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Bili's Journey

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ABSTRACT

This poster will trace the path of a single piece of data and identify all the regulatory and standards compliance considerations that dot the landscape from initial data collection all the way through submission through the eCTD. We'll follow the journey of the lab parameter Total Bilirubin, NCI Thesaurus Code C38037, and affectionately known in this poster as "Bili", while demonstrating every influencing factor in the standards and regulatory environment as Bili's data values and metadata are transformed along the way from start to finish. Standards concepts of CDASH, SDTM and ADaM will be considered along with all the regulations defined in the FDA Data Standards Catalog. Other items will be demonstrated such as data anonymization and Define-XMLv2.0 which have an effect of transforming data or metadata for data sharing and submission. From start to finish, Bili's journey is truly remarkable.

INTRODUCTION

The purpose of this poster is to visually show the sheer numbers of guidance documents, regulations, standards models, and conversions that are to be considered as data is collected and transformed for an electronic submission to the FDA. This poster does not give every possible consideration because each submission is unique and the regulations and standards documents will change over time. The intent is to just give a high-level picture to make the reader aware of the many controls placed on data from its inception all the way through submission and show where to go for more information.

WHY BILI AND HIS JOURNEY?

The idea to use lab data as an example gives an opportunity to show some important data conversions but any piece of study data would suffice and could be used to trace through the path from study collection to submission. Before any study protocol is written, there is usually an idea of what data is important for analyzing safety or efficacy. This data is usually well defined and in Bili's case, well understood. This is a common lab parameter with an example definition in the poster along with typical normal ranges for the result according to Fischbach. Other organizations in the healthcare landscape that don't involve clinical trials may know Bili from the LOINC definition with code 1975-2 highlighted in the poster. Bili's journey begins as he gathers badges, such as LOINC, for some of the important regulations, standards or transformations accomplished along the path.

GUIDANCE AND REGULATIONS ALONG THE PATH TO SUBMISSION

PDUFA V performance goals describes the process FDA intends to follow to require submissions using the eCTD format, thus the CTD triangle is at the heart of the submission and central to our poster. But to get this far, there are many CFR, ICH and FDA guidance and regulations to follow. Data cannot be collected until study participants have signed an informed consent as can be seen quite early in the path with the PART 50 document. The List of Standard, Guidance, Regulations, etc. has the items in an approximate order during this path. Use this list as a start and go to the ucm535180.htm FDA page for more information about eCTD submissions. One of the goals of PDUFA V stated that FDA will publish guidance that will require study data in conformance to CDISC standards and you can see related documents to these toward the end of the list.

STANDARDS AND TRANSFORMATIONS ALONG THE PATH TO SUBMISSION

The FDA Data Standards Catalog shows the supported standards and the required dates for conformance to those standards. The terminology example shows the requirement for LOINC use in the SDTM for studies starting after 03/15/2020. Currently the NCI Thesaurus codes are included in the SDTM controlled terminology and Bili's example (C38037) was presented in the poster.

The FDA issued a Position on the Use of SI Units for Lab Tests. To include these standardized values within the SDTM, conventional values are multiplied by a conversion factor in order to get the SI standardized result. A method for doing this can be seen in the SAS dataset with an example conversion for BILI from conventional (mg/dL) to SI (umol/L).

An XML document containing metadata for all SDTM and ADaM datasets in a submission is developed and included in the appropriate submission folder with the name define.xml. The poster shows an excerpt from this file for the SDTM-IG 3.1.2 Value Level Metadata. The standard for define.xml has been updated to version 2. This example highlights one of the biggest benefits of this upgrade. The "Where" clause will allow metadata values to point to the exact record in tall thin (normalized) data where the controlled values identify the lab result in original units (LBORRES) associated with the lab test code "BILI". This is a vast improvement over the original standard which didn't have the ability to link the lab result values with the individual lab test code values.

Data sharing is something else to consider regarding data associated with the values of BILI collected in study data. In the US, HIPPA is the primary regulation protecting personally identifiable information within healthcare data. The EU developed Policy 70 and GDPR to protect personally identifiable information. PhUSE has de-identification standards and there were some great presentations about this at the PARIS SDE in 2015. The poster shows an example of some records containing BILI values within an ADaM dataset to be shared. Fields that could potentially identify an individual (shown in yellow highlight) contain anonymized values which protect the privacy of the individual subjects but still allow for analysis of the data.

CONCLUSION

Without a clear methodology for conducting clinical trials and submitting the results electronically, including the underlying standardized data, it simply would not be possible for regulatory agencies to review and give their approval within the allotted timeframes. On a macro scale, the benefits of having well-defined regulations and standards are immense and enable industry and regulatory agencies to quickly bring new therapies to market. On a micro scale, a glance at this poster reveals the daunting challenge of working clinical study data through these regulations, guidelines and standards on the path to submission. The longest journey begins with a single step. The study programmer should be aware of the guidance documents, standards and transformations presented in the poster, even as they are upgraded, and use Bili's remarkable path as a first step for identifying and finding information needed along the path to submission.

REFERENCES

Frances Fischbach. A Manual of Laboratory Diagnostic Tests. Third Edition. Philadelphia: J.B. Lippincott Company; 1988. p.280-281

Please visit these websites to learn more about privacy:
PhUSE SDE Archive [Internet] https://www.phuse.eu/paris2015
CSDR [Internet] https://www.clinicalstudydatarequest.com/Default.aspx
HIPAA [Internet] https://www.hhs.gov/hipaa/for-professionals/privacy/index.html
EMA [Internet]
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac05809f363e
GDPR [Internet] https://www.eugdpr.org/

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RECOMMENDED READING

FDA [Internet]
HTTPS://WWW.FDA.GOV/DRUGS/DEVELOPMENTAPPROVALPROCESS/FORMSSUBMISSIONREQUIREMENTS/ELECTRONICSUBMISSIONS/UCM535180.HTM

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