Streamline Assessing Clinical Trial Data with Standards

Using FDA NDAs and CRs as Examples

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Board of Director and C3C Member of CDISC

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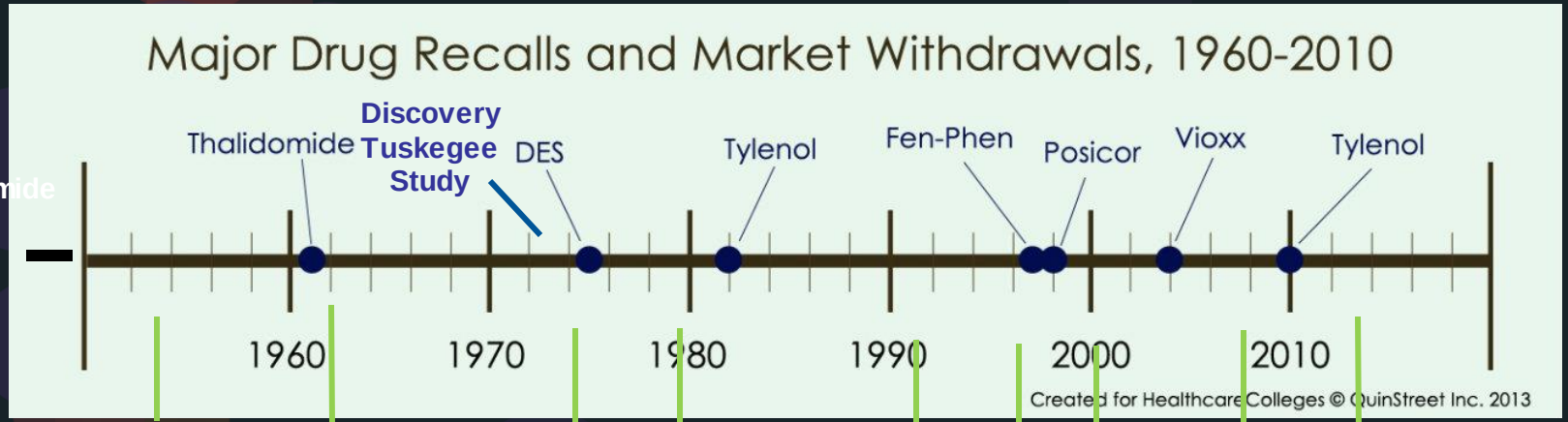
JMP STATISTICAL DISCOVERY

Drug Safety

Standardized Requirements and Procedures



1937 — Elixir Sulfanilamide

1938 — FDA — Federal Food, Drug, and Cosmetic Act

1953 — NIH — IRBs

1962 — FDA — Kefauver-Harris Amendments FDA Regulation

1974 — National Research Act Passed

1979 — The Belmont Report

1991 — The Common Rule

1996 — ICH GCP

2000 — Clinical Trials.gov

2007 — WHO ICTRP

2013 — EMA Expands Trial Database

http://ictd2015.lillycoi.com

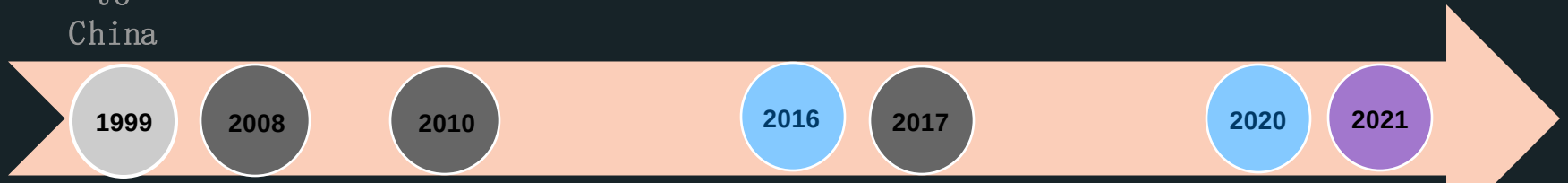
http://www.healthcarecolleges.com/news/medicine-gone-wrong-timeline-major-drug-recalls.html

FDA Required Training for Reviewers

https://www.fda.gov/media/80047/download 4/25/2018

	6-9 Months	
	CDER NDA/BLA Regs and Policies (classroom or online)	
	CDER Review of Clinical Trials	OND: Office of New Drugs
	OND Ready, Set, Review	OTS: Office of Translational Sciences
	OND 2017 Clinical Review Template Introduction	OCS: Office of Computational Science
	OND The Road to Assessing Benefit and Risk	
	CDER MaPP 6010.3 Clinical Review Template Attachment B (Safety Review, p. 36 – print resource) http://inside.fda.gov:9003/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm080121.pdf	
	CDER Learn the Safety Dance	
	OTS MedDRA Training – I & II	Standard Terminology
	OCS Data standards training	Standard Data
	OCS JMP and JMP Clinical Training (multiple modules)	Standard Analysis Procedures
	FDA Library Electronic Resources	
	FDA Library Training: Introduction to PubMed/EBSCO Host/Research Tool	

CDISC is the Standard to Use



Why ?

Why Not ??

Required

Suggested

FDA

pmda

国家药品监督管理局
National Medical Products Administration

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

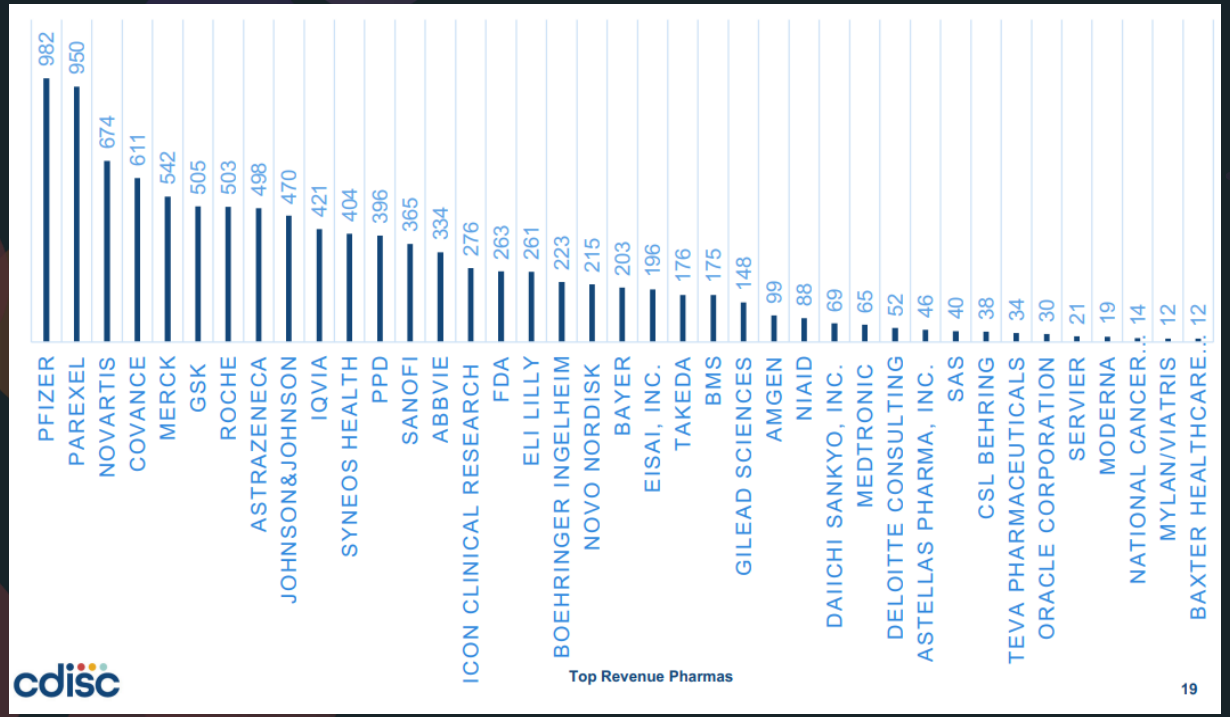
cdisc

Standards
Education
Membership
Communication

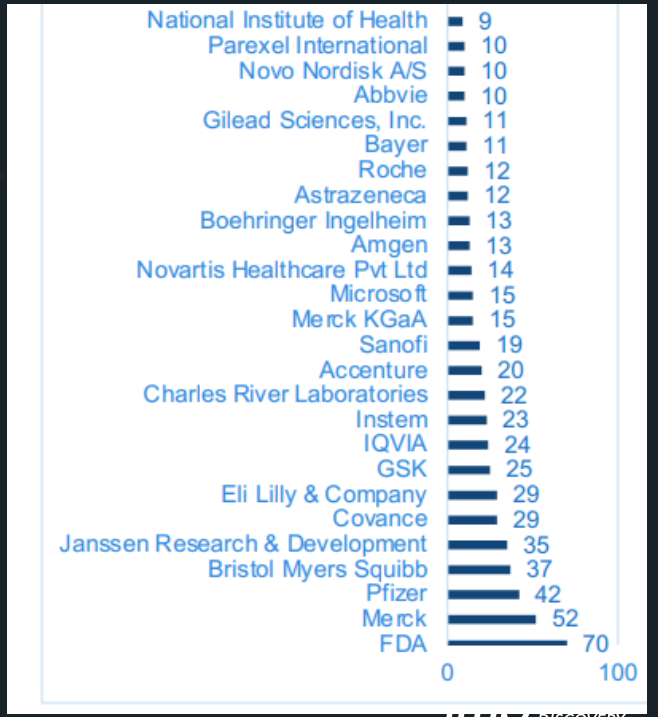
jmp STATISTICAL DISCOVERY

Widely Used in Industry and Regulatory Agency

CDISC Accounts per Organization
2022



Volunteers per Organization
2022



CDISC Enables Efficient Streamlining of Clinical Trial Safety Evaluation

Geoffrey Mann, Thomas J. Pedersen, Rebecca Lyzinski, Anisa Scott, John Cromer, Meichen Dong, Andrew J Foglia, Nora Varga, Sam Gardner, Christopher J. Kirchberg, Byron A. Wingerd, Russell D. Wolfinger*, Wenjun Bao*

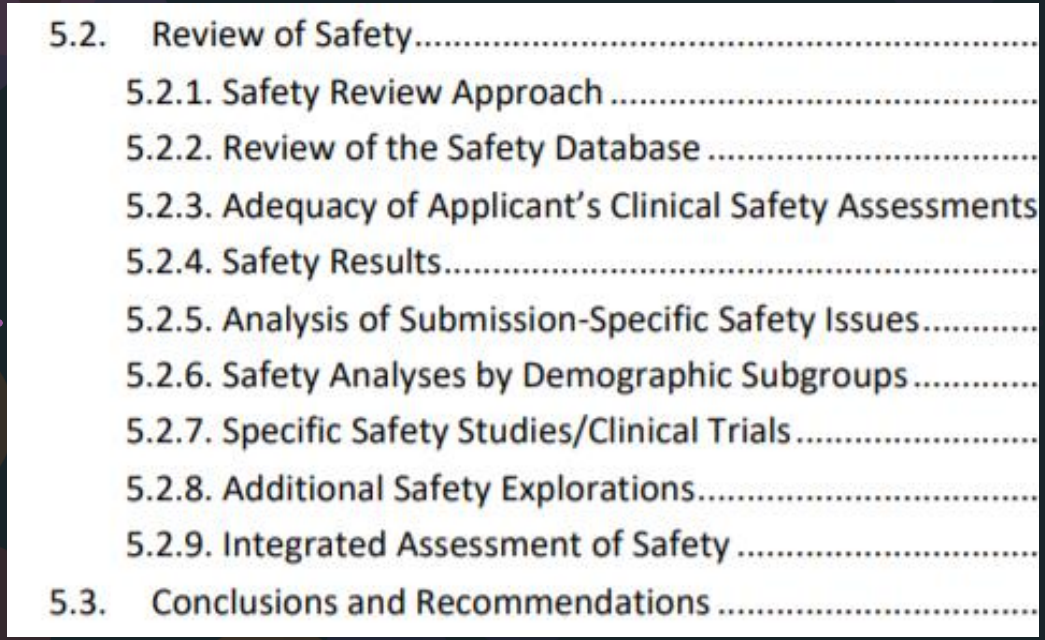
JMP, SAS Institute Inc., Cary, NC 27513

CDISC Special Issue in:

Papers in this issue also by:

US FDA
Japan PMDA
Danish Medicines Agency

FDA NDAs or CRs for Safety



5.2. Review of Safety
- 5.2.1. Safety Review Approach
- 5.2.2. Review of the Safety Database
- 5.2.3. Adequacy of Applicant's Clinical Safety Assessments
- 5.2.4. Safety Results
- 5.2.5. Analysis of Submission-Specific Safety Issues
- 5.2.6. Safety Analyses by Demographic Subgroups
- 5.2.7. Specific Safety Studies/Clinical Trials
- 5.2.8. Additional Safety Explorations
- 5.2.9. Integrated Assessment of Safety

5.3. Conclusions and Recommendations

Mydayis https://www.fda.gov/media/142063/download

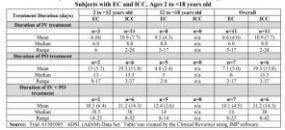
NDA: New Drug Application CR: Clinical Review

A. Safety Review Approach

The Analysis Data Model (ADaM) and Study data Tabulation Model (SDTM) datasets were intact and evaluable using JMP programs for the clinical team and for evaluation by our Biometrics team.

Vyvanse https://www.fda.gov/media/151943/download

B. Review of Safety Database



Vfend https://www.fda.gov/media/113616/download

C. Adequacy of Applicant's Clinical Safety Assessments

Demographics of Safety Database

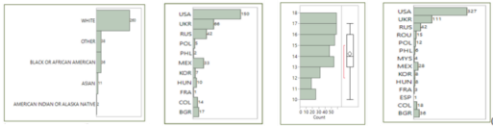


Table 11: Treatment by age group in Study D1050326

Age Group	Lurasidone 20-80 mg Count	Lurasidone 20-80 mg Column %	Placebo Count	Placebo Column %	Count	% of Total
age >=6 and age <=12	38	21.7%	37	21.5%	75	21.61%
age >=13 and age <=17	137	78.3%	135	78.5%	272	78.39%
All	175	100.0%	172	100.0%	347	100.00%

Latuda https://www.fda.gov/media/103749/download

E. Safety Analyses by DM Subgroups

TEAEs & ARs by Age, Sex, Race, Ethnicity & location

Table 36: Treatment-Emergent Adverse Reactions Occurring in ≥2 Subjects in Any Subgroup Treated With Arazlo Lotion or Vehicle Lotion, by Age Group (ISS, Safety Analysis Set)

Preferred Term	Age 9 to <12 Years (N=26) Arazlo Lotion, n=14 n (%)	Age 9 to <12 Years (N=26) Vehicle Lotion, n=12 n (%)	Age ≥12 Years (N=1542) Arazlo Lotion, n=764 n (%)	Age ≥12 Years (N=1542) Vehicle Lotion, n=778 n (%)
Application site pain	1 (7.1)	0	40 (5.2)	2 (0.3)
Application site dryness	0	0	28 (3.7)	1 (0.1)
Combined PTs for application site: rash/dermatitis/erythema/hypersensitivity	1 (7.1)	0	24 (3.1)	0
Application site exfoliation	0	0	16 (2.1)	0
Application site pruritus	2 (14.3)	0	7 (0.9)	0
Application site irritation	0	0	6 (0.8)	0
Application site acne	0	0	1	2 (0.3)

Arazlo https://www.fda.gov/media/134644/download

G. information was verified by reviewers

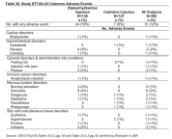


Table 14: Enrollment by Country

Country	ABP 710 (N=279)	US-Remicade (N=279)	Total (N=558)
Australia	5 (1.8%)	4 (1.4%)	9 (1.6%)
Bulgaria	14 (5.0%)	11 (3.9%)	25 (4.5%)
Canada	2 (0.7%)	1 (0.4%)	3 (0.5%)
Czech Republic	52 (18.6%)	49 (17.6%)	101 (18.1%)
Germany	15 (5.4%)	11 (3.9%)	26 (4.7%)
Hungary	7 (2.5%)	14 (5.0%)	21 (3.8%)
Poland	125 (44.8%)	133 (47.7%)	258 (46.2%)
Spain	7 (2.5%)	4 (1.4%)	11 (2.0%)
United States	52 (18.6%)	52 (18.6%)	104 (18.6%)

Source: Study 20140111 CSR, Table 14-1.2.1; clinical reviewer verified using JMP and ADSL dataset by TRT01A.

Quzyttir https://www.fda.gov/media/133034/download

Avsola https://www.fda.gov/media/134460/download

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- B 5.2.2. Review of the Safety Database .....
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- E 5.2.6. Safety Analyses by Demographic Subgroups.....
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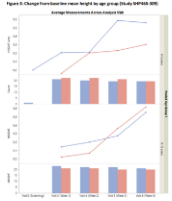
- 5.2.9. Integrated Assessment of Safety .....

5.3. Conclusions and Recommendations .....

Mydayis https://www.fda.gov/media/142063/download

F. Specific Safety Studies/Clinical Trials & other assessments

F.1. Specific Safety Issues



F.2. Additional Safety Explorations

Vyvanse https://www.fda.gov/media/151943/download

Mydayis https://www.fda.gov/media/142063/download

D. Safety Results

D.1. Death and SAE

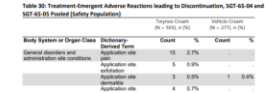
Participant: 101014
Randomized Arm: NIC .15
Investigator Name: 101B

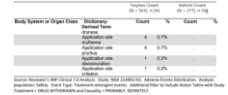
Participant 101014 was a 74-year-old white female. Her medical history included focal deficit, headache, hypertension, vomiting, hypertension, allergies, diabetes mellitus, and other medical condition.]

The participant discontinued the trial on 21MAR1989 (Day 6) due to death.

Latuda https://www.fda.gov/media/103749/download

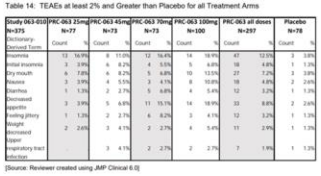
D.2. Discontinuations due to AEs

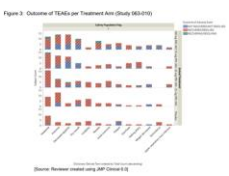




Twyneo https://www.fda.gov/media/151645/download

D.3. Treatment Emergent AEs and ARs





Adhansia XR https://www.fda.gov/media/124188/download

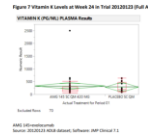
Table 25. FMQs with Events in ≥2% of Dasiglucagon Treated Subjects Over Entire Observation Period – Placebo-Controlled Pool

FMQ	0.6 mg Dasiglucagon n=116	Placebo n=53	1 mg GlucaGen n=43	RR*	95% CI
Nausea	66 (56.9%)	2 (3.8%)	23 (53.5%)	15.1	(3.8, 59.3)
Hypoglycemia	29 (25%)	7 (13.2%)	9 (20.9%)	1.9	(0.9, 4)
Vomiting	29 (25%)	1 (1.9%)	9 (20.9%)	13.3	(1.9, 94.7)
Headache	14 (12.1%)	2 (3.8%)	5 (11.6%)	3.2	(0.8, 13.6)
Infections	8 (6.9%)	4 (7.5%)	0 (0%)	0.9	(0.3, 2.9)
Diarrhea	6 (5.2%)	(0%)	1 (2.3%)	N/A	N/A
Injection Site Reactions	4 (3.4%)	2 (3.8%)	3 (7%)	0.9	(0.2, 4.8)

*RR= risk ratio (dasiglucagon versus placebo)
Source: Generated by reviewer in JMP with ADSL and ADAE datasets

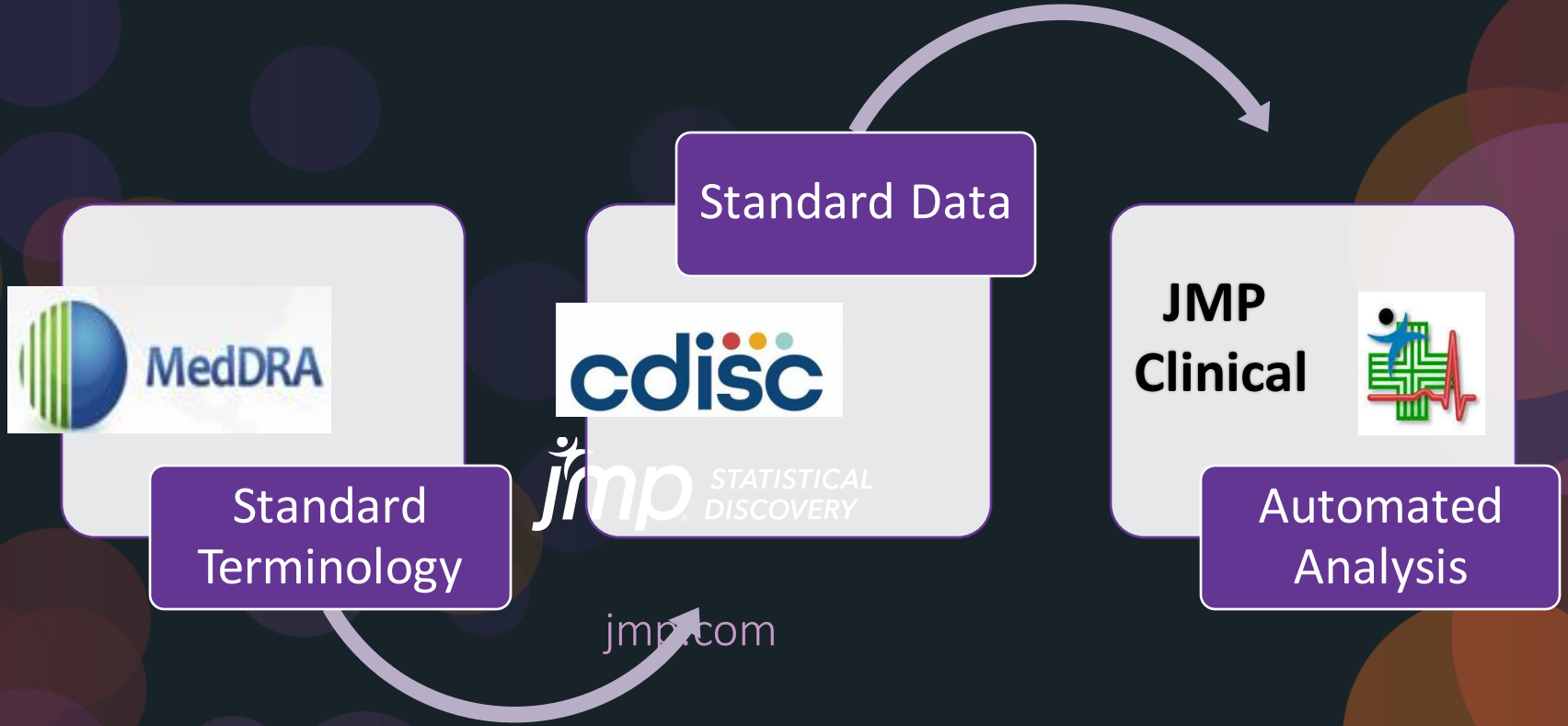
Zegalogue https://www.fda.gov/media/147791/download

D.4. Laboratory Finding



Repatha https://www.fda.gov/media/154402/download

Speedy Clinical Trial Goals Achieved by Standards: Quality, Efficiency, Reproducibility and Reusability



Thanks!