

Individual Patient Records and the Critical Path

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PRISM

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Disclaimer

Views expressed in this presentation
are those of the speaker and not,
necessarily, of the Food and Drug
Administration

My New Disclaimer

Acknowledgements

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- Randy Levin, *CDER, FDA*
- Ed Nevius, *CDER, FDA*
- Bill Qubeck, *Pfizer*
- Norm Stockbridge, *CDER, FDA*
- Stan Woolen, *OC, FDA*

Outline

- FDA Mission
- White Oak and OBPS
- Critical Path
- Standards Development and the FDA
 - Data Standards Council
 - CDISC/HL7/RCRIM
- Review of Safety
 - Patient Profile Viewer
 - Do-It-Yourself SDTM
- Updates/Opportunities
 - NCI Janus/CRIX
 - CDISC eSDI
 - Academic Consortia

The **Critical Path** to New Medical Products

- “... a new focus on updating the tools currently used to assess the safety and efficacy of new medical products”
- “... develop this list through extensive consultation with private and public stakeholders...”
- Directly references CDISC SDTM as a “Critical Path” initiative

<http://www.fda.gov/oc/initiatives/criticalpath/>

FDA's Mission & Innovation

- “protecting the public health”
 - Organization
 - Electronic submissions and review
 - Study design, data quality and analysis
- “advancing the public health by helping to speed innovations”
 - Improvements: collection, review & submission processes
 - Standards
 - Shared repositories
 - Registries
 - Electronic data capture
 - Individual patient records

White Oak, MD: CDER's New "Home"



Office of Business Process Support -- OBPS

(the Office formerly known as OIM)

- Immediate Office (IO)
- Project Development Staff (PDS)
- Business Analysis and Reporting Staff (BARS)
- Regulatory Review Support Staff (RRSS)
- Division of Records Management (DRM)

OBPS: Some of It's Responsibilities

- Develops tools for access to and analysis of data used to support regulatory decisions
- Business process changes and/or implementation of information technology
- Standardizes information management processes
- Publishes regulations, guidance documents and MaPPs to support electronic submissions
- Develops information management project proposals
- Coordinates IT systems development projects
- Standardizes information management processes
- Develops and maintains business and data layers of the enterprise architecture
- Operates and manages the document rooms

Standards Development and the FDA

FDA's Motivation for Standards

Improve time to market for safe and effective treatments (increased patient safety and reduced costs) by...

- Improving efficiency of evaluation of safety and efficacy of investigational treatments
 - Facilitates communication between regulatory authority and applicant
 - Facilitates development of efficient review environment (e.g., training, analysis tools)
- Improving efficiency for clinical research
 - Facilitates design and conduct of clinical trials
 - Facilitates communication between researchers and study sponsor (e.g., between CRO and drug company)

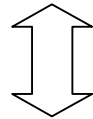
FDA Data Standards Council

- Coordinates the evaluation, development, maintenance, and adoption of health and regulatory data standards
- Ensures that common data standards are used throughout the agency
- Ensures that these standards are consistent with those used outside the FDA.
- Accomplished through
 - strategically focused and systematic analysis of health and regulatory data standards requirements; and
 - evaluation of existing standards and adoption or development and maintenance of standards.
- <http://www.fda.gov/oc/datacouncil/>

FDA Data Standards Council Procedures

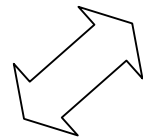
Business Process Planning

Identify data or terminology standard need

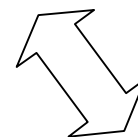
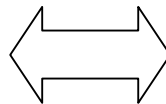


FDA Data Standards Council

Coordinate adoption or development

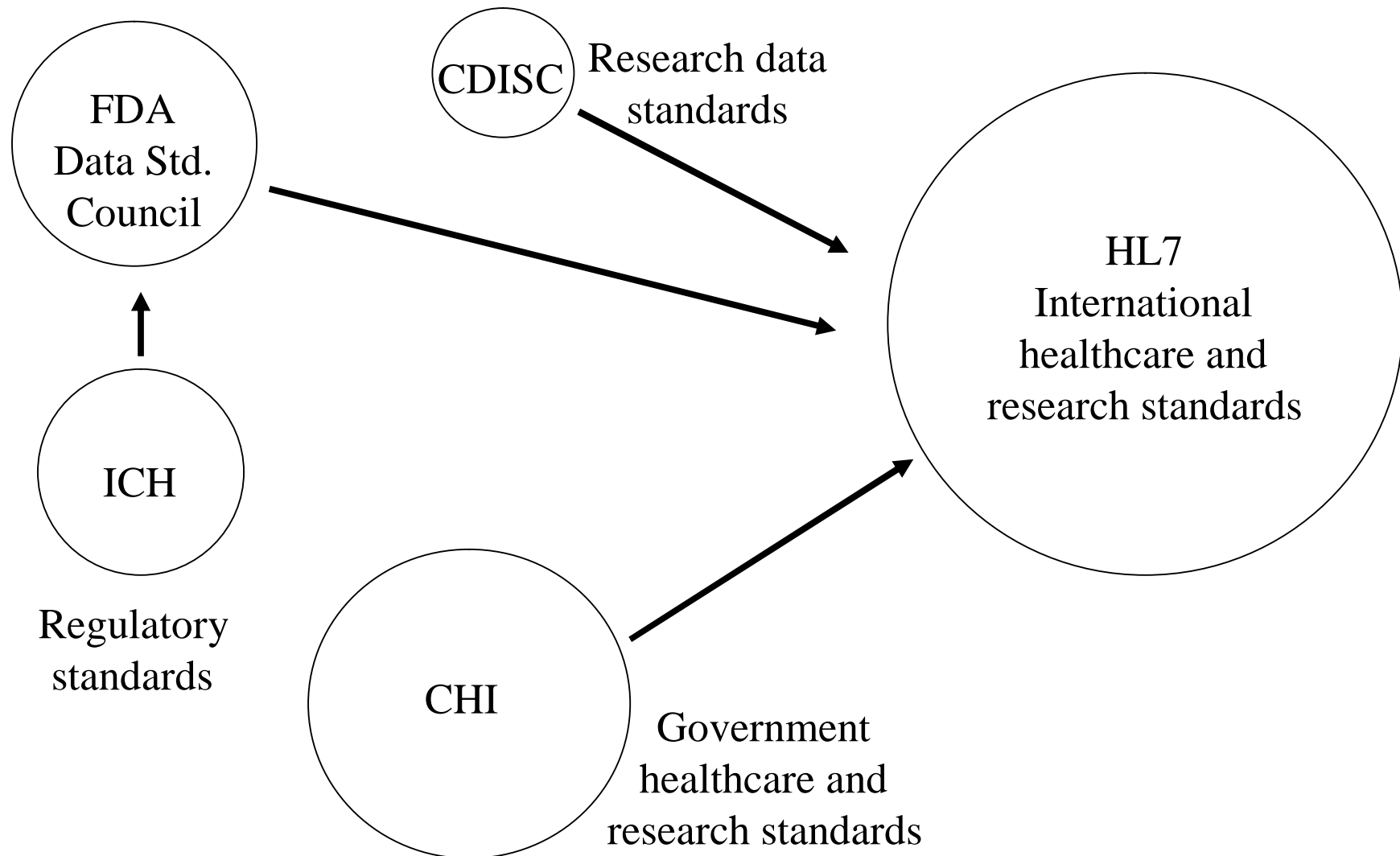


Working group of
FDA experts



Standard Development
Organization

Standards Organization

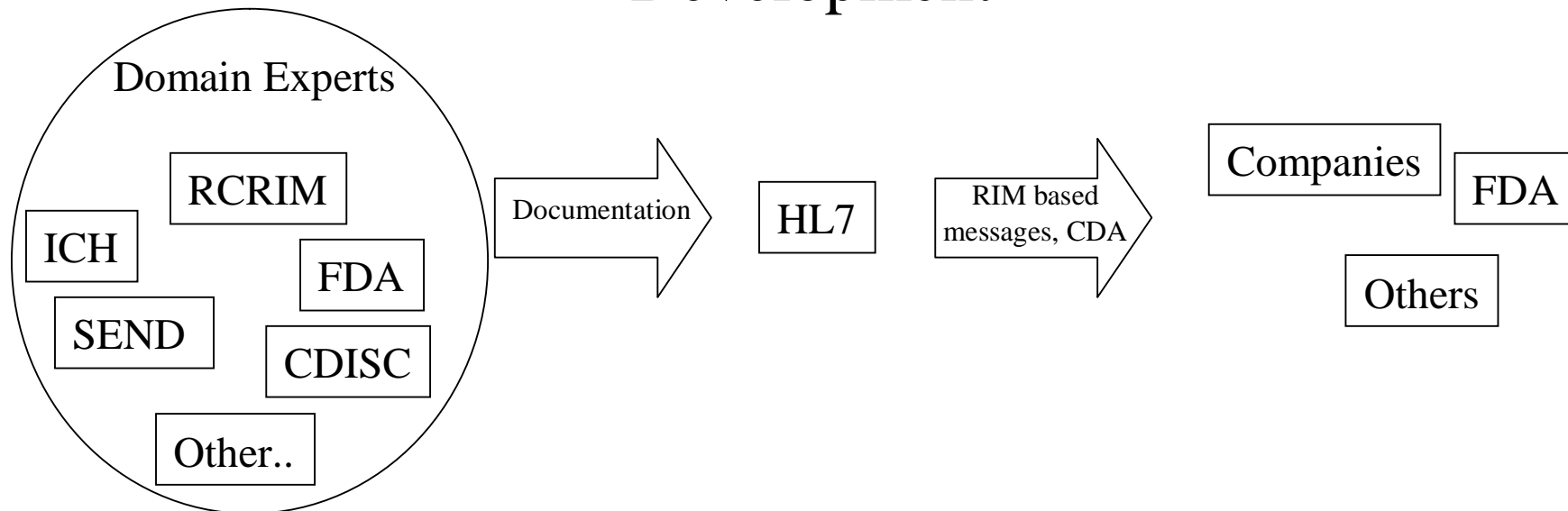


Standards Development

Requirements

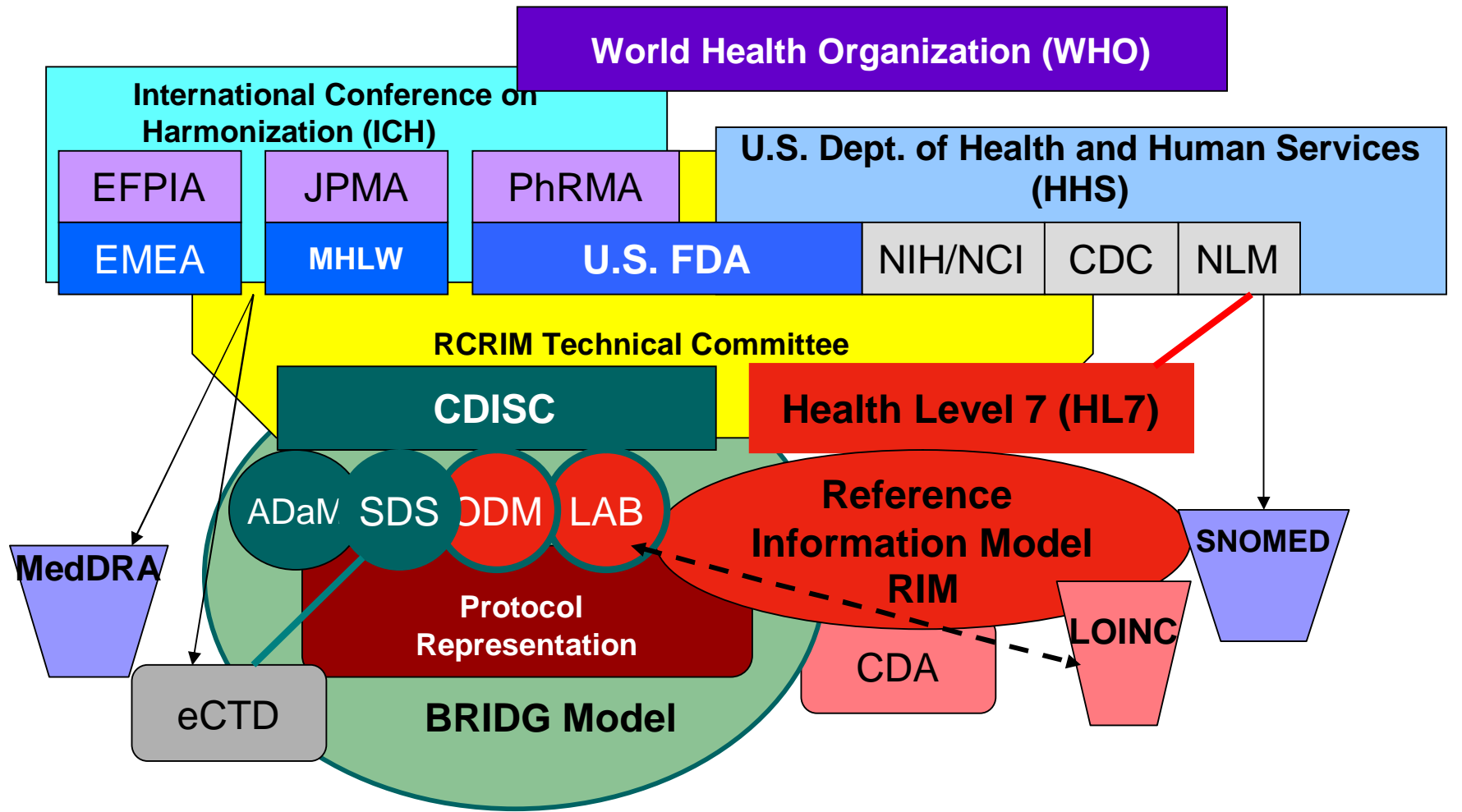
Specification
Development

Implementation



“World of Standards” 2005

Becky Kush/CDISC Interchange, 2005



- = Organization
- = Dictionary, Codelist
- = Standard
- = Model
- = Document Standard, or Architecture

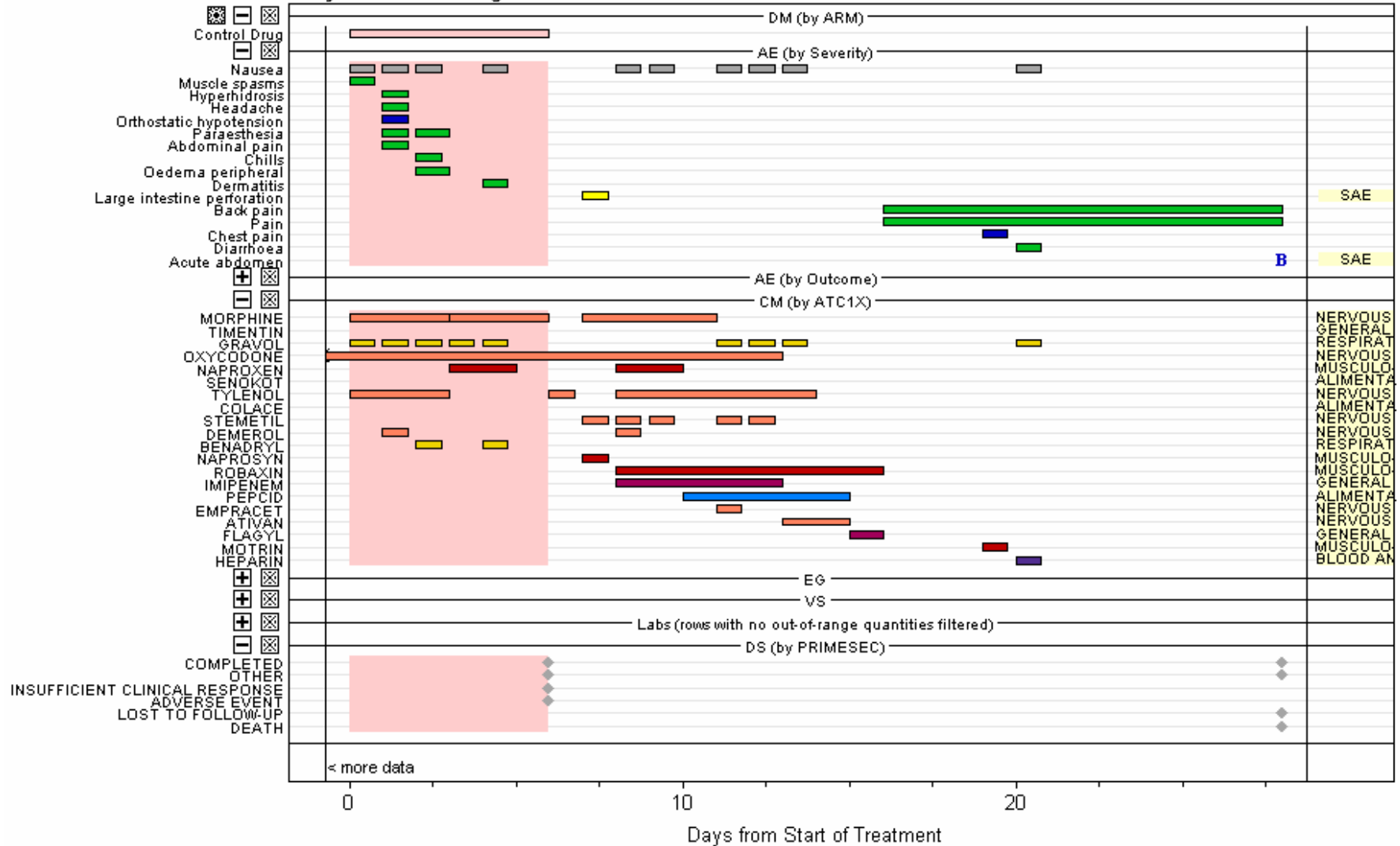
Safety Review & Individual Patient Records

- Patient Profile Viewer
- Do-It-Yourself SDTM

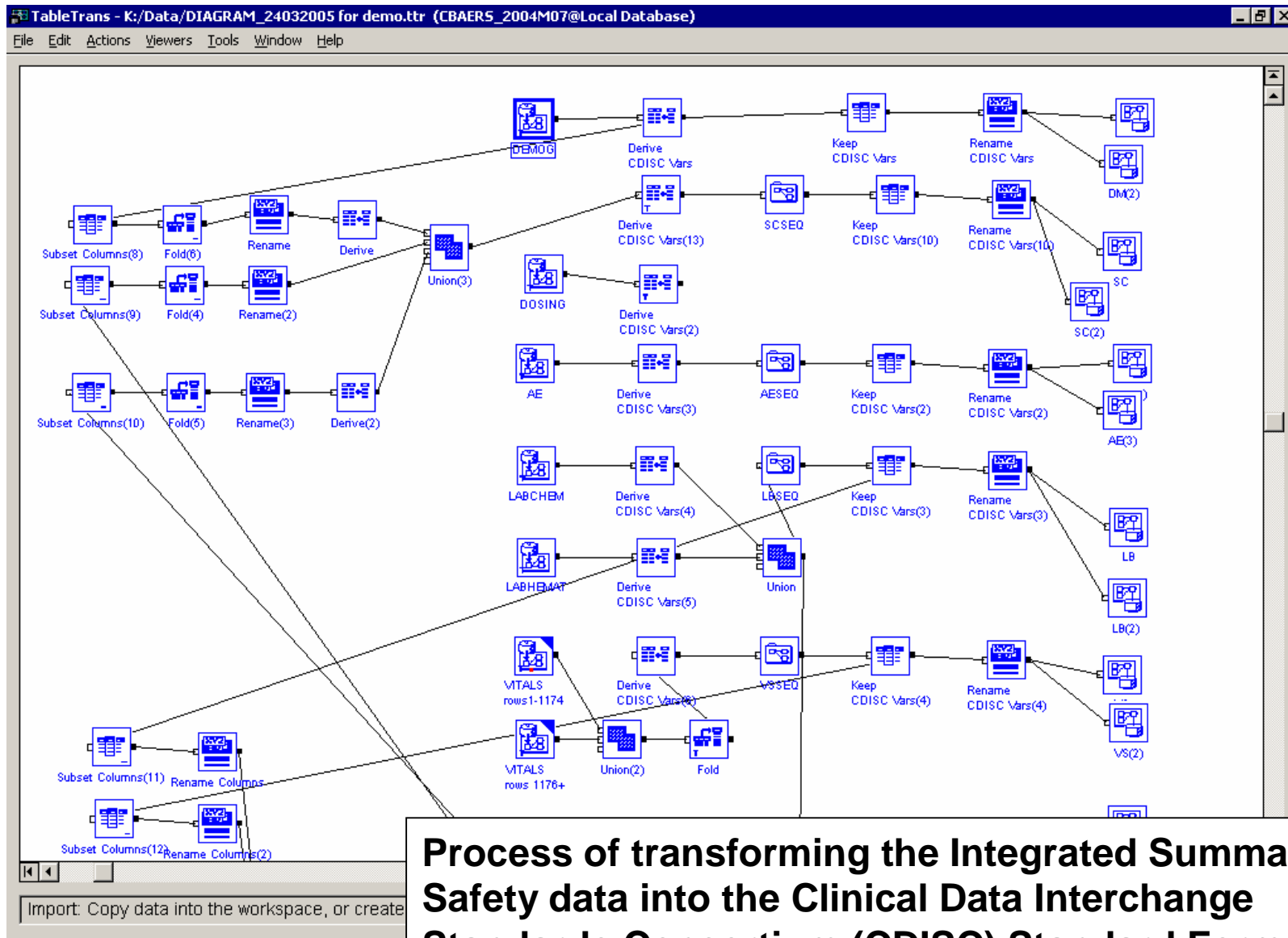
Patient Profile Viewer

Wonderdrug NDA - ISS Data

Subject: XXXXXX - Age: 29 - Sex: M - Race: White



Do-It-Yourself SDTM



Station	Time	Depth	Temperature	Direction	Speed	Remarks
101	10:00	10	15.5	120	1.5	Light breeze
102	10:15	20	15.0	130	1.5	
103	10:30	30	14.5	140	1.5	
104	10:45	40	14.0	150	1.5	
105	11:00	50	13.5	160	1.5	
106	11:15	60	13.0	170	1.5	
107	11:30	70	12.5	180	1.5	
108	11:45	80	12.0	190	1.5	
109	12:00	90	11.5	200	1.5	
110	12:15	100	11.0	210	1.5	
111	12:30	110	10.5	220	1.5	
112	12:45	120	10.0	230	1.5	
113	13:00	130	9.5	240	1.5	
114	13:15	140	9.0	250	1.5	
115	13:30	150	8.5	260	1.5	
116	13:45	160	8.0	270	1.5	
117	14:00	170	7.5	280	1.5	
118	14:15	180	7.0	290	1.5	
119	14:30	190	6.5	300	1.5	
120	14:45	200	6.0	310	1.5	
121	15:00	210	5.5	320	1.5	
122	15:15	220	5.0	330	1.5	
123	15:30	230	4.5	340	1.5	
124	15:45	240	4.0	350	1.5	
125	16:00	250	3.5	360	1.5	
126	16:15	260	3.0	370	1.5	
127	16:30	270	2.5	380	1.5	
128	16:45	280	2.0	390	1.5	
129	17:00	290	1.5	400	1.5	
130	17:15	300	1.0	410	1.5	
131	17:30	310	0.5	420	1.5	
132	17:45	320	0.0	430	1.5	
133	18:00	330	-0.5	440	1.5	
134	18:15	340	-1.0	450	1.5	
135	18:30	350	-1.5	460	1.5	
136	18:45	360	-2.0	470	1.5	
137	19:00	370	-2.5	480	1.5	
138	19:15	380	-3.0	490	1.5	
139	19:30	390	-3.5	500	1.5	
140	19:45	400	-4.0	510	1.5	
141	20:00	410	-4.5	520	1.5	
142	20:15	420	-5.0	530	1.5	
143	20:30	430	-5.5	540	1.5	
144	20:45	440	-6.0	550	1.5	
145	21:00	450	-6.5	560	1.5	
146	21:15	460	-7.0	570	1.5	
147	21:30	470	-7.5	580	1.5	
148	21:45	480	-8.0	590	1.5	
149	22:00	490	-8.5	600	1.5	
150	22:15	500	-9.0	610	1.5	
151	22:30	510	-9.5	620	1.5	
152	22:45	520	-10.0	630	1.5	
153	23:00	530	-10.5	640	1.5	
154	23:15	540	-11.0	650	1.5	
155	23:30	550	-11.5	660	1.5	
156	23:45	560	-12.0	670	1.5	
157	24:00	570	-12.5	680	1.5	
158	24:15	580	-13.0	690	1.5	
159	24:30	590	-13.5	700	1.5	
160	24:45	600	-14.0	710	1.5	
161	25:00	610	-14.5	720	1.5	
162	25:15	620	-15.0	730	1.5	
163	25:30	630	-15.5	740	1.5	
164	25:45	640	-16.0	750	1.5	
165	26:00	650	-16.5	760	1.5	
166	26:15	660	-17.0	770	1.5	
167	26:30	670	-17.5	780	1.5	
168	26:45	680	-18.0	790	1.5	
169	27:00	690	-18.5	800	1.5	
170	27:15	700	-19.0	810	1.5	
171	27:30	710	-19.5	820	1.5	
172	27:45	720	-20.0	830	1.5	
173	28:00	730	-20.5	840	1.5	
174	28:15	740	-21.0	850	1.5	
175	28:30	750	-21.5	860	1.5	
176	28:45	760	-22.0	870	1.5	
177	29:00	770	-22.5	880	1.5	
178	29:15	780	-23.0	890	1.5	
179	29:30	790	-23.5	900	1.5	
180	29:45	800	-24.0	910	1.5	
181	30:00	810	-24.5	920	1.5	
182	30:15	820	-25.0	930	1.5	
183	30:30	830	-25.5	940	1.5	
184	30:45	840	-26.0	950	1.5	
185	31:00	850	-26.5	960	1.5	
186	31:15	860	-27.0	970	1.5	
187	31:30	870	-27.5	980	1.5	
188	31:45	880	-28.0	990	1.5	
189	32:00	890	-28.5	1000	1.5	
190	32:15	900	-29.0	1010	1.5	
191	32:30	910	-29.5	1020	1.5	
192	32:45	920	-30.0	1030	1.5	
193	33:00	930	-30.5	1040	1.5	
194	33:15	940	-31.0	1050	1.5	
195	33:30	950	-31.5	1060	1.5	
196	33:45	960	-32.0	1070	1.5	
197	34:00	970	-32.5	1080	1.5	
198	34:15	980	-33.0	1090	1.5	
199	34:30	990	-33.5	1100	1.5	
200	34:45	1000	-34.0	1110	1.5	

Handwritten notes on a grid background, detailing medical observations and lab results. The notes are organized into columns and rows, with some entries highlighted in red. A red circle with '100%' is visible on the left side.

100%

ni base, ALT to 113, then 153, neg sero, probable drug
base abnl ALT 153, AST90, hep C pos, no change, unrelated
base ALT abnl 137, no major change, ANA as high as 1:640, unrelated
base ALT el abnl 39, increase to 113 and then fall, possible
ni abnl base ALT 62, with rise to 129, then 152, possible, need F/U
time frame of el consis, possible
ni base, ALT increase to 159, normalized, possible
mild inc base ALT3,AST46, rise to 137/80 w el ALP152, poss
el base ALT78,AST137, rise to 203/233, ni bill and ALP, only 1 f/u, possible
base abnl ALT68,AST94, inc 143,200, severe underlying cardiac disease,unrel
abnl base ALT254,AST139, increased, but refused f/u
abnl base ALT122/AST83,inc216/141,dec116/92, poss inc trans in hep C
abnl base ALT49/42,inc ALT104, hap C pos, ANA1:80,likely hep C,unrelated drug
ni base, rise ALT365/AST153,fall172/100,autoimm and sero neg,possible
base abnl ALT121/AST49,rise 242/120, no decel, hep sero neg, possible
base ALT213/AST133PRE with el ALP, only 2days rx, improved, unrelated
base abnl ALT369/AST216, not much change, nbili, unrelated
ni base, inc ALT396/AST270,fall178/56,CVA(valve thrombus) prior to el LFT,poss
abnl base, ALT243/AST142,fall 59/46, unrelated
abnl base ALT198/ALP322,riseALT350with decline, possible
abnl base ALT108/AST70,rise329/195, hep C+,etoh, possible
ni base, rise ALT160/AST172, resolve, possible
abnl base ALT173/AST83, no change, unrelated
hep C X15 years, ETOH and tylenol, unrelated
sl base abnl, rise ALT112, then fall, possible
abnl base ALT214/AST142, "no major change" unrelated, pt refused V3 lab
abnl base ALT84/AST38, inc159/168, dec near ni, hep sero neg, poss
mild abnl base ALT53/AST48, inc 145/85, found hep C, poss
base ALT122/AST103, peak ALT175, hep sero neg, unrelated
ni base, inc ALT236, then ni, rash 2 weekspost rx, poss, U/S-,prior chole
abnl base, ALT84/AST93, inc ALT/AST/bili during rx, poss drug
ni base, inc ALT266,AST142, no F/U, possible
base rise ALT to 109, hep sero neg, poss
base lab

agree, trans stable with ALT 3.3 xULN
agree, AST=ALT, weak ANA 1:40, improved during rx
base ALT 44, rx 235/303/187, when rx began, agree hep C, but trans rise with drug, also lower
agree, trans inc: AST=ALT
agree, although inc to threshold ALT after drug therefore ? Drug impact need to check patient with the
agree,unresolved, ? any F/U
agree, U/S ? fatty liver, el with drug possible, also mild inc ALP and eos, resolved
agree, baseline or without change
2K at V2, then at ALT to 142 (but after levaspin), agree, poss, still with el inc: TPA
agree,NT/AD and tylenol and cipro prior, still mild el sero, base f/u
agree, tests rd 2 mos later of drug and ETOH, had assoc rise in bill with ALT123/AST129, no lab ser
agree, trans improve during study, but eos and pos ASMA
agree
agree, late F/U back at base, enticology?, did rise with drug
agree, int/roomcom med, but none listed, cholelithiasis picture
agree, hep sero neg, ANA 1:40, stable ALT
agree, soft case for CEC endpoint, ?any late F/U, rd ALP, bil
agree, el trans and bil, ALP, eos
agree, biopsy chronic active hepatitis chx hep C
agree, f/u (V2) LFT done after levaspin (el trans with sero)
agree, although study drug 7.2 day, then comd, comaxuron, rise F/U
agree, absolute eos inc although ALT improved el at V2
agree, abnl prior without major change, pos ANA
agree, also could have been due to increased alcohol?
agree, trans up, still up at late F/U, ? Contrib of alcohol?
agree, may have had underlying liver dz with former hx ETOH, also concor simvastatin
agree, assoc w inc ALP, not bili, no eos count done, neg viral serologies, visit times early
agree, levels still rising at f/u, any late f/u?, losartan can el LFT
agree, there is no F/U recorded or data sheet prepared, any late F/U??
death secondary to MI, no F/U beyond V2, disagree, can't r/o drug
rise to ALT424/AST222, rise occurred, I'm not sure you can separate from study drug,
agree, can't separate out hep C, U/S lat liver, cholelithiasis
hep C pos, abnl base with <3X base rise, still can't r/o drug!
agree, assoc inc ALP, no eos, needs F/U (May near ni ALT45/AST34)
agree, F/U needs check, trans still rise
agree
pt baseALT404, no neg impact by study drug on LFT, but concern hep C subgroup
ni ALT45/AST30 when hosp with stroke, rise noted 1 week after admission, possible, hosp more
hospitalized for pneumonia/?hepatitis,look only 1 day study med,LFT declined, rise late hep sero
abnl base with worsening, ni LFT following month, pos eos as LFT improves, hep sero neg
course shortened due to syncope, dx hep C,transam still inc ?any late F/U
rise after treatment, resolution off, agree poss/prob
agree likely unrelated, but incomplete F/U with ALT down from 4 to 3XULN, no V3 lab
disagree, had rise with rx, hep C vs drug, also pos DNA7sig
agree, also noted + ASMA, sig ?
agree?, ALT declined after treatment, hx hep C, tests ordered, not recorded, confirm ?
agree,V2 lab still w el, but less than base
agree, F/U back to base, still mild abnl
?disagree, abnl base with further inc, still inc at last lab, hep and auto neg, ?any
agree, possible, but pravachol also concern new med?
agree,still abnl 2/02,3/02 but baseline,no eos
agree, needs f/u info - any late F/U?, looks like lost to f/u, no CBC, hep sero
agree, despite early f/u, lab time OK and trans ni, hep sero neg
abnl pre, ni 2 weeks, inc 1 month out, dec ALT113/AST61, remote dx hep A
agree, bil did rise to 19 (0.9 from 10-0.48) and late bill sl over ULN, ? any

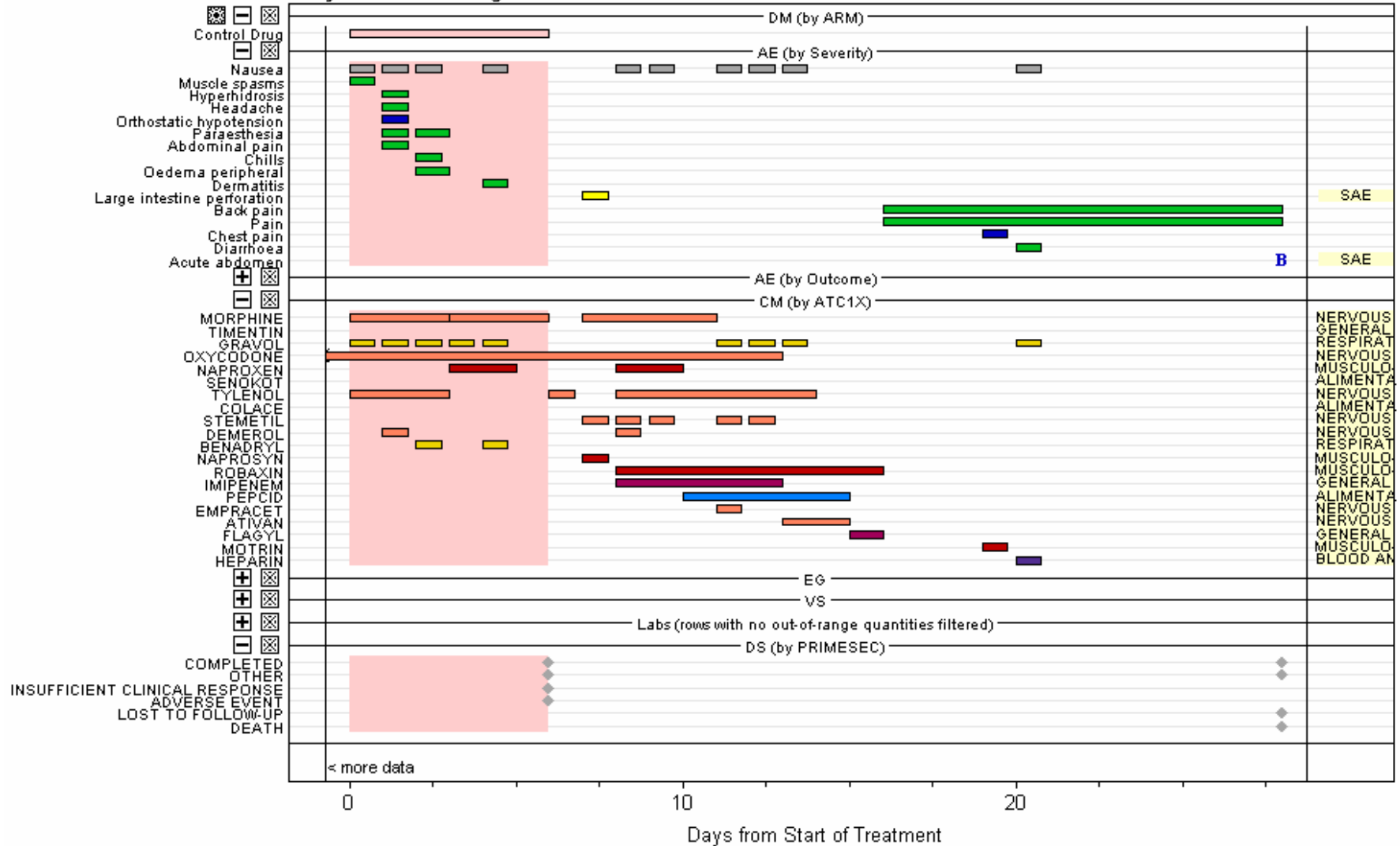
abn
B/L

abnl base ALT122/AST83,inc216/14
abnl base ALT49/42,inc ALT104, ha
nl base, rise ALT365/AST153,fall17
base abnl ALT121/AST49,rise 242
base ALT213/AST133PRE with el
base abnl ALT369/AST216, not n
nl base, inc ALT396/AST270,fall
abnl base, ALT243/AST142,fell
abnl base ALT198/ALP322,rise
abnl base ALT108/AST70,rise
nl base, rise ALT160/AST172,
abnl base ALT173/AST83, no
hep C X15 years, ETOH and
sl base abnl , rise ALT112, t
abnl base ALT214/AST142
abnl base ALT84/AST38, i
ALT52/AST

Patient Profile Viewer

Wonderdrug NDA - ISS Data

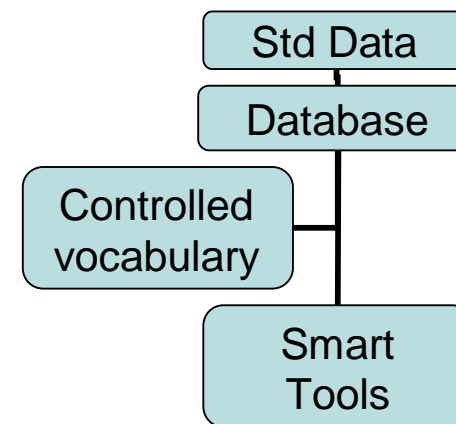
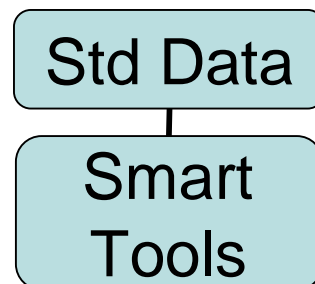
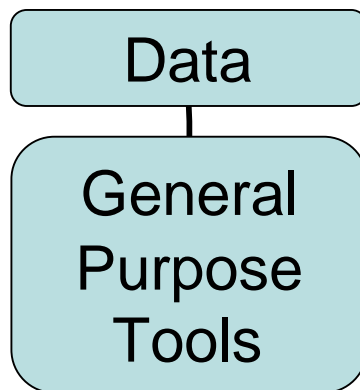
Subject: XXXXXX - Age: 29 - Sex: M - Race: White



Updates/Opportunities

- NCI Janus/CRIX
- CDISC eSDI
- Academic Consortia

JANUS and the Evolution of Data Management

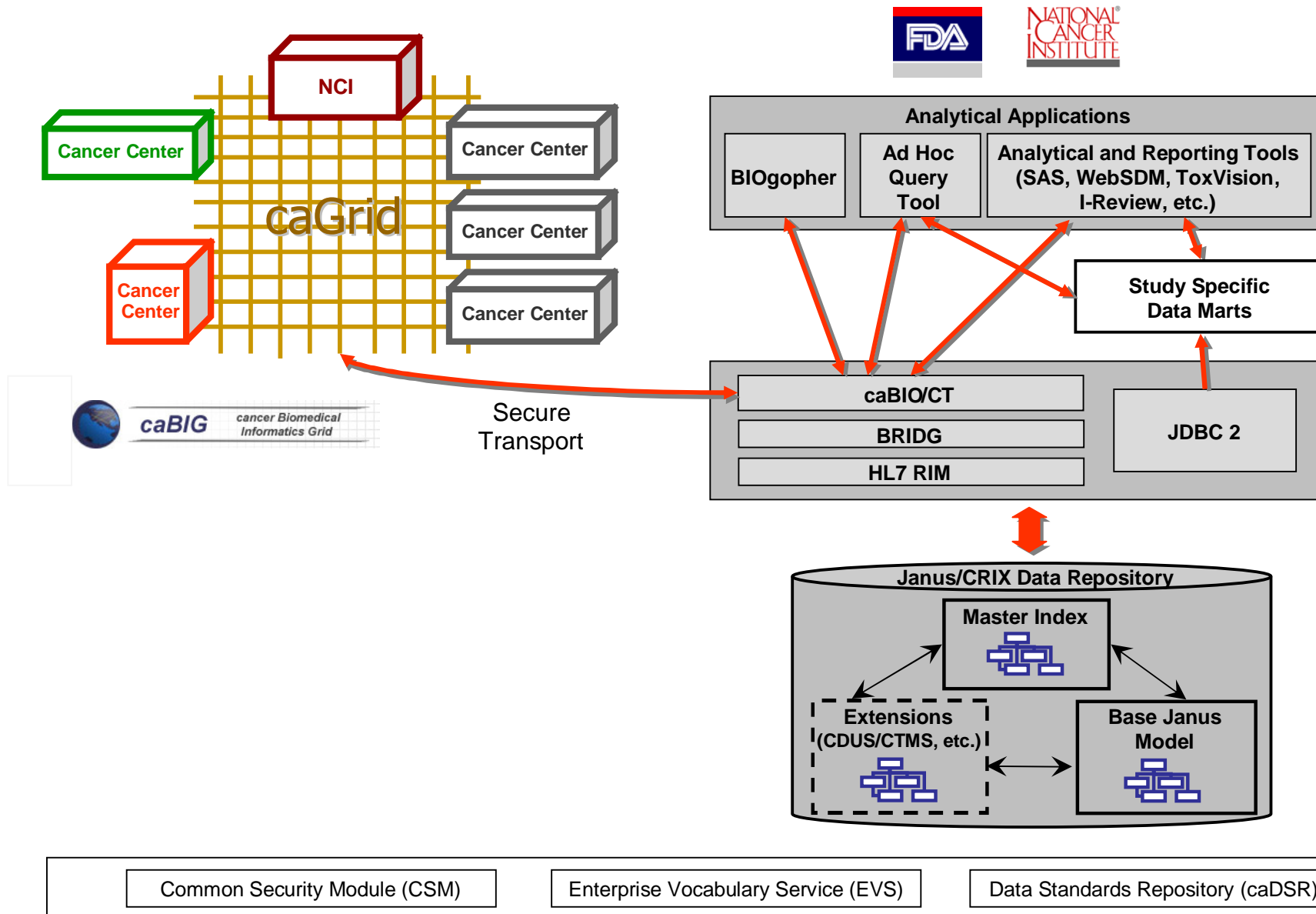


Cross-study analyses

- Integrated demographics
- Integrated safety review
- Historical controls
- Drug class-wide trends
- Disease modeling and other Critical Path Initiative activities

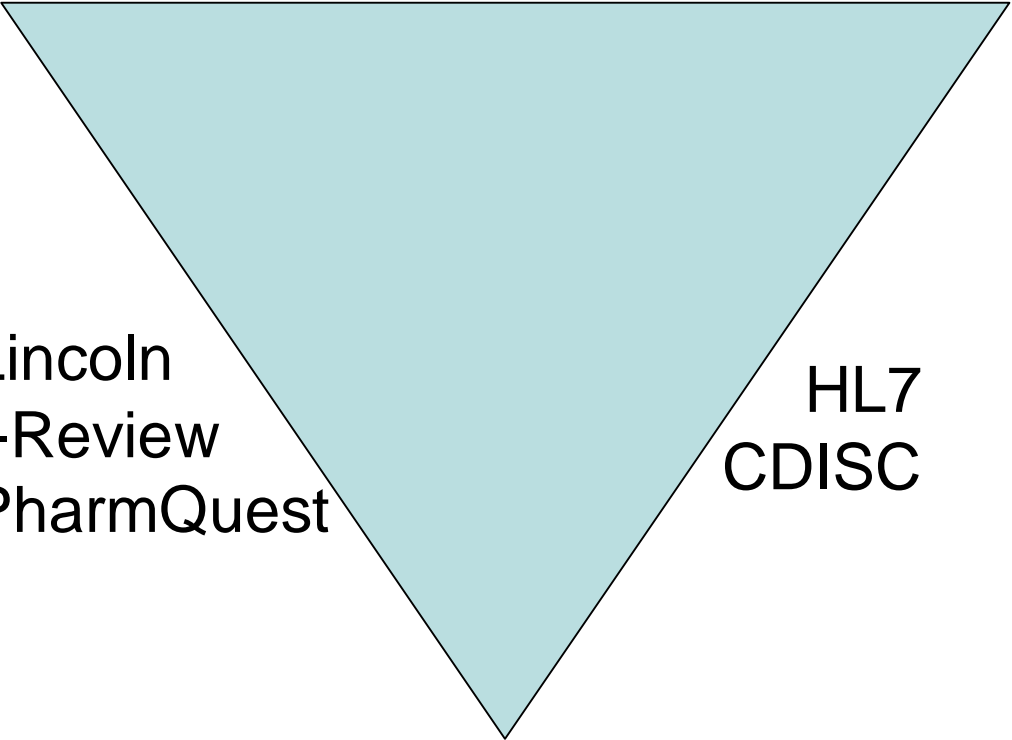


CRIX Data Access Vision



Vocabulary
Security
Etc.

NCI FDA



Lincoln
I-Review
PharmQuest

HL7
CDISC

Tools and viewers
Managed data
SAS
PPV
External data
aECG



eSource* Data Interchange (eSDI)

- **Purpose of eSDI Initiative**
 - to facilitate the use of electronic technology in the context of existing regulations for the collection of source data in clinical trials for regulatory submission by leveraging the power of the CDISC standards, in particular the Operational Data Model (ODM).
 - “Pave the path towards the vision of ‘research at the point of care and care at the point of research’ and ultimately to enable information system interoperability to improve medical research and related areas of healthcare, which is at the core of the CDISC mission.”
- **Document Posted for Open Public Review and Comment by 17 October**

**Note: eSource pertains to eDiaries, ePRO, eDCI, Electronic Health Record*

Requirements

PAPER

- **Requirement 1:** An instrument used to capture source data shall be an accurate representation of the protocol ensuring that the data as specified within the protocol is captured correctly.
- **Requirement 2:** Source data shall be Accurate, Legible, Contemporaneous, Original, Attributable, Complete and Consistent.
- **Requirement 3:** An audit trail shall be maintained as part of the source documents for the original creation and subsequent modification of all source data..

Requirements

- **Requirement 4:** The storage of source documents shall provide for their ready retrieval.
- **Requirement 5:** The investigator shall maintain the original source document or a certified copy.
- **Requirement 6:** The mechanism used to maintain source documents shall ensure that source data cannot be modified without the knowledge or approval of the investigator.
- **Requirement 7:** Source documents and data shall be protected from destruction.

Requirements

- **Requirement 8:** The source document shall allow for accurate copies to be made.
- **Requirement 9:** Source documents shall be protected against unauthorized access.

Electronic

- **Requirement 10:** The sponsor shall not have exclusive control of a source document.

The Critical Path and MIT's Center for Biomedical Innovation

- The **MIT Center for Biomedical Innovation (CBI)** is a new Institute-wide collaboration of faculty from the MIT Schools of Engineering, Management, and Science, the Harvard-MIT Division of Health Sciences & Technology (HST), and their counterparts from government and industry.
- CBI is identifying, researching and enabling the implementation of innovative methodologies and approaches which will transform the discovery, development and distribution of accessible therapeutics, diagnostics and medical devices.
- <http://cbi.mit.edu/>

CBI Planning Workshop Participants,

June 16-17, 2005

Abbott (Rx)
ALTANA
Amgen
AstraZeneca
Biogen Idec
Boehringer Ingelheim
Bristol-Myers Squibb
Centers for Medicare &
Medicaid Services (CMS)
Corning Life Sciences
Food and Drug
Administration (FDA)
GE Healthcare
Genzyme
Gene Logic
GlaxoSmithKline (GSK)
Guidant (J&J)
IBM
IMS Health

International Society for
Pharmaceutical Engineering
(ISPE)
Jackson Laboratory
Johnson & Johnson
Lehman Brothers
Eli Lilly
Massachusetts State Government
Mayo Clinic
Merck
Millennium
National Cancer Institute (NIH)
Novartis
Pfizer
Roche
Schering-Plough
Stryker
Wyeth

THANK YOU

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