NONMEM INPUT FILE CREATION FOR PK/PD MODELING BY SGS SECURE DATA OFFICE

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The Secure Data Office (SDO) is an independent team within SGS Biometrics group that works in a secured environment. SDO is authorized to have access to data that are still blinded to other parties. This approach is supported by well defined and strict procedures describing in detail how the blinded data will be handled and who is authorized to receive access. The creation of nonlinear mixed-effects modeling input files for PK/PD modeling (NONMEM) is also part of the SGS SDO services, as well as input files for Phoenix and NCA analysis.

Benefits of working with an independent provider for programming input files include:

- Dedicated team of programmers experienced in creation of input files for PK/PD modeling
- As an external and independent party, the team works together with data management group to ensure crucial issues in the clinical database are resolved before database lock (especially dose intake and PK sampling information)
  - Eliminates risk of unblinding your project team before DBL
  - Improves the quality of the PK/PD input files
  - Access to final input files for PK/PD modeling at database lock
- Allow sponsor programmers to focus on input files for the primary statistical analyses and sponsor modelers to focus on their core business: PK/PD modeling

THE SECURE DATA OFFICE CONCEPT

The SDO is a dedicated team within SGS that is completely separate from all other teams. All folders are on a secured server and all databases are accessible only for SDO employees. This specific and separate group gives SGS and our clients the confidence that any type of data unblinding will be performed in a safe and secure way throughout the duration of a study. Because no one from the SDO team is involved in any analysis or modeling activities, the team can also be involved in the creation of input files for PK/PD modeling. This robust process is supported by procedures Standard Operating Procedures (SOPs) and Work Instructions (WIs), and has passed several audits. The SDO concept can be implemented as a standalone activity or as part of our full service offering (including PK/PD modeling and simulation by SGS Exprimo).

In the SDO, there are six dedicated programmers, with multiple years of experience, who exclusively make input files for PK/PD analysis and modeling. For several of our pharmaceutical clients, NONMEM files are routinely created. This can either be done in collaboration with the sponsor's own pharmacometrics department, an external vendor, or directly with our modellers at SGS Exprimo. This integrated collaboration enables fast and efficient exchanges around suitable dataset structure and how data is to be used. For numerous compounds, integrated datasets across multiple studies were created.

The data programmers and modeling team work closely together. The programmers prepare the document describing the specifications of the files in collaboration with the modelers. The programmers stay in close contact with the modelers throughout programming in order to: add more details to the specifications, resolve questions, send draft files, implement feedback and make updates to the files. The SDO programmers are in contact with the responsible data management department, whether it's the sponsor's, a third party, or SGS's data management team, to understand the data structure and make sure the correct data required by the modeler is used. If requested, SGS will also use analysis datasets as source for the NONMEM file to ensure consistency between modeling and statistical analysis. The SDO group is familiar with CDISC and ADaM standards as source data.

BLINDED SOURCE DATA

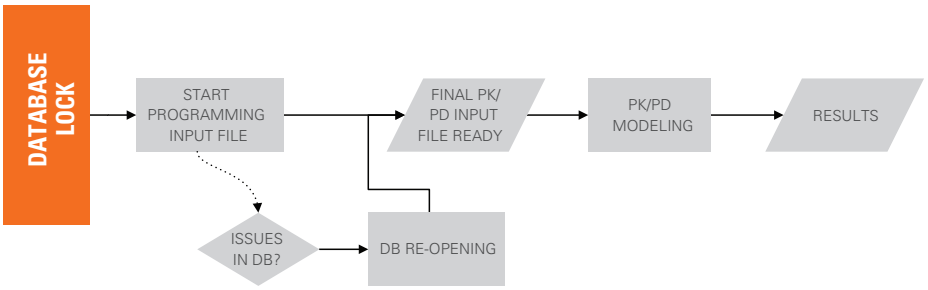
In a traditional CRO model, laboratory data (e.g. PK samples, biomarkers, antibodies, or immunogenicity data) is transferred to data management in a blinded manner and the unblinded results

are added to the laboratory data transfer only after database lock. As a result, the creation of the final SDTM datasets and the PK/PD input datasets needed for the analysis and modeling activities can only start after database lock. If a data issue is identified during programming of the input files, there is a risk that the database would have to be re-opened again to correct the issue, which can cause a significant delay in the availability of the data for modeling purposes.

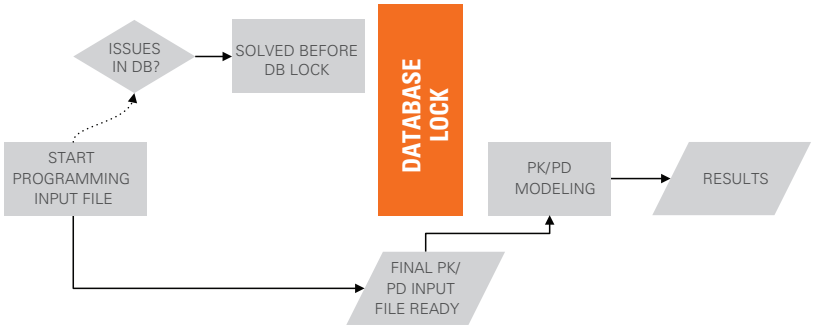
In order to mitigate this risk, SGS has set-up a working model in which our SDO works closely together with the data management team ensuring all issues are identified and resolved in a timely manner before database lock. In this model, the laboratory data is first transferred to the SDO. The SDO sends sample identifier transfers to the data management department for the purpose of reconciliation between CRF and lab vendor data. At this time the trial is still in ongoing. Any inconsistencies, such as missing samples or inconsistencies in the sample dates and/or times, can still be queried. This leads to an improvement of the data quality and integrity.

When sample results are ready, they are sent from the lab to the SDO at SGS. The data management department will also send the CRF data to the SDO. The SDO will make sure all the data received from the data management department and the lab will be merged and converted into the required SDTM dataset structure. They create the PC, (part of) LB, IS (and other datasets as needed) before the lock. During the lock process, the SDO will deliver the datasets to the data management department. As such, the PC and other unblinding data can be included immediately in the clinical database lock.

WITHOUT SD OFFICE



WITH SD OFFICE



CREATION OF THE PK/PD INPUT DATASETS

Because the unblinded lab data (PK, biomarkers, immunogenicity data) is already available at the SDO, the programming of the PK and PD input files can already start before the database lock. All datasets of the clinical database need to be shared between the data management department and the SDO. This will include all the demographic data, vital sign and meal information, all outcome parameters of the study such as survival, time-to-event, questionnaires, ECG, EEG and viral load data. In addition, the programmers at the SDO have access to the randomisation information and the unblinding data.

Provided the SDO is involved prior to the database lock, the SDO programmers together with the modellers will start writing the document describing the specifications prior to the first deliverable. Once the specifications are in good shape, the SDO will begin programming based on the clinical database before the database lock. Any strange and unexpected values can be reported to the data management team. This advance work leads to improved data quality. If the source data is confirmed to be correct, the PK/PD modeler will be contacted in a blinded manner to discuss how to handle this unexpected data. If required SAS scripts can be written by the SDO programmers to deal with the unexpected data: e.g. exclude certain records based on rules or impute missing data. At the time of the database lock, only a rerun of the prepared scripts needs to be done. This results in a significant time gain. Usually, a NONMEM input file can be delivered a few working days after database lock.

In case of very short timelines between database lock and study report writing or submission to the authorities, even more is possible. A blinded PK/PD input file can be delivered to the modeler before unblinding of the study. By using dummy subject IDs and removing all treatment information, the analyst can already have a look at the data before the study is unblinded. It is crucial here, that the analyst does not have access to other clinical data containing real subjectIDs. They can already start to build their models. After database lock, a compare of values before and after can be done, or small modifications can be made to the model. Also for studies where database lock has already occurred or several studies for a compound were already conducted, the programmers experienced in creation of the NONMEM files will facilitate the modeling part.

ADVANTAGES:

- Dedication and Experience of programmers in NONMEM files
- Quality gain
- Time gain (after DBL)
- Off the critical path
- Access to blinded PK input files before DBL

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