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Preventing Premature Unblinding in PK/PD Related Studies

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ABSTRACT

Blinding is commonly used in clinical research study designs and is one of the critical methodologic features intended to reduce the risk of bias allowing a realistic statistical comparison of the study outcomes. Premature unblinding carries the risk of invalidating the entire clinical study which would be a costly mistake. Unblinding brings special challenges for performing Pharmacokinetic(PK) and Pharmacodynamic(PD) related studies. During the various stages of a blinded PK/PD study, there are inherit high risks of accidental unblinding that may occur during study conduct, sample processing and bioanalysis, data analysis and reporting, or modeling and simulation. This presentation is designed to create an awareness of the challenges and identify operational procedures, processes and programming tips intended to prevent PK/PD related studies from premature unblinding.

INTRODUCTION

In addition to statistical analysis and modeling, pharmacokinetics (PK) and pharmacodynamics (PD) describe the time course and effect of a drug. Pharmacometrics (PM) provides an understanding of the quantification of PK/PD relationships by developing models and simulations. These activities play critical roles in all phases of drug development, from drug discovery, preclinical to clinical and post marketing.

Maintaining blinding during the blinded trial period had always been challenging. Many blinded clinical trials have PK related components. These components carry their own special characteristics which bring additional challenges. Understanding these special characteristics will help prevent premature unblinding.

New advances sciences including ADA (Anti-Drug-Antibodies), TE (Target Engagement), RO (Receptor Occupancy) and other biomarkers are now routinely included in clinical trials. Some of them carry similar characteristics as PK data and processing these new data streams introduces additional risk factors of premature unblinding.

Handling data is a core component of clinical studies. Data flow, data collection, transfer, tabulation, cleaning, and reconciliation are efforts that occur during trial conduct. Assembling data and graphical evaluation are major components of analysis, modeling, and reporting. Each of the data preparation stages carries some similar and unique risk factors of premature unblinding. Data handling for early-stage or late-stage clinical trials, different analysis methods, techniques and approaches may also introduce different risk factors.

The complexities of data sciences is a growing challenge. With the globalization of drug development data has often traveled through a handful of databases from different functional groups, multiple Contract Research Organizations (CROs) or even different sponsors. Very likely, the data files are handled by many colleagues in different areas with expertise in different backgrounds. The heterogenicity of data sources brings various sources of risks of premature unblinding.

Clinical efficiency is always one of the major goals of drug development. Clinical protocols and project timeline planning must seriously consider risks of premature unblinding. Understanding which activities can be accomplished before official database lock and unblinding, and which ones need to wait, is important. Pre-planning can provide insights and guidance for optimizing processes, ultimately providing opportunities for gains in efficiency.

Last but not least, good practice is always a must throughout the multi-dimensional metrics of PK related drug development processes. We would like to share the five key criteria that we consider from our experiences to ensure good practices.

MAINTAIN BLINDING – WHY IT IS SPECIAL FOR PK RELATED ACTIVITIES

Once a trial is designed to be blinded, a series of procedures and processes must be in place for study setup and conduct to maintain the blinding. Throughout the trial blinded period, only pre-identified designated personnel have access to the treatment information. Blinding and unblinding clinical trials are relatively mature procedures. A typical blinding procedure is to utilize and maintain a randomization schedule or randomization code. Official unblinding usually happens at the end of trial, or has been planned for an unblinded interim analysis, e.g. for adaptive design. Standard procedures must be in place for unplanned unblinding during the trial conduct, e.g. in case of emergency unblinding due to a subject's drug-related medical emergency.

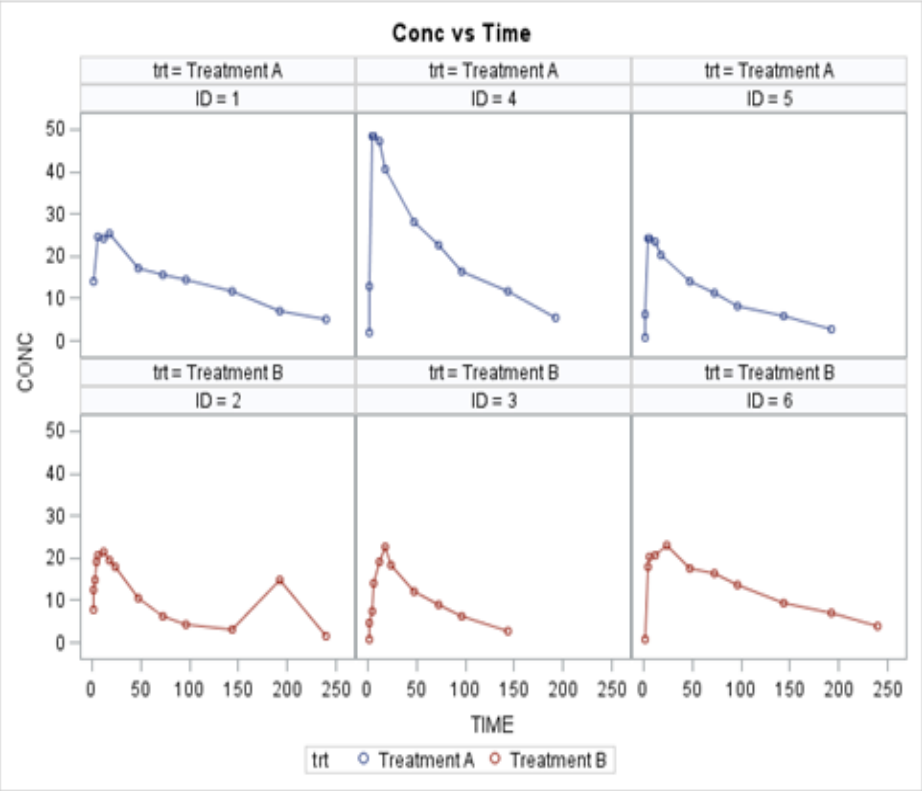
Preparation for final study reports include processes intended to minimize the risk of premature unblinding. The safest way is to start all reporting related activities after official unblinding. However, this may not be preferred. First, this may cause missing some optimal opportunities for data cleaning prior to analysis. Second, timelines often do not allow for the delay. If proper procedures and processes are in place, some activities can be strategically planned and performed in blinded fashion during the blinded trial period. The goal is to be prepared and once the database is locked and unblinded, "click the button", so that the reports are ready in the shortest time.

From a statistical perspective, standard procedures are developed and typically shared across the industry. Usually the statistical analyses are pre-defined. Statistical Analysis Plan (SAP), detailed data derivation documentations, Data Release Plan (DRP), detailed mockup tables can be ready as early as when the protocol is finalized. Standard procedures are implemented for maintaining blinding, e.g. mask treatment assignments, mask actual dose information, logics of creating dummy test data, methods of scrambling data, schedule of dry-runs.

The above are all effective operational procedures to ensure timelines are met while protecting trials from premature unblinding, However, if the trial has a PK component, additional special challenges and concerns maybe introduced.

Pharmacokinetics (PK) is broadly defined as "what the body does to a drug." PK drug concentration results imply what treatment a subject had received. If PK drug concentration results over time are below lower level of quantification (BLQ), then it is very likely the subject is on placebo treatment. Conversely, if high PK drug concentrations are measured, it indicates that the subject had been on active treatment.

PK related analysis and modeling studies the time course of drug behaviors and body reactions. Data in chronological order is critical for data cleaning and analysis. This introduces special challenges of maintaining blinding. Display 1. shows some typical individual PK concentrations vs time profiles.[1] Each graph may indicate some data issues. If these issues are detected at the end of the study and after official unblinding, it may be too late, and the entire clinical study may be rendered invalid. Early data inspection during the blinded trial period provides benefits in many ways and the PK data in chronological order must be taken into account. Scrambled data without considering time course will not serve the purpose.



Display 1. Sample PK Drug Concentration vs Time profile

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A cross-check against dose administration information is often needed, including checking dose amount, date and time, even dose route, form, frequency etc. e.g. Graph 2 in Display 1. may imply much higher dose amount administered to ID 4 when compared to the other subjects.

Other PK related data streams share similar characteristics, e.g. Anti-Drug Antibody (ADA or unwanted immunogenicity) data, Target Engagement (TE), Receptor Occupancy (RO) data and other biomarker data. Using ADA data as an example, the detection of ADAs in blood samples may indicate immune response by a subject against a therapeutic antigen. Whether a reaction is positive or negative, or the onset time of a positive ADA response also implies the drug treatment that a subject was given.

Unlike statistical activities in which almost all analyses are pre-defined, pharmacometric activities are more exploratory, as the model building process may take multiple learn-and-confirm cycles. During these cycles and with additional information being added, risk factors of premature unblinding also accumulate. Therefore, ongoing risk assessments are needed throughout the blinded trial period and ongoing timeline adjustments maybe needed.

SCENARIO 1: AREAS WITH POTENTIAL RISKS OF PREMATURE UNBLINDING DURING DATA COLLECTION, TRANSFER, TABULATION, CLEANING AND RECONCILIATION

The bio-analytical lab is front and center of processing PK related data. There are typically two major PK data processes; without a central lab and with central lab. The operational processes using a central lab for PK sample management may be more complicated than the more direct processes of working without a central lab, but many risks exist in both processes. Sample handling for ADA, TE, RO and other biomarkers have similar challenges.

OBTAINING PLACEBO LISTINGS FOR SAMPLE BIOANALYSIS

Typically, only samples with active treatment administration should be analyzed. This will significantly reduce bioanalytical time, bioanalytical staff needs, and reduce reagent and supply cost. However, the process of separating these samples from placebo samples may introduce unintentional unblinding. Placebo sample listings can be subject-level or visit-level. Some study designs will need to identify samples at a visit-level, e.g. cross-over study design or early escape study design. A crossover design is a repeated measurements design such that same subject receives different treatments during the different study periods, i.e., the subject cross over from one treatment to another during the course of the trial. An early-escape design allows a subject to switch to other treatment groups based on certain predetermined evaluation criteria, i.e. switch from placebo treatment to active treatment due to lack of clinical response. In these situations, in order to identify placebo samples, not only the subject identifiers are needed, but the subject visit identifiers are also needed. Many organizations find their effective ways to securely handle the information and ensure blinding, while some find contracting the activities to a third-party secure data office with expertise may also work out well.

DATA CLEANING AND RECONCILIATION

The primary source for the PK sample metadata (subject identifiers, protocol event identifiers / nominal times, sample collection date/time) may be separate from the primary source for the PK bioanalysis (e.g. drug concentration) data. The PK sample metadata is usually collected using lab requisition forms, or the combination of electronic case report form (eCRF) and lab requisition forms. Data collected through eCRFs is directly captured in the clinical database, while data collected through lab requisition forms must be transferred to the clinical database via a separate file. When samples are shipped from a central laboratory to a bioanalysis laboratory, an additional shipment specific manifest is provided with the samples. Therefore, a reconciliation step may be required to ensure that the cumulative record of samples received at the central laboratory is consistent with the cumulative record of samples also received by the bioanalysis laboratory. Prior to a formal unblinding, a sample tracking file can be considered to accomplish this task without providing the bioanalytical results in the file. A typical sample result file starts from the sample identification information and includes analyte information as it is set up in the bio-analysis data repository, e.g. Laboratory Information Management System(LIMs), and includes the assay result information. We recommended to only keep minimal information in the sample result file. When the time is appropriate, the primary source files will be merged together into the final database. It may be necessary to provide “test files” to check the programming for this merging of data. If common information exists in multiple files, e.g. sample nominal time event identifiers exist in two or three files, ongoing data reconciliation during trial conduct may be necessary. During the process of data cleaning and reconciliation, the following are highly recommended:

1. Include minimal number of columns in the data file which are sufficient for the particular task e.g. data reconciliation.
2. If results data are needed in order to program the merging of the data, do not include result file with real assay results, rather use un-populated or dummy result field in the data.
3. Separate sample tracking file and sample result file. Do use the full sample tracking file with all subjects and all visits in it for reconciliation. Do not use the subset sample result file which excluded placebo subjects or samples for reconciliation purpose, in order to avoid providing a blinded recipient with the ability of identifying placebo records.
4. Use re-masked subject ID if needed when providing results files for programming in preparation for merging.

DATA TABULATION, STANDARD DATA TABULATION MODEL (SDTM) MAPPINGS

SDTM mapping is a major initiative needed for a trial database during study setup and conduct. Risks of unintentional unblinding exist during this process. Our aim is not to discuss the process of mapping treatment group or dosing related domains. Rather, our discussions will focus on the PK related data mapping, specifically the PC (Pharmacokinetic Concentration) domain, and PP (Pharmacokinetic Parameters) domain. For large molecule drugs, or drugs with a protein component, the IS

(Immunogenicity Specimen Assessments) domain is designated for the anti-drug antibody data. Since target engagement, receptor occupancy and other pharmacodynamic or biomarker data are relatively new data streams, SDTM mappings are being discussed at the CDISC (Clinical Data Interchange Standards Consortium) level. Until CDISC provides the SDTM recommendations, it is up to the trial sponsor to map the data into the LB (Lab) domain together with other lab data, or create self-defined stand-alone domains per company standards. All of these finding domains interact with SV (Subject Visits) domain. Whether an organization chooses to perform data cleaning and reconciliation before SDTM mapping, or after, risk factors of premature unblinding exist throughout the process, and the same concerns and recommendations apply.

Use of external suppliers for data management, data analysis, or bioanalysis as Contract Research Organizations (CROs) adds additional layers of process complexity. Assurance of Standard Operation Procedures, (SOPs) that address both sample accountability and data security must be in place and trainings should be conducted prior to the handling of any data.

QUERIES AND EDIT-CHECKS

Some typical PK related data management edit checks are: pre-dose samples with high drug concentration values; samples obtained immediately post IV bolus/infusion with below level of quantification (BLQ) result; pre-or post-dose sample collection date and time consistent with dose administration date and time etc. The first two checks may be performed in the bioanalytical laboratory, if the laboratory has access to the dosing information. Otherwise an unblinded data management group would need to perform the checks. No matter which method is chosen, the standard procedures and guidelines should be clearly defined and personnel trained to prevent unintentional unblinding. For example, the checks for date and time logic should only include date and time tracking information in the comparison files, it should not allow any access that includes real dose level, dose amount or assay results.

SCENARIO 2: AREAS WITH POTENTIAL RISKS OF PREMATURE UNBLINDING DURING DATA ANALYSIS, MODELING AND REPORTING

PK related analysis, modeling and reporting are often on the critical path of the drug development and regulatory decision-making process. Most of the time, either because of scientific reasons or timeline concerns, these activities are needed before the official unblinding. Study teams must either carefully unblind a small group of personnel, or manage the activities in blinded fashion during the blinded period. All these activities involve a certain level of data merging and assembling, and the risks of premature unblinding are embedded throughout the data preparation processes.

All PK related analysis and modeling can be roughly classified as two approaches; individual subject approach and population based approach. The discussions below are not based on scientific rationale for different types of analysis or modeling, but rather based on different analysis data preparation needed for different activities, and the risk factors of premature unblinding will be illustrated respectively.

In this section, “interim” refers to the activities in blinded fashion which occurs before any official / formal unblinding.

INTERIM NON-COMPARTMENTAL ANALYSIS (NCA), DATA VISUALIZATION AND COHORT-BY-COHORT ANALYSIS

These types of analysis are often for early phase PK studies with intensive PK sampling, or for a subgroup analysis with intensive sampling. Several standard software packages are available for these types of analysis, but regardless of the software, analysis input data can be assembled into standard structure and format. Often, there are legitimate needs of generating interim PK results before the final database lock and unblinding. Using dose-escalation studies as an example, individual PK profile plots are provided to the safety review committee while the trial is ongoing. Cohort-by-cohort analysis and NCAs may be performed, and results are often used to support the next dose-level selection. When these activities are performed in blinded fashion during the blinded trial period, the following are some of the common areas to prevent premature unblinding:

1. Subject ID needs to be masked to avoid matching back to the clinical database.
2. Use nominal dose and nominal time. Do not use actual dose or actual relative time as these can easily identify a specific subject's sample, especially when there are only a few subjects in a cohort.
3. Only include minimal information that directly contributes to the analysis result in the data set. Do not include unnecessary information that can be used to identify the subject. These analyses are often based on small data set, e.g. cohort one of 0.1mg treatment group include a total of 8 subjects, 6 subjects are on active treatment and 2 on placebo. It takes little demographic information to easily identify the study subject. Therefore, if personal identifiers such as age, gender, height and body weight data are not contributing to the analysis, then do not include them in the data set. Otherwise it can be very easy to identify the subject even when the subject ID is masked.
4. Thoroughly evaluate whether ADA, TE, RO or biomarker etc. data are absolutely needed. If yes, data extraction, transfer, data merging and assembling may be needed if these pieces of data are from different databases. Risks are increased during each step of these data flow processes and the security of the data needs to be considered.
5. The data for these activities usually can be obtained directly from the bioanalytical lab, but in some organization, analysis automation tools are built based on using SDTM data. In those cases, the above preventative actions need to be taken into consideration prior the SDTM mapping is done.
6. Detailed data transfer agreements must be in place defining needs, formats, and secure methods of transfer.

INTERIM POPULATION PHARMACOKENETIC (POPPK) MODELING

Population pharmacokinetics (POPPK) is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest. Certain patient demographical, pathophysiological, and therapeutic features, such as body weight, excretory and metabolic functions, and the presence of other therapies, can regularly alter dose-concentration relationships. Population pharmacokinetics seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified.[2] A POPPK approach can be used for studies in any study phase, can be for a single study or pooled studies, and PK results data can be from intensive sampling or sparse sampling. Ideally it should be performed after the official unblinding, however since the modeling building is a long learn-and-confirm process, often, due to timeline constrains, some data assembling and visualization activities are planned and executed in the blinded fashion during the trial blinded period.

Several software packages are available for Population Pharmacokinetic (POPPK) and Pharmacokinetic/Pharmacodynamic (PK/PD) modelling and simulation. NONMEM® is widely accepted as the gold standard software package for this purpose. Its name is an acronym for non-linear mixed effects modeling. Display 2. shows a sample POPPK data set of one subject in NONMEM® required data format. POPPK data set for other software packages can be similar in data structure. Dosing records and PK drug concentration records are stacked and sorted in chronological order. In this example, rows 2,6,9,12,15 and 19 are dosing records, the rest are PK drug concentration records. PK drug concentration values are in the DV (Dependent Variable) column. Column PTIM is relative elapsed nominal time since first active dose.

	C	STDY	ID	PTIM	TIME	TAD	DOSE	DV	CMT	EVID	MDV	AGE	SEX	RACE	WGT	HGT	WBC	ALB	ALT	AST	CRCL
2		A01	10001	0	0	0	0.15	.	1	1	1	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
3		A01	10001	0	0	0	.	0	1	0	1	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
4		A01	10001	0.042	0.042	0.042	.	3.313	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
5		A01	10001	90.958	89.938	89.938	.	0.08	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
6		A01	10001	91	89.98	0	0.15	.	1	1	1	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
7		A01	10001	91.042	90.022	0.042	.	3.104	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
8		A01	10001	181.958	184.968	94.988	.	0.09	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
9		A01	10001	182	185.01	0	0.15	.	1	1	1	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
10		A01	10001	182.042	185.051	0.041	.	3.453	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
11		A01	10001	272.958	272.944	87.934	.	0.122	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
12		A01	10001	273	272.985	0	0.15	.	1	1	1	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
13		A01	10001	273.042	273.027	0.042	.	1.094	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
14		A01	10001	363.958	366.962	93.977	.	0.123	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
15		A01	10001	364	367.003	0	0.15	.	1	1	1	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
16		A01	10001	364.042	367.045	0.042	.	4.194	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
17		A01	10001	371	381	13.997	.	1.42	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
18		A01	10001	454.958	447.954	80.951	.	0.26	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
19		A01	10001	455	447.996	0	0.15	.	1	1	1	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4
20		A01	10001	455.042	448.038	0.042	.	6.393	1	0	0	50	1	1	70.1	172.1	3.75	3.7	20	21	110.4

Display 2. Sample POPPK data set

Since POPPK analysis and modeling may be performed in any trial phase, all of the considerations discussed in 1-6 above for interim NCA and early phase trials apply here. Because of the extra complexity of assembling POPPK data sets, the following also need to be considered:

1. POPPK data set can be a large data set in terms of the number of records and the number of variables, especially for late-stage clinical trials. Per modeling needs, the data set can be easily extended by adding tens of covariates from various data sources. But more data processing across multiple databases usually introduces more risks of unintentional unblinding.
2. Records associated with placebo dosing are excluded from POPPK input data set, for early-escape design or cross-over design with placebo treatment. Relative time or relative nominal time will need to be calculated according to the time of active dose administration. Any downstream data processing with merging back to the full database will introduce risks of identifying placebo subjects and visits.
3. POPPK analysis and modeling can be for individual studies and pooled studies. When pooling studies, coordination between study teams is important, and documentation needs to be in place, especially when pooled studies are from both blinded trials and unblinded trials.

Moreover, with today's data mining techniques and capabilities, a merged data set with tens of variables can be easily used to trace back to the clinical database and identify the subject treatment assignment, and break the blinding. A more conservative practice is to use dummy data or scrambled data as much as possible during the trial blinded period, or list all who handle POPPK analysis and data processing as segregated, unblinded personnel.

INTERIM POPULATION PD MODELING, DISEASE-REGRESSION MODELING, DOSE-RESPONSE MODELING AND PK/PD MODELING:

Pharmacodynamics (PD) is defined as "what the drug does to the body" and is a way of describing the mechanisms of drug action and defining the relationship between drug concentration and effect. Population PD evaluates physiological and biochemical effects of drugs on the body or disease-causing agents at the population level.[3] Pharmacokinetic/pharmacodynamics (PK/PD) modeling provides the link between drug effects and time. Studying PKPD provides the basis to understand the time course of onset, the duration and the extent of effects caused by drugs.

PD of interest can be outcomes, such as adverse events, efficacy end points, or other physiological responses. Although the PK/PD modeling methods and techniques are still advancing and are complex, the data preparation is relatively manageable. All risk factors discussed above for POPPK data preparation apply. In addition, the followings are some major differences of PK/PD data sets from POPPK data sets:

- PK/PD data set is bigger in size longitudinally than POPPK data set. A simplified thinking of PK/PD data is adding PD measurement values into dependent variable (DV) column and stacking the records vertically to the POPPK data set. sorted Adding a flag variable to differentiate dosing records,

PK drug concentration records and PD records, sort the stacked data in chronological order.

- Multiple PD measurements can be stacked into one PK/PD data set.
- PK/PD data set is bigger in size horizontally than POPPK data set, because there may be more covariates of interest to be included in the models.
- Unlike POPPK data that exclude non-PK related records, e.g. placebo records, PK/PD data include all subjects all visits.

Because PK/PD modeling studies PK and PD relationships and requires real dosing information, the PK measurements and PD measurements are often merged into one data set. This introduces an extremely high risk of breaking the efficacy blinding. Because of the high risk, some trial sponsors have strict rules that do not allow performing PK/PD(efficacy) modeling during a trial blinded period.

EXPOSURE-RESPONSE (E-R) ANALYSIS AND MODELING:

Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs. That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known.[4] Per broad definition, people use the term Exposure-Response analysis and modeling interchangeably with Dose-Response or PK/PD analysis and modeling. In these cases, all the risk factors we discussed above also apply here. In a more narrow and advanced sense, there are a couple of special aspects that differentiate E-R modeling from PK/PD modeling.[5]

- The exposure variables in E-R modeling are PK parameters (e.g. AUC, Cmax, Cmin, Css) rather than PK drug concentration timecourse in PK/PD modeling;
- The response is often an efficacy endpoint, typically expressed as the change of response variable from baseline to the end of trial.

When these aspects reflect modeling input data preparation, they introduce additional risk factors of premature unblinding. Typical input data preparation for E-R analysis and modeling usually follows three steps:

1. Create the POPPPK input data set, build the final POPPK model, output the subject-level PK parameters (e.g. AUC, Cmax, Cmin, Css).
2. Create the PK/PD modeling input data set, use efficacy end points as dependent variables.
3. Merge the above PK parameter data set with the PK/PD data set.

Since the exposure variables for the E-R analysis and modeling are the PK parameters and they are the outputs from POPPK modeling, they do imply an actual treatment received. Because of a narrow definition, Exposure-Response analysis and modeling input data set often include merged actual subject drug exposure information and efficacy end points measurements into one data set. Therefore, the E-R analysis and modeling should only be performed after the official database lock and unblinding. Data explore, data cleaning, or data assembling for programming maybe performed during the trial blinded phase only when using not-merged data or dummy/scrambled data.

Exposure-Response analysis model building and modeling is probably one of the most time-consuming activities on the model-based drug development path. In addition, the start of the activities has contingencies, e.g. completion of POPPK modeling, time of formal database lock and unblinding, multi-source of data, complexity of data assembly requirement etc. Having realistic timelines and effective strategies and processes are very challenging.

GOOD PRACTICES FOR OPERATIONAL STEPS: 5 CRITERIA TO CONSIDER

From past experiences, we have identified five key criteria that are the most considered for ensuring good practices.

JUSTIFICATION

Provide the relevant justification for requesting transfers of potentially unblinding data. Document the request and the authorization for providing potentially unblinding information to various persons or groups.

RECIPIENTS

Ensure the information is provided to the correct recipients. Identify the individuals performing the necessary tasks, and their designated contractors, if applicable. Remember to include all groups that need to see the unblinded data in order to complete their work. For example, an additional functional area representative providing compliance or peer review of the data for quality purposes before it is transferred.

Recipients of the data must prevent any further unauthorized dissemination of the data. Actions should be taken and documented to prevent access to the documents for persons other than the intended recipient.

ACCESS

Secure data access must be restricted to unblinded parties during the blinded study phase.

Clear and protected communication, storage and archiving of blinded information must be planned in advance to protect the trial integrity, and minimize the potential for influence or bias.

Identify the types of secure data transfers expected for the study to ensure the data is provided in secure manner. Examples include encryption, password protected media or restricted access to data sharing platforms.

Data evaluation, data cleaning, and data queries for resolution of issues must be done in a manner to prevent unauthorized unblinding. When a question arises with regard to treatment assignment, communications should not involve other blinded personnel.

Both internal and external parties should be given access only to the data required to perform the relevant job functions or contracted services. Access to a combination of secure data and other clinical data should be avoided if not required.

PERIODIC TRAINING

Ensure all parties associated with handling unblinded data have appropriate training on the applicable policies and procedures. When contract research organizations are used, the Sponsor must insure the contracted personnel are instructed in the procedures to follow to ensure the study blind is maintained.

PREVENT RECURRENCE

Any unintentional/unauthorized unblinding should be reported and explained. The evaluation can then be documented, and steps taken to mitigate, and prevent recurrence of situations in which the blind is broken in error.

CONCLUSION

Premature unblinding is very costly. Handling PK related data has special challenges for maintaining blinding. Risk factors exist from multiple data processing steps throughout the trial blinding period and includes data collection, transfer, tabulation, cleaning, reconciliation, data analysis, modeling and reporting.

Model-based drug development continuous to grow rapidly. In addition to the fast advancement of methodologies and technologies, the requirements for data preparation is also advancing quickly, as a result, more risk factors of premature unblinding are introduced. Meanwhile, with the fast advancing computational power and data mining techniques, intentional tracing the actual subject treatment information becomes easy. Maintaining blinding takes knowledge and effort.

Different prevention actions are recommended for different scenarios. However, the followings are general fundamental recommendations:

- Mask subject ID as a minimal action for all PK related data processing activities during the whole blinded period.
- Only include minimal required information when assembling analysis and modeling data sets.
- Perform PK/Efficacy modeling after official unblinding. Some data preparation, e.g. data cleaning, graphical evaluation of data, finding trend and outliers, can be arranged before official unblinding, but plan cautiously. We recommend breaking data and activities into pieces, avoid mergeability. Document the scope in modeling plans.
- IT infrastructure support in line with data management, analysis and modeling activities.
- For NCA and POPPK, even if protection actions are taken for analysis in blinded fashion during the trial blinded period, consider to list the personnel working as unblinded personnel.
- Plan realistic timelines for PK scientists, pharmacometricians and PKPD/PM programmers.

Above all, ensure good practices and always consider the following five key criteria for operational procedures: justifications, recipients, access, periodic training, and preventing recurrence.

REFERENCES

1. Zong, A. 2013. "SAS® 9.3: Better graphs, Easier lives for SAS programmers, PK scientists and pharmacometricians". *Proceedings of the PharmaSUG 2013 Conference. SP09.* http://www.pharmasug.org/proceedings/2013/SP/PharmaSUG-2013-SP09.pdf
2. Guidance for Industry: Population Pharmacokinetics. https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf
3. Upton, RN and Mould, DR. 2014. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development: Part 3—Introduction to Pharmacodynamic Modeling Methods. CPT Pharmacometrics Syst Pharmacol.2014 Jan; 3(1): e88.
4. Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf
5. Overgaard RV, Ingwersen,SH and Tornøe CW. 2015. Establishing Good Practices for Exposure–Response Analysis of Clinical Endpoints in Drug Development. CPT Pharmacometrics Syst Pharmacol. 2015 Oct; 4(10): 565–575.

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PK/PD programming forum: http://community.amstat.org/sxp/pk-pd-programmer-forum56

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RECOMMENDED READING

Guidance for Industry: E9 Statistical Principles for Clinical Trials https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf

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