Standard SDTM Methodology with Legacy Data

Nth Analytics

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Legacy Data

- Old studies never die …
- Legacy studies are often required for submissions or pharmacovigilence
- Two types:
  - Well-documented
  - Less well-documented
- This presentation focuses on the worst case
  - Large pharmacovigilence project with lots of issues

Legacy Study Scenarios

- Best case
  - Requires no/little additional Data Management intervention
  - Maps “easily” to SDTM format
- Worst case
  - Becomes a Data Management problem with high level of intervention prior to mapping to SDTM
  - May require heavy statistician involvement for validation
  - Problematic data, may be excluded or imputed, so long as a reasonable, well-documented process can be defined

Case Study

A Large, Messy Database

- Large pharmacovigilence project
  - Sponsor required to address questions from regulatory authorities regarding safety issues.
- Convert demography, concomitant medications, and labs to SDTM
  - Minimum set of SDTM files required: DM, SC, CM, LB
  - SUPPCM and SUPPLB also needed
- 42 studies from 1987 to 2001 comprising 400 sites, 5,000 subjects, 1.2M lab records, 92,000 medication records
  - Original CRFs and study reports unavailable for some studies

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Staff

- Production
  - Data Manager
  - Clinician
  - Programmer
- Validation
  - Statistician
- Coordinator
  - Project Manager

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Strategy

- Start with analysis datasets
  - Already pooled
  - Already gone through one round of cleaning
  - Some consistency issues resolved
  - Working with 42 individual trial datasets was infeasible
- Three-Stage Process
  1. Data Management
  2. Validation
  3. SDTM Mapping
- Once Data Management straightens out the data, SDTM is the easy part

Why Convert to SDTM

- SDTM offers many added benefits beyond just cleaning the data
  - Integrate with current database, if necessary
  - Possible submissions to FDA
  - Ease of use
  - Not that hard, compared with data cleaning problems

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Conmeds - Problems

- Inconsistent data collection
- Inconsistent variable naming conventions
- Inconsistent/missing medication coding
  - Use of multiple medication dictionaries
- 92,000+ medication records in the file
  - 20,000 meds with a populated verbatim term
  - 56,000 meds with a dictionary term but no verbatim term
  - Remaining medications had neither verbatim nor dictionary term
    - Instead, there was a 3-digit code from an old internal dictionary (existing only in hard-copy)

Conmeds - Solutions

- Create new dataset and new derived term to be autoencoded, using lowest level of granularity available on each record
  - verbatim, dictionary term, 3-digit code
- Recreate electronic version of old 3-digit codes/decodes dictionary.
- Use the latest WHO Drug Dictionary to recode all the medication terms.

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Labs

- Lab data was a mess
- The sponsor did not have a good “comfort level” in addressing safety issues
- Twenty-eight (28) lab analytes of importance
  - Out of 40 total

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Labs - Problems

- Normal ranges missing, incomplete, wrong compared to result
  - 88,112 records had no range at all
  - 9,413 records had the low end of the range missing
  - 123 records had the high end of the range missing
- Normal range flags (H,L) inconsistent with ranges
- Implausible lab values
  - questionable, suspicious, or outright wrong
- Implausible units
- Questionable value/unit conversions

Labs - Solutions

- Data Management review
  - Determine extent of the problem
  - Ranges and units of measure fixed where possible
  - Determined when rule-based changes could be applied
  - Remaining issues passed to clinician for review
- Clinical review
  - Final approval on proposed changes
  - Provided referenced normal ranges to replace missing ranges
- Programmer
  - Applied changes from data manager and clinician
  - Derived standard lab values/units from the corrected data
- Statistician
  - Validated the whole thing
- Complete audit trail maintained

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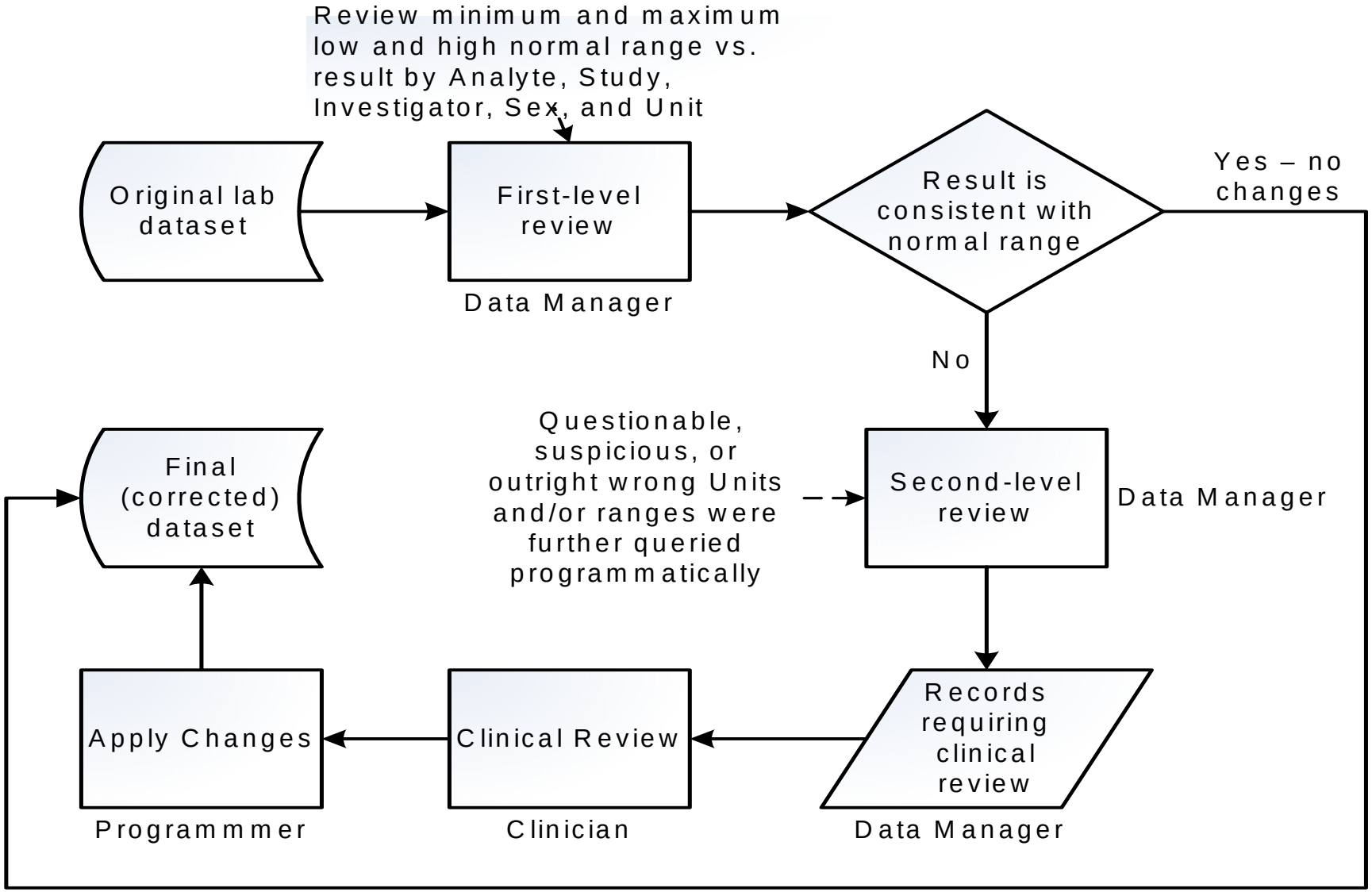
Lab Review Process



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Labs - First Level Review

- The original lab value was the bedrock on which everything depended.
  - Only units and normal ranges were subject to change after review and authorization by the clinician.
  - No lab values were changed
- The magnitude of the range was compared with the magnitude of the lab value.
  - by analyte, investigator, study, unit and sex
- The unit was reviewed for appropriateness with the range, the result and the analyte
- Units and/or ranges that were questionable, suspicious, or outright wrong examined in more detail.
  - Identify patient numbers and the context and extent of the problem.
  - This tabulation formed the basis of the second level review.

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Labs - Second Level Review

- Lab data were transferred to Excel for clinical review.
- Possible actions (if any), included:
  - No change
  - Correct the units
  - Apply generic normal ranges
  - Exclude the value as implausible

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Lab Data - Programming Steps

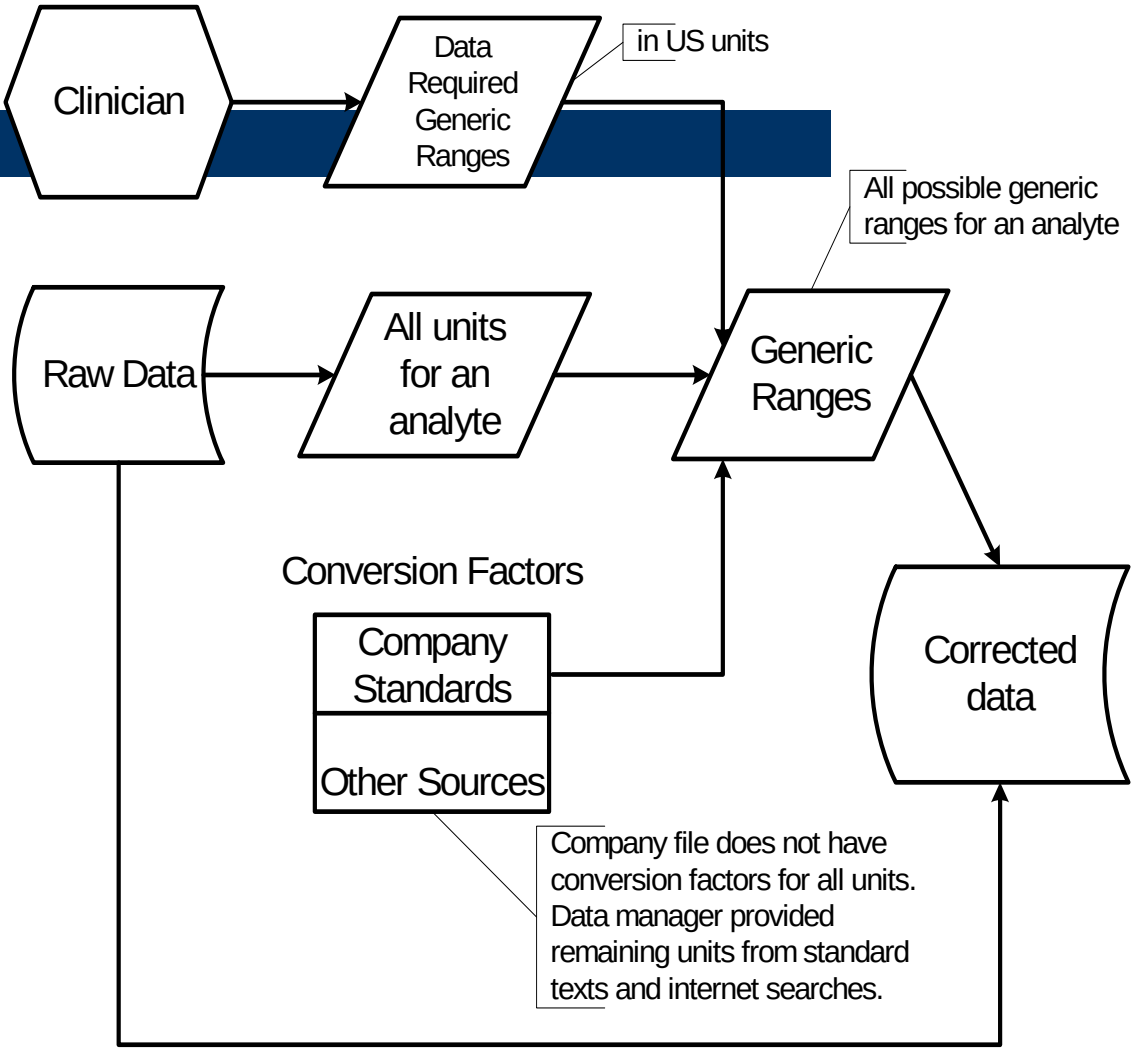
1. Programmers applied imputed values to the database
2. Missing ranges were replaced with generic ranges programmatically
3. Programmers converted to standard units and assigned high/low normal range flag after all imputations and generic ranges were applied.
4. Clinicians identified implausible values to be flagged in the database and excluded from analysis.

Generic Normal Ranges

- Since more than 50% of ranges were missing from lab records, the clinician established generic ranges that would be used in the absence of the laboratory-specified normal range.
  - References included the Merck manual and Harriet Lane Handbook (for pediatric ranges)
- Due to sheer volume of issues, the project team agreed that researching the original normal ranges through extensive review of the original CRFs for each subject affected was infeasible given the resources available.

Generic Normal Ranges

- Replace missing normal ranges with generic ranges provided by the clinician if either low or high or both are missing,
- All normal range flagging is done on the original results in the original units.
- Clinician provides generic ranges in US units. However, final normal ranges have to be in original units, and these are programmatically converted back to the original units.



Implausible Values

- After all possible imputations were applied, some results simply did not make sense.
  - Questionable values were presented to the clinician to review for plausibility.
  - A flag was set in the database on each record for which there was an implausible value.
- Results that were ambiguous, i.e. the value could have been a reasonable outlier, or the unit of measure could have been in error, were left as is.
- Results that had no unit of measure and no normal range were flagged as implausible (i.e. unusable for analysis).

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Implausible Values

Analyte	Unit	Study	Subject	Result	Normal Range		Comment
					Low	High	
SODIUM	mmol/L	STUDY1	S1-001	4.1			Possibly a potassium value.
SODIUM	mmol/L	STUDY1	S1-005	11.3	.	.	Possible data entry error or result from another test.
ALBUM	g/dL	STUDY3	S3-006	0.47	3.2	5.5	Possible data entry error.
POTASS	mmol/L	STUDY4	S4-034	141	.	.	Likely sodium value.
POTASS	mEq/L	STUDY5	S5-011	25.2	3.5	5.3	Obvious error of some sort.
POTASS	mEq/L	STUDY6	S6-039	20.2	3.5	5.3	Obvious error of some sort.
POTASS	mmol/L	STUDY4	S4-112	74	.	.	Sodium and potassium values likely switched.
POTASS	mEq/L	STUDY8	S8-309	17.4	3.5	5.3	Obvious error of some sort.
POTASS	mmol/L	STUDY9	S9-237	149	.	.	Likely sodium value.
POTASS	mg/L	STUDY9	S9-247	100	.	.	Unit and value make no sense.
POTASS	mmol/L	STUDY9	S9-651	243.4	.	.	Sodium and potassium values likely switched.
POTASS	mmol/L	STUDY9	S9-112	35	.	.	Possible data entry error.
POTASS	mEq/L	STUDY9	S9-126	0.7	.	.	Obvious error of some sort.
ALT	U/L	STUDY11	S11-212	2.1	0	39	Possible data entry error.
ALT	IU/L	STUDY11	S11-335	0.5	0	31	Error of some sort.

Validation

- Obviously, such a multi-layered cleaning and imputation process requires extensive validation
- Validation performed by statistician
  - Statisticians are detailed oriented, and are experts in findings errors in data
  - Statisticians have an entirely different perspective than data managers, which is a plus when independent confirmation is required
- The entire process was independently programmed using different methodology to the extent possible.
  - All validation was performed using SAS Enterprise Guide
- The goal was to confirm, through independent programming, that all of the records that should have changed did change, and records that should not have changed did not change

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Validation Steps

1. Identify all records that are changed comparing original vs. final datasets. Potential changes fell into 6 categories:
   - Normal range flags
   - Normal range upper/lower limits
   - Results
   - Units
   - Invalid data flags
   - Conversions
- Note that results should not have changed. The validation step simply verified that there were in fact no changes to the RESULT variable

Validation Steps (cont)

2. Independently create a dataset containing the generic normal ranges, using ranges provided in the emails from the clinician as the source
3. Independently program high/low flags, normal range limits, results, units, valid flags, and converted values and units
4. Compare the results, and send any discrepancies back to data manager and programmer for resolution. Repeat until all discrepancies are resolved.

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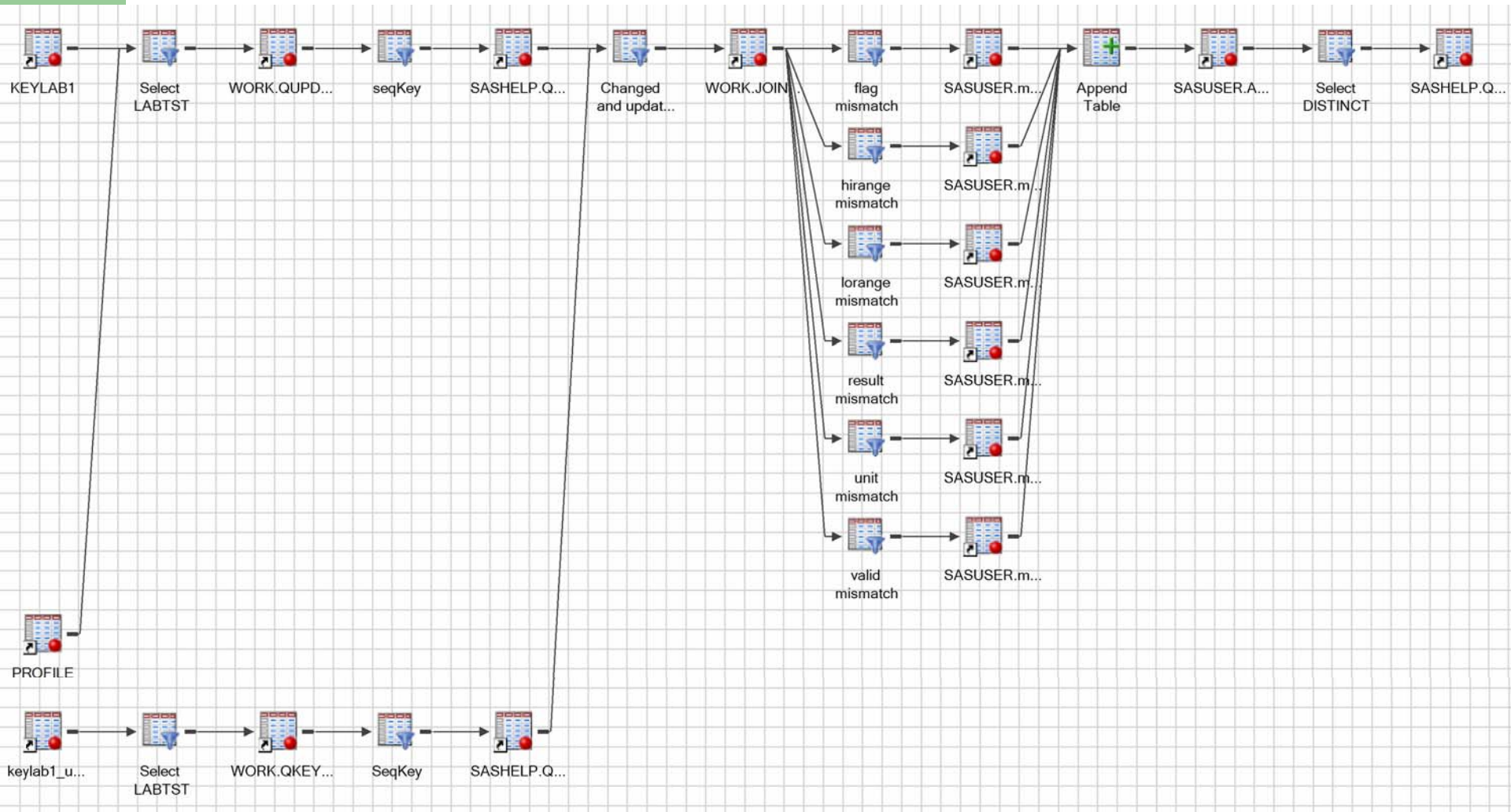
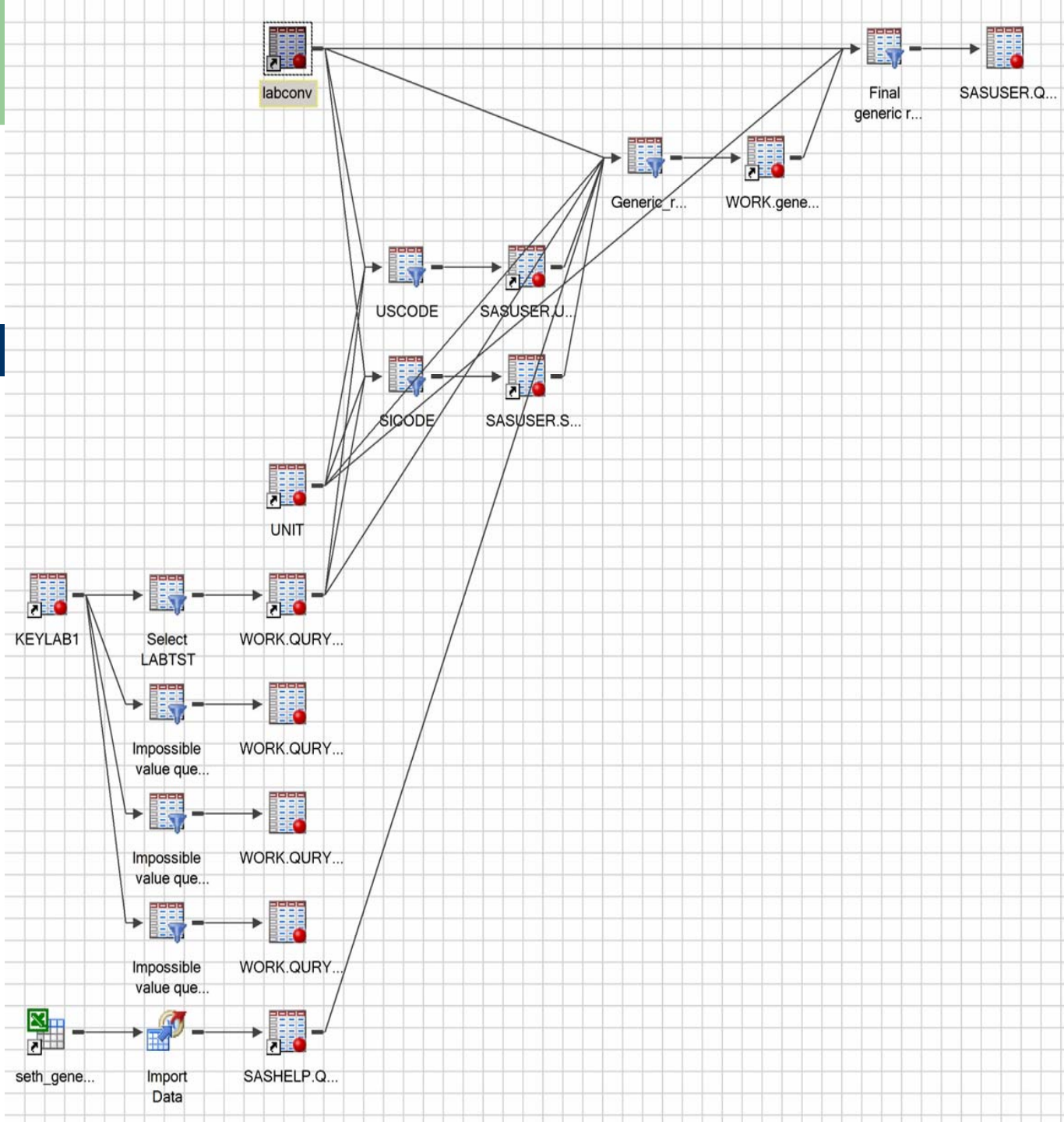
Differences between new and old datasets



Recreate Generic Normal Ranges



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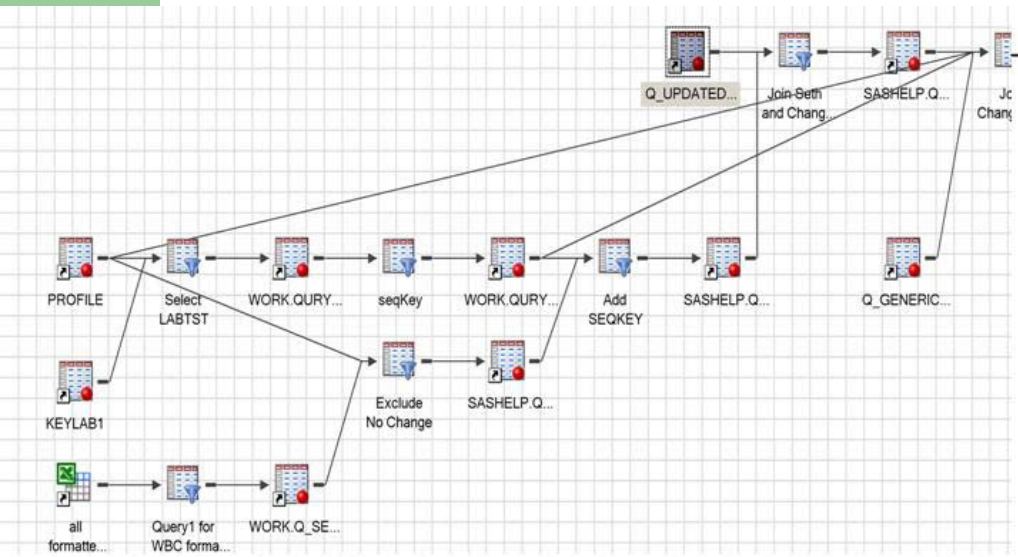
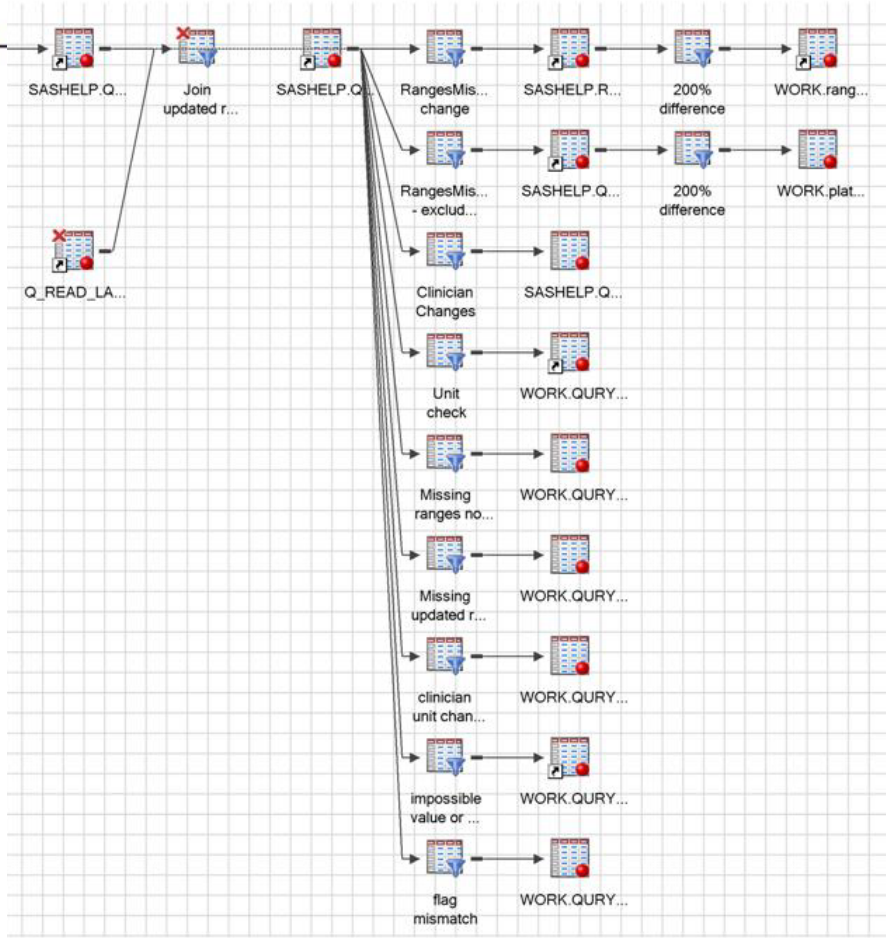
Changes vs. Independently Programmed Results





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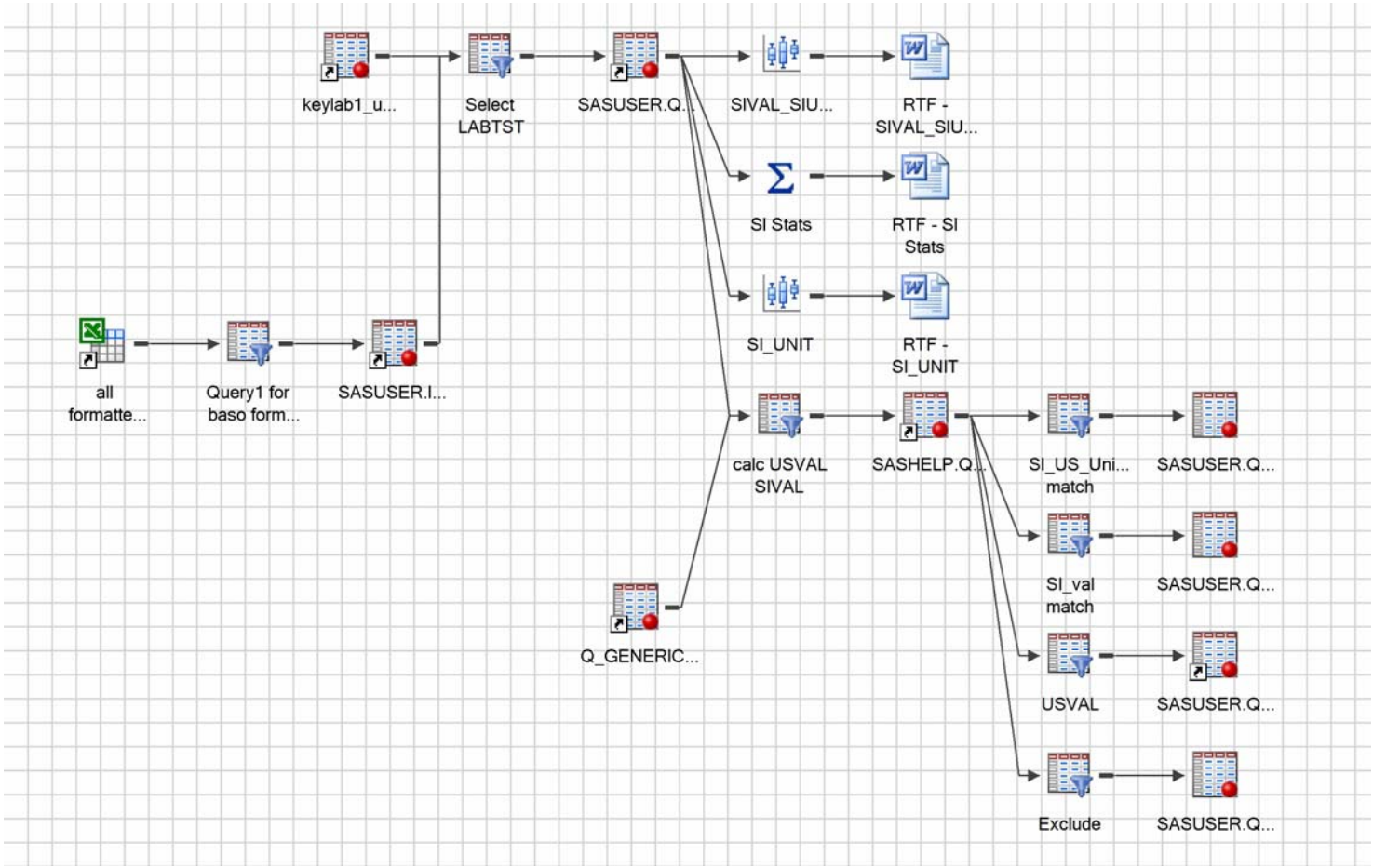
Check Conversions



SDTM Mapping

Domains

- DM
- SC
- CM
- SUPPCM
- LB
- SUPPLB

Strategy

- Map the minimum number of variables
  - Required
  - Expected
  - Permissable if absolutely necessary (or easy)
- Analysis dataset strategy

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DM

All DM variables mapped directly from analysis dataset.

Variable Name	Variable Label	Type	Mapping	Core
STUDYID	Study Identifier	Char	LEGACY_DEMOG.PNO	Req
DOMAIN	Domain Abbreviation	Char	='DM'	Req
USUBJID	Unique Subject Identifier	Char	LEGACY_DEMOG.UPATNO	Req
SUBJID	Subject Identifier for the Study	Char	LEGACY_DEMOG.UPATNO	Req
RFSTDTC	Subject Reference Start Date/Time	Char	%ISODATE(LEGACY_DEMOG.FRSTDOSE)	Exp
RFENDTC	Subject Reference End Date/Time	Char	=' '	Exp
SITEID	Study Site Identifier	Char	LEGACY_DEMOG.INO	Req
INVID	Investigator Identifier	Char		Perm
INVNAM	Investigator Name	Char	LEGACY_DEMOG.INVNAME	Perm
BRTHDTC	Date/Time of Birth	Char		Perm
AGE	Age in AGEU at RFSTDTC	Num	LEGACY_DEMOG.AGE	Exp
AGEU	Age Units	Char	='YEARS'	Exp
SEX	Sex	Char	LEGACY_DEMOG.SEX	Req
RACE	Race	Char	LEGACY_DEMOG.RACE	Exp
ETHNIC	Ethnicity	Char		Perm
ARMCD	Planned Arm Code	Char	LEGACY_DEMOG.TRT_CODE	Req
ARM	Description of Planned Arm	Char	LEGACY_DEMOG.TRTF	Req
COUNTRY	Country	Char	LEGACY_DEMOG.CNTRY	Req
DMDTC	Date/Time of Collection	Char		Perm
DMDY	Study Day of Collection	Num		Perm

SC

- Baseline weight goes in SC
- Repeat for baseline height
- SCDTC – date not in analysis dataset, leave blank

Variable Name	Variable Label	Type	Comments	Core
STUDYID	Study Identifier	Char	LEGACY_DEMOG.PNO	Req
DOMAIN	Domain Abbreviation	Char	='SC'	Req
USUBJID	Unique Subject Identifier	Char	LEGACY_DEMOG.UPATNO	Req
SCSEQ	Sequence Number	Num	%SEQ	Req
SCSTAT	Status of SC Measurement	Char		Perm
SCDY	Study Day of Examination	Num		Perm
SCGRPID	Group ID	Char		Perm
SCSPID	Sponsor-Defined Identifier	Char		Perm
SCTESTCD	Subject Characteristic Short Name	Char	='BASEWGT'	Req
SCTEST	Subject Characteristic	Char	='BASELINE WEIGHT'	Req
SCCAT	Category for Subject Characteristic	Char		Perm
SCSCAT	Subcategory for Subject Characteristic	Char		Perm
SCORRES	Result or Finding in Original Units	Char	LEGACY_DEMOG.BASEWGT	Exp
SCORRESU	Original Units	Char	='KG'	Perm
SCSTRESC	Character Result/Finding in Std Units	Char	PUT(LEGACY_DEMOG.BASEWGT,BEST8.)	Exp
SCSTRESN	Numeric Result/Finding in Standard Units	Num	LEGACY_DEMOG.BASEWGT	Perm
SCSTRESU	Standard Units	Char	='KG'	Perm
SCREASND	Reason Not Performed	Char		Perm
SCDTC	Date/Time of Collection	Char	=' '	Exp
SCEVAL	Evaluator	Char		Perm
SCGRPID	Group ID	Char		Perm
SCSPID	Sponsor-Defined Identifier	Char		Perm

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CM – Variables Mapped

Variable Name	Variable Label	Type	Mapping	Core
STUDYID	Study Identifier	Char	LEGACY_DEMOG.PNO	Req
DOMAIN	Domain Abbreviation	Char	='CM'	Req
USUBJID	Unique Subject Identifier	Char	LEGACY_DEMOG.UPATNO	Req
CMSEQ	Sequence Number	Num	%SEQ	Req
CMTRT	Reported Name of Drug, Med. Or Therapy	Char	LEGACY_CM.PSEUDOVB	Req
CMDECOD	Standardized Medication Name	Char	LEGACY_CM.PREFTERM	Perm
CMCAT	Category for Medication	Char	CASE WHEN LEGACY_CM.AEDYN='Y' THEN 'AED' ELSE 'NON-AED' END	Perm
CMINDC	Indication	Char	LEGACY_CM.INDICT	Perm
CMDOSTXT	Dose Description	Char	LEGACY_CM.TOTDOSE	Perm
CMROUTE	Route of Administration	Char	LEGACY_CM.ROUTE	Perm
CMSTDTC	Start Date/Time of Medication	Char	%ISODATE(LEGACY_CM.CSTARTDT)	Perm
CMENDTC	End Date/Time of Medication	Char	%ISODATE(LEGACY_CM.CSTOPDT)	Perm
CMSTDY	Study Day of Start of Medication	Num	%RELDAY(LEGACY_CM.CSTOPDT)	Perm
CMENDY	Study Day of End of Medication	Num	%RELDAY(LEGACY_CM.CSTARTDT)	Perm
CMDUR	Duration of Medication	Char	CASE WHEN LEGACY_CM.DUR IS NOT NULL THEN ='Y' THEN TRIM(INPUT(LEGACY_CM.DUR,8.)) || ' DAYS' 'ELSE ' ' END	Perm

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CM – Variables Not Mapped

Variable Name	Variable Label	Type	Mapping	Core
CMGRPID	Group ID	Char		Perm
CMSPID	Sponsor-Defined Identifier	Char		Perm
CMMODIFY	Modified Reported Name	Char		Perm
CMSCAT	Subcategory for Medication	Char		Perm
CMOCCUR	CM Occurrence	Char		Perm
CMSTAT	Concomitant Medication Status	Char		Perm
CMREASND	Reason Medication Not Collected	Char		Perm
CMCLAS	Medication Class	Char		Perm
CMCLASD	Medication Class Code	Char		Perm
CMDOSE	Dose per Administration	Num		Perm
CMDOSU	Dose Units	Char		Perm
CMDOSFRM	Dose Form	Char		Perm
CMDOSFRQ	Dosing Frequency per Interval	Char		Perm
CMDOSTOT	Total Daily Dose Using CMDOSU	Num		Perm
CMDOSRGM	Intended Dose Regimen	Char		Perm
CMSTRF	Start Relative to Reference Period	Char		Perm
CMENRF	End Relative to Reference Period	Char		Perm
VISITNUM	Visit Number	Num		Perm

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SUPPCM

- ATC codes (1 to 10) and Level 1, 2, 3, and 4 decodes for each ATC code go in SUPPCM

Variable Name	Variable Label	Type	Mapping	Core
STUDYID	Study Identifier	Char	LEGACY_DEMOG.PNO	Req
RDOMAIN	Related Domain Abbreviation	Char	='CM'	Req
USUBJID	Unique Subject Identifier	Char	LEGACY_DEMOG.UPATNO	Req
IDVAR	Identifying Variable	Char	='CMSEQ'	Req
IDVARVAL	Identifying Variable Value	Char	%SUPPSEQ	Req
QNAM	Qualifier Variable Name	Char	='LEVEL1_1'	Req
QLABEL	Qualifier Variable Label	Char	='LEVEL 1 DECODE FOR ATC CODE 1'	Req
QVAL	Data Value	Char	LEGACY_CM.LEVEL1_1	Req
QORIG	Origin	Char	='DERIVED'	Req
QEVAL	Evaluator	Char		Perm

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SUPPCM

- Prior medication flag

Variable Name	Variable Label	Type	Mapping	Core
STUDYID	Study Identifier	Char	LEGACY_DEMOG.PNO	Req
RDOMAIN	Related Domain Abbreviation	Char	='CM'	Req
USUBJID	Unique Subject Identifier	Char	LEGACY_DEMOG.UPATNO	Req
IDVAR	Identifying Variable	Char	='CMSEQ'	Req
IDVARVAL	Identifying Variable Value	Char	%SUPPSEQ	Req
QNAM	Qualifier Variable Name	Char	='PRIOR'	Req
QLABEL	Qualifier Variable Label	Char	='PRIOR MEDICATION'	Req
QVAL	Data Value	Char	LEGACY_CM.PREVMED	Req
QORIG	Origin	Char	='DERIVED'	Req
QEVAL	Evaluator	Char		Perm

LB – Variables Mapped

Variable Name	VariableLabel	Type	Comments	Core
STUDYID	Study Identifier	Char	LEGACY_DEMOG.PNO	Req
DOMAIN	Domain Abbreviation	Char	='LB'	Req
USUBJID	Unique Subject Identifier	Char	LEGACY_DEMOG.UPATNO	Req
LBSEQ	Sequence Number	Num	%SEQ	Req
LBTESTCD	Lab Test or Examination Short Name	Char	LEGACY_LB.LABTST	Req
LBTEST	Lab Test or Examination Name	Char	LEGACY_LB.LABDESC	Req
LBCAT	Category for Lab Test	Char	CASE WHEN LEGACY_LB.LABCAT='C' THEN 'CHEMISTRY' WHEN LEGACY_LB.LABCAT='H' THEM 'HEMATOLOGY' WHEN LEGACY_LB.LABCAT='U' THEN 'URINALYSIS' ELSE ' ' END	Exp
LBORRES	Result or Finding in Original Units	Char	PUT(LEGACY_LB.RESULT,BEST8.)	Exp
LBORRESU	Original Units	Char	LEGACY_LB.UNIT	Exp
LBORNRLO	Normal Range Lower Limit of Orig Units	Char	PUT(LEGACY_LB.LORANGE,BEST8.)	Exp
LBORNRHI	Normal Range Upper Limit of Orig Units	Char	PUT(LEGACY_LB.HIRANGE,BEST8.)	Exp
LBSTRESC	Character Result/ Finding in Std Format	Char	PUT(LEGACY_LB.SIVAL,BEST8.)	Exp
LBSTRESN	Numeric Result/ Finding in Std Units	Num	LEGACY_LB.SIVAL	Exp
LBSTRESU	Standard Units	Char	LEGACY_LB.SIUNIT	Exp
LBSTNRLO	Normal Range Lower Limit of Std Units	Num	=.	Exp
LBSTNRHI	Normal Range Upper Limit of Std Units	Num	=.	Exp
LBNRIND	Reference Range Indicator	Char	LEGACY_LB.FLAG	Exp
LBBLFL	Baseline Flag	Char	LEGACY_LB.BASEFLAG	Exp
VISITNUM	Visit Number	Num	LEGACY_LB.VISITNUM	Req
LBDTC	Date/Time of Specimen Collection	Char	%ISODATE(LEGACY_LB.SAMPDT)	Exp
LBDY	Study Day of Specimen Collection	Num	LEGACY_LB.STUDYDAY	Perm

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LB – Variables Not Mapped

Variable Name	VariableLabel	Type	Comments	Core
LBGRPID	Group ID	Char		Perm
LBREFID	Specimen ID	Char		Perm
LBSPID	Sponsor-Defined Identifier	Char		Perm
LBSCAT	Subcategory for Lab Test	Char		Perm
LBSTNRC	Reference Range for Char Rslt-Std Units	Char		Perm
LBSTAT	Lab Status	Char		Perm
LBREASND	Reason Test Not Done	Char		Perm
LBNAM	Vendor Name	Char		Perm
LBLOINC	LOINC Code	Char		Perm
LBSPEC	Specimen Type	Char		Perm
LBSPCCND	Specimen Condition	Char		Perm
LBMETHOD	Method of Test or Examination	Char		Perm
LBDRVFL	Derived Flag	Char		Perm
LBFAST	Fasting Status	Char		Perm
LBTOX	Toxicity	Char		Perm
LBTOXGR	Standard Toxicity Grade	Char		Perm
VISIT	Visit Name	Char		Perm
VISITDY	Planned Study Day of Visit	Num		Perm
LBENDTC	End Date/Time of Specimen Collection	Char		Perm
LBTPT	Planned Time Point Name	Char		Perm
LBTPTNUM	Planned Time Point Number	Num		Perm
LBELTM	Elapsed Time from Reference Point	Char		Perm
LBTPTREF	Time Point Reference	Char		Perm

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- Impossible value flag

Variable Name	Variable Label	Type	Mapping	Core
STUDYID	Study Identifier	Char	LEGACY_DEMOG.PNO	Req
RDOMAIN	Related Domain Abbreviation	Char	='LB'	Req
USUBJID	Unique Subject Identifier	Char	LEGACY_DEMOG.UPATNO	Req
IDVAR	Identifying Variable	Char	='LBSEQ'	Req
IDVARVAL	Identifying Variable Value	Char	%SUPPSEQ	Req
QNAM	Qualifier Variable Name	Char	='VALIDFG'	Req
QLABEL	Qualifier Variable Label	Char	='IMPOSSIBLE VALUE FLAG'	Req
QVAL	Data Value	Char	LEGACY_LB.VALID	Req
QORIG	Origin	Char	='DERIVED'	Req
QEVAL	Evaluator	Char	='SPONSOR'	Perm

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SUPPLB

- Impossible value flag reason

Variable Name	Variable Label	Type	Mapping	Core
STUDYID	Study Identifier	Char	LEGACY_DEMOG.PNO	Req
RDOMAIN	Related Domain Abbreviation	Char	='CM'	Req
USUBJID	Unique Subject Identifier	Char	LEGACY_DEMOG.UPATNO	Req
IDVAR	Identifying Variable	Char	='LBSEQ'	Req
IDVARVAL	Identifying Variable Value	Char	%SUPPSEQ	Req
QNAM	Qualifier Variable Name	Char	='VALIDCOM'	Req
QLABEL	Qualifier Variable Label	Char	='IMPOSSIBLE VALUE FLAG REASON'	Req
QVAL	Data Value	Char	LEGACY_LB.COMMENT	Req
QORIG	Origin	Char	='DERIVED'	Req
QEVAL	Evaluator	Char	='SPONSOR'	Perm

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Summary

- Enter process took 5 months
- Resouces:
  - Data Manager: 100%
  - Clinician: 25%
  - Programmer: 50%
  - Project Manager: 25%
  - Statistician: 100% (for one month)

Discussion

- Messy legacy studies require a lot of data management expertise before automated methods can be used
  - A range of problems in the legacy data had to be resolved to make the data usable prior to mapping to SDTM
- While the approach used in cleaning the conmed and lab data might be applicable to other types of data, clearly caution must be taken, as each type of data typically has its own set of unique problems
- Legacy conversion to SDTM may appear on the surface to be costly, however, non-conversion can be more costly
  - The ability to respond to regulatory requests can be greatly reduced if working with multiple “old” databases in varying structures.