BASAS 2019

Learnings from Statistical Programming supporting audits for regulatory agencies (FDA and EMA)

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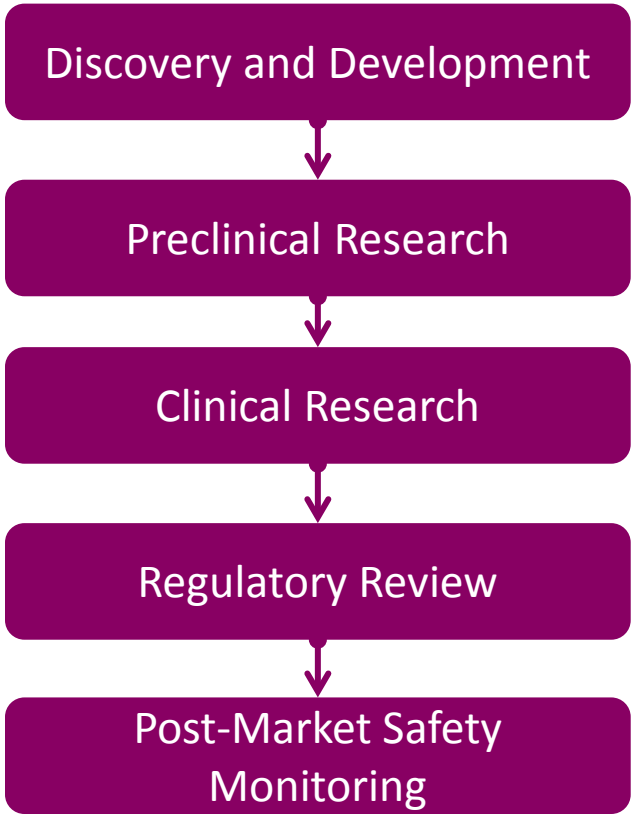
Agenda

- Overview of Drug Development
- Background on Food and Drug Administration (FDA) Requirements.
- European Medicines Agency (EMA) – Overview
- EMA – Inspection guidelines
- Implementation
- Questions and discussion.

Overview of Drug Development



Food and Drug Administration (FDA)

Background on FDA Requirements

- FDA uses onsite inspections to ensure that clinical investigators ,sponsors, and Institutional Review Boards (IRB) comply with FDA regulations while developing investigational drugs or biologics.

- In 1977, FDA established the **Bioresearch Monitoring** (BIMO) Program to develop cross-center guidelines for inspections of clinical investigators, sponsors, and IRBs.

- The BIMO Program for drugs is managed by the **Office of Scientific Investigations** (OSI) and for biologics by the Office of Inspections and Surveillance.

- Medical reviewers, who are responsible for approving or disapproving a product, consult with BIMO reviewers to choose which clinical trial sites to inspect.

Background on FDA Requirements (Continued)

- OSI requests sponsor to submit:
  - Part I: General study related information and specific Clinical Investigator Information
  - Part II: Subject Level Data Listings by Site
  - Part III: Summary Level Clinical Site Data (SLCS)
- Each major study (phase 2 or phase 3) should be prepared.
- For clinical site involved in multiple studies in support of an application, provide the data independently for each study within dataset.

Part I: General study related information and specific Clinical Investigator Information

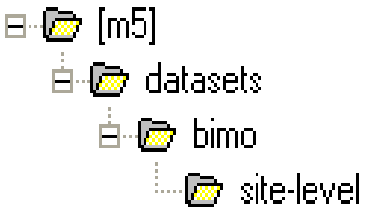
- Item 1: include the site information in a tabular format: site number; Principal investigator; site location (address and contact information);current location.
- Item 2: include by site information in a tabular format: Number of subjects screened; randomized; treated who prematurely discontinued.
- Item 3: include the information in a tabular format: location of Trial Master File; CROs information (name, address and contact); location of source data generated by CROs; location of study-related documents.
- Item 4: Annotated CRF.
- Item 5: Protocol and all amendments

Part II: Subject Level Data Listing by Site

- a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
- b. Subject listing for treatment assignment (randomization).
- c. Subject listing of drop-outs and subjects that discontinued with date and Reason
- d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
- e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
- f. By subject listing, of AEs, SAEs, deaths and dates
- g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
- h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
- i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
- j. By subject listing, of laboratory tests performed for safety monitoring

Part III: Summary Level Clinical Site Data (SLCS)

- Guidance for Industry: Providing Submissions in Electronic Format—Summary Level Clinical Site Data for CDER's Inspection Planning.
- Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning.
- Should be provided in a single dataset containing data from all major Studies used to support safety and efficacy, with totally 39 variables.
- Should be provided by clinical site and treatment arm for the ITTpopulation.
- Should be submitted in the eCTD format belongs in Module 5 –Clinical Study Reports

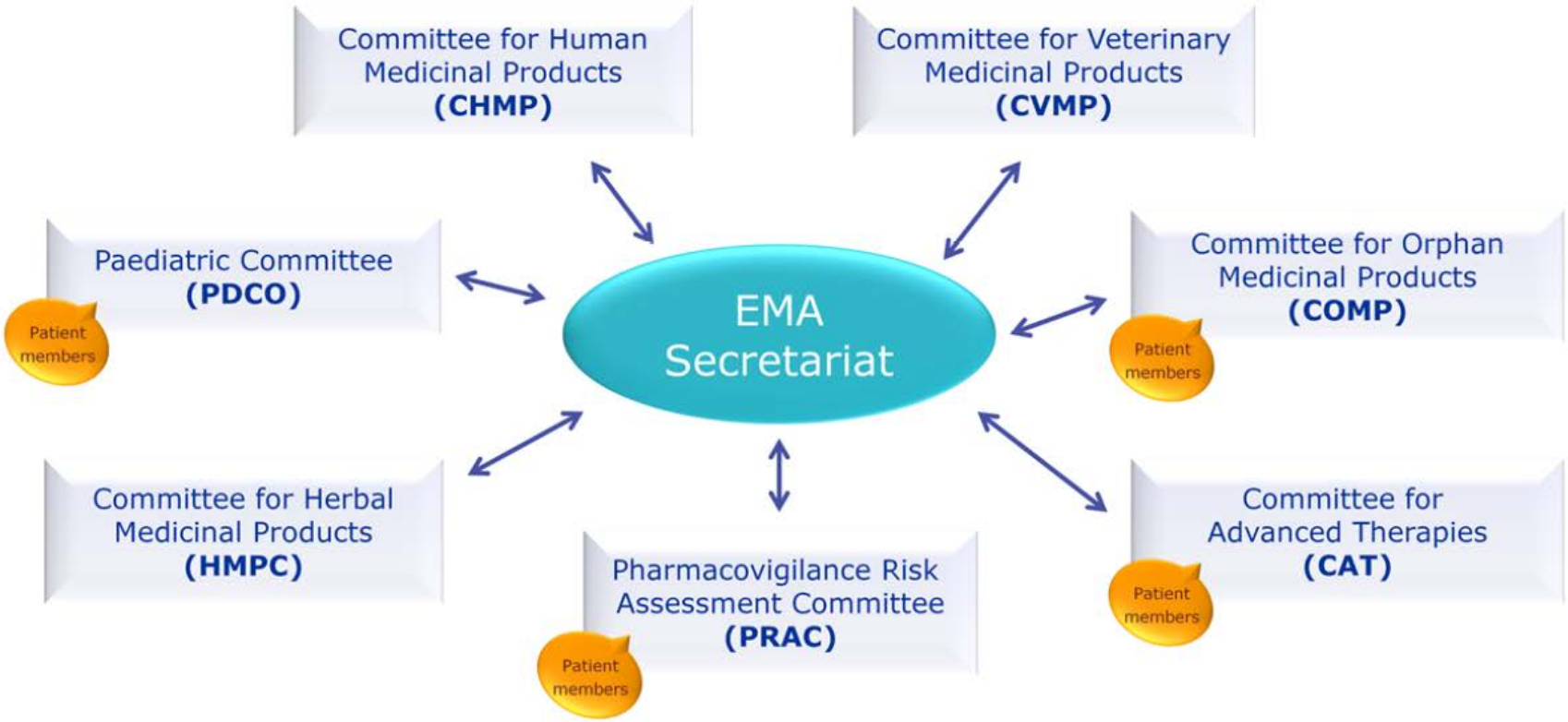


Part III: Summary Level Clinical Site Data (SLCS) (continued)

- 39 variables include:
- General information (Sponsor, IND/NDA/BLA number)
  - Study Conduct:
  - Enrollment
  - Subjects Discontinuations
  - Protocol Violations
- Safety Perspective:
  - Deaths
  - AEs
  - SAEs
- Site-specific Efficacy
- Site Information
  - Financial Disclosure
  - Name, Address and Contact information of the Primary Investigator

European Medicines Agency (EMA)

European Medicines Agency (EMA) – Overview



European Medicines Agency (EMA) – Overview (continued)

- CHMP responsibilities
  - Conduct the initial assessment of EU-wide marketing authorization applications.
  - Assess modifications or extensions ('variations') to an existing marketing authorization.
  - Consider the recommendations of the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) on the safety of medicines.
  - Assessment based on comprehensive scientific evaluation of data.

- In connection with centralized applications, the CHMP often requests a GCP inspection of one or more sites to be performed.

- Inspections may be routine or may be triggered by issues arising during the assessment of the dossier or by other information such as previous inspection experience

EMA – Inspection guidelines

- Prior to such GCP inspections, EMA sends an announcement letter to the applicant which details a list of documents to be provided to the inspection team, among other details.

- Data requested
  - All data for the selected sites, including CRF and vendor data.
  - Raw data set and Analysis data set, including any imputation.
  - Data provided should be exactly the same as that submitted in the Clinical Study Report (CSR).
  - Additional specifications are provided regarding format and name of the variables, columns etc.

- Format of the listings – PDF and Excel.

EMA – Inspection guidelines (continued)

- Report format of the patient data listings.
  - Unless otherwise agreed with the inspection team, the data should be collected in the groups defined below – each to be presented in a different Excel spreadsheet.
    - Study populations & conduct data
    - Subjects' data
    - Treatment data
    - Specific efficacy
    - Safety data
    - Laboratory type data
    - Concomitant medication data
    - Subject questionnaire data (if not part of efficacy)
- The columns ”study site ID”, ”subject ID” and ”treatment group” and where applicable “visit ID” and/or ”visit Date” should be in all spreadsheets.
- If in doubt on where to group data, please raise the question to the inspector.

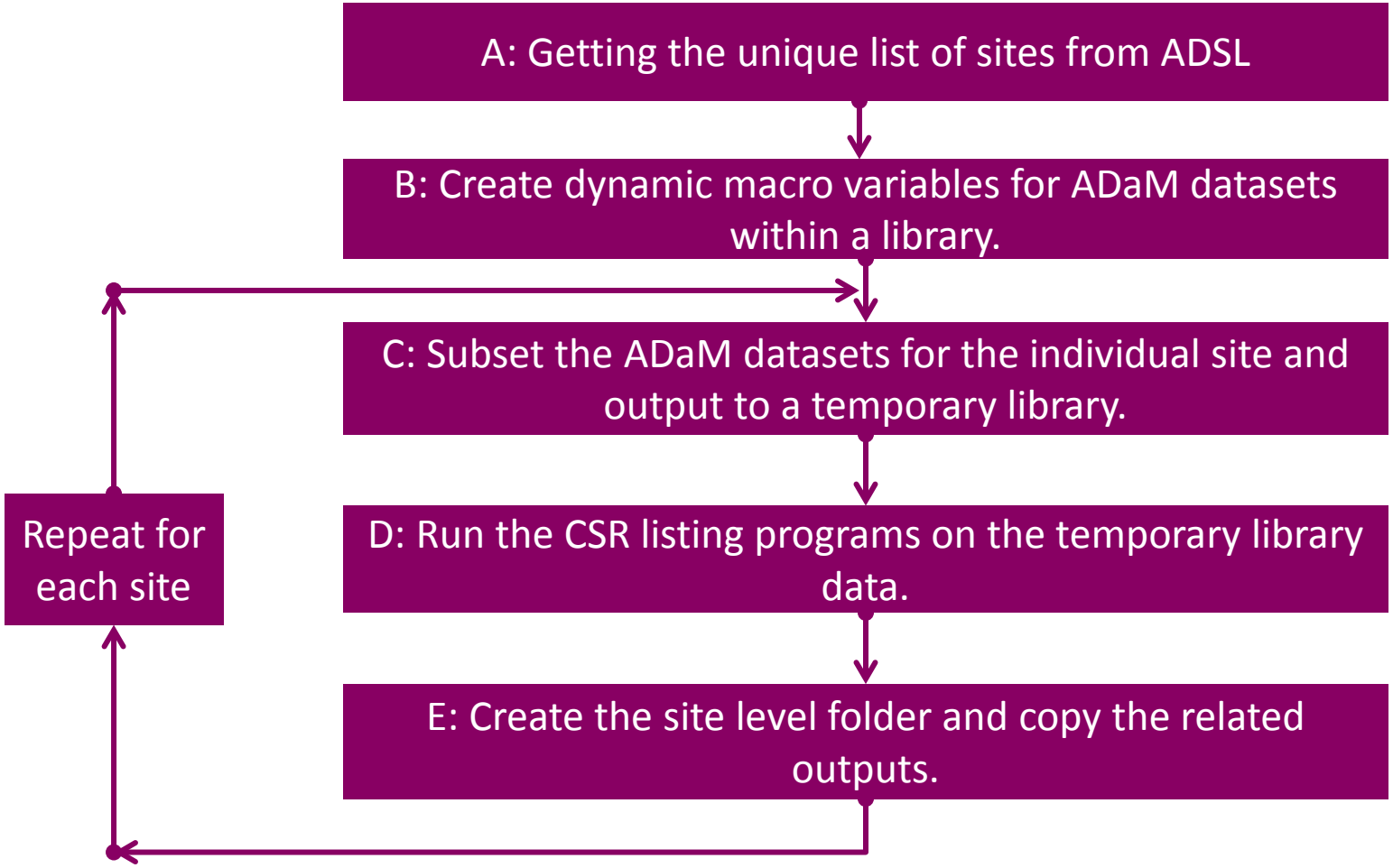
Implementation

Implementation

- Top goals
  - Create site level data output
  - Adhere to Regulatory agency's general guidelines.
  - Code reusability to retain efficiency and quality.
  - Time sensitive

- Challenges
  - More sites = more data = more space = more time.
  - Some guidelines are too generic, open for interpretation, both curse and boon.
  - Additional format for analysis data sets and patient data listings – Excel. (EMA)
  - Grouping for patient data listings. (EMA).

Implementation



Implementation Code

```
proc freq data=iplib.adsl;
  tables siteid/list out=sites(keep=siteid);
run;

proc contents data=iplib._all_ out=content;
run;

proc sort data=content nodupkey;
  by memname;
run;

data _null_;
  set content end=eof;
  call symputx(catt("dsn",_n_),memname);
  if eof then call symputx("totdsn",_n_);
run;
```

Implementation Code

```
%macro bimo(siteid=);
 %local i;
    %do i= 1 %to &totdsn.;
    data bimo.&&dsn&i.;
     set iplib.&&dsn&i.;
        where siteid="&siteid.";
   run;
 %end;

%let dir=C:\SASData\xxx\xxx;
options noxwait noxsync;
X MKDIR "&dir.&siteid.";

data _null_;
 rc=sleep(20);
run;

x listings.bat;
data _null_;
 rc=sleep(200);
run;
```

Implementation Code

```
X COPY  "&dir."  "&dir.&siteid.";
data _null_;
 rc=sleep(30);
run;

filename filrf "&dir.";
data _null_;
  did = dopen('filrf');
  memcount = dnum(did);
  do while (memcount>0);
    fname = dread(did,memcount);
    if scan(lowcase(fname),2,'.')='rtf'
                or
        scan(lowcase(fname),2,'.')='xlsx'
                or
        scan(lowcase(fname),2,'.')='sas7bdat'
    then do;
        rcref = filename('fref',catx('\',"&dir.",fname));
        rcdel = fdelete('fref');
    end;
    memcount+-1;
  end;
  stop;
run;

%mend;
data _null_;
 set sites;
 call execute('%'||"bimo(siteid="||strip(siteid)||")");
run;
```

E

Summary

- Regulatory agency requirements.
- Setup worked efficiently for our systems.
- Points to consider:
  - Plan ahead.
  - Work with the regulatory agencies.
  - Broad outlook on the submission.

Links and References

Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

Guidance for Industry - Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

Presentation - EMA role and activities
https://www.ema.europa.eu/documents/presentation/presentation-european-medicines-agency_en.pdf

The Drug Development Process
https://www.fda.gov/forpatients/approvals/drugs/

European Medicines Agency
https://www.ema.europa.eu/