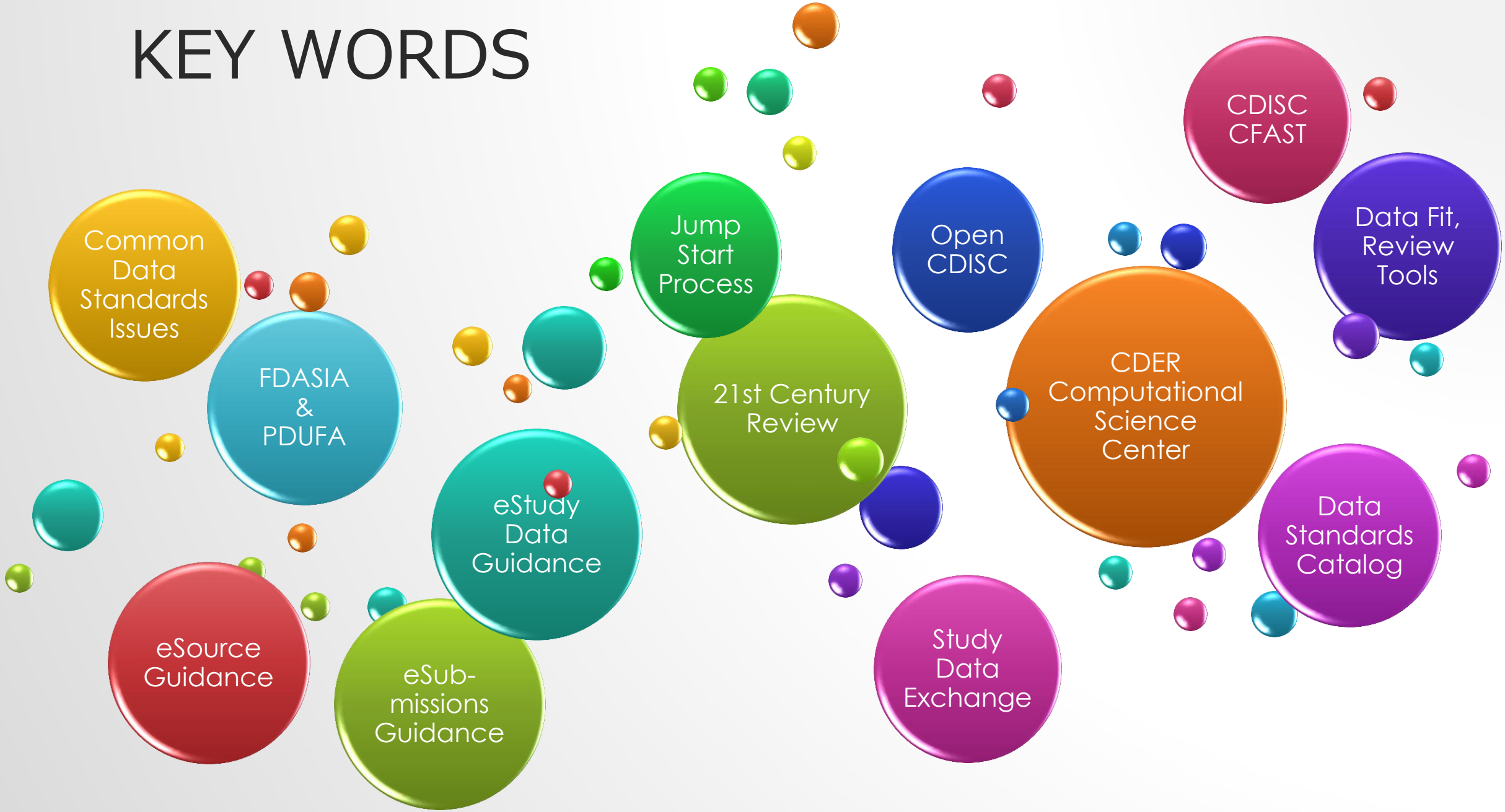
FDA REVIEW CAPABILITIES

CDISC Japan User Group - SDTM Team
September 2013

KEY WORDS


Common Data Standards Issues
FDASIA & PDUFA
Jump Start Process
21st Century Review
Open CDISC
CDISC CFAST
Data Fit, Review Tools
CDER Computational Science Center
Data Standards Catalog
eStudy Data Guidance
eSource Guidance
eSub-missions Guidance
Study Data Exchange

FDA REVIEW CAPABILITIES

- **Data Validation**
  - DataFit: CDER's Data Validation Platform
- **Review Tools**
  - Clinical: eDISH, MAED, jREVIEW, FIRRS, etc.
  - Non-Clinical: NIMS
  - Data Warehouse: Janus

What is the “DataFit“

- **Objectives**
  - レビューツールで利用可能なデータかどうかを評価するための、バリデーション レポートを生成すること
  - FDAのバリデーション仕様を、業界全体に共有すること
    - 例：CDISCとは異なる、もしくは定義されていない、FDA特有の要件（例えば、DILIの解析に必要な変数、SDTMではPermissibleだが重要である場合など）について
- **Values**
  - 申請データの質や機能性を向上させる
  - どのようにデータを申請するか、スポンサーにとっての不確定要素を減らす
  - 申請後の追加要求・照会を減らす
  - データ標準の導入に関して、IND時点での議論のたたき台となる

*Source1: Modernizing the Review Process through Innovation, Lilliam Rosario, CSC-CDER FDA, FDA/PhUSE CSS 2013

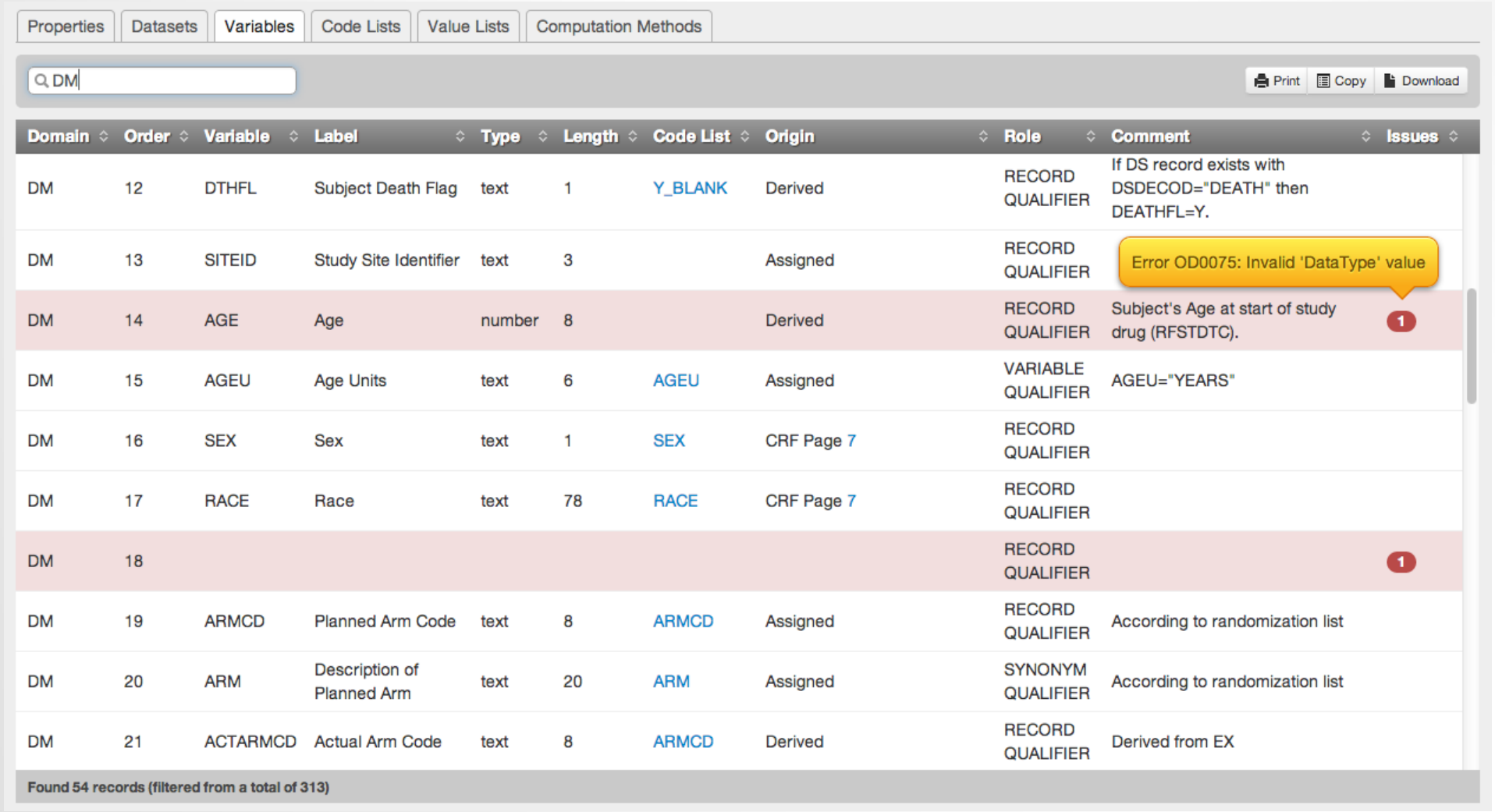
DataFit - Profiles

Profile	Score	Pass/Fail	Domains	Issues	Failures	Errors	Warnings	Notices
General Data Quality (2 Profiles)								
CDER Common Data Standards Issues	60	Pass	39	16	53	0	53	0
SDTM v3.1.2 General Data Quality	93	Pass	39	42	253,649	764	252,882	3
Laboratory Findings Analysis (6 Profiles)								
Liver Function Analysis Panel	40	Fail	3	5	2,453	2,452	0	1
eDISH	43	Fail	6	5	3,692	2,465	13	1,214
JReview Liver Function Baseline Box Whiskers	58	Pass	3	0	2,453	0	2,452	1
JReview Labs Baseline vs Max/Min Scatter Plots	100	Pass	3	0	1	0	0	1
JReview Hy's Law Plots	100	Pass	3	0	1	0	0	1
JReview Hy's Law Patient Listing	100	Pass	3	0	1	0	0	1
Metadata (1 Profiles)								
Study Metadata	100	Pass	39	0	0	0	0	0
Overall Survival Analysis (1 Profiles)								
Overall Survival Analysis Panel	100	Pass	7	1	14	0	10	4
Standards Compliance (2 Profiles)								
SDTM v3.1.2 Compliance	94	Pass	39	32	30,521	0	30,502	19
SDTM v3.1.2 Controlled Terminology	100	Pass	39	0	49	0	0	49

Found 30 records

*Source2: CDISC Standards in FDA Submissions, Max Kanevsky, NJ CDISC User Group June 17, 2013

DataFit - Define Viewer



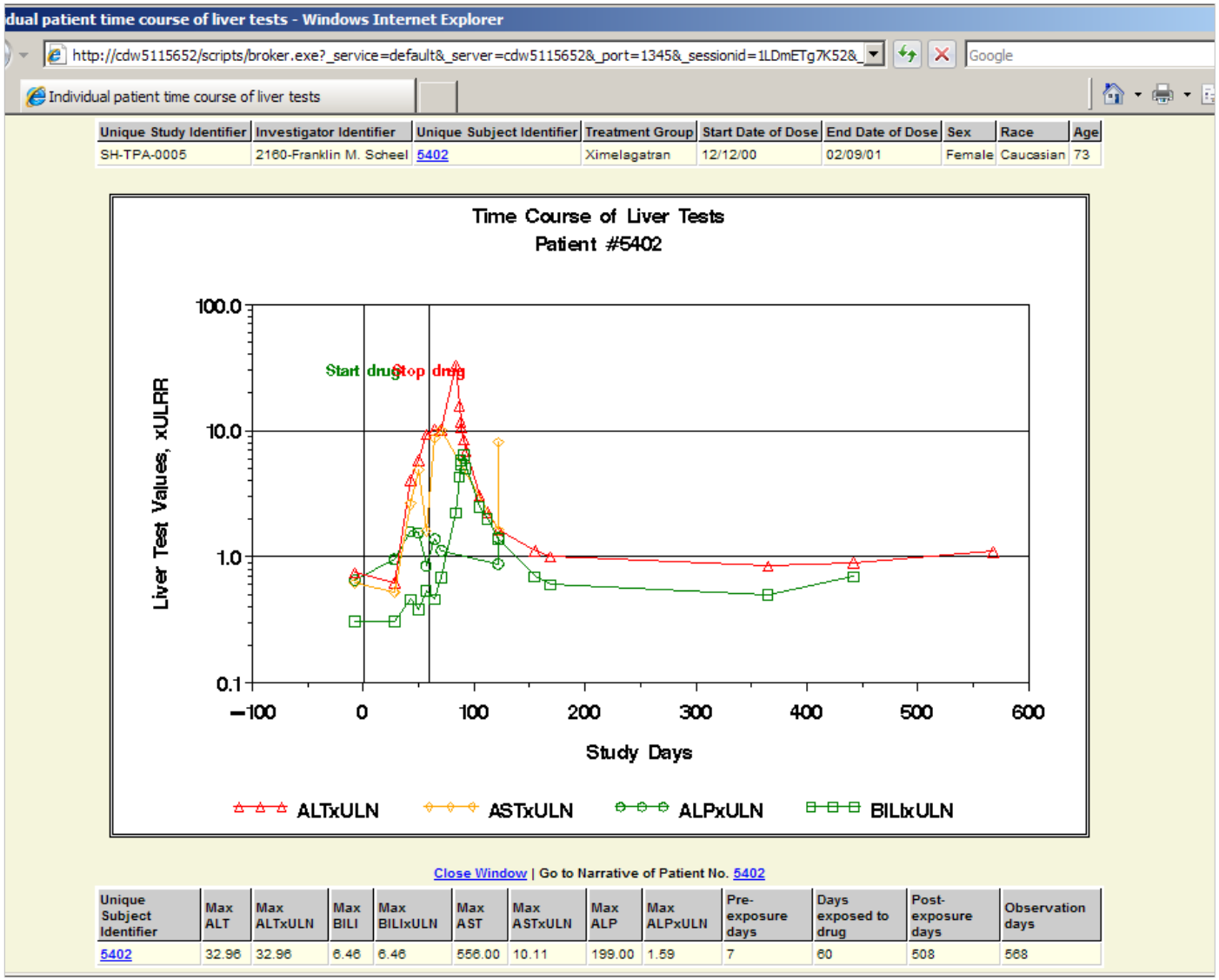
Domain	Order	Variable	Label	Type	Length	Code List	Origin	Role	Comment	Issues
DM	12	DTHFL	Subject Death Flag	text	1	Y_BLANK	Derived	RECORD QUALIFIER	If DS record exists with DSDECOD="DEATH" then DEATHFL=Y.	
DM	13	SITEID	Study Site Identifier	text	3		Assigned	RECORD QUALIFIER		
DM	14	AGE	Age	number	8		Derived	RECORD QUALIFIER	Subject's Age at start of study drug (RFSTDTC).	1
DM	15	AGEU	Age Units	text	6	AGEU	Assigned	VARIABLE QUALIFIER	AGEU="YEARS"	
DM	16	SEX	Sex	text	1	SEX	CRF Page 7	RECORD QUALIFIER		
DM	17	RACE	Race	text	78	RACE	CRF Page 7	RECORD QUALIFIER		
DM	18							RECORD QUALIFIER		1
DM	19	ARMCD	Planned Arm Code	text	8	ARMCD	Assigned	RECORD QUALIFIER	According to randomization list	
DM	20	ARM	Description of Planned Arm	text	20	ARM	Assigned	SYNONYM QUALIFIER	According to randomization list	
DM	21	ACTARMCD	Actual Arm Code	text	8	ARMCD	Derived	RECORD QUALIFIER	Derived from EX	

*Source2: CDISC Standards in FDA Submissions, Max Kanevsky, NJ CDISC User Group June 17, 2013

eDISH (evaluation of Drug Induced Serious Hepatotoxicity)

- 肝毒性を引き起こす薬剤かどうかを審査するための解析ツール
- 関心を持つべき被験者データを特定し、また同時に、その被験者の解析データを提供する
- “干し草の中で針を見つける”ように、大規模試験において、特別に関心を持つべき稀な被験者（機能障害や入院など臨床的に重篤もしくは悪化の事例があり、かつ、それが薬剤により引き起こされたのかどうかを、より注意深く究明する必要がある少数の被験者）を素早く発見できる

*Source3: Drug Drug-Induced Liver Injury: Making Decisions, Making Progress, Douglas C. Throckmorton MD, CDER FDA, March 20, 2013



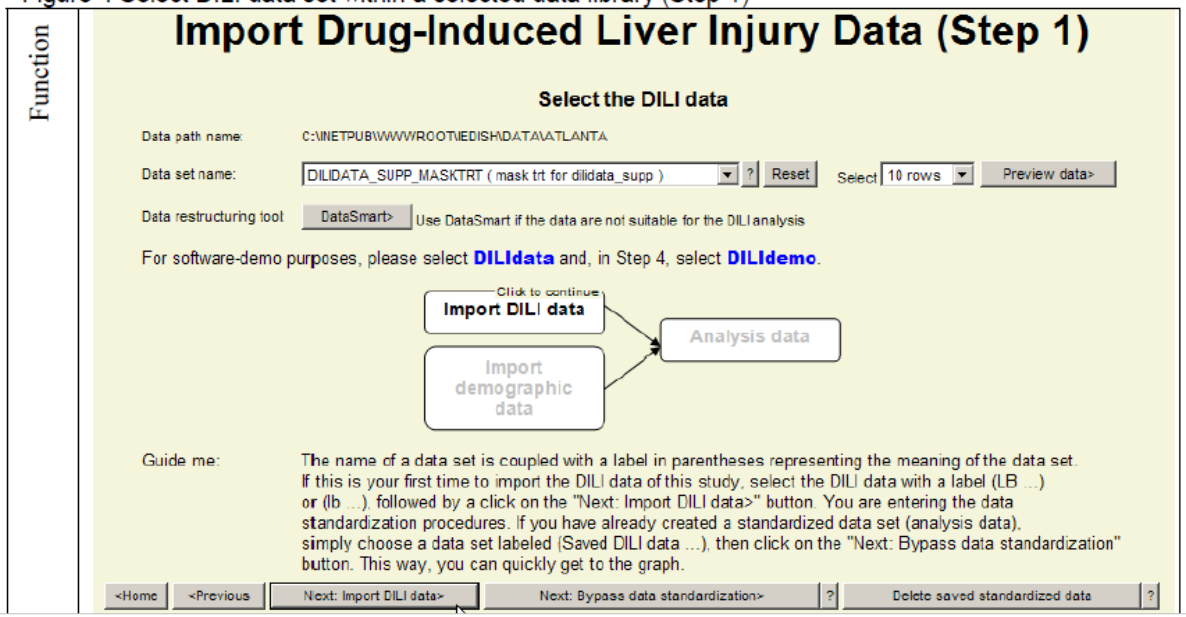
*Source4: Leveraging High Quality Standard Data to Benefit the Public Health, Chuck Cooper, FDA, NIH Data Standards Forum October 19, 2012

eDISH (evaluation of Drug Induced Serious Hepatotoxicity)

- 長期かつ大規模試験における肝機能データの解析に強み
- 1試験のすべての臨検データを1画面の中に凝縮し、一目でわかる要約を提供
- すべての被験者のデータを、要約画面から時系列の個別データ（背景因子や肝機能検査、臨床的な叙述など）にまで掘り下げることができる
- DILI（薬物性肝障害）の評価
- ハイレベルなデータ標準を要求し、eDISHのスムーズな実行のために、CDISCに準拠した入力データが必要

Figure 3 Portal of eDISH

Figure 4 Select DILI data set within a selected data library (Step 1)

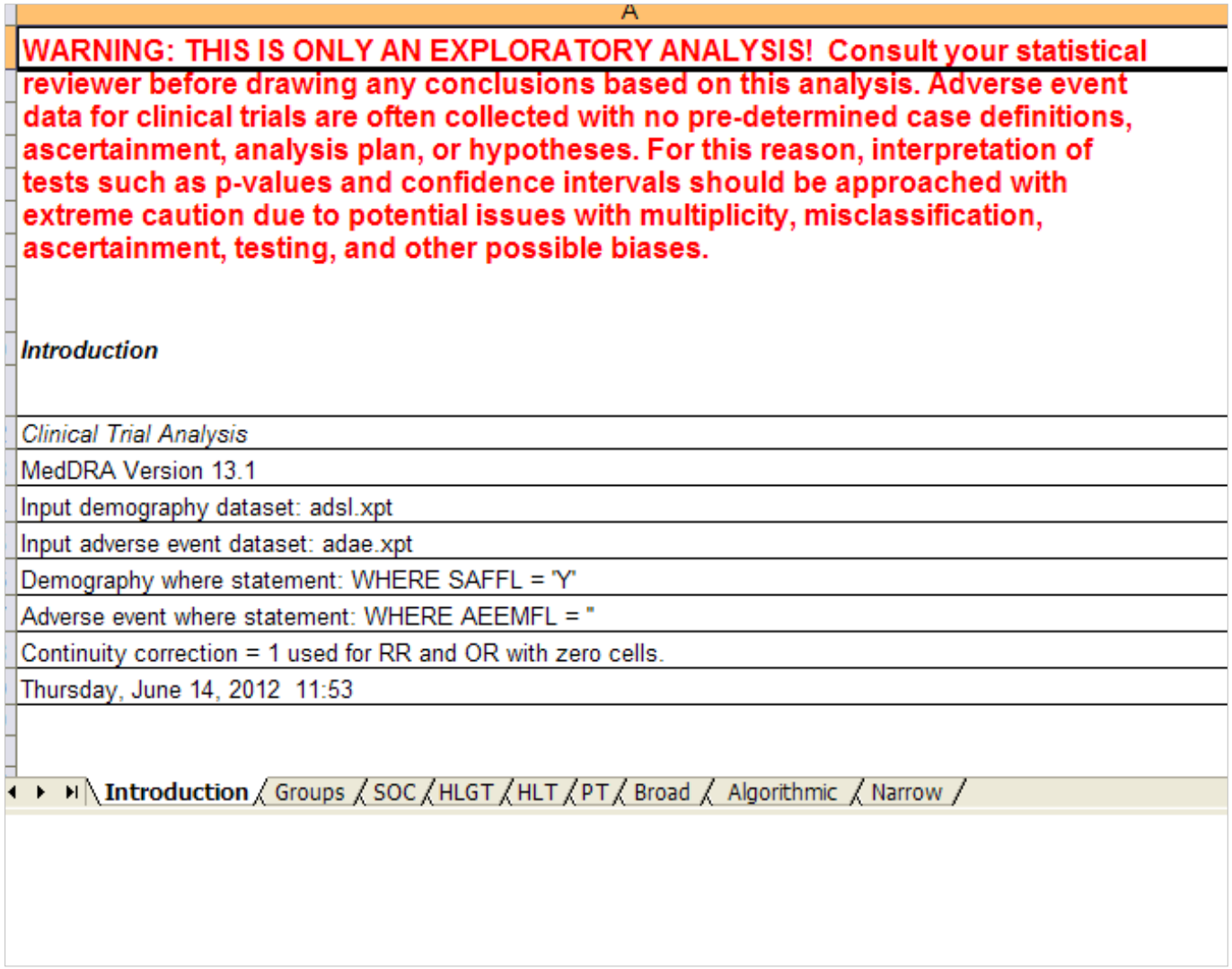


*Source5: How a SAS/IntrNet tool was created at the FDA for the detection of potential drug-induced liver injury using data with CDISC standard, Ted Guo, John Senior and Kate Gelperin, FDA, WUSS September 2, 2009

MAED (MedDRA-based Adverse Event Diagnostics)

(pronounced like "maid")

- サーバーベースの有害事象解析ツール
- 大規模試験での有害事象の解析を、審査官が素早く行うことを可能にする
- MedDRA Hierarchyのすべてのレベルでの解析が可能
- すべてのMeDRA標準検索式 SMQsでの解析が可能
- もともとは2009年に開発、2013年時点でのユーザーは約110人であり、限定的に使用



A

WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS! Consult your statistical reviewer before drawing any conclusions based on this analysis. Adverse event data for clinical trials are often collected with no pre-determined case definitions, ascertainment, analysis plan, or hypotheses. For this reason, interpretation of tests such as p-values and confidence intervals should be approached with extreme caution due to potential issues with multiplicity, misclassification, ascertainment, testing, and other possible biases.

Introduction

Clinical Trial Analysis

MedDRA Version 13.1

Input demography dataset: adsl.xpt

Input adverse event dataset: adae.xpt

Demography where statement: WHERE SAFFL = 'Y'

Adverse event where statement: WHERE AEEMFL = ''

Continuity correction = 1 used for RR and OR with zero cells.

Thursday, June 14, 2012 11:53

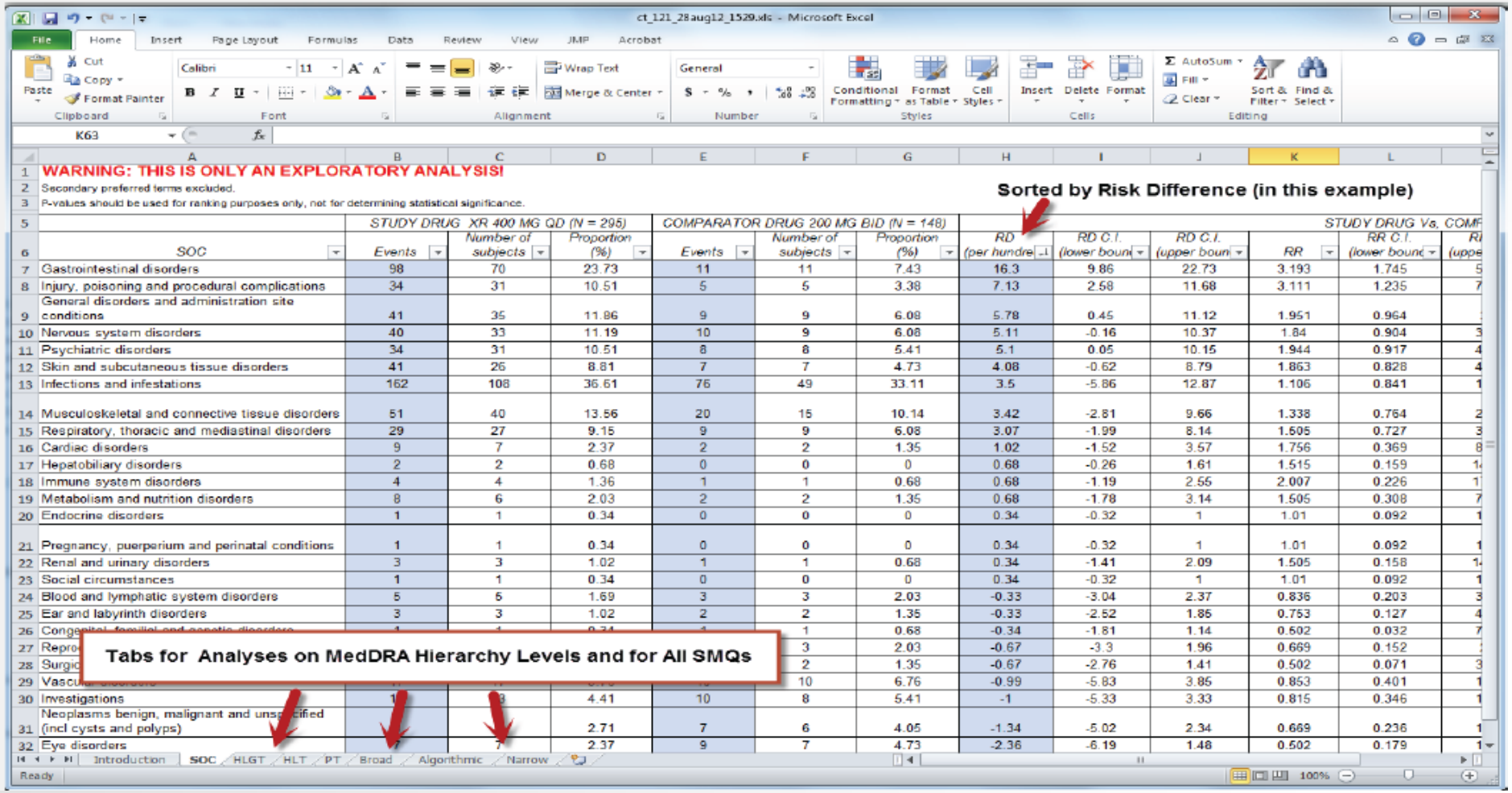
Introduction Groups SOC HLGT HLT PT Broad Algorithmic Narrow

*Source1: Modernizing the Review Process through Innovation, Lilliam Rosario, CSC-CDER FDA, FDA/PhUSE CSS 2013

*Source6: MedDRA-based Adverse Event Diagnostic Service, Joy Li, MS, CSC-CDER, FDA, June 26, 2012

MAED - RESULTS OF MAED ANALYSIS

Table 1: AE MedDRA Hierarchy summary at SOC level



WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!

Secondary preferred terms excluded.

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

Sorted by Risk Difference (in this example)

SOC	STUDY DRUG XR 400 MG QD (N = 295) Events	Number of subjects	Proportion (%)	COMPARATOR DRUG 200 MG BID (N = 148) Events	Number of subjects	Proportion (%)	RD (per hundre	RD C.I. (lower boun	RD C.I. (upper boun	RR	RR C.I. (lower boun	RR C.I. (upper
Gastrointestinal disorders	98	70	23.73	11	11	7.43	16.3	9.86	22.73	3.193	1.745	5
Injury, poisoning and procedural complications	34	31	10.51	5	5	3.38	7.13	2.58	11.68	3.111	1.235	7
General disorders and administration site conditions	41	35	11.86	9	9	6.08	5.78	0.45	11.12	1.951	0.964	
Nervous system disorders	40	33	11.19	10	9	6.08	5.11	-0.16	10.37	1.84	0.904	3
Psychiatric disorders	34	31	10.51	8	8	5.41	5.1	0.05	10.15	1.944	0.917	4
Skin and subcutaneous tissue disorders	41	26	8.81	7	7	4.73	4.08	-0.62	8.79	1.863	0.828	4
Infections and infestations	162	108	36.61	76	49	33.11	3.5	-5.86	12.87	1.106	0.841	1
Musculoskeletal and connective tissue disorders	51	40	13.56	20	15	10.14	3.42	-2.81	9.66	1.338	0.764	2
Respiratory, thoracic and mediastinal disorders	29	27	9.15	9	9	6.08	3.07	-1.99	8.14	1.505	0.727	3
Cardiac disorders	9	7	2.37	2	2	1.35	1.02	-1.52	3.57	1.756	0.369	8
Hepatobiliary disorders	2	2	0.68	0	0	0	0.68	-0.26	1.61	1.515	0.159	1
Immune system disorders	4	4	1.36	1	1	0.68	0.68	-1.19	2.55	2.007	0.226	1
Metabolism and nutrition disorders	8	6	2.03	2	2	1.35	0.68	-1.78	3.14	1.505	0.308	7
Endocrine disorders	1	1	0.34	0	0	0	0.34	-0.32	1	1.01	0.092	1
Pregnancy, puerperium and perinatal conditions	1	1	0.34	0	0	0	0.34	-0.32	1	1.01	0.092	1
Renal and urinary disorders	3	3	1.02	1	1	0.68	0.34	-1.41	2.09	1.505	0.158	1
Social circumstances	1	1	0.34	0	0	0	0.34	-0.32	1	1.01	0.092	1
Blood and lymphatic system disorders	5	5	1.69	3	3	2.03	-0.33	-3.04	2.37	0.836	0.203	3
Ear and labyrinth disorders	3	3	1.02	2	2	1.35	-0.33	-2.52	1.85	0.753	0.127	4
Congenital, familial and genetic disorders	1	1	0.34	1	1	0.68	-0.34	-1.81	1.14	0.502	0.032	7
Reproductive system and breast disorders	3	3	1.02	3	3	2.03	-0.67	-3.3	1.96	0.669	0.152	1
Surgical and medical procedures	2	2	0.68	2	2	1.35	-0.67	-2.76	1.41	0.502	0.071	3
Vascular disorders	9	9	3.05	10	10	6.76	-0.99	-5.83	3.85	0.853	0.401	1
Investigations	13	13	4.41	10	8	5.41	-1	-5.33	3.33	0.815	0.346	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8	8	2.71	7	6	4.05	-1.34	-5.02	2.34	0.669	0.236	1
Eye disorders	7	7	2.37	9	7	4.73	-2.36	-6.19	1.48	0.502	0.179	1

Tabs for Analyses on MedDRA Hierarchy Levels and for All SMQs

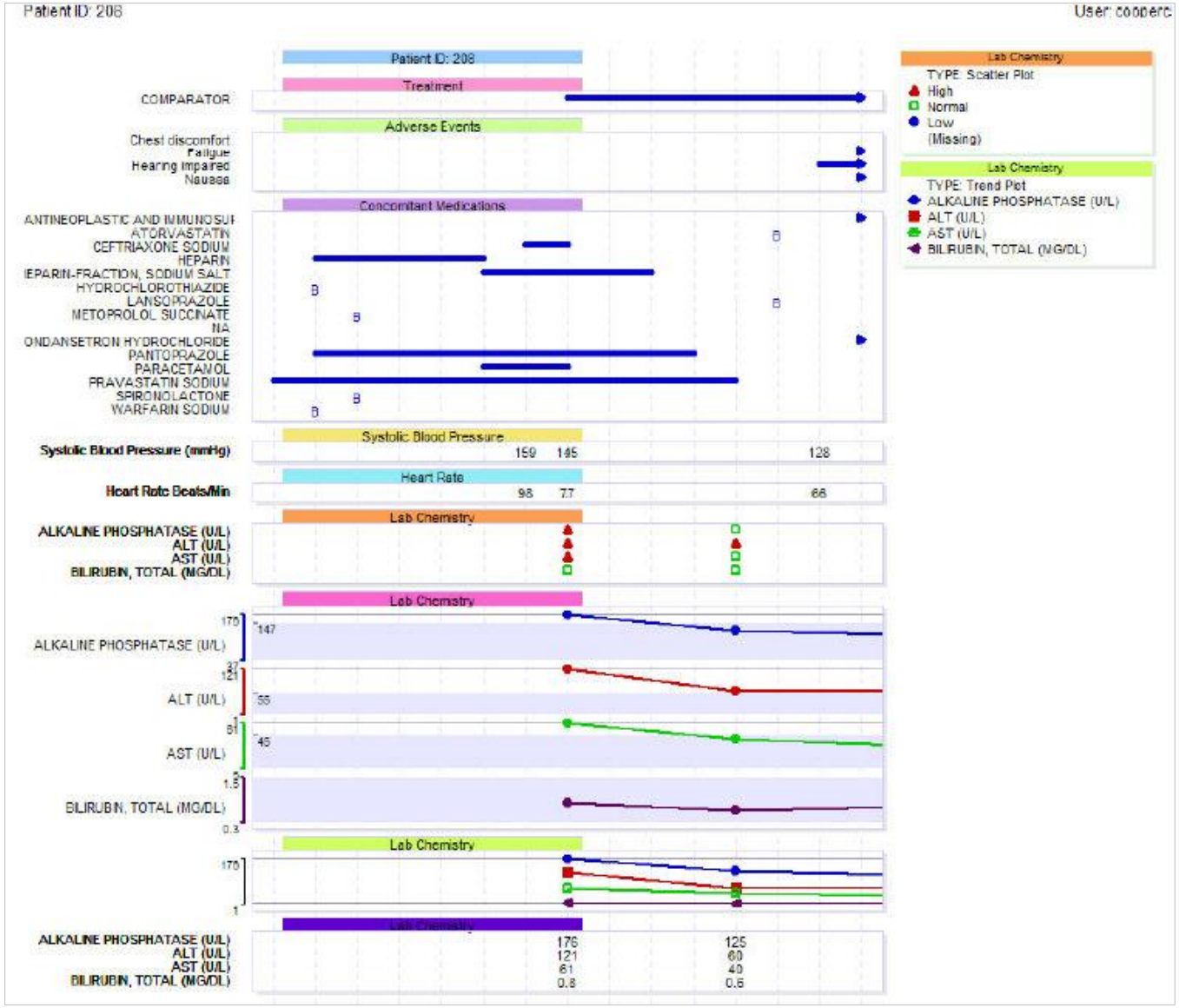
Introduction | SOC | HLGT | HLT | PT | Broad | Algorithmic | Narrow

*Source7: MAED Service: FDA-Developed Tool for Clinical AE Data Signal Detection, Xin (Joy) Li; Chuck Cooper; Zhongjun Luo, CSS-CDER FDA, FDA/PhUSE Computational Science Symposium 2013

jReview

- 標準化されたデータのもとで、標準的な解析を行うことができる
- 様々な種類の解析を自動で行うことができ、同時に、審査を行う上で十分な品質を持ったドキュメントを生成できる
- CDERで現在使用されており、四半期毎に新しい解析パターンが追加されている
- Integrated Clinical Systems, Inc.の製品がベース
  - iReview: stand-alone
  - jReview: web-based

*Source1: Modernizing the Review Process through Innovation, Lilliam Rosario, CSC-CDER FDA, FDA/PhUSE CSS 2013



*Source8: Use of New Tools for Safety Analysis, Chuck Cooper, CSC-CDER FDA

NIMS (Nonclinical Information Management System)

- 非臨床データのロード、検索、解析、可視化およびレポジトリの機能を持ち、効率的かつ素早い安全性審査を可能にする
- Web-basedで、SENDを利用
- PointCross社のNonclinical Study Data Repository (NSDR)という製品がベース
  - Study Data Integration and Search System (SDIS)
  - ToxVision++
  - XTEND

*Source9: NIMS User Guide, CSC-CDER FDA

Page 57; Figure 86: z-Transformation (Box-Plot)

FIRRS (FDA Investigators Rapid Review System)

- 解析をサポートする目的での、申請データの質や機能性の評価を、審査官が迅速に実施することを助けるツール
- スポンサーの標準的なデータマネジメント業務（コーディングや辞書の使用、また、重要な臨床検査値についてなど）の、品質評価を実施するために開発されている

*Source1: Modernizing the Review Process through Innovation, Lilliam Rosario, CSC-CDER FDA, FDA/PhUSE CSS 2013

SOURCES/REFERENCES

1. Modernizing the Review Process through Innovation, Lilliam Rosario, CSC-CDER FDA, FDA/PhUSE CSS 2013
2. CDISC Standards in FDA Submissions, Max Kanevsky, NJ CDISC User Group June 17, 2013 (Special thanks to Mr. Max, who gives us the snapshots of "Datafit")
3. Drug-Induced Liver Injury: Making Decisions, Making Progress, Douglas C. Throckmorton MD, CDER FDA, March 20, 2013
4. Leveraging High Quality Standard Data to Benefit the Public Health, Chuck Cooper, FDA, NIH Data Standards Forum October 19, 2012
5. How a SAS/IntrNet tool was created at the FDA for the detection of potential drug-induced liver injury using data with CDISC standard, Ted Guo, John Senior and Kate Gelperin, FDA, WUSS September 2, 2009
6. MedDRA-based Adverse Event Diagnostic Service, Joy Li, MS, CSC-CDER FDA, June 26, 2012
7. MAED Service: FDA-Developed Tool for Clinical AE Data Signal Detection, Xin (Joy) Li; Chuck Cooper; Zhongjun Luo, CSC-CDER FDA, FDA/PhUSE CSS 2013
8. Use of New Tools for Safety Analysis, Chuck Cooper, CSC-CDER FDA
9. NIMS User Guide, CSC-CDER FDA