International Journal of Clinical Trials
Kala NG et al. Int J Clin Trials. 2021 Nov;8(4):323-329
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: https://dx.doi.org/10.18203/2349-3259.ijct20214112

Review Article

Overview of clinical data management and statistical analysis of bioequivalence study

Kala N. G.*, O. Shruti, Aishwarya B. M.

Department of Biotechnology, RV College of Engineering, Autonomous Institute Affiliated to Visvesvaraya Technological University, Belagavi, Bengaluru, Karnataka, India

Received: 20 June 2021
Accepted: 19 July 2021

***Correspondence:**
Dr. Kala NG,
E-mail: ngkala25@gmail.com

ABSTRACT

Owing to the demands of both pharmaceutical industry and the regulatory authorities' clinical data management (CDM) field came into practice. CDM plays a vital role in the study data gathering stage of clinical research. In order to meet this goal, specialized tools i.e. software applications are used to maintain audit trials that offer easy identification and resolution of data discrepancies even in huge and complex clinical trials. Hence a proper and effective clinical data management is required for generating high-quality, accurate, reliable and statistically sound dataset. Such dataset are relatively easy to interpret which is a key step in statistical analysis of a bioequivalence study. Performance of a thorough analysis is dependent on the quality of the trial data. This review highlights how data is processed after it is captured through eCRF, data validation, data cleaning and statistical analysis specially focused on Bioequivalence studies.

Keywords: Clinical trials, Case report form, Edit checks, Pharmacokinetics, Bioequivalence

INTRODUCTION

Clinical trials are majorly designed to observe and analyse the outcomes of human subjects under the experimental conditions which are controlled by the researcher or scientist.[1,2] The evolution of clinical trials travels quite a long and fascinating journey.[3-5] In the "Book of Daniel" (562 BC - 1537), the world's first clinical trial was recorded where an experiment was carried out by the King named 'Nebuchadnezzar' where he ordered the subjects in his kingdom to live on a strict diet of meat and wine to compare the nourishment of vegetarians against the meat eaters. In 1537, the first clinical trial was conducted in an accident manner by the famous surgeon by name Ambroise Pare where he was responsible for the treatment of the wounded soldiers in the battlefield. James Lind is considered as the first physician for conducting a controlled clinical trial around 1747 in the modern era. He conducted a comparative trial for scurvy.[4,6] The Nuremberg Code of 1947 stressed on the voluntarily given consent and this interest of informed consent was later regulated in the US along with the 1962 Kefauver-Harris amendments. Then the Helsinki Declaration of 1964 added some of the specific recommendations for the involvement of humans as subjects in the clinical trials.[3] With the support of ethical guidelines clinical trials started to become incorporated in regulation in the early 20th century. The Food and Drug Administration (FDA) was founded in 1862 as a scientific institution and later became a law enforcement organization after the passing of the Food and Drugs Act by US Congress in 1906. After this, the FDA gained more power over drug related legislation.[3,7]

A clinical trial is conducted to validate a new drug, vaccine, diagnostic procedure involving therapy or a machine. These trials need detailed pre-designed setup to respectively collect data. These setups are created along

with an analysis plan called statistical analysis plan (SAP). These documents will describe all events in detail and will guide the entire trial through the study design. These designs allow data collection in a pattern specifically created for the study.[8] Such collections are not just to control the entry but also to decide its purpose similar to CRFs. The latter helps with cleaning and management of the data. Certain platforms like SAS and R are known to have built-in packages just for such events.[9,10] All the analyses are performed on these cleaned and validated data sets suggesting that the better the validation, stronger and more reliable the statistical results will be. Poorly arranged data when analysed will include error and is prone to falsely reject hypotheses contributing to type-I or type-II errors. Hence management is vital for a reliable analysis.

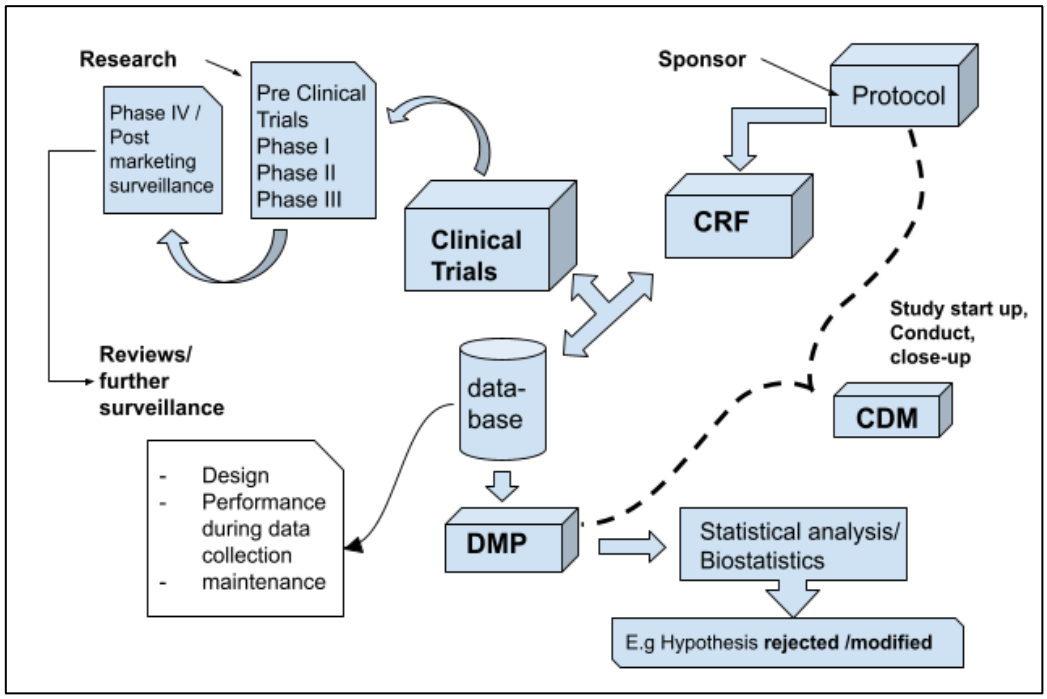

Figure 1: Overview of clinical data management.

The entire process of capturing, validation, and organization of subject research data is done in compliance with standard procedures to obtain high-quality data that is complete and error-free. The main aim is to collect maximum data by reducing the sum of flaws as low as possible for analysis.[11,12] In order to meet this goal, specialized tools i.e. software applications are used to maintain audit trials that offer easy identification and resolution of data discrepancies even in huge and complex clinical trials. CDMS are the computer applications that are accessible for data management. CDMS are particularly important in multicenter trials in order to handle enormous amounts of database produced. Both commercial and few open source CDMS tools are available. Some examples are Oracle Clinical, Macro, Rave (Commercial) and open CDMS, PhOSCo, TrialDB (open sources).[13]

Data management plan covers 3 phases: Set up phase, Conduct phase and Close out phase. The Setup phase includes study protocol interpretation, CRF designing and development, writing edit checks specifications, database design and User Acceptance testing (UAT). Whereas, the conduct phase comprises data collection, validation, discrepancy management, Med coding, SAE. Finally the close out phase ends with Database audit and locking. The concept of statistical analysis comes into sight after the trial data is loaded, cleaned and locked generating a full trial dataset. This article highlights the processes involved in CDM and gives the reader an overview of how statistical analysis of bioequivalence study is designed.[22]

SET UP PHASE

A specialized document for data capture in CDM is Case Report Form (CRF). CRF is developed in order to capture the subject data which is a significant part of the clinical research and can have an impact on study success.[14] Currently there are 2 classes of CRFs used in clinical data management, i.e., traditional paper CRF and improvised Electronic Case Report Form (eCRF). For larger studies eCRF is preferred whereas paper CRF is best chosen for smaller studies. Moreover in the present scenario eCRF is chosen over paper CRF as they are less time-consuming.[15-18] Apart from CRF design, CDMS also includes data validation programming. Edit checks are used for discrepancies management during data capturing from the end user. It is used to map some data points from one CRF to another, to fire a pop-up message when discrepant data is entered. It is also used to calculate certain fields like Body Mass Index (BMI), Subject's age

etc. Use of validation specifications improves the quality of the clinical trial data. All Electronic Data Capturing (EDC) systems have their own discrepancy management tool and they make use of different programming language like Java, Python, SAS, C#, SQL.[11,18-21]

Table 1: CI range based on log-transformed data.[20]

Test	Reference	Ratio	Percentage	ln(ratio)
0.3	1.0	0.8	80	-0.223
0.9	1.0	0.9	90	-0.105
1.0	1.0	1.0	100	0
1.1	1.0	1.1	110	0.095
1.2	1.0	1.2	120	0.182
1.25	1.0	1.25	125	0.223

Protocol interpretation

Protocol is called as the master document of the trail. The study protocols are considered as both a resource for the regulators and an end result of a study. A protocol is the trial document that defines the objectives, background, and rationale for the trial, design, methodology, statistical considerations, and an organisation of a trial. A protocol is provided by the Clinical trial team (sponsor) to the Clinical management team before developing the DMP. Protocol interpretation is the first and foremost step in all clinical data management platforms, as they provide the data points to be considered for data management and statistical analysis. The management team must focus on the few important contents of the protocol that is needed for designing the case report form. From the study protocol we first look into the general and background information of that particular study. General information includes title, identifying number, year, name and place of the sponsor, investigator, clinical laboratories and additional departments involved in the trial. Background involves a report that the trial will be conducted in compliance with the protocol, GCP and the relevant regulatory requirement. The most significant part of the protocol is the objective, which comprises thorough explanation of the primary and secondary study goal and clearly states the research hypothesis/ research question. Once the objective is cleared we will look for the next content of the protocol which are Clinical study design, Inclusion and exclusion criteria, Informed consent form, treatment of subjects, predicted adverse events etc. Study design includes information about single, double blind, observational, randomized study etc.[23-26]

Case report forms

Case Report Form is one of the main components of clinical data management, which is used to capture the subject data of any clinical research.[14,18,20] CRF should be designed in accordance with regulatory requirements and must have all the material to collect the study specific data. Although paper CRFs are yet used on a larger scale, eCRFs are attracting consumers as they offer more benefits such as enhanced data quality, online discrepancy management and rapid database lock etc.[14] It should be protocol driven and robust in content and the design requires enormous preparation and consideration to every minute detail. While designing an e-CRF, if there is data repeating in more than one CRF such as subject ID, protocol ID, subject initials will be generated by the system robotically from first page to all others. The CRF must be designed keeping the end-user in mind and must be implemented based on scientific practices. In order to augment easy reading and precise data entry, an uncrowded CRF layout should be preferred and must avoid insertion of too many particulars on the same page.[27,28]

Almost all CDMS maintain standard CRF templates that can be modified accordingly. The standard templates are of boundless help while handling large numbers of studies in the similar research area. Most frequently used standard CRF templates are demography, inclusion and exclusion criteria, medical history, physical examination, AE and study outcome modules. The units of all the dimensions should be indicated in the CRFs to keep up uniformity. Standard formats must be used for date, time. After designing the first version of the CRF, it will be verified by a reviewer team. Once the second version is developed, it will be again checked by a team for tuning if any. Overall comments will be considered for designing the final version of CRF and then the reviewed one will be sent to the project manager for approval. Few sponsors provide their own Blank CRF, if then we can directly start designing e-CRF. If not then we need to develop a mock CRF for our reference and then we begin with the e-CRF. The CRF should be formatted in such a way that repeated observations recorded such as BP, pulse, temperature can be documented in distinct lines rather than single line horizontally.[48,49]

In order to synchronize each element in the CRF with its parallel dataset id, an annotated CRF is used. Annotation is a very much required phase in converting the CRFs into a database application. Basically CRFs are annotated via creating unique variables for every field to be entered. In order to maintain uniformity in annotating the CRFs throughout all CDMS and regulatory bodies, standards given by Clinical Data Interchange Standard Consortium (CDISC) are referred to.

CONDUCT PHASE

Data validation plan

Data validation can be defined as a process of evaluating the validity of data according to the protocol requirements. The edit specifications list is created which explains about the data which should be tested and corrected. The programming of the tests occurs as per the logic condition mentioned in this Data Validation Plan (DVP). These edit check programs are written in order to recognize the discrepancies in the data entered for

assurance of trial data validation. Before the programming, the customer will be asked for consent on the plan before programming is applied to them. Initially these programs are tested with dummy (fake or not real) data containing the discrepancies (data point that fails to pass a validation check). It can be caused due to inconsistency in the data, missing values, out of range data and deviations from the specified study values.[29] In e-CRF based clinical trials, data validation processes will be running on frequent mode in order to identify the discrepancies in the entered data.[30] The discrepancies will be highlighted in the system and Data Clarification Form (DCF) is generated.

Discrepancy management

It is a process of subject data cleaning and gathering enough proofs for the observed data deviations in CDMS. It consists of both manual and system checks. CDMS includes a separate database for discrepancies in which all the occurred discrepancies are captured and preserved with the audit trail. Depending on the type of discrepancy they are either highlighted or notified to the investigator for the internal checking of the data entered or else closed by the manager through Self-Evident corrections without notifying it to the investigator whereas for the discrepancies which require appropriate clarifications from the investigator's side DCFs are sent to the site. In eCRFs the site investigator has the authority to check the discrepancies notified/sent to him/her and provide the suitable clarifications online where the same will be updated in the database.[29,30]

CDM team evaluates each one of the discrepancies regularly and the resolved data discrepancies are recorded as 'closed'. Not usually but in some cases the investigator will not be able to provide suitable answers for the discrepancy caused. Those discrepancies are considered as irresolvable and the same will be revised in the database. Discrepancies management is one of the most critical procedures in the entire CDM process.[30]

Medical coding

Medical coding helps in identifying and classifying the medical terminologies properly which are associated with the clinical trial. The medical coding is done as per the project specific protocol requirement. It helps in classifying the reported medical terms mentioned on the CRF to standard dictionary terms to achieve consistency in data and avoid the unnecessary duplication.

Usually, Medical Dictionary for Regulatory Activities (MedDRA) is used for coding of the adverse events. World Health Organization-Drug Dictionary Enhanced (WHO-DDE) is used for codicating the medications.[31]

SAE reconciliation

Serious Adverse Event (SAE) data reconciliation is the comparison of key safety data variables between clinical data management system and sponsor. Reconciliation is performed to ensure that the events existing in both the systems are consistent.[32]

CLOSE OUT PHASE: DATABASE LOCKING AND DATASET GENERATION

Database lock is performed to ensure that there will be no further modification of the study data during the analysis final stage. The locking of the database is performed when all the clinical data management events are finished. A Separate checklist for locking the database is maintained and was ensured to manage the locking of the database. The events which are part of this list are whether all the discrepancies are closed, DCFs received and revised accordingly, medical coding completed etc. When this checklist is completed consent for locking procedure is obtained from all of the stakeholders, then the database will be finally locked and clean data i.e. dataset is generated for statistical analysis. After this process no other modification in the database is further possible. But in some cases of critical issues, users will be given permission and authority to modify data even after the database locking.[29]

ROLE OF CDM IN STRENGTHENING STATISTICAL ANALYSIS

The concept of statistical analysis comes into sight after the trial data is loaded, cleaned and locked generating a full trial dataset. It includes all the data collected through CRFs with the provided annotations. Such data needs cleaning as not all fields have edit checks performed on them. This is to avoid missing out any outlier or a rare occurrence and hence requires manual validation. When the dataset is undertaken for statistics, subjects need to fulfil specific requirements for analysis. Although screening is always performed to check the compliance with both inclusion and inclusion criteria, based on the lab data further selection is required. This entire process depends on both clinically specified and sponsor specified requirements. In this study, lab reports provide the plasma drug concentration revealing the exposure of the treatment at defined timestamps in all the subjects.[22]

For analysis, clinically defined pharmacokinetics parameters are used which include the maximum concentration (Cmax), area under the plasma drug concentration curve (AUC0-t), the time at which Cmax was obtained (Tmax). These are used for analysis to indicate the treatment pattern of a test based on reference. The bioequivalence analysis requires the test drug to be analysed with no significant difference in mean compared to reference drug. For a detailed analysis, it is followed by the safety analysis in which the adverse event and other vital measurements are analysed for test treatment with reference as the baseline. Following the same timestamps, concentration values relate to the drug performance in the individual, which is why AUC0-t is used along with Cmax. If any outlier is there, the former

will change drastically, so we need another parameter Cmax to confirm the results. The design here is a crossover study which involves treating the subject with both the drugs i.e. the same will act as a control as well as the test. The parameters to be analyzed here are the test (T) vs. reference (R) treatments which come under categorical variables indicating certain specific statistical tests. They serve as the independent variable depending on which the concentration (quantitative) values are assessed. Before starting the analysis, sample size estimation (SE) is done to decide on the sample size for analysis. Ideally in both categories equal samples should be there during trial.[33-37]

Category - A and B

n(A)=n1; n(B)= n2

n1=n2 - Ideal case

n1=! n2 - Requires SE

For SE, we need 6 parameters- bioequivalence (BE) margin (example- 80-125% i.e. 0.8-1.25), expected T/R ratio, Significance level α (type-I error), Type-II-error β, Intra-individual coefficient of variation CV. to define the BE margin we have to find the intra-subject coefficient of variation of the reference formulation. When we talk about the main BE analysis the nature of data becomes crucial and is important for it to fit our model. The statistical model for this study involves normal data which is not what we get in real life.[30,38,39] The raw data is highly skewed and needs some power transformation to fit the model. Log-transformation is one option as it decreases such skewness between data points resulting in a better fit data for our model. Such data when uploaded for analysis will produce reliable data. Statistical tests are based on normality and non-normality dividing them into parametric (for normal data) and non-parametric data (non-normal data).[40]

According to the protocol, subjects with all the data points within specified range can be analysed for the bioequivalence test which is the primary objective. To remove the effects of sequence, period and treatment, certain measures are taken. An initial Intra-subject Coefficient of variation (ISCV) analysis is required to find the variation in the reference formulation. This is done to set a baseline on which test will be assessed. Cmax values of both the reference treatments are used to find the mean and standard deviation. By dividing the S.D with mean, we get the coefficient of variation (CV). From this the CV% is calculated by multiplying with 100 which serves as the values to set the 90%CI range as shown in table 1. Through statistics we need to prove that there is no significant difference in the T and R drug. We can conclude that 2 treatments are not different from one another if the 90% CI of the ratio of a log-transformed exposure measure falls completely within the range 80-125%. We conclude that they are "not different "and not that "they are the same". Regulatory bodies decided that a difference up to 20% of the systemic drug exposure is not clinically significant.[41]

Based on the variable type and number of them, ANOVA is selected as the statistical test. Others like the Wilcoxon test can also be used but the reliability is more on ANOVA as it is fit for normal data. Such tests have been studied much more than the non-parametric ones. Every test has 2 hypotheses, null and alternate. For ANOVA the null hypothesis states that there is no significant difference in the means and alternate states that there is a difference. For the drug to be bioequivalent, we have to prove that there is no difference in both treatments i.e. to reject the alternative hypothesis. This should be done for both Cmax and AUC0-t along with the 90% CI values. This happens when p-value is less than 0.05 or else null hypothesis is rejected indicating no bioequivalence.

When BE is finished, its safety is validated using adverse event information. Unlike BE analysis, this takes all the patients even if they have left the study after any no. of visits/period with all the test data recorded being the only condition. To perform all these analysis and calculation, the data needs to be arranged respectively. There are different assessments and the basis change for each i.e. some are based on T versus R on the other hand they need to be separated based on period/visits or else the sequence of treatments they are categorized into. Hence this is the most time taking part in the entire analysis after the individual analysis of each subject for outliers and missing data. CDM helps in generating an accurate dataset which strengthen the statistical assessments

CONCLUSION

To meet the expectations of ever-growing demand of pharmaceutical companies there is a gradual shift from paper-based to the electronic systems of data management. The efficient usage of these electronic data-capturing tools will make sure that high-quality data are generated from clinical trials for easy review and fast decision making. The main aim of the study is to deliver high quality, error-free, maximum data for analysis. It includes functioning with a range of computer applications, database systems, validation specifications, and management of clinical trial data. The integrity of clinical trial data is the main trait for new drug approval by regulatory agencies which is covered by CDM. An essential companion to well-designed clinical trial is its suitable statistical analysis. The clinical data management is being performed taking a lot of measures and have improved with the amendments in clinical guidelines, standards and regulations. However, there is still room for improvements in terms of data capturing. Not everyone is comfortable with systems and prefers paper CRFs over electronic data capturing. This makes the confidentiality and accuracy of data questionable. Adapting best CDM practices in clinical trials will make sure that trial data is consistent, comprehensive and

checked thoroughly. Our study concludes that the pharmaceutical companies and sponsor research need a sound and effective CDM for better clinical trials output.

ACKNOWLEDGEMENTS

We thank Uma Janapareddy (Founder and Managing Director of SyMetric system) for providing SyMetric C6 and her guidance to complete this review paper.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Kwan JL, Lo L, Ferguson J, Goldberg H, Diaz-Martinez JP, Tomlinson G et al. Computerised clinical decision support systems and absolute improvements in care: Meta-analysis of controlled clinical trials. BMJ. 2020;370
2. Umscheid CA, Margolis DJ, Grossman CE. Key concepts of clinical trials: A narrative review," Postgraduate medicine. 2011;123(5):194-204.
3. Bhatt A. Evolution of clinical research: A history before and beyond james lind. Perspectives in clinical research. 2010;1(1):6.
4. Piantadosi S. Clinical trials: a methodologic perspective. John Wiley & Sons. 2017.
5. Viergever RF, Li K. Trends in global clinical trial registration: An analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. BMJ Open. 2015;5(9).
6. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in clinicaltrials. gov, 2007- 2010. JAMA. 2015;307(17):1838-47.
7. Chen ML, Shah V, Patnaik R, Adams W, Hussain A, Conner D et al. Bioavailability and bioequivalence: An fda regulatory overview. Pharma Res. 2001;18(12):1645-50.
8. Meinert CL. Clinical trials, overview. Wiley Handbook of Current and Emerging Drug Therapies. 2006.
9. Weber B, Hochhaus G. A systematic analysis of the sensitivity of plasma pharmacokinetics to detect differences in the pulmonary performance of inhaled fluticasone propionate products using a model-based simulation approach. AAPS J. 2015;17(4):999-1010.
10. Sarkar S, Pramanik A, Khatedi N, Maiti J. An investigation of the effects of missing data handling using 'r'-packages," in Data Engineering and Communication Technology. Springer. 2020;275-84.
11. Krishnankutty B, Bellary S, Kumar NB, Moodahadu LS. Data management in clinical research: An overview. Indian J Pharmacol. 2015;44(2):168.
12. Benedetti MG, Catani F, Leardini A, Pignotti E, Giannini S. Data management in gait analysis for clinical applications. Clin Biomec. 2015;13(3):204-15.
13. Nourani A, Ayatollahi H, Dodaran MS. A review of clinical data management systems used in clinical trials. Rev Recent Clin Trials. 2015;14(1):10-23.
14. Nahm M, Shepherd, J Buzenberg A, Rostami R, Corcoran A, McCall J et al. Design and implementation of an institutional case report form library. Clinical Trials. 2011;8(1):94-102.
15. Bellary S, Krishnankutty B, Latha M. Basics of case report form designing in clinical research. Perspectives Clin Res. 2014;5(4):159.
16. Fleischmann R, Decker AM, Kraft A, Mai K, Schmidt S. Mobile electronic versus paper case report forms in clinical trials: A randomized controlled trial. BMC Med Res Methodol. 2017;17(1):1-10.
17. W¨ubbelt P, Fernandez G, Heymer J. Clinical trial management and remote data entry on the internet based on xml case report forms. Medical Infobahn for Europe, IOS Press. 2000;333-7.
18. Powell G, Bonnett L, Tudur-Smith C, Hughes D, Marson T, Williamson. Using routinely recorded data in a clinical trial: The feasibility, agreement and additional benefits compared to standard prospective data collection methods. Biomed Central. 2017;8.
19. Richesson RL, Nadkarni P. Data standards for clinical research data collection forms: Current status and challenges. Journal of the American Medical Informatics Association. 2011;18(3):341-6.
20. Coons SJ, Eremenco S, Lundy JJ, O'Donohoe P, O'Gorman H, Malizia W. Capturing patient-reported outcome (pro) data electronically: The past, present, and promise of epro measurement in clinical trials. The Patient-PatientCentered Outcomes Research. 2015;8(4):301-9.
21. Thriemer K, Ley B, Ame SM, Puri MK, Hashim R, Chang NY et al. Replacing paper data collection forms with electronic data entry in the field: Findings from a study of community acquired bloodstream infections in pemba, Zanzibar. BMC Res Notes. 2012;5(1):1-7.
22. Deepa M, Ranganath B, Gopa R. Clinical Data Management Importance. Clinical Research. Asian J Pharm Clin Res. 2016;9(2):59-62.
23. Al-Jundi A, Sakka S. Protocol writing in clinical research. J Clin Diagnos Res. 2016;10(11):ZE10.
24. Cipriani A, Barbui C. What is a clinical trial protocol? Epidemiol Psychiatric Sci. 2016;19(2):116-7.
25. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, KrleˇzaJeri´c K et al. Spirit 2013 statement: Defining standard protocol items for clinical trials. Revista Panamericana de Salud P´ublica. 2015;38:506-14.
26. Li G, Taljaard M, Van den Heuvel ER, Levine MA, Cook DJ et al. An introduction to multiplicity issues in clinical trials: The what, why, when and how. Int J Epidemiol. 2017.

27. Moon KK. Techniques for designing case report forms in clinical trials. ScianNews. 2006.
28. Le Jeannic A, Quelen C, Alberti C, Durand-Zaleski I. Comparison of two data collection processes in clinical studies: Electronic and paper case report forms. BMC Med Res Methodol. 2015;14(1):1-10.
29. Vijayananthan A, Nawawi O. The importance of good clinical practice guidelines and its role in clinical trials. Biomedical Imaging Intervention J. 2008;4(1).
30. Matkar S, Gangawane A. An outline of data management in clinical research. Int J Clin Trials. 2011;4(1):1-6.
31. Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. Biomedical imaging and intervention J. 2008;4(1):e5.
32. Koppula M. Clinical Data Management. 2016.
33. Anderson S, Hauck WW. A new procedure for testing equivalence in comparative bioavailability and other clinical trials. Communications in Statistics-Theory and Methods. 1983;12(23):2663-92.
34. Patterson SD, Jones B. Bioequivalence and statistics in clinical pharmacology. Chapman and Hall/CRC; 2005.
35. Alloway RR, Vinks AA, Fukuda T, Mizuno T, King EC, Zou Y et al. Bioequivalence between innovator and generic tacrolimus in liver and kidney transplant recipients: A randomized, crossover clinical trial. PLoS medicine. 2016;14(11):e1002428.
36. Ott RL, Longnecker MT. An introduction to statistical methods and data analysis. Cengage Learning. 2015.
37. Meinert CL. Clinical trials, overview. Wiley Handbook of Current and Emerging Drug Therapies. 2006.
38. Knief U, Forstmeier W. Violating the normality assumption may be the lesser of two evils. Behavior Research Methods. 2021;1-15.
39. Kaur P, Jiang X, Duan J, Stier E. Applications of in vitro–in vivo correlations in generic drug development: Case studies. The AAPS journal. 2015;17(4):1035-9.
40. Wang J, Zhang H, Wang R, Cai Y. Pharmacokinetics, bioequivalence and safety evaluation of two ticagrelor tablets under fasting and fed conditions in healthy chinese subjects. Drug Design, Development and Therapy. 2015;15:1181.
41. Lu C, Chim C. Generic medications: A primer for pharmacists and patients. US Pharm. 2015;43(6):6-8.

Cite this article as: Kala NG, Shruti O, Aishwarya BM. Overview of clinical data management and statistical analysis of bioequivalence study. Int J Clin Trials 2021;8(4):323-9.