PDUFA Update on Data Standards

Institute of Medicine Workshop: Sharing Clinical Data

Mary Ann Slack
Office of Planning and Informatics
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

October 4, 2012

Electronic Submissions and Standardization of Electronic Application Data

Problem to be Addressed

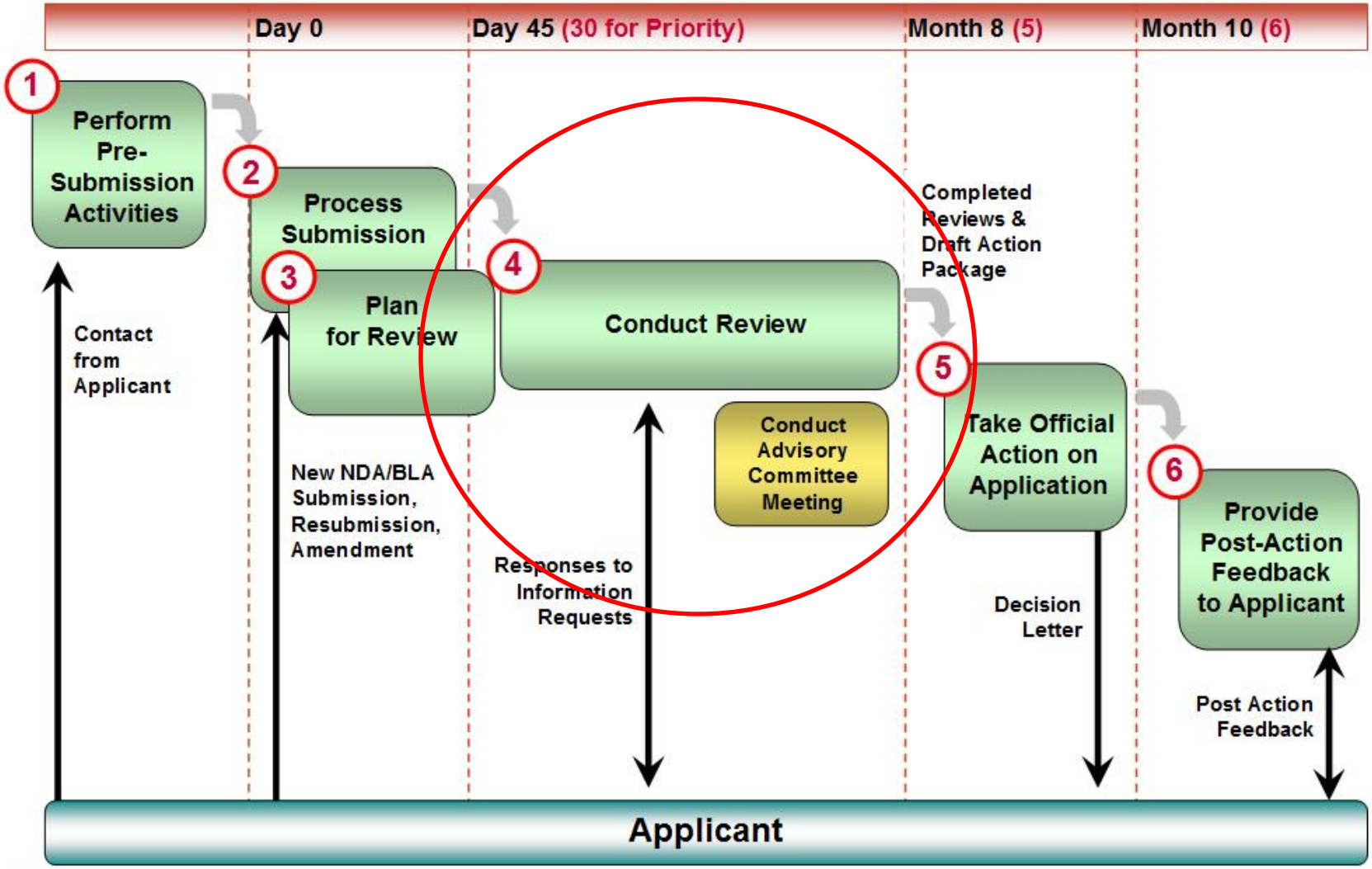
- Extreme variability and unpredictability of the format and content of submitted application data present a major obstacle to timely, consistent, and efficient review within current PDUFA timeframes.

- Lack of Standardized Clinical Data
  - Limits ability to address in-depth questions and late-emerging issues in a timely manner
  - Impedes timely safety analysis to inform REMS decisions
  - Limits ability to transition to more standardized and quantitative approaches to benefit-risk assessment

New Drug Review: Workload

Unit	7/1/2011 - 6/30/2012
Drugs/Biologic Commercial INDs with Activity	6,102
IND Special Protocol Assessments	271
IND Meetings Scheduled	1,737
Original NDA/BLAs	128
NDA/BLA Meetings Scheduled	253
Efficacy Supplements	116
Manufacturing Supplements	1,912
NDA/BLA Labeling Supplements	1,270
NDA/BLA Annual Reports	2,751

21st Century Review Timelines



FDA Safety and Innovation Act (FDASIA) – Reauthorizes PDUFA

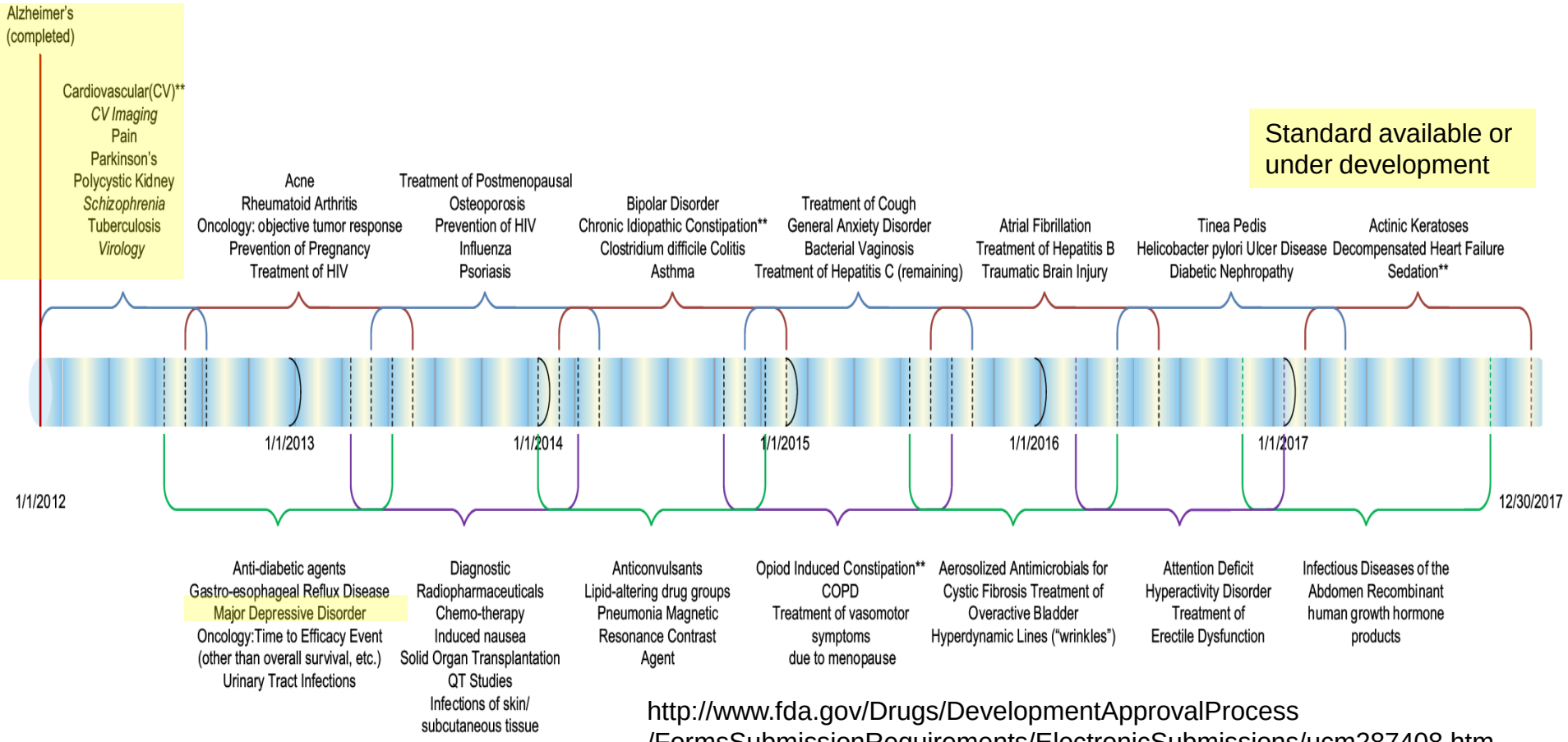
XII. E. Clinical Terminology Standards: Using a public process that allows for stakeholder input, FDA shall develop standardized clinical data terminology through open standards development organizations (i.e., the Clinical Data Interchange Standards Consortium (CDISC)) with the goal of completing clinical data terminology and detailed implementation guides by FY 2017.

1. FDA shall develop a project plan for distinct therapeutic indications, prioritizing clinical terminology standards development within and across review divisions. FDA shall publish a proposed project plan for stakeholder review and comment by June 30, 2013. FDA shall update and publish its project plan annually.

G. FDA shall periodically publish final guidance specifying the completed data standards, formats, and terminologies that sponsors must use to submit data in applications. In the case of standards for study data, new data standards and terminology shall be applicable prospectively and only required for studies that begin 12 months after issuance of FDA's final guidance on the applicable data standards and terminology.

http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf

~58 Therapeutic/Disease Area Standards in 5 Yrs!



http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm287408.htm

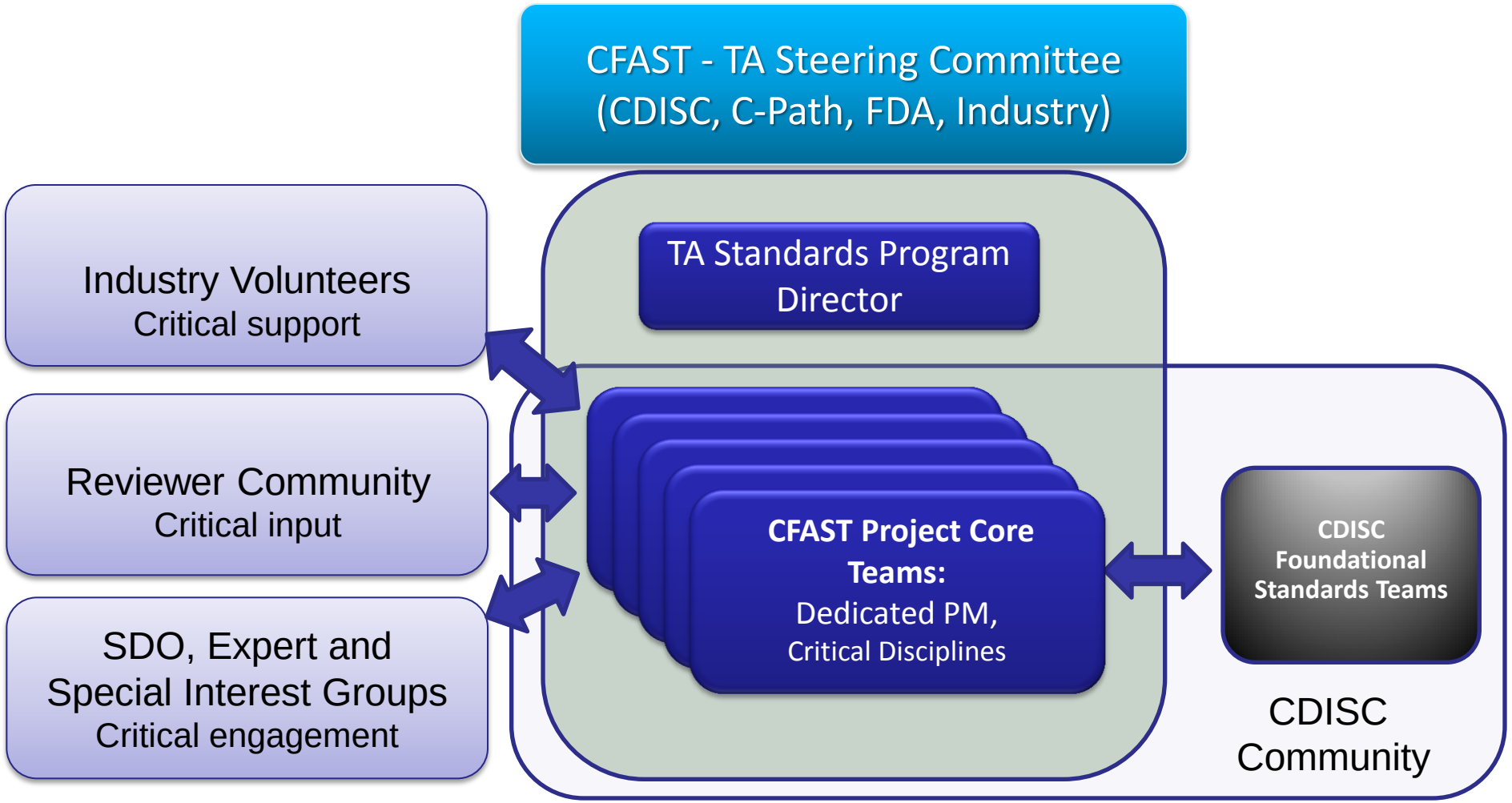
Converging on Shared Need

- **CFAST – Coalition for Accelerating Standards and Therapies**
  - CDISC and Critical Path Institute Partnership
  - Key Initiative: Define, develop and maintain initial set of data standards for therapeutic areas identified by FDA.
- **TransCelerate BioPharma**
  - Clinical study execution identified as initial area of focus
  - Development of clinical data standards **one** of 5 projects
- **Health Level 7**
  - Works with the clinical community to define therapeutic & domain specific data elements and relationships supporting data reuse across healthcare, surveillance, registries and research
  - Collaborative interaction between HL7 CIC and CDISC

Converging on Shared Need

- **FDA's participation in areas such as**
  - Scientific and technical direction in TA prioritization
  - Participate in TA scoping
  - FDA subject matters experts to advise on work streams & for final consensus review
  - Publish draft and final guidance on completed standards – that will be enforceable.

CFAST TA Standardization Initiative - Collaboration and Governance



Example - SAS Clinical Data Integration Pilot – Prepare SDTM Submission Data for Liver Toxicity Assessment (eDISH)

Map SDTM submission data to demography and liver lab data structures as defined by eDISH -

Drug-Induced Serious Hepatoxicity

Standardvariable	variablemeans	Variabletype
STUDYID	Unique identifier for a study within the submission	Char
USUBJID	Unique subject identifier within the submission	Char
TRTCD	Treatment Code	Num
TRTGRP	Treatment Group	Char
EXSTDT	Start Date of Dose	Char (ISO 8601 YYYY-MM-DD)
EXDT	Date of Exam	Char (ISO 8601 YYYY-MM-DD)
EXENDT	End Date of Dose	Char (ISO 8601 YYYY-MM-DD)
ALT	Serum alanine aminotransferase activity (U/L)	Num
ALT_REF_HIGH	ALT High Normal Range (U/L)	Num
BILI	Total serum bilirubin concentration (mg/dL)	Num
BILI_REF_HIGH	BILI High Normal Range (mg/dL)	Num
AST	Serum aspartate aminotransferase (U/L)	Num
AST_REF_HIGH	AST High Normal Range (U/L)	Num
ALP	Alkaline phosphatase (U/L)	Num
ALP_REF_HIGH	ALP High Normal Range (U/L)	Num
ONPROTOC	Subject on Protocol at the Time of exam (Y/N)	Num
GGT	Gamma glutamyl transferase (U/L)	Num

Standardvariable	variablemeans	Variabletype
STUDYID	Unique identifier for a study within the submission	Char
USUBJID	Unique subject identifier within the submission	Char
INVID	Investigator Identifier	Char
INVNAM	Investigator Name	Char
INVDESC	Investigator Description	Char
BIRTHDT	Date of birth	Char (ISO 8601 YYYY-MM-DD)
AGE	Age in years at randomization	Num
SEX	Sex (M/F)	Char
RACE	Race (WHITE, BLACK, OTHER)	Char
COUNTRY	Country	Char
HEIGHT	Height in cm	Num
WEIGHT	Weight in kg	Num
COMPLETE	Subject completing the study (Y/N)	Char
DROPDT	Date subject discontinued the study	Char (ISO 8601 YYYY-MM-DD)
DROPREAS	Reason for discontinuation	Char

Courtesy of SAS Corporation, 08/2012

Current Process

- Ask the sponsor for data
  - PDUFA V – minimize duplicative data.
  - Lack of traceability.
  - No confirmation of data quality.
  - Longer waiting period with more sponsor burden.

Pilot Process

- Use of data integration tool to transform SDTM.
- Demonstrated transformed eDISH data results. same as manual process.

Peak TBL vs. Peak ALT - Windows Internet Explorer

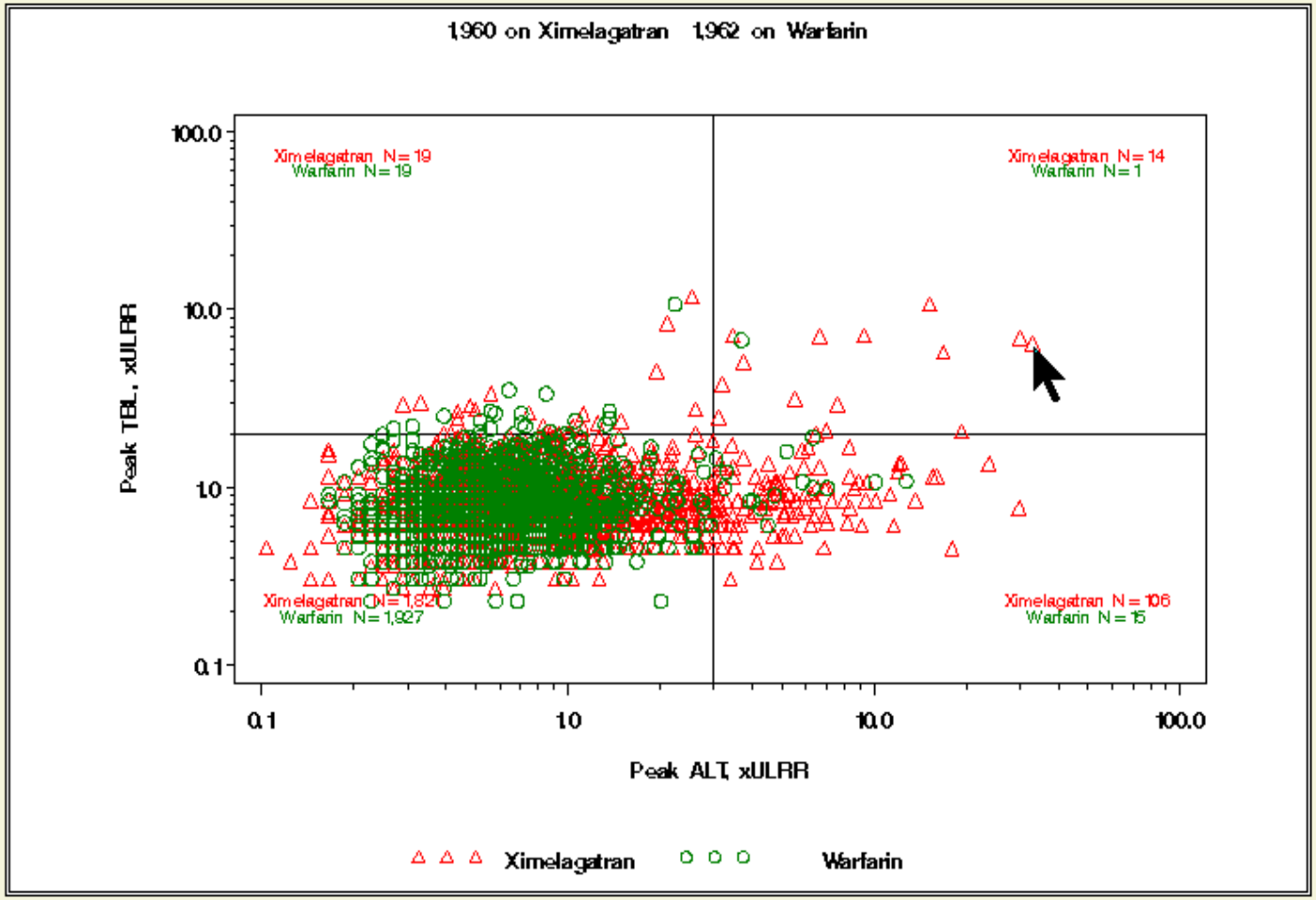
http://cdw5115652/scripts/broker.exe?_service=default&_program=n21686p.ExantaPeak.sas&libreforig=exanta&libref=S

Peak TBL vs. Peak ALT

eDISH

Evaluation of Drug-Induced Serious Hepatotoxicity

| Export SAS data set JRSDATA2_DILISUMMARYSAVED to *PeakValues[1].CSV* for MS Excel | Show number of patients | How to Access Individual-Patients' Data | Close Window |

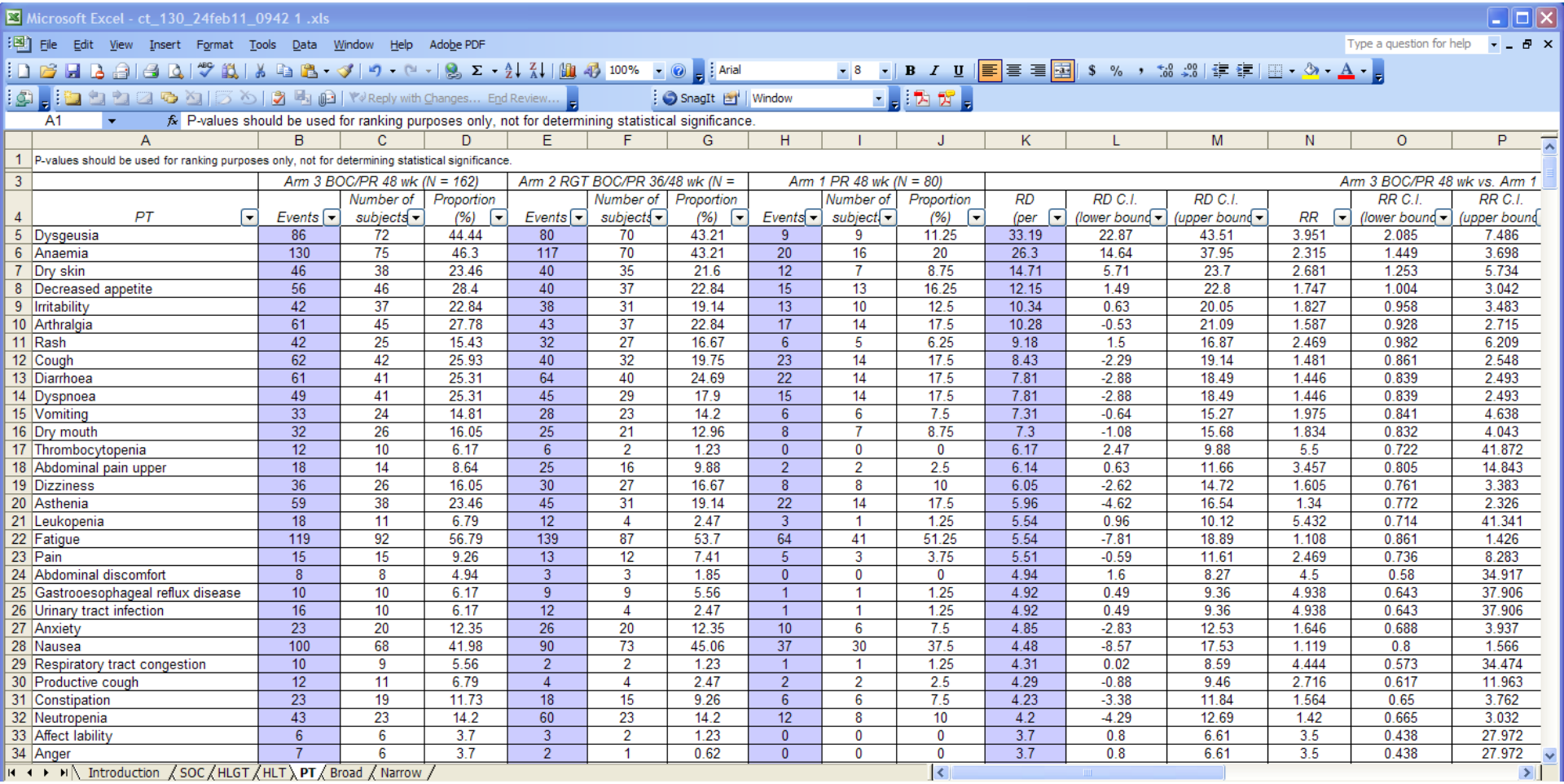


| Export SAS data set JRSDATA2_DILISUMMARYSAVED to *PeakValues[1].CSV* for MS Excel | Show number of patients | How to Access Individual-Patients' Data | Close Window |

Example - Data Standards and Clinical Trial AE Trends & Signals

- Adverse Event Diagnostics Tool
  - Developed by CDER Reviewers
    - Performs over 200 automated complex safety signal detection assessments
    - Equivalent amount of work has never before been possible
    - Successes - Within 1 month of being available to reviewers
      - Medical officer discoveries:
        - » Anaphylaxis – unrecognized by sponsor, now in WARNINGS section of product label
        - » Pancreatitis – now being explored for other products
        - » Multiple other examples

Example:
MedDRA Adverse Event Diagnostic (MAED)



Microsoft Excel - ct_130_24feb11_0942 1 .xls

P-values should be used for ranking purposes only, not for determining statistical significance.

		Arm 3 BOC/PR 48 wk (N = 162)			Arm 2 RGT BOC/PR 36/48 wk (N =			Arm 1 PR 48 wk (N = 80)								Arm 3 BOC/PR 48 wk vs. Arm 1
	PT	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	Events	Number of subject	Proportion (%)	RD (per	RD C.I. (lower bound	RD C.I. (upper bound	RR	RR C.I. (lower bound	RR C.I. (upper bound
5	Dysgeusia	86	72	44.44	80	70	43.21	9	9	11.25	33.19	22.87	43.51	3.951	2.085	7.486
6	Anaemia	130	75	46.3	117	70	43.21	20	16	20	26.3	14.64	37.95	2.315	1.449	3.698
7	Dry skin	46	38	23.46	40	35	21.6	12	7	8.75	14.71	5.71	23.7	2.681	1.253	5.734
8	Decreased appetite	56	46	28.4	40	37	22.84	15	13	16.25	12.15	1.49	22.8	1.747	1.004	3.042
9	Irritability	42	37	22.84	38	31	19.14	13	10	12.5	10.34	0.63	20.05	1.827	0.958	3.483
10	Arthralgia	61	45	27.78	43	37	22.84	17	14	17.5	10.28	-0.53	21.09	1.587	0.928	2.715
11	Rash	42	25	15.43	32	27	16.67	6	5	6.25	9.18	1.5	16.87	2.469	0.982	6.209
12	Cough	62	42	25.93	40	32	19.75	23	14	17.5	8.43	-2.29	19.14	1.481	0.861	2.548
13	Diarrhoea	61	41	25.31	64	40	24.69	22	14	17.5	7.81	-2.88	18.49	1.446	0.839	2.493
14	Dyspnoea	49	41	25.31	45	29	17.9	15	14	17.5	7.81	-2.88	18.49	1.446	0.839	2.493
15	Vomiting	33	24	14.81	28	23	14.2	6	6	7.5	7.31	-0.64	15.27	1.975	0.841	4.638
16	Dry mouth	32	26	16.05	25	21	12.96	8	7	8.75	7.3	-1.08	15.68	1.834	0.832	4.043
17	Thrombocytopenia	12	10	6.17	6	2	1.23	0	0	0	6.17	2.47	9.88	5.5	0.722	41.872
18	Abdominal pain upper	18	14	8.64	25	16	9.88	2	2	2.5	6.14	0.63	11.66	3.457	0.805	14.843
19	Dizziness	36	26	16.05	30	27	16.67	8	8	10	6.05	-2.62	14.72	1.605	0.761	3.383
20	Asthenia	59	38	23.46	45	31	19.14	22	14	17.5	5.96	-4.62	16.54	1.34	0.772	2.326
21	Leukopenia	18	11	6.79	12	4	2.47	3	1	1.25	5.54	0.96	10.12	5.432	0.714	41.341
22	Fatigue	119	92	56.79	139	87	53.7	64	41	51.25	5.54	-7.81	18.89	1.108	0.861	1.426
23	Pain	15	15	9.26	13	12	7.41	5	3	3.75	5.51	-0.59	11.61	2.469	0.736	8.283
24	Abdominal discomfort	8	8	4.94	3	3	1.85	0	0	0	4.94	1.6	8.27	4.5	0.58	34.917
25	Gastrooesophageal reflux disease	10	10	6.17	9	9	5.56	1	1	1.25	4.92	0.49	9.36	4.938	0.643	37.906
26	Urinary tract infection	16	10	6.17	12	4	2.47	1	1	1.25	4.92	0.49	9.36	4.938	0.643	37.906
27	Anxiety	23	20	12.35	26	20	12.35	10	6	7.5	4.85	-2.83	12.53	1.646	0.688	3.937
28	Nausea	100	68	41.98	90	73	45.06	37	30	37.5	4.48	-8.57	17.53	1.119	0.8	1.566
29	Respiratory tract congestion	10	9	5.56	2	2	1.23	1	1	1.25	4.31	0.02	8.59	4.444	0.573	34.474
30	Productive cough	12	11	6.79	4	4	2.47	2	2	2.5	4.29	-0.88	9.46	2.716	0.617	11.963
31	Constipation	23	19	11.73	18	15	9.26	6	6	7.5	4.23	-3.38	11.84	1.564	0.65	3.762
32	Neutropenia	43	23	14.2	60	23	14.2	12	8	10	4.2	-4.29	12.69	1.42	0.665	3.032
33	Affect lability	6	6	3.7	3	2	1.23	0	0	0	3.7	0.8	6.61	3.5	0.438	27.972
34	Anger	7	6	3.7	2	1	0.62	0	0	0	3.7	0.8	6.61	3.5	0.438	27.972

Introduction / SOC / HLGT / HLT / PT / Broad / Narrow

Example - Common Key Analyses

- CDER Standard Review Analysis Panels
  - Over 50 standard analyses automated
    - Including: demographics, exposure, adverse events, disposition, liver toxicity
    - Typical clinical reviewer has not previously been able to produce this degree of output on their own
    - Corroborates sponsors' analyses
    - Improves reviewer efficiency, consistency, quality
- Standard Panels Require Standard Data To Run Successfully

Links & Contacts

FDA Data Standards website:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm249979.htm

Data Standards Catalog:

http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Questions: CDER-edata@fda.hhs.gov

Contact: MaryAnn.Slack@fda.hhs.gov