FDA SEND CT-Compatible Simulated Study
- Process streamlining and implementation -

T. Anzai[1, 2], R. Aerni[2], M. Wasko[2], F. Mura[2], S. Horikawa[3], S. Sato[3], Y. Murase[3], H. Hatakeyama[3]

[1] Showa University School of Medicine / PDS Life Science, Hamamatsu-shi, Japan [2] PDS Lifesciences, Basel, Switzerland [3] Ina Research Inc., Nagano, Japan

Introduction

SEND (Standard for the Exchange of Nonclinical Data) was implemented by the US FDA in December, 2016, actuating a monumental shift toward electronic submission and evaluation. Although these changes are only applicable to submissions made in the US, non-US pharmaceutical companies, CRO's and the like are joining the rush to become SEND-compatible.
Since becoming the first Japanese CRO to make a successful FDA SEND trial submission in 2015, Ina Research (INA) has been pro-active in educating the Japanese community regarding the steps toward SEND submission success. This includes process and precaution considerations for those planning to incorporate SEND into their research planning. In light of the gradual standardization of SEND Controlled Terminology (CT), INA recently conducted a simulated CT-compliant study. In order to expedite final report terminology and CT unification in a standard study, INA investigated 1) planning stage considerations, 2) system issues observed when collecting mock data, and 3) methods allowing quicker, more efficient SEND conversion. INA also considered the visualization of SEND datasets, and how it may improve study evaluation.

Materials and methods SEND CT-compatible simulated study overview

Parameters	Content
Type of study	Four-week repeated oral dose toxicity study in dogs with a 4-week recovery period
Groups	4 groups, 32 animals in total Control: 5 animals/sex (2/sex for recovery) Low dose: 3 animals/sex Mid dose: 3 animals/sex High dose: 5 animals/sex (2/sex for recovery)
Parameters	Clinical observations, body weights, food consumption, ECG, ophthalmology, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, histopathology and TK
CT-compatible parameters	Organ names, clinical laboratory parameters, units of measurement and histopathological lesions[1]
System information	SENDIG 3.0 Controlled Terminology Ver.2016-09-30 In particular, the LB, MA and MI domains were investigated when using a SEND dataset conversion system.

[1] The practicality of CT for lesions was investigated.

Implementing a CT-compliant study

1.Current trends
The following 2 methods are widely employed to attain CT-compliance:
A. Create a legend of in-house terms and the applicable CT (conversion done at SEND dataset preparation)
B. Amend In-house terms employed to CT (conversion not necessary)

While 'A' seems more commonplace, it involves conversion of terminology during dataset creation. This method makes data confirmation difficult, because it allows the existence of several terms (those used in the final report vs. CT) to describe the same parameter/lesion.
The examples below are groups of terms used at INA in data collection and final report-writing and their respective CT-compatibility rates (incl. recognition and comparison of upper and lowercase letters):
- Specimens (MA & MI domains): 40% (match to CT)
- Laboratory Test Codes (LB domain): 37%
- Laboratory Test Names (LB domain): 18%

2. Purpose of a CT-compliant study
Assuming that the SEND system will also be implemented in Japan and the use of CT will become more commonplace, a simulated study implementing common terminology used in the protocol, safety study system, final report and SEND dataset was conducted.

3. Methods of CT-compliance
I. Study protocol
To avoid confusion that might have effected the results of this investigation, the study protocol was written using standard terminology implemented at INA. A table was attached with the corresponding CT.
II. Safety study system
- Specimens (**Table 1**)
Standard organ names altered in the various dictionaries to match CT in individual studies.
- Laboratory Test Codes, Laboratory Test Names (**Table 2**)
Raw data is collected as usual and terms are altered at tabulation to match CT.

III. Final report
The final report (including tables) is written using CT. A list of all CT used was also included in the final report.

4. SEND dataset
Assessment of a visual format for evaluation purposes, as well as how this format may be utilized.

Problems and solutions of CT-compliancy

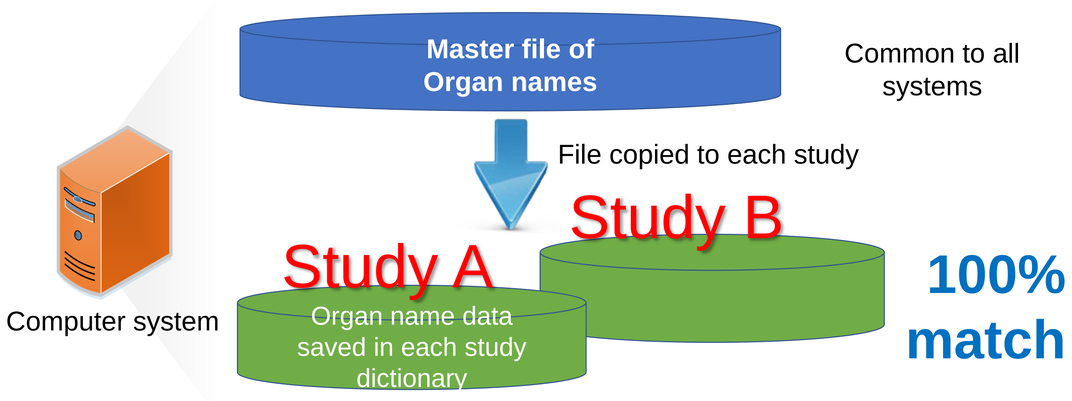
1.Computer system – Problems posing a CRO
No problems were encountered altering the system employed at INA to the specifications required for "Specimen" descriptions. However, if all "Laboratory Test" parameters were to be adjusted to match CT, including raw data, it was necessary to change overall facility standards, not just for individual studies, throughout the applicable timeframe.

Since this required careful consideration into whether or not it was possible, when and how it could be done, as well as agreement from clients, it was not feasible to amend such terminology straight away. Therefore, in this study, it was investigated whether or not amendments could be made on an individual study basis, limiting CT-compatibility to the final report only. Regular terminology was applied to the protocol with a table attached describing the applicable CT. This prevented inadvertent mistakes being made due to sudden changes to regular writing styles but allowed clarification of the terminology to be used in the final report.

2.Collection of lesion data
Non-neoplastic CT is still very limited. Problems encountered in this simulation are summarized in **Table 3**.

3.Evaluation using a SEND dataset
Using a SEND 'Viewer', the calculation of group means and standard deviations, as well as generation of charts or diagram is easily performed. The frequency of clinical signs or the grade of histopathological lesions can also be color-coded. All this assists in the visualization of data at evaluation, but it is also a very valuable tool prior to preparation of the final report. Therefore, it is optimal that a dataset be generated as soon as possible after data are fixed. A viewer that can be used at different facilities is also required.

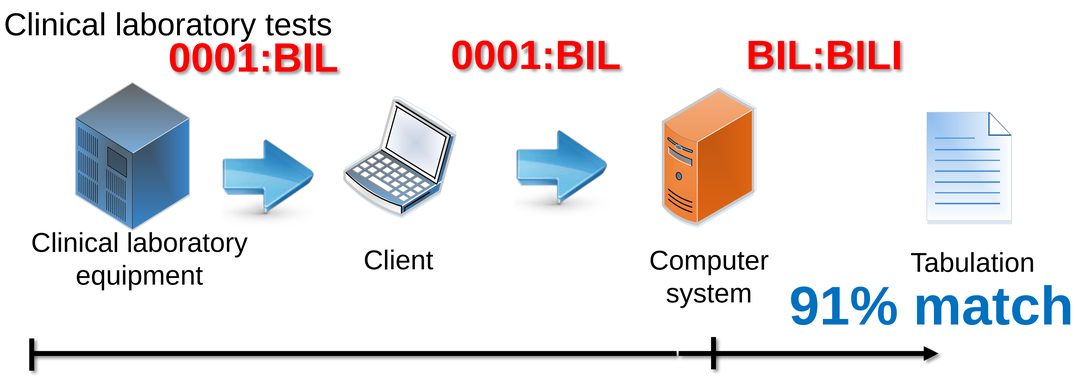
Table 1: Specimen Applying CT to organ names (histopathology)



Point By copying the master file to individual studies, amendments can be made within a study that won't alter all systems

Example of terms registered at INA	Applicable CT
Kidneys	KIDNEY
Femoral bone marrow	BONE MARROW, FEMUR
Cecum	LARGE INTESTINE, CECUM

Table 2: Laboratory Tests Applying CT to test parameters



Point Data to represented by a code (0001) and is changed to match CT at final output only.

Example of terms registered at INA	Applicable CT
BIL	BILI
UN	UREAN
CRE	CREAT

System constraints prevent the use of CT (100% match impossible)

Parameters	Clinical chemistry	Urinalysis
Sodium (NA)	SODIUM	SODIUM .
Potassium (K)	K	K .
Chloride (CL)	CL	CL .

Table 3: Basic pathological lesions MI domain (MISTRESC variables)

Basic histopathological lesions with/without applicable CT

Organ/ tissue	Raw data	CT
Thymus	Atrophy	Match
Kidney	Pyelonephritis	Match
Vagina	Mucification, increased	Match
Liver	Microgranuloma	No match
Eye	Keratitis	No match
Heart	Necrosis/inflammatory cell infiltrate, cardiomyocyte (Murine progressive cardiomyopathy)	No match

Although there is no need to convert this data in the final report to CT, there is a need to collect data that is CT-compatible in anticipation of future SEND requirements. Since non-neoplastic terminology is still lacking, INHAND-recommended terms are routinely employed.

Conclusion

1) Planning is a MUST
Create a list of parameters, confirm whether the system/raw data is SEND-compatible and adjust the master dictionary accordingly.

2) System issues that became obvious only when collecting mock data in the same manner as a real study
Within the current system, it is difficult to unify clinical chemistry and organ weight values in the dataset with those in the raw data. However, terminologies used in the tables of the final report were almost completely CT-compatible for all other parameters (parameters which do not contain notation common to any other parameter). As for histopathological lesions, sufficient CT does not yet exist. Therefore, it is advantageous to monitor developments in this area and fine-tune the system as necessary.

3) Streamlining the SEND conversion process
From just over 40% matching to nearly 100% CT-compatibility, the time required to create a SEND dataset decreased notability. CT-compatibility dramatically effects the time and resources required to create a SEND dataset.

4) Visualization of SEND-converted data in evaluation
SEND is expected to reduce the time required to evaluate study data, as well as clarify fundamental criteria. However, a stable Viewer is still not available. It is expected that, with the growing number of companies implementing SEND, that a suitable viewer will also be established.