PP15

An End User's Perspective of Clinical Dosing Data Used for Population PK / PD Analysis with Nonlinear Mixed Effects Modeling

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ABSTRACT

Observing how clinical dosing data are used in building population pharmacokinetic/pharmacodynamic (PK/PD) analysis datasets lead to a more comprehensive collection and representation of vital clinical data.

A model is only as good as the data! Population PK/PD modeling is an important part of a regulatory submission and data integrity is a crucial component to all successful models. Here, we explore the challenges end-users face when the provided dosing data are incomplete, insufficient, or ambiguous, as well as solutions and best practices to address such challenges.

Population PK/PD modeling depends on an accurate time-ordered analysis dataset. For example, when dosing times are not collected, imputations and assumptions are made which lowers the integrity of the model. The representation of dosing start and stop dates and times differ for different routes of administration (for example, intravenous versus oral). Accurately reflecting changes in dose amounts administered is equally important.

INTRODUCTION

Datasets intended for population pharmacokinetic/pharmacodynamic (PK/PD) analyses are built by using the information collected from the subjects enrolled in a clinical trial. Such datasets require a potentially complex arrangement of data in a format that can be used by the analysis program.

Population PK/PD datasets are time-ordered arrangements of records that represent the events related to administration of a drug, resulting blood concentration, and/or pharmacodynamic (PD) responses occurring within the individuals enrolled in a clinical trial.[1] The order of the event's dose, pharmacokinetic (PK) concentration, and PD response measures inform the model. The complexity of the dataset depends on the complexity of the system being modeled. When working with complex data, building these datasets can be a complicated process, thus, it is important to have discussions and understanding of the data needed as well as the modeling goals. It is critical to capture and arrange meaningful data to perform such analysis because data are the backbone of modeling, and a model is only as good as the data!

DOSING DATA

Dosing data is an informative component of PK/PD analysis datasets, especially for population PK analysis. It is vital to have the accurate amount that was administered along with the units to have a successful model. Population PK datasets are time-ordered in relation to the first dose. These are generally sorted by a time variable, for example, actual relative time from first dose (ARLFT), while population PK/PD datasets use time since first event and are time-ordered in relation to the first PD measure. It is important to collect actual dose date/time because of the time-ordered dependency of analysis dataset. Typically, at a minimum, dose date/time is collected prior to a PK sample and the date and time of dose administration may also be collected during the same clinic visits, Typically, out-of-clinic dose administration are not collected and must be estimated based on actual times administered throughout each subject.

When administering intravenous (IV) doses, particularly IV infusions, it is important to record the start and stop date/time of the infusion along with the total amount administered. If the IV infusion administration was interrupted for any reason, it is critical to have the time of the interruption as well as the infusion resume time and end time recorded. This prevents from having inaccurate and prolonged IV dosing periods.

Instances when dosing data are inadequate, lacking, or unclear, imputations and assumptions are made which compromise the integrity of the model.

GOOD PRACTICES

Transparent communication between the team members is the key to creating successful PK/PD analysis datasets. Imputation rule(s) should be clearly communicated and documented. Understanding the study design (expected dosing regimen, planned sampling scheme, etc.) assists in building the analysis dataset and can also provide insight into what to expect in the data. Additionally, it is essential to review the created PK/PD analysis dataset before modeling the data.

CONCLUSIONS

- Dosing data can be very complex, as the few examples describe within the poster.
- It is vital to capture, record, and utilize accurate clinical trial dose administration information to create the analysis dataset to inform PK/PD modeling.
- Awareness is key. It is important to understand the modeling goal, available data, and how the data will inform the model.
- It is critical to be able to reproduce results.
- A **population PK/PD model** is only as **good** as the **data**.
- **Capturing** and **sharing** good data is key to **accurate** modeling.
- Observing how clinical dosing data are used in population PK/PD modeling will lead to a more comprehensive collection and representation of clinical data.

RECOMMENDED READING

Capture and Use of Meaningful Data for Population PK/PD Analysis with Nonlinear Mixed Effects Modeling

SDTM Domains

ADPPK Guidance

REFERENCES

1. Owen JS, Fiedler-Kelly J. Introduction to population pharmacokinetic / pharmacodynamic analysis with nonlinear mixed effects models. Hoboken (NJ): John Wiley & Sons, Inc.; 2014.

CONTACT INFORMATION

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