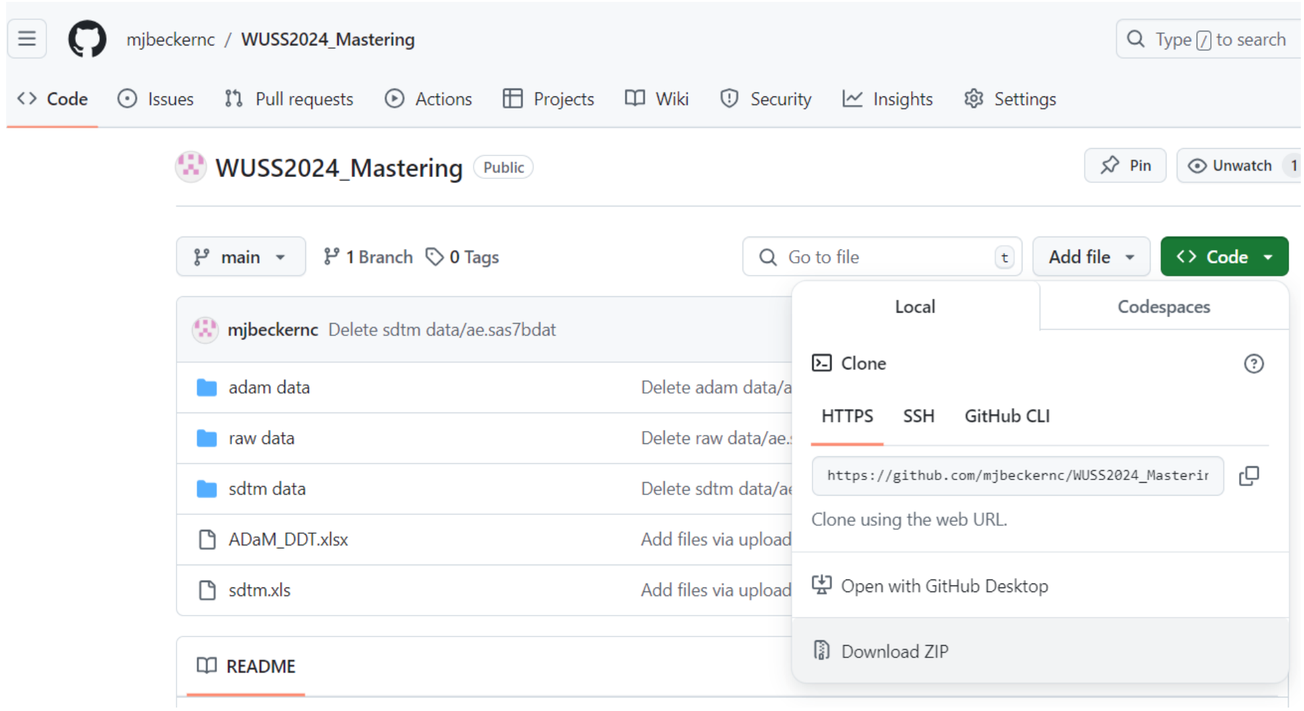
Download data / Documents

- Go to: https://github.com/mjbeckernc/WUSS2024_Mastering.git

- Go to <> Code, Download Zip
- Unzip to your laptop



Mastering Clinical Trial Reporting

Matt Becker, Life Science Strategic Advisor, HLS

Clinical Trials

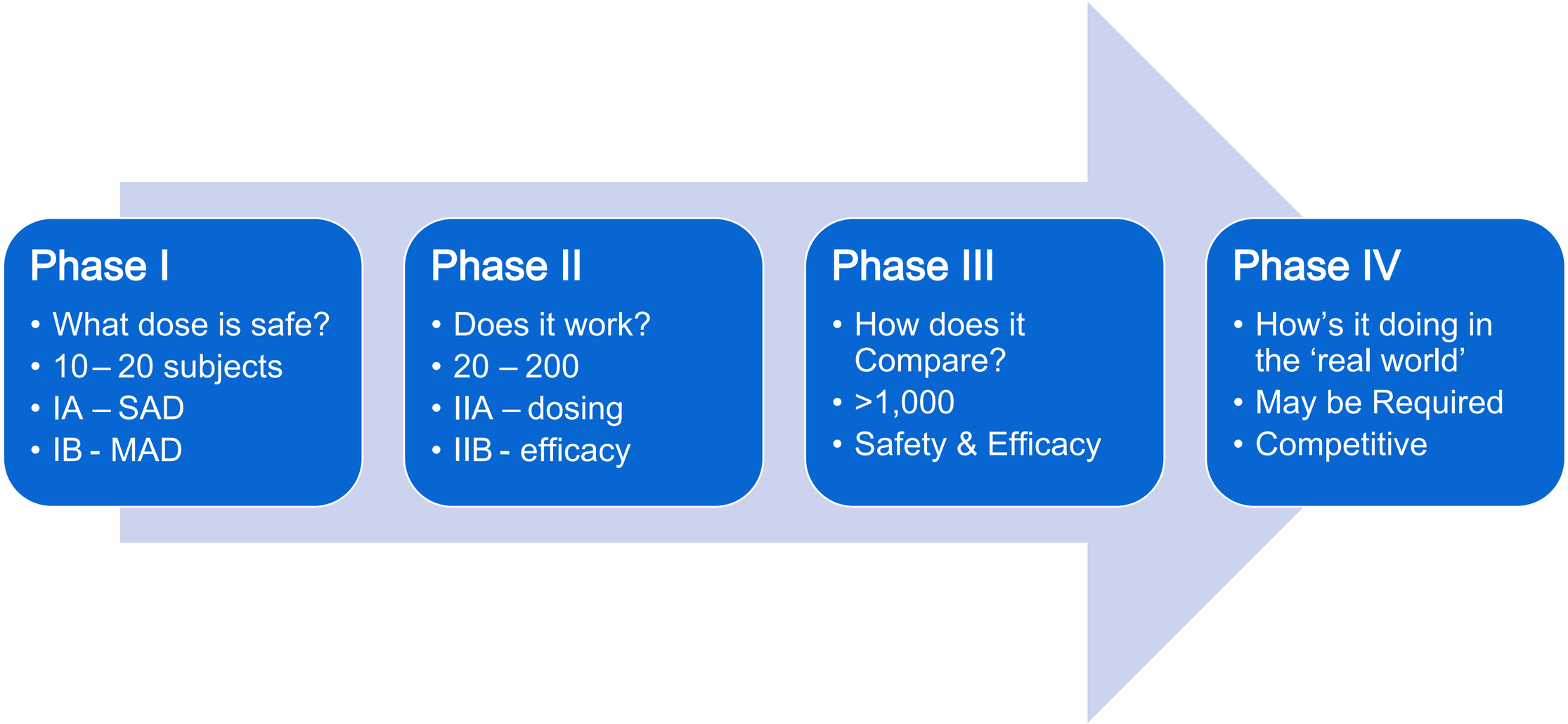
What are They

- "Clinical trials are research studies that explore whether a medical strategy, treatment, or device is **safe** and **effective** for humans. These studies also may show which medical approaches work best for certain illnesses or groups of people. Clinical trials produce the best data available for health care decision making."

NIH: https://www.nhlbi.nih.gov/studies/clinicaltrials

Clinical Research

Types of Trials



Clinical Research

Trial Setup & Execution

Execution

Data Standards

- Standard Data Tabulation Model (SDTM)
  - Raw structure to standard metadata structure

- Analysis Dataset Model (ADaM)
  - Analysis ready metadata structure for tables, listings*, figures (TLFs)

Execution

SDTM – Demographics (DM)

D	E	F	G	H	I	M	N	O
t Name	Variable Name	Variable Label	Type	Described Value Domain	Role	Definition	Notes	Examples
	STUDYID	Study Identifier	Char		Identifier	A sequence of characters used by the sponsor to uniquely identify the study.		
	DOMAIN	Domain Abbreviation	Char		Identifier	An abbreviation for a collection of observations, with a topic-specific commonality.	2-character abbreviation, which must be "DM".	
	USUBJID	Unique Subject Identifier	Char		Identifier	A sequence of characters used to uniquely identify a subject across all studies for all applications or submissions involving the product.		
	SUBJID	Subject Identifier for the Study	Char		Topic		Subject identifier, which must be unique within the study. Often the ID of the subject as recorded on a CRF.	
	RFSTDTC	Subject Reference Start Date/Time	Char	ISO 8601 datetime or interval	Record Qualifier	The start date or date and time of the sponsor-defined study reference period, represented in a standardized character format.	Usually equivalent to date/time when subject was first exposed to study treatment. Required for all randomized subjects; will be null for all subjects who did not meet the milestone the date requires, such as screen failures or unassigned subjects.	
	RFENDTC	Subject Reference End Date/Time	Char	ISO 8601 datetime or interval	Record Qualifier	The end date or date and time of the sponsor-defined study reference period, represented in a standardized character format.	Usually equivalent to the date/time when a subject was determined to have ended the trial. Often equivalent to either date/time of last exposure to study treatment or date/time of last contact with the subject. Required for all randomized subjects; null for screen failures or unassigned subjects.	
						The start date or date and time of		

SDTM Hands-On

Execution

ADaM – Subject Level Analysis Dataset (ADSL)

B	C	D	E	F	G	H	I	J
a Structure Name	Dataset Name	Variable Group	Variable Name	Variable Label	Type	Codelist/Controlled Terms	Core	CDISC Notes
ect-Level Analysis aset	ADSL	Identifier	STUDYID	Study Identifier	Char		Req	DM.STUDYID
ect-Level Analysis aset	ADSL	Identifier	USUBJID	Unique Subject Identifier	Char		Req	DM.USUBJID
ect-Level Analysis aset	ADSL	Subject Demographics	AGE	Age	Num		Req	DM.AGE. If analysis needs require a derived age that does not match DM.AGE, then AAGE must be added
ect-Level Analysis aset	ADSL	Subject Demographics	AGEU	Age Units	Char		Req	DM.AGEU
ect-Level Analysis aset	ADSL	Subject Demographics	AGEGRy	Pooled Age Group y	Char		Perm	Character description of a grouping or pooling of the subject's age for analysis purposes. For example, AGEGR1 might have values of "<18", "18-65", and ">65"; AGEGR2 might have values of "Less than 35 y old" and "At least 35 y old".
ect-Level Analysis aset	ADSL	Subject Demographics	SEX	Sex	Char		Req	DM.SEX.
ect-Level Analysis aset	ADSL	Subject Demographics	RACE	Race	Char		Req	DM.RACE.
ect-Level Analysis aset	ADSL	Population Indicator	SAFFL	Safety Population Flag	Char		Cond	These flags identify whether or not the subject is included in the specified population. A minimum of one subject-level population flag variable is required in ADSL. \n Not all of the indicators listed here need to be included in ADSL. As stated in Section 3.1.4, Flag Variable Conventions, only those indicators corresponding to populations defined in the statistical analysis plan or populations used as a basis for analysis need be included in ADSL. \n This list of flags is not meant to be all-inclusive. Additional population flags may be added. \n The values of subject-level population flags cannot be blank. If a flag is used, the corresponding numeric version (*FN, where 0 = No and 1 = Yes) of the population flag can also be included. Please also refer to Section 3.1.4, Flag Variable Conventions.
ect-Level Analysis aset	ADSL	Treatment	ACTARM	Description of Actual Arm	Char		Perm	DM.ACTARM
ect-Level Analysis aset	ADSL	Treatment Timing	TRTSDT	Date of First Exposure to Treatment	Num		Cond	Date of first exposure to treatment for a subject in a study. TRTSDT and/or TRTSDTM are required if there is an investigational product. Note that TRTSDT is not required to have the

ADaM Hands-On

Execution

Data Mapping - Common Code

- Data step / Proc SQL
  - Variable creation
  - Variable assignment
  - Merging data
  - Saving data
- Macros for common algorithms
  - Study day calculations
  - Date variable creation
  - Others as desired
- Common Procs
  - Proc SQL, Sort, Transpose, Freq, Means, Summary

```
data ae(drop=visit aestdtc aeendtc aeacn aerel aeout
        rename=(visitnew=visit aestdtc_new=aestdtc aeendtc_new=aeendtc aeacn_new=aeacn aerel_new=aerel aeout_new=aeout));
  set &rawdata..ae;
  length usubjid $25 visitnew $25 aesev aecat $50 aeenrf $15;
  usubjid=trim(left(studyid))||'-'||trim(left(site))||'-'||trim(left(randomno));
  domain='AE';
  if aenone='Y' then aeoccur='N';
  else aeoccur='Y';
  if aeoccur='Y' then do;
    %msdtmdt(datepart=aestdt, datevar=aestdtc_new);
    %msdtmdt(datepart=aeendt, datevar=aeendtc_new);
  end;
  aecat='ADVERSE EVENTS';
  aeseq='14';
  visitnum=visit;
  visitnew=upcase(put(visitnum,visitf.));
  if aeongo='Y' then aeenrf='ONGOING';
  aesev=aetoxgrc;
  aeacn_new=aeacnc;
  aerel_new=aerelc;
  aeout_new=aeoutc;
  aecontrt=aecontr;
run;

%msdtmdy(inds=ae, todate=aestdtc, studyday=aestdy);
%msdtmdy(inds=ae, todate=aeendtc, studyday=aeendy);

proc sort data=ae;
  by aeterm;

proc sort data=raw.codeae out=codeae;
  by aeterm;

data ae;
  merge ae(in=x) codeae(in=y);
  by aeterm;
  length aebodsys aedecod $200;
  if x;
  aebodsys=upcase(socterm);
  aedecod=upcase(prefterm);
run;

proc sort data=ae;
  by studyid domain usubjid aeseq aespid;

%mimpsdtm(micsv=AE, miin=AE, miout=sdtm.ae, mlbl=AE SDTM Dataset);
```

Execution

Data Mapping - Common Code

```
%macro mstudydy (todate=, basedate=, studyday=studyday);

 %if &todate= |&basedate= %then %do;
  put 'missing parameters - aborting...'
 %end;

 %else %do;
  &studyday=&todate-&basedate+(&todate ge &basedate);
 %end;

%mend mstudydy;
```

```
%macro msuppq (outfile=, rdomain=, idvar=, qnam=, qlabel=, qorig=, qeval=, filter=);

   RDOMAIN=upcase("&rdomain");
   label rdomain='Related Domain Abbreviation';
   IDVAR=upcase("&idvar");
   %if &idvar^=  %then %do; IDVARVAL=&idvar; idvarval=left(idvarval); %end;
   QNAM=upcase("&qnam");
   QLABEL=upcase("&qlabel");
   QVAL=left(upcase(&qnam));
   QORIG=upcase("&qorig");
   QEVAL=upcase("&qeval");
   &filter output &outfile;

%mend msuppq;
```

Execution

Baseline - Listing

ABCD, Inc.
XMB-111 Draft

Appendix 16.2.4-1: Demographics and Subject Characteristics

Subject	Date of Birth	Age (Years)	Gender	Race	Height (cm)	Weight (kg)	TBSA[a]
111-1001							

[a]Total Body Surface Area (mL/m²) = square root of [Ht (cm) * Wt (kg) divided by 3600]

PROGRAM: rldemo.sas (FINAL) 27APR2022 09:58

Listing Hands-On

SDTM DM

Columns for ARM, Subject ID, Start Date, End Date, Age, Sex, Race, Ethnicity

Execution

Listings - Common Code

- Data step / Proc SQL
  - Variable creation
  - Variable assignment
  - Merging data
- Macros for common algorithms
  - As needed(e.g. case)
- Common Procs
  - SQL, Sort, Transpose, Report
- ODS statements

```
proc sort data=sdtm.vs out=vs;
  by usubjid;
  where visitnum=0 and vstestcd in('ORNHT','ORNWT');

proc transpose data=vs out=tranvs(drop=_name_);
  by usubjid;
  var vsstresn;
  id vstest;
run;

proc sort data=sdtm.dm out
  by usubjid;

data dm;
  merge dm(in=x) tranvs(in=y);
  by usubjid;
  length tbsa 8;
  if x;
  tbsa=sqrt((height*weight)/3600);
run;

proc sort data=sdtm.suppdm out=suppdm(keep=usubjid qval);
  by usubjid;
  where qnam='INIT';

data dm(rename=(qval=init));
  merge dm(in=x) suppdm(in=y);
  by usubjid;
  if x;
  page=int(_n_/8)+1;
run;

%mcase(inds=dm, exceptl=%str('USUBJID','INIT','BRTHDTC'));

%mtitle(progid=ldemo);

proc report data=dm headline headskip nowindows split='|' missing spacing=1;
  column page usubjid init brthdtc age sex race height weight tbsa;
  define page / order noprint;
  define usubjid / order 'Subject' style={just=left cellwidth=7%};
  define init / display 'Initials' style={just=left cellwidth=6%};
  define brthdtc / display 'Date of Birth' style={just=left cellwidth=10%};
  define age / order 'Age|(Years)' format=4.1 style={just=center cellwidth=7%};
  define sex / display 'Gender' style={just=left cellwidth=7%};
  define race / display 'Race' style={just=left cellwidth=22%};
  define height / display 'Height|(cm)' format=3. style={just=left cellwidth=8%};
  define weight / display 'Weight|(kg)' format=3. style={just=left cellwidth=8%};
  define tbsa / display "TBSA`{super a}" format=4.1 style={just=left cellwidth=8%};
  break after page / page;
```

Execution

Baseline - Table

ABCD, Inc.
XMB-111 Draft

Table 14.1.1-1: Demographics and Subject Characteristics

		Age Group (years)					
		0 - 2	3 - 6	7 - 11	12 - 17	3 - 17 Total	Total
Age (years)	n	11					
	Mean (SD)						
	Median						
	Min, Max						
Gender, n(%)	Male	5 (45.5%)					
	Female						
Race, n(%)	American Indian/Alaska Native						
	Black or African American						
	Hispanic						
	White						
Height (cm)	n						
	Mean (SD)						

[a]Total Body Surface Area = square root of [Ht (cm) * Wt (kg) divided by 3600]

PROGRAM: rtdemog.sas, (FINAL) 15OCT2015 10:23

Table Hands-On

ADaM ADSL

Summarize Age, Gender, Race

Execution

Tables - Common Code

- Data step / Proc SQL
  - Variable creation
  - Variable assignment
  - Merging data
- Macros for common algorithms
  - Categorical analysis
  - Discrete analysis
  - P-values
  - Others as desired
- Common Procs
  - SQL, Sort, Transpose, Report, Means, Freq, Summary, Ttest, Lifetest
- ODS Statements

```
%mss(msdata=lb, msout=plat2, msvar=lbstresn, msstats=n meansd median range, msprec=1, msorder=17, mswhere=(lbtestcd='PLAT' and visitnum=2));
%mss(msdata=lb, msout=plat3, msvar=chg, msstats=n meansd median range, msprec=1, msorder=18, mswhere=(lbtestcd='PLAT' and visitnum=2));
%mss(msdata=lb, msout=plat4, msvar=lbstresn, msstats=n meansd median range, msprec=1, msorder=19, mswhere=(lbtestcd='PLAT' and visitnum=29));
%mss(msdata=lb, msout=plat5, msvar=chg, msstats=n meansd median range, msprec=1, msorder=20, mswhere=(lbtestcd='PLAT' and visitnum=29));

data final;
  set hgb1 hgb2 hgb3 hgb4 hgb5 hct1 hct2 hct3 hct4 hct5 rbc1 rbc2 rbc3 rbc4 rbc5 p      plat3 plat4 plat5;
run;

proc sort data=final;
  by order sorder;

data final;
  set final;
  by order sorder;
  length page 4 firstcol $40 secondcol $40;
  retain page;
  if first.order then page=floor(order/5.1)+1;
  if first.order and order=1 then firstcol="Hemoglobin (mmol/L)";
  else if first.order and order=6 then firstcol="Hematocrit (fraction of 1)";
  else if first.order and ord      then firstcol="Red Blood Cells (10E12/L)";
  else if first.order and          hen firstcol="Platelets (10E9/L)";
  if first.order then se           t(order,orderf.);
run;

proc sort data=f
  by page ord          firstcol secondcol;

%mtitle(p          logid);

proc report data=final headline headskip nowindows split='|' missing spacing=1 style(header)=[protectspecialchars=off];
  column page order sorder firstcol secondcol text ("Age Group (years) \brdrb\brdrs" trt1 trt2 trt3 trt4 trt5) trt6;
  define page /order noprint;
  define order /order noprint;
  define sorder /order noprint;
  define firstcol / "Lab Test" style={just=l cellwidth=8%};
  define secondcol / "Timepoint" style={just=l cellwidth=12%};
  define text/ " " style={just=l cellwidth=7%};
  define trt1 / "     0 - 2 |     (N=&pop1)" style={cellwidth=10% asis=on pretext="\tqdec\tx450 "};
  define trt2 / "     3 - 6 |     (N=&pop2)" style={cellwidth=10% asis=on pretext="\tqdec\tx450 "};
  define trt3 / "     7 - 11 |     (N=&pop3)" style={cellwidth=10% asis=on pretext="\tqdec\tx450 "};
  define trt4 / "     12 - &up_limit |     (N=&pop4)" style={cellwidth=10% asis=on pretext="\tqdec\tx450 "};
  define trt5 / "     3 - &up_limit Total |     (N=&pop5)" style={cellwidth=10% asis=on pretext="\tqdec\tx450 "};
  define trt6 / "     Total |     (N=&pop6)" style={cellwidth=10% asis=on pretext="\tqdec\tx450 "};
  break after page / page;
  compute before order;
    line " ";
  endcomp;
run;
```

Execution

Common Code Examples

```
proc means data=ms0&msorder nway
  %IF %UPCASE(&MSPRT) NE Y %THEN %DO;
    noprint
  %END;;
  var &msvar;
  %IF &MSBY NE or &MSTRT NE %THEN %DO;
    class &MSBY &MSTRT;
  %END;
  %IF &MSWHERE NE %THEN %DO;
    where &MSWHERE;
  %END;
  output out=ms&msorder    n=nn
                        mean=nmean
                         std=nstd
                      median=nmedian
                         min=nmin
                         max=nmax
                       nmiss=nnmiss
                         sum=nsum
                      stderr=nse
                          ql=nql
                          q3=nq3
                         var=nvar
                        uclm=nuclm
                        lclm=nlclm;
run;
```

```
proc freq data=&mfdata noprint;
  %IF &MFWHERE NE %THEN %DO;
    where &MFWHERE;
  %END;
  tables &mftable / out=mf2;
run;
```

```
%macro msdtmdt (datepart=, datevar=);

 %if &datepart= | &datevar= %then %do;
  put 'missing parameters - aborting...'
 %end;

 %else %do;
  &datevar= trim(left(substr(&datepart.yy,1,4
  if compress(&datevar)='--' then &datevar=''
 %end;

%mend msdtmdt;
```

Challenges

Concerns for Clinical Trials

- System must be validated – 21 CFR Part 11
- Tight access controls required – Blinded & Unblinded Data
- Data standards adherence
- Managing multiple workflows and multiple users
- Following SOPs – Traceability & Auditability
- FDA Submission – Risk Adverse