

Mission Possible: Your Assignment is to Validate Output for a Study

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Introduction The biopharmaceutical industry is the most heavily regulated industry in the US, even ahead of banking and finance. The Food and Drug Administration (FDA) is the US regulatory body that has approval authority of drugs and devices. The EMEA is the FDA's equivalent in the European Union and the HPB in Canada. All agencies have requirements that the clinical trials data are correct and the output 'makes sense'. This paper will refer to the FDA, though the other worldwide agencies have similar requirements. Validation of the programs creating derived or analysis data sets, CDISC SDTM or ADaM, and the programs creating tables, listings, and figures (TLFs) assures the correctness of subject data for a submission. The regulations of submitting clinical trials data are not within the scope of this poster. This poster assumes familiarity with CDISC SDTM. Why Validate? •The FDA has guidances for submitting clinical trial data as well as requirements for clean subject data •Your company management will have a validation requirement that may vary depending on the task and the possible risk assessment related to data importance. •Validating programs and their output reduces development costs, especially if validation begins as soon as the data sets have been created •Validation provides correct conclusions about the safety and efficacy of drugs and devices •Without correct conclusions drawn from TLFs, the drug may be incorrectly approved •If the FDA were to find issues or errors, they may come to the biopharmaceutical company to do a full audit, they may levy a substantial fine against the company, and/or they may issue a "refusal to file." •Would there be a "pink slip" in your future??? •Make the FDA's job easier – don't let them find programming issues or errors. •Prove that what was supposed to have been done, has been done - correctly. Where to Start? •Read the protocol! –Study conduct location, –Study design (double blind, single blind, or crossover), –Efficacy objectives and parameters, including statistical models used, –Study population, –Safety parameters, including laboratory tests, –Questionnaires (check the version!) •Read the annotated Case Report Form (aCRF), paper or electronic version •Note what data were collected in each data set •Read the Analysis Plan (AP) / Statistical Analysis Plan (SAP) / Report and Analysis Plan (RAP) •Check how dosing information was collected •Are the data collected in CDISC SDTM format? •Read and understand programming considerations, and •Read and study the layouts for the output TLFs General Checks for All Data Sets •Run a PROC CONTENTS with order=varnum for the data sets/domains that you are validating to make sure all of the variables in the data set are in the correct SDTM order •Check the CONTENTS output for controlled terminology, numeric or character •Are date variable values in correct format? YYYY-MM-DDThh:mm:ss •Do the data "make sense?" •Run a PROC FREQ on all <u>required</u> variables to be sure there are NO null values •Get familiar and knowledgeable about the data Demography (DM) •The demography (DM) domain is the first to be programmed •DM = one record per subject •Run a PROC FREQ on all required variables •Since COUNTRY is required, check the FREQ output against the protocol – are the values in the output the only values in the protocol? •Check expected variables – should any of them really have null values? It is rare that RFSTDTC is ever null – there are few clinical trials without a dose/treatment start date •All of the following domains/data sets come after DM •Run a PROC FREQ to check one record per subject •If values for COUNTRY are not in the RAW data, check that the DM creation program populates it correctly Laboratory (LB) •A lot of data!!! •The downside of sending additional tests is that the data must be cleaned and reported •Lots of PROC FREQs to check the data – –LBTESTCD * LBSTRESU –LBCAT * LBTESTCD * LBTEST •Read the protocol to see which lab tests are required. It is up to the pharmaceutical company whether to include other lab tests that MAY have been sent from the central lab Vital Signs (VS) •Very similar validation to LB •Run PROC FREQs: –VSTESTCD * VSTEST –VSTESTCD * VSSTRESN –VSSTRESN * VSSTRESC •Check protocol for which vital signs must be reported Questionnaire (QS) •Check the version in protocol, usually is an appendix, and the aCRF to make sure the printed questions are the same •One questionnaire that often has issues is SF-36 SF-36® Health Survey - Version 1 3i. Walking one block 4d. Had difficulty performing the work or other activities (for example, it took extra time) 5c. Didn't do work or other activities as carefully as usual 9a. Did you feel full of pep? 9f. Have you felt downhearted and blue? SF-36v2® Health Survey Walking one hundred yards Had <i>difficulty</i> performing the work or other activities (for example, it took extra effort) Did work or activities <i>less carefully than usual</i> Did you feel full of life? Did you feel downhearted and depressed? References •A good website to check for current information from the Bioresearch Monitoring Program (BIMO) is www.fda.gov/oc/gcp •For standard lab values and conversion factors: http://www.unc.edu/~rowlett/units/scales/clinical_data.html Contact Information Susan Fehrer Coulson BioClin, Inc. Emporia, KS 66801 Work Phone: 011.609.351.3302 susanfehrer@yahoo.com
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