

Implementing JumpStart at Novo Nordisk A/S



Lina Ulkjær, Novo Nordisk

Implementing Scripts contributed by FDA at Novo Nordisk A/S



Lina Ulkjær , Novo Nordisk

Agenda

- About Scripts contributed by FDA
- Show outputs
- Recommendation
- Implementing and stakeholders
- Computational Science Symposium group:
 - Standard Analyses & Code Sharing, Script discovery and acquisition

Scripts contributed from FDA

- FDA's JumpStart program: Supporting drug innovation
- JumpStart is developed by FDA and runs a series of drug clinical trial data analyses early in the review process to assess data composition, quality, analyses options, and tools for the analyses, so reviewers better understand the data and have the information to conduct an effective evaluation of the drug submission

Link to FDA's web site for *Scripts contributed by FDA*:

- <https://www.fda.gov/drugs/resourcesforyou/consumers/ucm397921.htm>

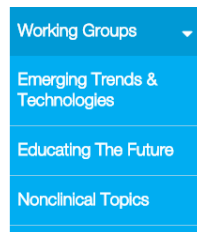
PhUSE Standard Analyses & Code Sharing

Project group: Script discovery and acquisition

- First 7 FDA Scripts programs shared on the PhUSE GitHub site
- Enable the Industry to use the FDA scripts programs



Home > Standard Analyses & Code Sharing



Standard Analyses & Code Sharing

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Script Discovery & Acquisition: The aim of the FDA/PhUSE repository is to make available a set of scripts/tools/programs for data manipulation, reporting and analyses of medical data. There are currently many such tools already available on the internet, but they are disparate and many are not easy to locate. This project aims to bring as many of these together into our open source Code Repository, making them more accessible to the community of statisticians and programmers across pharma, regulators and academia. Key tasks will be identifying, contracting and negotiating with the current owners of the scripts/tools/programs to bring them into the FDA/PhUSE repository.

- **Now tested in real life at Novo Nordisk A/S on our data**
- **but Outputs in this presentation is on PhUSE data**

What did we do:

- Joined the FDA project:
 - Script discovery and acquisition
- From GitHub downloaded:
 - Program
 - Documentation



phuse ADVANCE
CONNECTED SHARE ADVANCE

March 4th–6th
Silver Spring Civic Center
Silver Spring, Maryland, USA

US 2018
The Computational
Science Symposium

Home > Standard Analyses & Code Sharing

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Emerging Trends & Technologies

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Nonclinical Topics

Standard Analyses & Code Sharing

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Script Discovery & Acquisition: The aim of the FDA/PhUSE repository is to make available a set of scripts/tools/programs for data manipulation, reporting and analyses of medical data. There are currently many such tools already available on the internet, but they are disparate and many are not easy to locate. This project aims to bring as many of these together into our open source Code Repository, making them more accessible to the community of statisticians and programmers across pharma, regulators and academia. Key tasks will be identifying, contracting and negotiating with the current owners of the scripts/tools/programs to bring them into the FDA/PhUSE repository.

GitHub

- GitHub is a web-based version control repository and Internet hosting service, used by the Standard Analyses & Code Sharing group to host programs
- https://github.com/phuse-org/phuse-scripts/blob/master/contributed/Scripts_Top_Dir.zip

GitHub, the Scripts

 This repository Search Pull requests Issues Marketplace Explore

phuse-org / phuse-scripts

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[Code](#) [Issues 0](#) [Pull requests 0](#) [Projects 0](#) [Wiki](#) [Insights](#)

Branch: master [phuse-scripts / contributed / Scripts_Top_Dir.zip](#) [Find file](#) [Copy path](#)

 **RebekaMT** Add files via upload acec3fe on Dec 14 2016

1 contributor

1.24 MB [Download](#) [History](#)  

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(Sorry about that, but we can't show files that are this big right now.)

How to run

GitHub

Branch: master

phuse-scripts / contributed / Scripts_Top_Dir.zip

Download



SAS programs

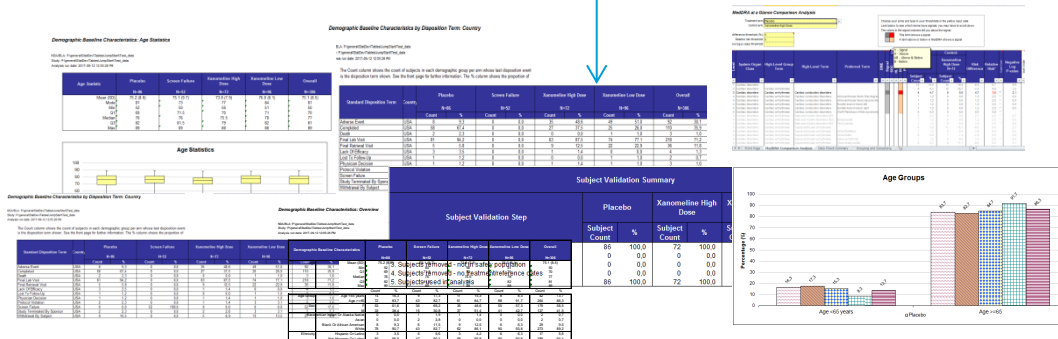
Set a pointer to data

SDTM
Data

Excel
Templates

Run SAS programs on PC SAS

It's easy to
download
and run the
scripts



Outputs from Scripts provided by FDA:

- Graphic view of Adverse Events (Adverse Events Panel Relative Risk and Adverse Events Panel Odds Ratio)
- AE Severity
- Excluded AEs
- Demographics
- Disposition
- Exposure
- Liver analysis (HY's low)
- MedDRA at a Glance.

View your study in a split second(or 10 min)

Outputs are from data from PhUSE

Data from PhUSE: phuse-scripts/data/sdtm/cdiscpilot01/

Name	Date modified	Type	Size
 Adverse_Events_Relative_Risk_Analysis.xls	16-01-2013 03:35	Microsoft Excel 97...	1.108 KB
 Adverse_Events_Odds_Ratio_Analysis.xls	12-09-2017 12:03	Microsoft Excel 97...	2.235 KB
 AE_Severity.xls	12-09-2017 12:02	Microsoft Excel 97...	330 KB
 Demographics.xls	12-09-2017 12:05	Microsoft Excel 97...	4.833 KB
 Disposition.xls	12-09-2017 12:08	Microsoft Excel 97...	3.847 KB
 excluded_AEs.xls	12-09-2017 12:21	Microsoft Excel 97...	37 KB
 Exposure.xls	12-09-2017 12:07	Microsoft Excel 97...	967 KB
 Liver_Labs.xls	15-02-2016 23:48	Microsoft Excel 97...	3.302 KB
 Liver_Labs_Error_Summary.xls	12-09-2017 12:08	Microsoft Excel 97...	18 KB
 MedDRA_at_a_Glance_Analysis_Panel.xls	12-09-2017 12:11	Microsoft Excel 97...	2.052 KB
 aebodsys_dne_mdhiersoc.csv	12-09-2017 12:11	Microsoft Excel C...	3 KB
 excluded_AEs.csv	12-09-2017 12:20	Microsoft Excel C...	12 KB

View your study

Data from PhUSE

Adverse Events by Treatment Arm

NDA/BLA: P:\general\StatDev\Tables\JumpStart\Test_data

Study:

P:\general\StatDev\Tables\JumpStart\Test_data

Analysis run date: 2017-09-12 12:02:39 PM

Counts are the number of subjects in each treatment arm experiencing at least one adverse event per body system/organ class and dictionary-derived term. Only adverse events occurring in greater than 2% of subjects in any treatment arm are included.

Body System or Organ Class	Dictionary-Derived Term	Placebo		Xanomeline High Dose		Xanomeline Low Dose		Total	
		N=86		N=72		N=96		N=254	
		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Skin And Subcutaneous Tissue Disorders	Pruritus	8	9,3	25	34,7	21	21,9	54	21,3
Skin And Subcutaneous Tissue Disorders	Erythema	8	9,3	14	19,4	14	14,6	36	14,2
Skin And Subcutaneous Tissue Disorders	Rash	5	5,8	8	11,1	13	13,5	26	10,2
Skin And Subcutaneous Tissue Disorders	Hyperhidrosis	2	2,3	8	11,1	4	4,2	14	5,5
Skin And Subcutaneous Tissue Disorders	Skin Irritation	3	3,5	5	6,9	6	6,3	14	5,5
Skin And Subcutaneous Tissue Disorders	Blister	0	0,0	1	1,4	5	5,2	6	2,4
Skin And Subcutaneous Tissue Disorders	Rash Pruritic	0	0,0	2	2,8	1	1,0	3	1,2

NOTES:

1 This analysis uses the safety population and only counts adverse events that start between a subject's first exposure and 30 days after the subject's last exposure

1 AEs by Arm / 2 SAEs by Arm / 3 AEs by Max Severity / 4 SAEs by Max Severity / Data Check Summary / Grouping and Subsetting

View your study

Data from PhUSE

Serious Adverse Events by Treatment Arm

NDA/BLA: P:\general\StatDev\Tables\JumpStart\Test_data

Study: P:\general\StatDev\Tables\JumpStart\Test_data

Analysis run date: 2017-09-12 12:02:39 PM

Counts are the number of subjects in each treatment arm experiencing at least one serious adverse event per body system/organ class and dictionary-derived term. Only adverse events with a 'Y' in the AESER variable from the AE domain are used.

Body System or Organ Class	Dictionary-Derived Term	Placebo		Xanomeline High Dose		Xanomeline Low Dose		Total	
		N=86		N=72		N=96		N=254	
		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Nervous System Disorders	Syncopal	0	0,0	0	0,0	2	2,1	2	0,8
Nervous System Disorders	Partial Seizures With Secondary Generalisation	0	0,0	1	1,4	0	0,0	1	0,4

NOTES:

1 This analysis uses the safety population and only counts adverse events that start between a subject's first exposure and 30 days after the subject's last exposure

1 AEs by Arm 2 SAEs by Arm 3 AEs by Max Severity 4 SAEs by Max Severity Data Check Summary Grouping and Subsetting

View your study

Adverse Events Summary

Data from PhUSE

Adverse Events Data Validation Summary							
Reason for Exclusion	Placebo N=301		Xanomeline High Dose N=436		Xanomeline Low Dose N=454		
	Event Count	%	Event Count	%	Event Count	%	
1. Date missing or incomplete	7	2,3	4	0,9	0	0,0	
2. Date before study analysis period	13	4,3	14	3,2	27	5,9	

Subject Validation Summary								
Subject Validation Step	Placebo		Xanomeline High Dose		Xanomeline Low Dose		Total	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
1. Subjects in demographics (DM)	86	100,0	72	100,0	96	100,0	306	100,0
2. Subjects removed - unassigned/screen failure	0	0,0	0	0,0	0	0,0	52	17,0
3. Subjects removed - not in safety population	0	0,0	0	0,0	0	0,0	0	0,0
4. Subjects removed - no treatment/reference dates	0	0,0	0	0,0	0	0,0	0	0,0
5. Subjects used in analysis	86	100,0	72	100,0	96	100,0	254	83,0

1 AEs by Arm / 2 SAEs by Arm / 3 AEs by Max Severity / 4 SAEs by Max Severity / **Data Check Summary** / Grouping and Subsets

View your study

Data from PhUSE

Demographic Baseline Characteristics: Overview

NDA/BLA: P:\general\StatDev\Tables\JumpStart\Test_data

Study: P:\general\StatDev\Tables\JumpStart\Test_data

Analysis run date: 2017-09-12 12:05:26 PM

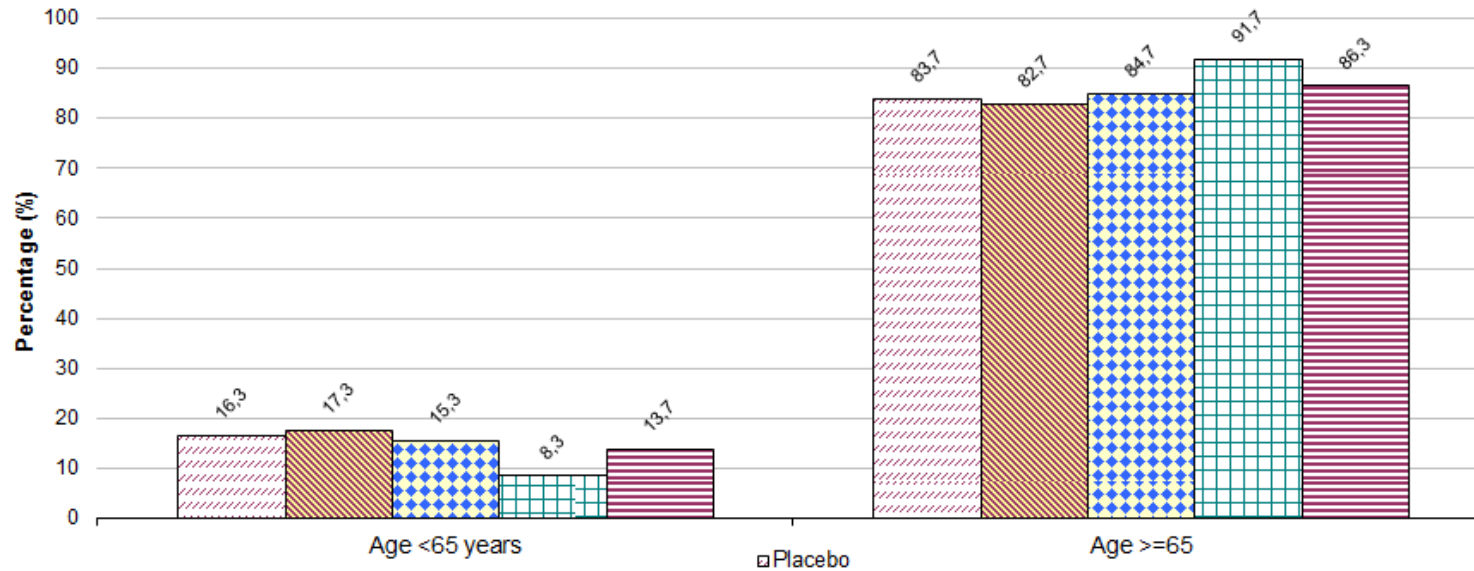
Demographic Baseline Characteristics		Placebo	Screen Failure	Xanomeline High Dose	Xanomeline Low Dose	Overall
		N=86	N=52	N=72	N=96	N=306
Age	Mean (SD)	75.2 (8.6)	75.1 (9.7)	73.8 (7.9)	76.0 (8.1)	75.1 (8.5)
	Min	52	50	56	51	50
	Q1	69	71.5	70	71	70
	Median	76	76	75.5	78	77
	Q3	82	81.5	79	82	81
	Max	89	89	88	88	89
		Count %	Count %	Count %	Count %	Count %
Age Group	Age <65 years	14 16,3	9 17,3	11 15,3	8 8,3	42 13,7
	Age >=65	72 83,7	43 82,7	61 84,7	88 91,7	264 86,3
Sex	F	53 61,6	36 69,2	35 48,6	55 57,3	179 58,5
	M	33 38,4	16 30,8	37 51,4	41 42,7	127 41,5
Race	American Indian Or Alaska Native	0 0,0	1 1,9	1 1,4	0 0,0	2 0,7
	Asian	0 0,0	2 3,8	0 0,0	0 0,0	2 0,7
	Black Or African American	8 9,3	6 11,5	9 12,5	6 6,3	29 9,5
	White	78 90,7	43 82,7	62 86,1	90 93,8	273 89,2
Ethnicity	Hispanic Or Latino	3 3,5	5 9,6	3 4,2	6 6,3	17 5,6
	Not Hispanic Or Latino	83 96,5	47 90,4	69 95,8	90 93,8	289 94,4

View your study

Demographic

Data from PhUSE

Age Groups



Front Page

1 Overview

2 Age Groups

3 Age Groups by Disp

4 Age Stats

5 Sex

6 Sex by Disp

7 Race

8 Race by Disp

View your study

Demographic Baseline Characteristics: Age Statistics

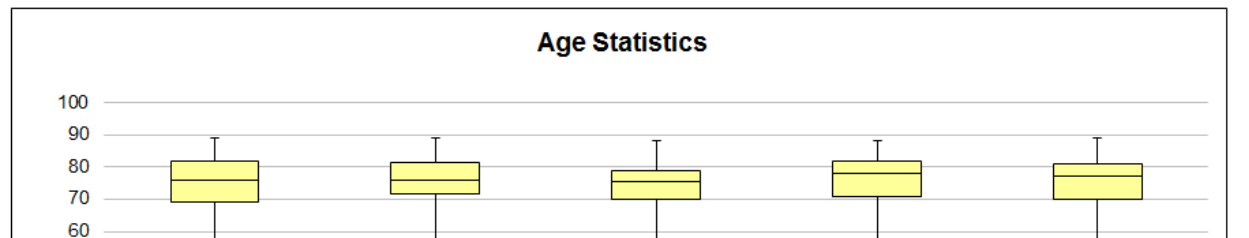
Data from PhUSE

NDA/BLA: P:\general\StatDev\Tables\UmpStart\Test_data

Study: P:\general\StatDev\Tables\UmpStart\Test_data

Analysis run date: 2017-09-12 12:05:26 PM

Age Statistic	Placebo N=86	Screen Failure N=52	Xanomeline High Dose N=72	Xanomeline Low Dose N=96	Overall N=306
Mean (SD)	75.2 (8.6)	75.1 (9.7)	73.8 (7.9)	76.0 (8.1)	75.1 (8.5)
Mode	81	73	77	84	81
Min	52	50	56	51	50
Q1	69	71.5	70	71	70
Median	76	76	75.5	78	77
Q3	82	81.5	79	82	81
Max	89	89	88	88	89



View your study

Data from PhUSE

Demographic Baseline Characteristics by Disposition Term: Country

NDA/BLA: P:\general\StatDev\Tables\JumpStart\Test_data

Study: P:\general\StatDev\Tables\JumpStart\Test_data

Analysis run date: 2017-09-12 12:05:26 PM

The Count column shows the count of subjects in each demographic group per arm whose last disposition event is the disposition term shown. See the front page for further information. The % column shows the proportion of

Standard Disposition Term	Country	Placebo		Screen Failure		Xanomeline High Dose		Xanomeline Low Dose		Overall	
		N=86		N=52		N=72		N=96		N=306	
		Count	%	Count	%	Count	%	Count	%	Count	%
Adverse Event	USA	8	9,3	0	0,0	35	48,6	49	51,0	92	30,1
Completed	USA	58	67,4	0	0,0	27	37,5	25	26,0	110	35,9
Death	USA	2	2,3	0	0,0	0	0,0	1	1,0	3	1,0
Final Lab Visit	USA	81	94,2	0	0,0	63	87,5	74	77,1	218	71,2
Final Retrieval Visit	USA	5	5,8	0	0,0	9	12,5	22	22,9	36	11,8
Lack Of Efficacy	USA	3	3,5	0	0,0	1	1,4	0	0,0	4	1,3
Lost To Follow-Up	USA	1	1,2	0	0,0	0	0,0	1	1,0	2	0,7
Physician Decision	USA	1	1,2	0	0,0	1	1,4	1	1,0	3	1,0
Protocol Violation	USA	2	2,3	0	0,0	1	1,4	3	3,1	6	2,0
Screen Failure	USA	0	0,0	52	100,0	0	0,0	0	0,0	52	17,0
Study Terminated By Sponsor	USA	2	2,3	0	0,0	2	2,8	3	3,1	7	2,3
Withdrawal By Subject	USA	9	10,5	0	0,0	5	6,9	13	13,5	27	8,8

6 Sex by Disp

7 Race

8 Race by Disp

9 Ethnicity

10 Ethnicity by Disp

11 Country

12 Country by Disp

13 Site ID

View your study

Data from PhUSE

Demographic Baseline Characteristics: Country and Site ID

NDA/BLA: P:\general\StatDev\Tables\UumpStart\Test_data

Study: P:\general\StatDev\Tables\UumpStart\Test_data

Analysis run date: 2017-09-12 12:05:26 PM

Country	Site ID	Placebo		Screen Failure		Xanomeline High Dose		Xanomeline Low Dose		Overall	
		N=86		N=52		N=72		N=96		N=306	
		Count	%	Count	%	Count	%	Count	%	Count	%
USA	701	14	16,3	10	19,2	12	16,7	15	15,6	51	16,7
	710	11	12,8	7	13,5	10	13,9	10	10,4	38	12,4
	708	9	10,5	7	13,5	5	6,9	11	11,5	32	10,5
	716	8	9,3	5	9,6	7	9,7	9	9,4	29	9,5
	704	9	10,5	0	0,0	8	11,1	8	8,3	25	8,2
	709	7	8,1	2	3,8	5	6,9	9	9,4	23	7,5
	705	5	5,8	5	9,6	5	6,9	6	6,3	21	6,9
	703	6	7,0	1	1,9	5	6,9	7	7,3	19	6,2
	718	4	4,7	0	0,0	4	5,6	5	5,2	13	4,2
	715	3	3,5	4	7,7	2	2,8	3	3,1	12	3,9
	711	1	1,2	8	15,4	1	1,4	2	2,1	12	3,9
	713	3	3,5	0	0,0	3	4,2	3	3,1	9	2,9
	717	2	2,3	0	0,0	3	4,2	2	2,1	7	2,3
	714	2	2,3	0	0,0	1	1,4	3	3,1	6	2,0
	707	1	1,2	3	5,8	0	0,0	1	1,0	5	1,6
	706	1	1,2	0	0,0	1	1,4	1	1,0	3	1,0
	702	0	0,0	0	0,0	0	0,0	1	1,0	1	0,3

City 10 Ethnicity by Disp 11 Country 12 Country by Disp 13 Site ID 14 Site ID by Disp 15 Country and Site ID

View your study

Data from PhUSE

Disposition Events by Arm for Exposed Subjects

_data

NDA/BLA: P:\general\StatDev\Tables\UmpStart\Test_data

Study: P:\general\StatDev\Tables\UmpStart\Test_data

Analysis run date: 2017-09-12 12:07:58 PM

Category of Disposition Event	Subcategory of Disposition Event	Disposition Event	Placebo		Xanomeline High Dose		Xanomeline Low Dose	
			Subject Count	%	Subject Count	%	Subject Count	%
Disposition Event	Missing	Completed	58	67,4	27	37,5	25	26,0
		Adverse Event	8	9,3	35	48,6	49	51,0
		Withdrawal By Subject	9	10,5	5	6,9	13	13,5
		Study Terminated By Sponsor	2	2,3	2	2,8	3	3,1
		Protocol Violation	2	2,3	1	1,4	3	3,1
		Lack Of Efficacy	3	3,5	1	1,4	0	0,0
		Physician Decision	1	1,2	1	1,4	1	1,0
		Death	2	2,3	0	0,0	1	1,0
		Lost To Follow-Up	1	1,2	0	0,0	1	1,0
Other Event	Missing	Final Lab Visit	81	94,2	63	87,5	74	77,1
		Final Retrieval Visit	5	5,8	9	12,5	22	22,9

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Excluded AEs

Data from PhUSE

USUBJID	arm	trtstdt	trtendt	aebodsys	aedecod	aeseq	aestdtc	AESEV	AES ER	err_desc		
01-701-1294	Xanomeline Low Dose	24-03-2013	14-06-2013	General Disorders And Administration Site Conditions	Application Site Pruritus	1	22-03-2013	MODERATE	N	2. Date before study analysis period		
01-701-1317	Xanomeline Low Dose	22-05-2014	20-11-2014	General Disorders And Administration Site Conditions	Cyst	2	13-05-2014	MILD	N	2. Date before study analysis period		
01-701-1317	Xanomeline Low Dose	22-05-2014	20-11-2014	Infections And Infestations	Onychomycosis	1	13-05-2014	MILD	N	2. Date before study analysis period		
01-701-1363	Placebo	30-05-2013	27-11-2013	Nervous System Disorders	Headache	2	1986	MODERATE	N	1. Date missing or incomplete		
01-701-1363	Placebo	30-05-2013	27-11-2013	Nervous System Disorders	Headache	4	1986	MILD	N	1. Date missing or incomplete		
01-703-1076	Xanomeline High Dose	25-10-2013	24-12-2013	Metabolism And Nutrition Disorders	Hypercholesterolaemia	3	2007	MODERATE	N	1. Date missing or incomplete		
01-703-1175	Placebo	20-12-2013	26-12-2013	Cardiac Disorders	Atrioventricular Block Second Degree	1	18-12-2013	SEVERE	N	2. Date before study analysis period		
01-703-1335	Xanomeline High Dose	17-03-2014	07-05-2014	Cardiac Disorders	Atrioventricular Block Second Degree	1	15-03-2014	MILD	N	2. Date before study analysis period		
01-703-1335	Xanomeline High Dose	17-03-2014	07-05-2014	Cardiac Disorders	Atrioventricular Block Second Degree	2	15-03-2014	MILD	N	2. Date before study analysis period		
01-704-1241	Xanomeline High Dose	25-08-2013	09-10-2013	Skin And Subcutaneous Tissue Disorders	Rash	1	14-08-2013	MODERATE	N	2. Date before study analysis period		
01-717-1357	Xanomeline High Dose	01-05-2013	14-10-2013	Nervous System Disorders	Dizziness	1	1994-04	MODERATE	N	2. Date before study analysis period		
01-718-1355	Placebo	28-02-2013	29-08-2013	Skin And Subcutaneous Tissue Disorders	Dermatitis Atopic	3	1982	MODERATE	N	1. Date missing or incomplete		

View your study in a split second(or 10 min)

Possible Hy's Law Cases

Data from PhUSE

NDA/BLA:

Study:

Analysis run date:

Combinations for Possible Hy's Law Cases: At the Same Visit

Liver Lab Test At Same Visit	0 N =		
	Event Count	Subject Count	% of Subjects
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP normal	0	0	0,00
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP normal	0	0	0,00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP normal	0	0	0,00
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP > normal	0	0	0,00
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP > normal	0	0	0,00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP > normal	0	0	0,00
Total Subjects	0	0	0,00
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN	0	0	0,00
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN	0	0	0,00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN	0	0	0,00
Total Subjects	0	0	0,00

Notes: All scores are post-baseline. Cases that have the lab combinations occurring at the same visit.

View your study

Data from PhUSE

Combinations for Possible Hy's Law Cases: At Any Time During the Study

Liver Lab Test Any Time During Study	0 N =	
	Subject Count	% of Subjects
ALT or AST $\geq$ 3 ULN, TB $\geq$ 1.5 ULN & ALP normal	0	0,00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 2 ULN & ALP normal	0	0,00
ALT or AST $\geq$ 5 ULN, TB $\geq$ 3 ULN & ALP normal	0	0,00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 1.5 ULN & ALP > normal	0	0,00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 2 ULN & ALP > normal	0	0,00
ALT or AST $\geq$ 5 ULN, TB $\geq$ 3 ULN & ALP > normal	0	0,00
Total Subjects	0	0,00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 1.5 ULN	0	0,00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 2 ULN	0	0,00
ALT or AST $\geq$ 5 ULN, TB $\geq$ 3 ULN	0	0,00
Total Subjects	0	0,00

Notes: All scores are post-baseline. Subjects that have the lab combinations occurring at any point during the study.

MedDRA at a Glance

- The output *MedDRA at a Glance* was judged highly valuable
- Information about adverse events merged with MedDRA hierarchy,
 - using the system organ class (SOC),
 - high-level group term (HLGT),
 - high-level term (HLT), and
 - preferred term (PT).
 - The user can choose which two arms to compare.
- To check that no safety signals have been overlooked.

MedDRA at a Glance Comparison Analysis

Data from PhUSE

Treatment arm:

Control arm:

difference threshold (%):

Relative risk threshold:

tive log p-value threshold:

Choose your arms and type in your thresholds in the yellow input cells

Look below to see which terms have signals; you may have to scroll down

The colors in the signal columns tell you about the signal:



This term shows a signal

A term above or below in MedDRA shows a signal

Level	System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	DME	Signal	Signal At					Treatment:		Control:		Risk Differen
							SOC	HLGT	HLT	PT	Placebo N=86		Xanomeline High Dose N=72			
											Subject Count	%	Subject Count	%		
1	Cardiac disorders										12	14,0	14	19,4	-5,5	
2	Cardiac disorders	Cardiac arrhythmias									8	9,3	12	16,7	-7,4	
3	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders								4	4,7	0	0,0	4,7	
4	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders	Atrioventricular block first degree							1	1,2	0	0,0	1,2	
4	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders	Atrioventricular block second degree							1	1,2	0	0,0	1,2	
4	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders	Bundle branch block left							1	1,2	0	0,0	1,2	
4	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders	Bundle branch block right							1	1,2	0	0,0	1,2	
4	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders	Wolff-Parkinson-White syndrome							0	0,0	0	0,0	0,0	
3	Cardiac disorders	Cardiac arrhythmias	Rate and rhythm disorders NEC								2	2,3	0	0,0	2,3	
4	Cardiac disorders	Cardiac arrhythmias	Rate and rhythm disorders NEC	Bradycardia							1	1,2	0	0,0	1,2	
4	Cardiac disorders	Cardiac arrhythmias	Rate and rhythm disorders NEC	Tachycardia							1	1,2	0	0,0	1,2	
3	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythmias								5	5,8	11	15,3	-9,5	
4	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythmias	Atrial fibrillation							1	1,2	2	2,8	-1,6	
4	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythmias	Atrial flutter							0	0,0	1	1,4	-1,4	
4	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythmias	Sinus arrhythmia							1	1,2	0	0,0	1,2	
4	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythmias	Sinus bradycardia							2	2,3	8	11,1	-8,8	

MedDRA at a Glance Comparison Analysis

Data from PhUSE

Treatment arm:

Control arm:

difference threshold (%):

Relative risk threshold:

ive log p-value threshold:

Choose your arms and type in your thresholds in the yellow input cells

Look below to see which terms have signals; you may have to scroll down

The colors in the signal columns tell you about the signal:



This term shows a signal

A term above or below in MedDRA shows a signal

Level	System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	DME	Signal	SOC	HL	HI	P	Treatment:		Control:		Risk Difference
											Placebo		Xanomeline High Dose N=72		
											Subject Count	%	Subject Count	%	
1	Cardiac disorders										12	14,0	14	19,4	-5,5
2	Cardiac disorders	Cardiac arrhythmias									8	9,3	12	16,7	-7,4
3	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders								4	4,7	0	0,0	4,7
4	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders	Atrioventricular block first degree							1	1,2	0	0,0	1,2
4	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders	Atrioventricular block second degree							1	1,2	0	0,0	1,2
4	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders	Bundle branch block left							1	1,2	0	0,0	1,2
4	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders	Bundle branch block right							1	1,2	0	0,0	1,2
4	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders	Wolff-Parkinson-White syndrome							0	0,0	0	0,0	0,0
3	Cardiac disorders	Cardiac arrhythmias	Rate and rhythm disorders NEC								2	2,3	0	0,0	2,3
4	Cardiac disorders	Cardiac arrhythmias	Rate and rhythm disorders NEC	Bradycardia							1	1,2	0	0,0	1,2
4	Cardiac disorders	Cardiac arrhythmias	Rate and rhythm disorders NEC	Tachycardia							1	1,2	0	0,0	1,2
3	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythmias								5	5,8	11	15,3	-9,5
4	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythmias	Atrial fibrillation							1	1,2	2	2,8	-1,6
4	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythmias	Atrial flutter							0	0,0	1	1,4	-1,4
4	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythmias	Sinus arrhythmia							1	1,2	0	0,0	1,2
4	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythmias	Sinus bradycardia							2	2,3	8	11,1	-8,8

Y - Signal
A - Above
AB - Above & Below
B - Below

MedDRA at a Glance Comparison Analysis Data from PhUSE

Treatment arm:

Control arm:

difference threshold (%):

Relative risk threshold:

tive log p-value threshold:

Choose your arms and type in your thresholds in the yellow input cells

Look below to see which terms have signals; you may have to scroll down

The colors in the signal columns tell you about the signal:



This term shows a signal

A term above or below in MedDRA shows a signal

Level	System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	DME	Signal At					Treatment:		Control:		Risk Difference
						Signal	SOC	HLGT	HLT	PT	Placebo N=86		Xanomeline High Dose N=72		
											Subject Count	%	Subject Count	%	
3	Cardiac disorders	Cardiac arrhythmias	Cardiac conduction disorders								4	4,7	0	0,0	4
2	Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions									11	12,8	3	4,2	8
3	Gastrointestinal disorders	Gastrointestinal motility	Diarrhoea (excl infective)								9	10,5	3	4,2	6
4	Gastrointestinal disorders	Gastrointestinal motility	Diarrhoea (excl infective)	Diarrhoea							9	10,5	3	4,2	6
2	Investigations	Cardiac and vascular investigations (excl enzyme tests)									7	8,1	1	1,4	6
4	Investigations	Cardiac and vascular investigations	ECG investigations	Electrocardiogram ST segment depression							4	4,7	0	0,0	4
1	Vascular disorders										3	3,5	0	0,0	3

NOTES:

1 This report is for data exploration only and should not be used for statistical inference

2 This analysis uses the safety population and only counts adverse events that start between a subject's first exposure and 30 days after the subject's last exposure

* Relative risk for the indicated term has been calculated after adjusting subject counts with a continuity correction of .5 to avoid dividing by zero

* Use caution with these results, since different continuity corrections yield different results and a notable relative risk statistic may only be an artifact of the correction used

Treatment arm:

Control arm:

difference threshold (%):

Relative risk threshold:

tive log p-value threshold:

Choose your arms and type in your thresholds in the yellow input cells

Look below to see which terms have signals; you may have to scroll down

The colors in the signal columns tell you about the signal:



This term shows a signal

A term above or below in MedDRA shows a signal

Level	System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	DME	Signal	Signal At					Treatment:		Control:		Risk Difference
							SOC	HLGT	HLT	PT	Placebo N=86		Xanomeline High Dose N=72			
											Subject Count	%	Subject Count	%		
1	Vascular disorders										3	3,5	0	0,0	3,5	
2	Vascular disorders	Decreased and nonspecific blood pressure disorders and shock									2	2,3	0	0,0	2,3	
3	Vascular disorders	Decreased and nonspe	Vascular hypotensive disorders								2	2,3	0	0,0	2,3	
4	Vascular disorders	Decreased and nonspe	Vascular hypotensive disorders	Hypotension							2	2,3	0	0,0	2,3	
4	Vascular disorders	Decreased and nonspe	Vascular hypotensive disorders	Orthostatic hypotension							1	1,2	0	0,0	1,2	
2	Vascular disorders	Vascular disorders NEC									0	0,0	0	0,0	0,0	
3	Vascular disorders	Vascular disorders NEC	Peripheral vascular disorders NEC								0	0,0	0	0,0	0,0	
4	Vascular disorders	Vascular disorders NEC	Peripheral vascular disorders NEC	Hot flush							0	0,0	0	0,0	0,0	
2	Vascular disorders	Vascular hypertensive disorders									1	1,2	0	0,0	1,2	
3	Vascular disorders	Vascular hypertensive	Vascular hypertensive disorders NEC								1	1,2	0	0,0	1,2	
4	Vascular disorders	Vascular hypertensive	Vascular hypertensive disorders	Hypertension							1	1,2	0	0,0	1,2	

NOTES:

1 This report is for data exploration only and should not be used for statistical inference

2 This analysis uses the safety population and only counts adverse events that start between a subject's first exposure and 30 days after the subject's last exposure

* Relative risk for the indicated term has been calculated after adjusting subject counts with a continuity correction of .5 to avoid dividing by zero

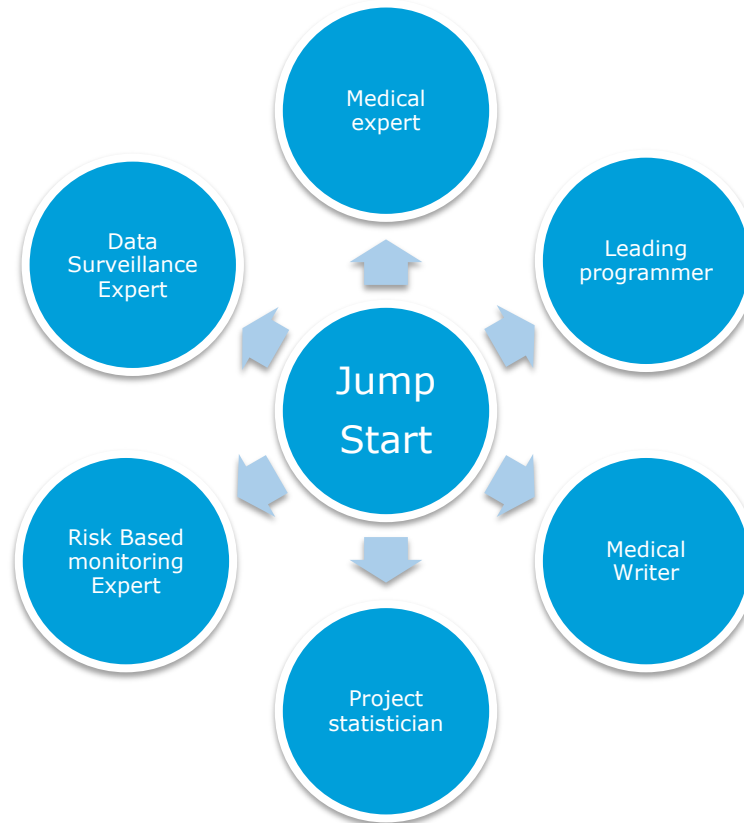
What did we do:

- Adaption of the script:
 - Corrected libname to Excel
 - Changed location of the log
 - Insert clearing of SAS work
- Fixed the script *MedDRA at a glance*
 - MedDRA version was hardcoded-> macro input
 - Designated Medical Event (DME) data from EMEA

Recommendation, Scripts contributed by FDA

- Run
 - on PC SAS / local on Enterprise Guide
 - on SDTM data (AE,DM,DS,EX)
 - AFTER Pinnacle 21 has checked data
 - best on trial design with 2 parallel arms.
- Max 6 arms (trial design), due to templates in Excel
- Cannot run on 64 Bits machines due to the Excel libname statement.
- Not good for crossover Trials
- Cannot run from affiliates due to data transfer issues to affiliates.

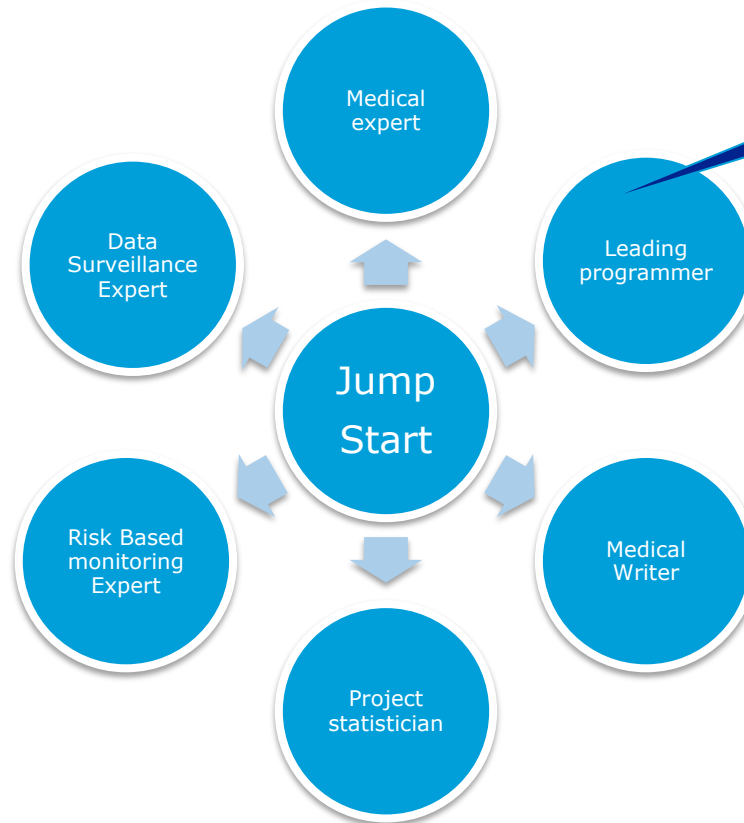
Implementation and stakeholders



Can you
run it on
my study?



Implementation and stakeholders

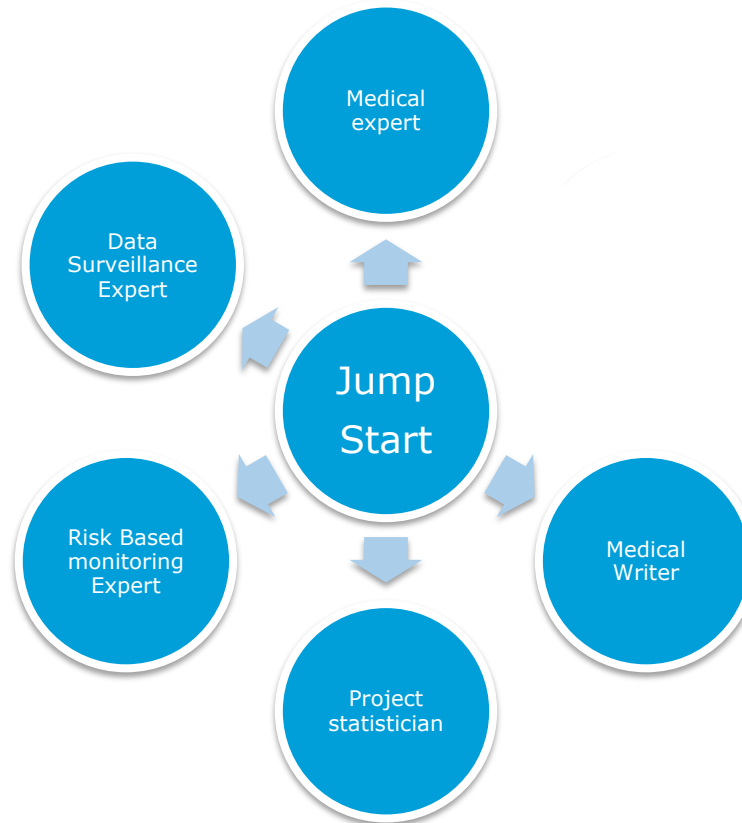


I cannot use it

Can you
run it on
my study?



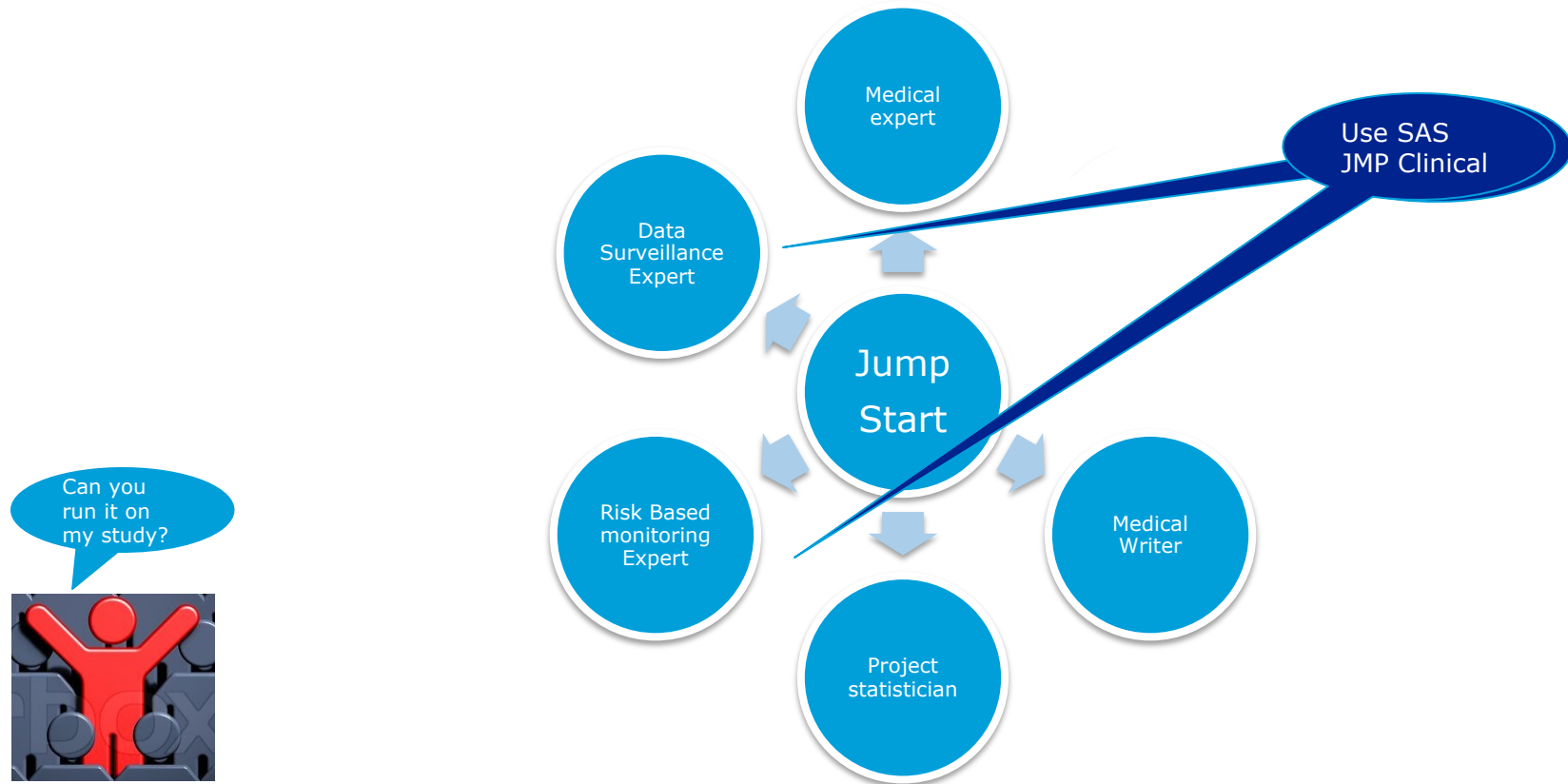
Implementation and stakeholders



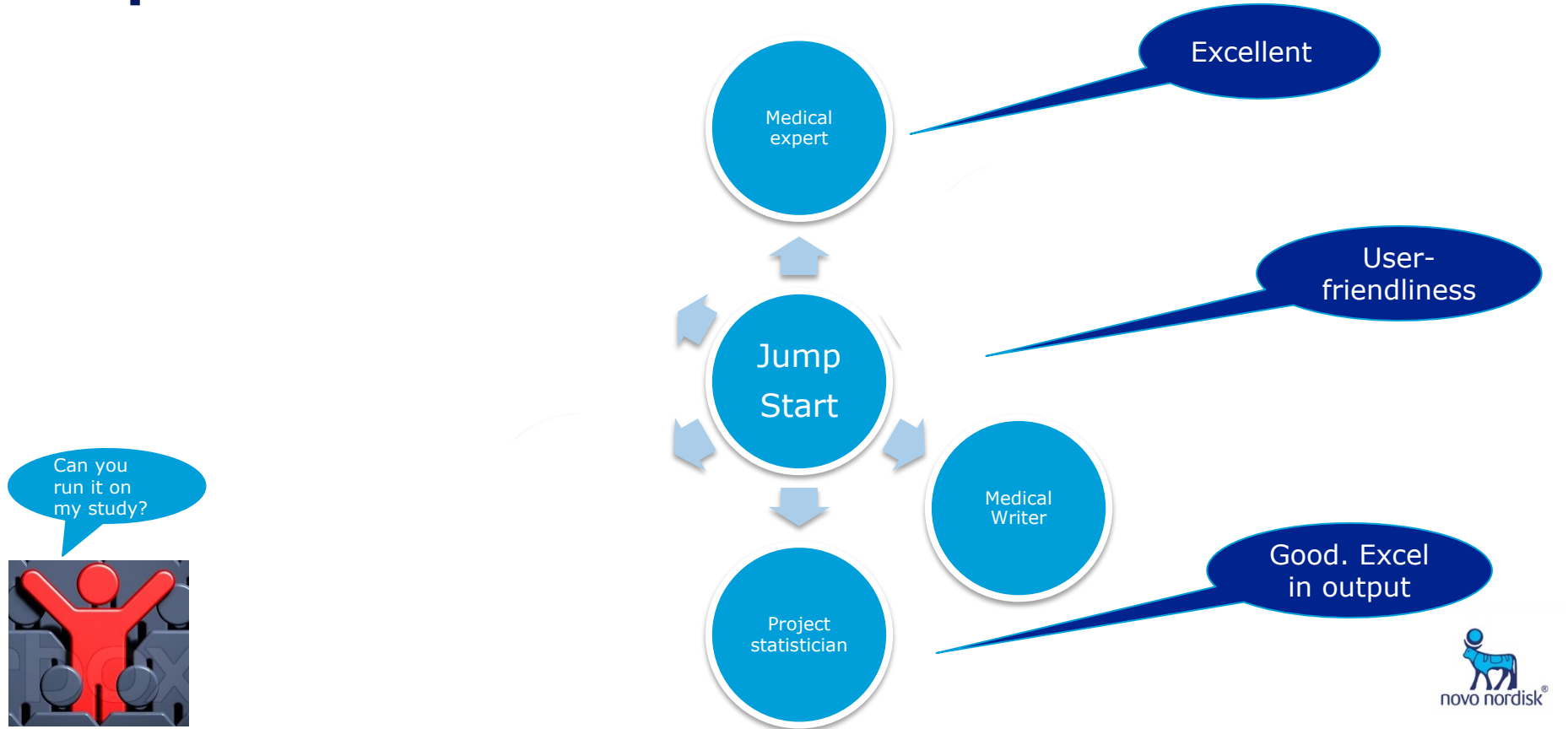
Can you
run it on
my study?



Implementation and stakeholders



Implementation and stakeholders



Novo Nordisk will use of Script contributed by FDA

- High level validation
 - Summary of a study data for statisticians and medical experts
 - Supplement for risk based monitoring, data surveillance and medical writer
 - For regulatory affairs
-
- The biggest advantage:
 - You see data as FDA see them
 - You see issues/signals that you may have overlooked.

It's highly recommend to use the scripts in the review process

Whom to run and when

- Run in Biostatistics Department.
 - Scheduled to run after key result meeting
 - By SAS JMP Clinical super users
- Output will be distributed to study group
- Will be run on all possible trials

Lesson learned until now

- Run on 4 trials and one test trial
- Until now no divergences has been found
- On the contrary confirmation were gained:



YES we have seen that signal!
YES we have those withdrawals

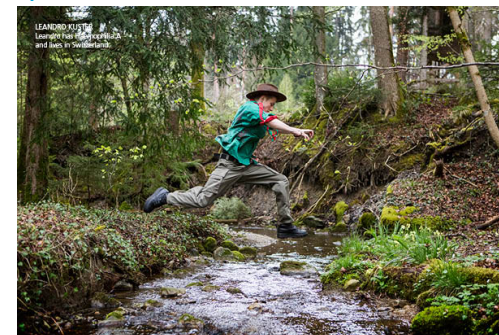
- The output from the scripts confirmed that nothing was overlooked
- The use of SAS JMP Clinical turned out to cover the outputs from the scripts

SDA: Script Discovery and Acquisition

- Project Next Steps
- Continue testing modified JumpStart Scripts
(need additional volunteers)
- Will continue to monitor for additional scripts
that may make sense for the PhUSE Repository

REFERENCES

- FDA homepage:
<https://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm397921.htm>
- White Paper:
<http://www.phuse.eu/documents/cswitepaperfdacontributedscripts-7164.pdf>
- The Scripts:
https://github.com/phuse-org/phuse-scripts/blob/master/contributed/Scripts_Top_Dir.zip
- SDA project:
http://www.phusewiki.org/wiki/index.php?title=Standard_Scripts
- Documentation:
<https://github.com/phuse-org/phuse-scripts/tree/master/tested/SAS/SpecDocs>
- Guide GitHub:
http://www.phusewiki.org/docs/2017_CSS_US/PP17_Final.pdf
- If you're interested in joining the SDA group:
- Please contact
 - Rojas, Alfredo alfredo.rojas@accenture.com or
 - Rebeka Revis, Rebeka_Revis@Lilly.com or
 - Mary E Nilsson nilsson_mary_e@lilly.com



Take home message

It's easy to
download
and run the
scripts

It's highly
recommend to
use the scripts
in the review
process



Questions

