies the healthy volunteers must not take any other medicinal products (including vitamins, diet-supplements, and medicinal herbs) within 14 days till the first product intake and during the whole study period till its completion [2]. If there is a need for concomitant therapy administration like in case of clinically significant abnormalities (CSA), the volunteer must be withdrawn from the study.

On the one hand, Phase I studies are also run on healthy volunteers and don't allow any concomitant therapy regardless prescribed or non-prescribed drugs, and even vitamins. On the other hand, there may be an exception in some cases when the Investigator considers the concomitant therapy to be unable to the study procedures. As an example, we want to present Phase I, randomized, crossover, open-label study designed to access safety, tolerability, PK equivalence, and bioequivalence of glycerol phenylbutyrate in healthy adults, carried out in Clinical and Diagnostics Center of National University of Pharmacy (CDC of NUPh) [1]. That study protocol allowed to give anti-emetic drugs in cases of nausea and specifically recommended the group of selective antagonists of 5-HT3-receptors of serotonine: Ondansetron, Dolasetron, Granisetron. Drugs such as Prochlorperazine, Promethazinum, Metoclopramide must not be given to volunteers because these drugs could cause the central nervous system disturbances. The study protocol also approved an occasional use of Paracetamol and the patient could continue participating in the CT with the corresponding notes in CRF. According to the protocol requirements, any other medication could be administered to volunteers at the Investigator's discretion but in contrast to bioequivalence studies such subjects weren't withdrawn from the study.

Inattentive identification, classification and determination of concomitant therapy during the study can affect the accuracy of study drug action assessment as well as CT in general. In clinical trials concomitant therapy assessment gets the most important meaning in cases when it is necessary to precisely justify, determine and closely assess its influence because such information may become the basis for further stages of CT, as well as future directions of pharmacovigilance. The ambiguity of situations / events in CT of drugs, when it is proved / forbidden to use concomitant therapy during the study, can lead to the initiation of discrepancies between the key parties of the study, also complicating the quality assurance of the clinical trial and reliability of data obtained.

Different interpretations of concomitant therapy in various types of clinical trials and non-systemic approach to revealing its nature have pre-determined the systematization and generalization approaches to its assessment. Therefore, the aim of this study is developing the algorithm for the Investigator's / Monitor's assessment of

concomitant therapy, whose usage may enhance the in-time monitoring and evaluation of clinically significant abnormalities, as well as actions which to be taken due to its initiation during CT.

EXPERIMENTAL SECTION

During our research we have studied documents of 12 clinical trials of bioequivalence with the participation of healthy volunteers and 5 clinical trials with the participation of patients with different diseases. These trials were run in Clinical and Diagnostics Center of National University of Pharmacy in 2006 – 2014. There were 17 study protocols and 1014 CRFs analyzed. All selected studies had different designs of protocols, different charts of drug administration, different duration of study, and different ways of drug administration; there were either different concomitant therapy or none, and some of these trials were performed in healthy volunteers and in patients with various probabilities and severity of CSA (Table 1). Domination of healthy volunteers is related to the specificity of CDC NUPh work, which focuses on the bioequivalence and Phase I studies.

Table 1. The concomitant therapy application according to CT type

Contingent of volunteers who took part in clinical trials conducted in CDC of NUPh in 2006 2014		Concomitant medications were administered due to	
		CSA	Main disease
1. Healthy volunteers	n=968	yes	-
2. Patients with liver disorders and liver cirrhosis	n=16	yes	yes
3. Patients with liver disorders and episodic encephalopathy	n=15	yes	yes
4. Patients with rheumatoid arthritis	n=6	yes	yes
5. Patients with Parkinson's Disease	n=9	yes	yes

RESULTS AND DISCUSSION

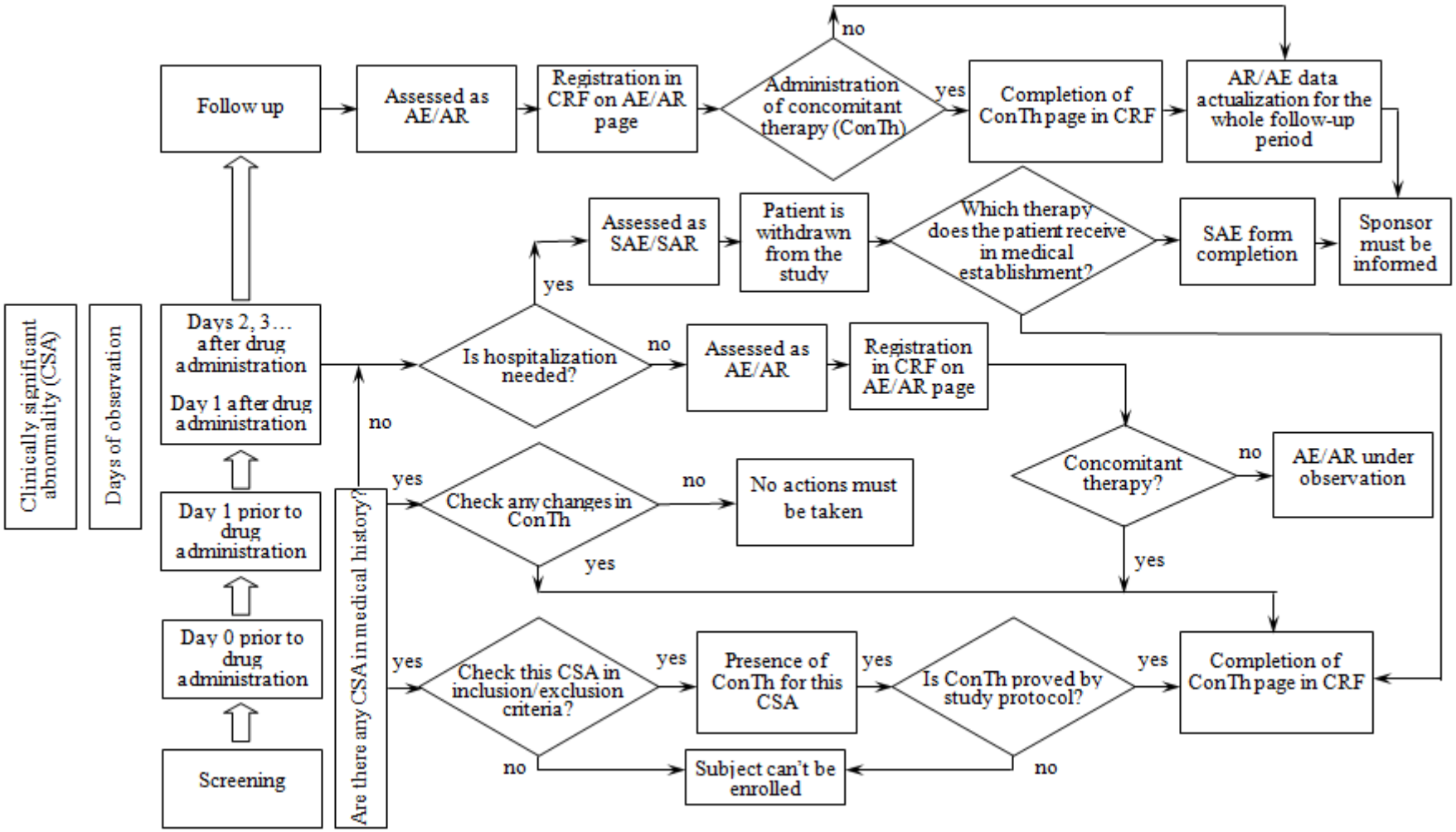
As a result the analysis of CT documents identified that to develop the general algorithm for concomitant therapy assessment it is necessary to enter the term which may capture the maximum quantity of possible responses of the human body to the drug action, as well as clinically abnormal results. Taking it into consideration, to define these manifestations we suggest using the general term "clinically significant abnormality" (CSA). And it includes changes in the clinical state of the study subject or such changes and deviations from normal ranges which need additional attention, and sometimes additional actions, including the administration of concomitant therapy.

The developed algorithm captures all Days of observation when the CSA was identified by the Investigator or the Monitor (Fig. 1). For example, if the Investigator detects any CSA in healthy volunteer / patient at Screening (or on Day 0, Day 1 prior to study drug administration) then he must check medical history regarding this abnormality. If it was mentioned there then the Investigator must check inclusion/exclusion criteria for this specific CSA. In case CSA corresponds to inclusion/exclusion criteria it is important to clarify the concomitant therapy which is administered and to clarify whether it is proved by protocol requirements.

If CSA isn't mentioned in medical history or appears after study drug administration then the hospitalization must be checked. In case patient is hospitalized such CSA is considered as serious AR/AE that requires additional therapy which must be reported to the Sponsor. If hospitalization isn't needed then CSA is considered as AR/AE which sometimes doesn't require any concomitant therapy.

Hence, the suggested structural algorithm for the registration and assessment of CSA during clinical trials and bioequivalence studies precisely assigns the place and the role of concomitant therapy, reflecting the system of procedures to manage the Investigators' actions taken at different stages of a clinical trial. It enhances the development of scientific approaches to ensuring the organizational aspects of trials and arranging the interaction between investigators, sponsors / monitors and health authorities in case of concomitant therapy need for all stages and types of the clinical trial.

Fig. 1. Structural algorithm of the Investigator's actions for the registration and assessment of CSA according to a Day of clinical trial



CONCLUSION

There has been an analysis of clinical trial documents carried out. This analysis has led to the discrepancies in the objectivization of the term "concomitant therapy" assessing. There have been protocols and CRFs of clinical trials with different designs, performed in Clinical and Diagnostics Center of National University of Pharmacy, analyzed. Consequently, on completion of analysis there have been various approaches to understanding and using concomitant therapy at a place of study determined. The developed algorithm of the Investigator's (or the Monitor's) assessment of registration and CSA assessment helps to conduct a comprehensive analysis of CSA, to minimize data entry mistakes, to standardize the process of fixation and assessment of concomitant therapy according to the ICH GCP requirements developed. Implementing the developed algorithm in the system of place of study will obviously help to facilitate the Monitor's work, as well as the work of investigators who are responsible for data capturing, data monitoring and data entry processing while conducting clinical trials.

REFERENCES

[1] BM McGuire; IA Zupanets; ME Lowe et al. *Hepatology*, **2010**, 51 (6), 2077-2085.
[2] Committee for Medicinal Products for Human Use (CHMP). Guideline on the Investigation of Bioequivalence, European Medicines Agency (EMA), London, **2010**, 27.
[3] D Simon. Dictionary for Clinical Trials, 2nd Edition, John Wiley and Sons, Ltd, New Delhi, **2007**, 262.
[4] E Nielsen; DA Hyder; C Deng. *Ther. Innov. Regul. Sci.*, **2013,** 48(2), 173-180.
[5] F Behrens; PP Tak; M Østergaard et al. *Ann Rheum Dis.*, **2014**, 0, 1-7.
[6] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH-Efficacy Topic 6: Guideline for Good Clinical Practice (CPMP/ICH/l35/95), ICH, Geneva, **1996**, 53.
[7] MM Laughon; DK Benjamin Jr; EV Capparelli et al. *Expert Rev Clin Pharmacol.*, **2011**, 4(5), 643-652.
[8] R Hattemer-Apostel; S Fischer; H Novak. *Drug Inform J.*, **2008**, 42, 123-130.
[9] V Tantsura; I Grimes; J Mitchel et al. *Drug Inform J.*, **2010**, 44, 745-756.
[10] V Ye Dobrova; KO Zupanets; KL Ratushna. *Management, Economy and Quality Assurance in Pharmacy*, **2013**, 27(1), 23-27.