Tales from the everyday life of a pharmaceutical statistician

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Disclaimer

Views and opinions expressed are those of the speaker and not necessarily Novo Nordisk

Novo Nordisk at a **glance**

Novo Nordisk is a leading global healthcare company, founded in 1923 and headquartered in Denmark.

Our purpose is to drive change to defeat serious chronic diseases, built upon our heritage in diabetes.

We do so by pioneering scientific breakthroughs, expanding access to our medicines, and working to prevent and ultimately cure disease.

1. https://companiesmarketcap.com/pharmaceuticals/largest-pharmaceutical-companies-by-market-cap/
(As of 25 January 2024).

Supplier of nearly
50%
of the world's insulin

Net sales
232.3
billion DKK

Affiliates in
80
countries

More than
64,000
employees

Total tax contribution
51
billion DKK

R&D centres in China, Denmark, India, UK and US

Strategic production sites in Denmark, Brazil, China, France and US

Globally, serving
41.6
million people living with diabetes and obesity

A top five
pharma company measured by market value[1]

Data Science

- at a glance

COMMUNITY OF PROFESSIONALS

- Automation Engineers
- Biostatisticians
- Computational Biologists
- Data Engineers
- Epidemiologists
- Machine Learning Scientists
- Pharmacologists
- … and many others!

Unlocking and driving value for patients, society and Novo Nordisk through data science

Creating the right data foundation and applying world-class analytics to transform data into business opportunities

DATA I ANALYTICS I PEOPLE

50/50 %

male/female

Novo Nordisk is a global healthcare leader powered by data, analytics and digital technologies

~1,100 colleagues

41 nationalities

CURRENT FOCUS

Faster and smarter product development by more *automation* and, *real time* data analytics

Increased insights and value of assets by modelling & simulation infirmed R&D + analytics across multiple data sources

Enable Precision Health through omics, imaging, digital biomarker data analyses

Ensure the right capabilities and culture and get access to best-in-class talents

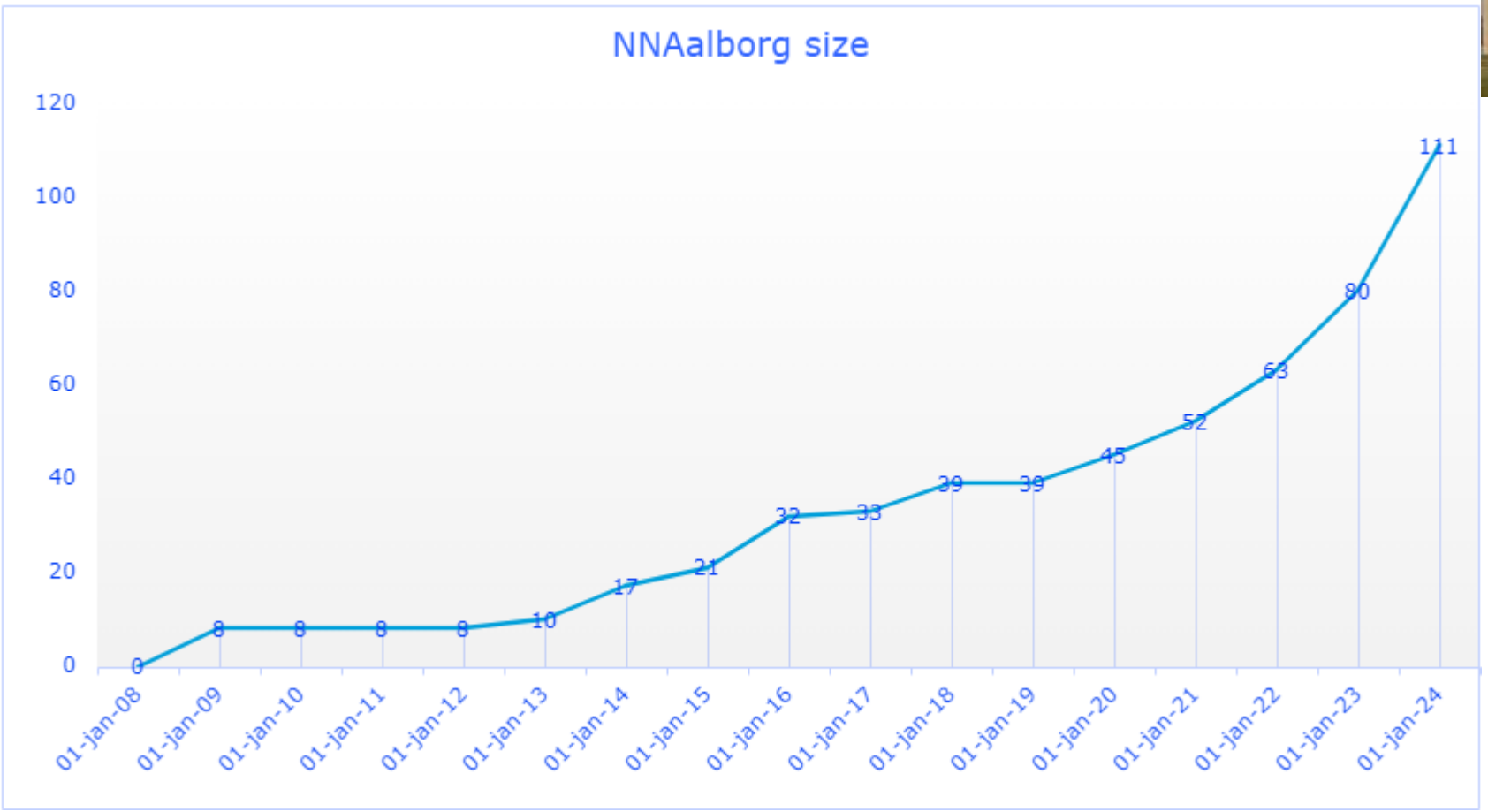
Automation

Data infrastructure

(Generative) AI / Machine learning

Outstanding workplace

NN Aalborg



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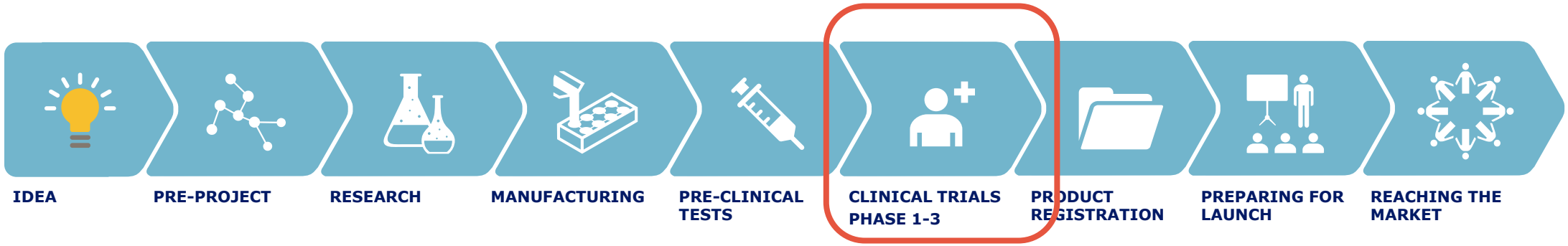
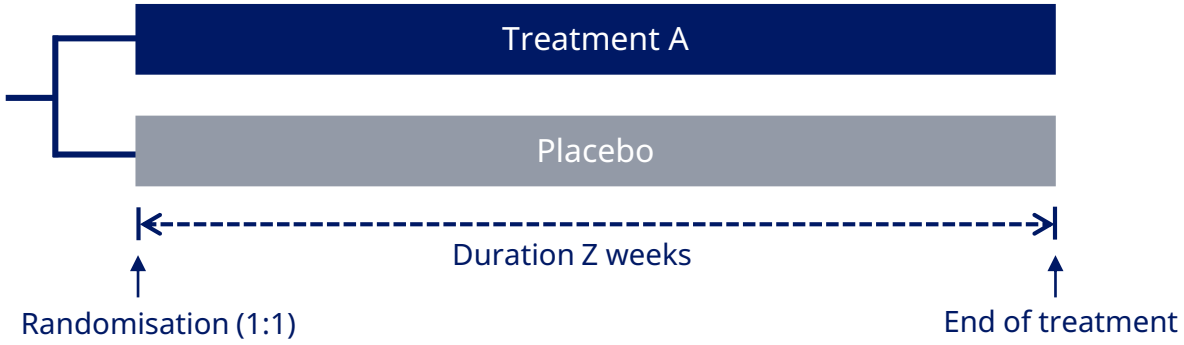
Setting the scene


IDEA
PRE-PROJECT
RESEARCH
MANUFACTURING
PRE-CLINICAL TESTS
CLINICAL TRIALS PHASE 1-3
PRODUCT REGISTRATION
PREPARING FOR LAUNCH
REACHING THE MARKET

Trial design – randomised clinical trial (RCT)

N patients



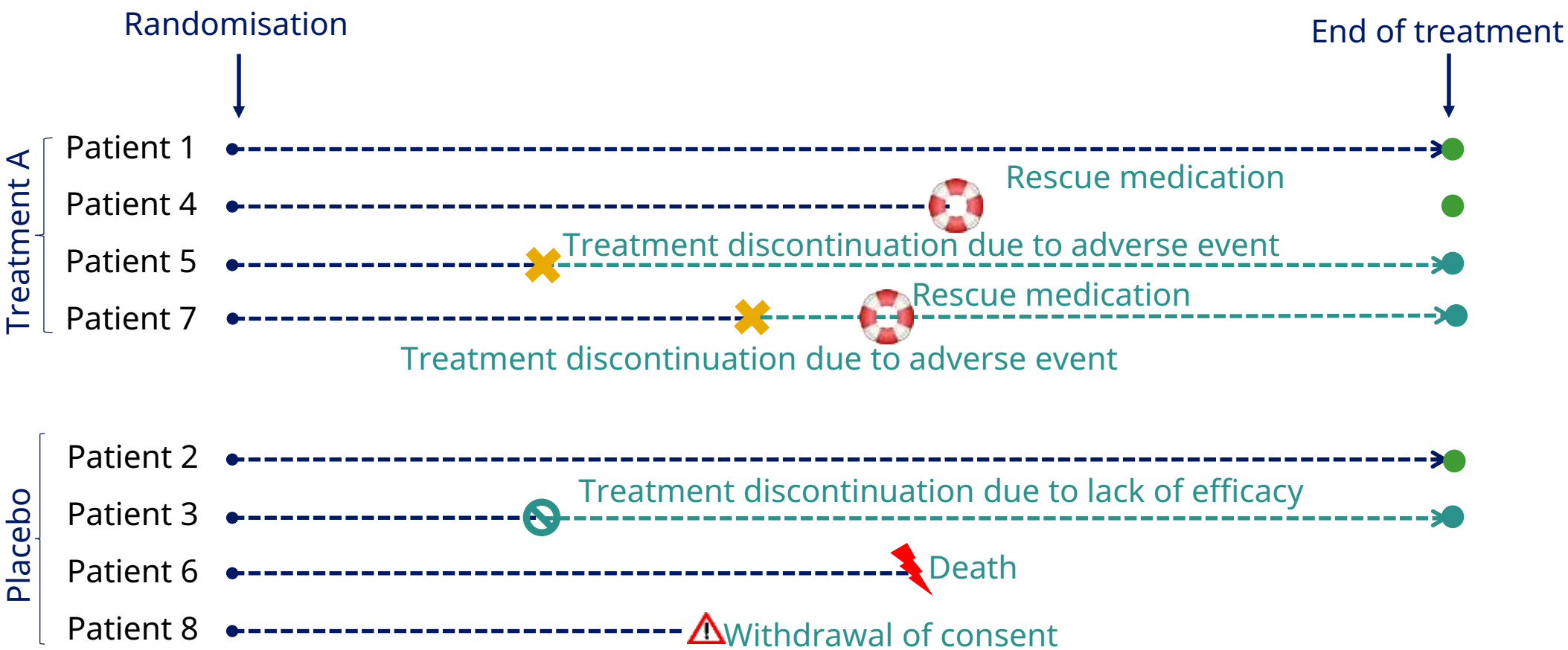
Trial objective	Key endpoints
To confirm superiority of Treatment A versus placebo on change in Y in participants “of this kind”	• **Primary:** Change in Y from baseline to week Z

Design and interpretation of clinical trials

The Answer to the Ultimate Question of Life, the Universe, and Everything is 42

Adams, Douglas, 1952-2001. The Hitchhiker's Guide to the Galaxy. New York :Harmony Books, 1980.

Intercurrent events



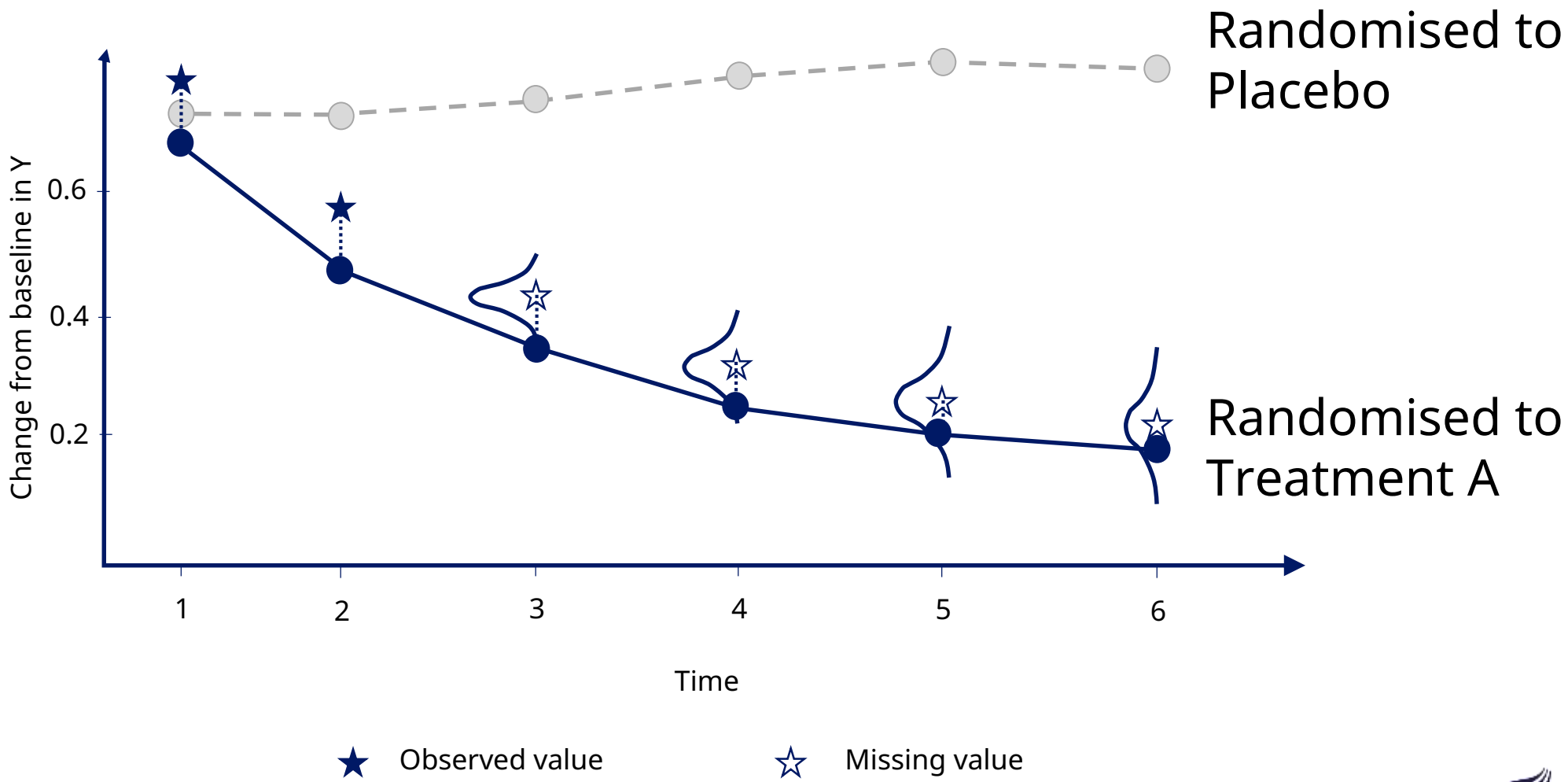
https://database.ich.org/sites/default/files/E9%28R1%29%20Training%20Material%20-%20PDF_0.pdf

Clinical questions

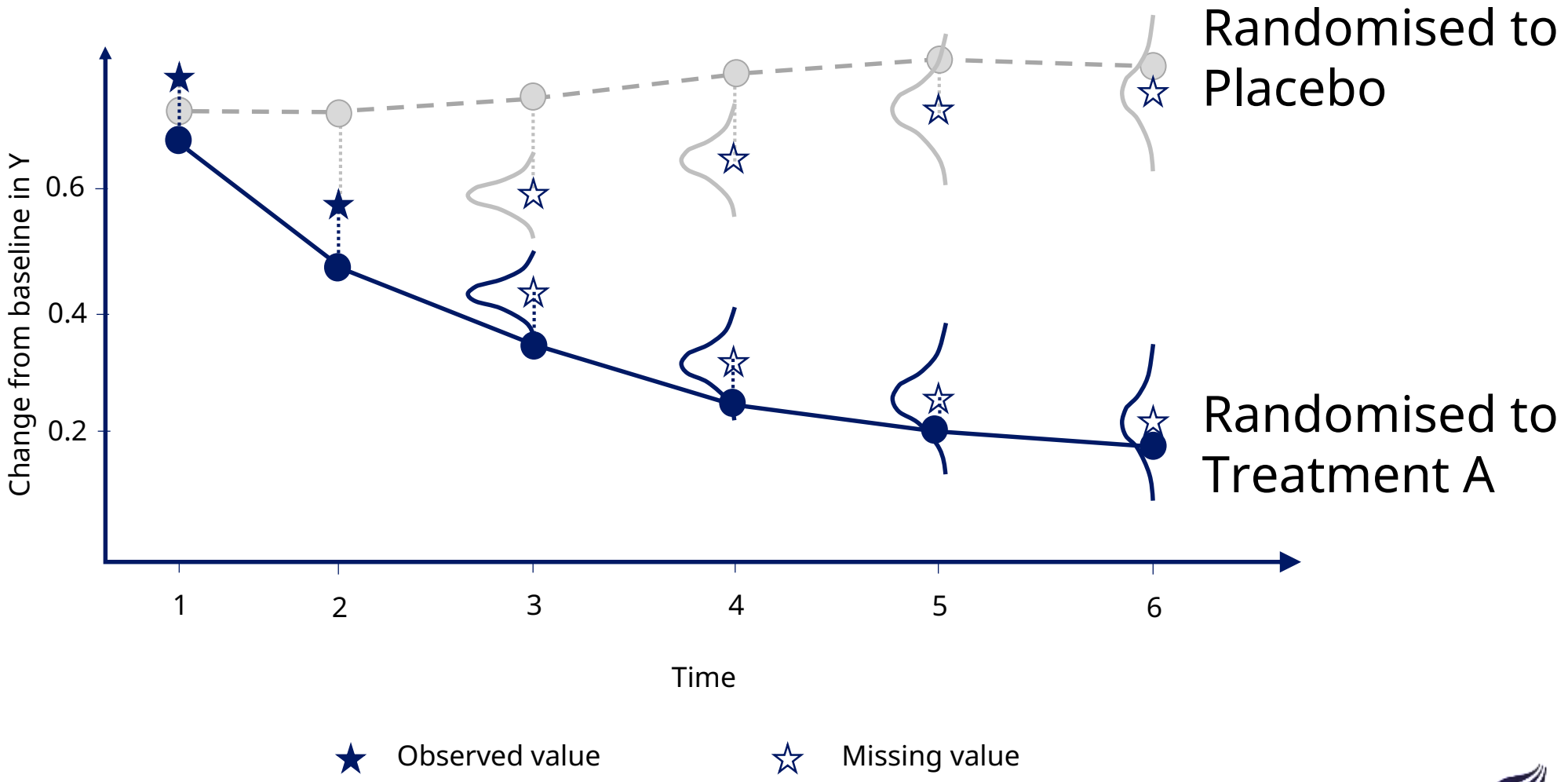
- What is the treatment effect of Treatment A versus placebo on change in Y from baseline to week T in participants with “Disease”, **regardless** of change in background medication and/or premature treatment discontinuation?

- What is the treatment effect of Treatment A versus placebo on change in Y from baseline to week T in participants with “Disease” **as if all participants adhered** to treatment and no rescue treatment was available?

“As if all adhered”



Alternative?



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Retrieved dropouts

- Participants continue in the trial, despite experiencing intercurrent events such as treatment discontination
- Missing values are e.g. imputed from participants in the same treatment arm that have the same treatment status (on/off treatment)

Historical/synthetic controls

Pocock's key criteria for selecting historical data
1976

1. Such a group must have received a precisely defined standard treatment which must be the **same as the treatment for the randomized controls**.
2. The group must have been **part of a recent clinical study** which contained the **same requirements for patient eligibility**.
3. The methods of **treatment evaluation must be the same**.
4. The distributions of **important patient characteristics** in the group should be comparable with those in the new trial.
5. The previous study must have been performed in the **same organization** with largely the same clinical investigators.
6. There must be **no other indications leading one to expect differing results** between the randomized and historical controls

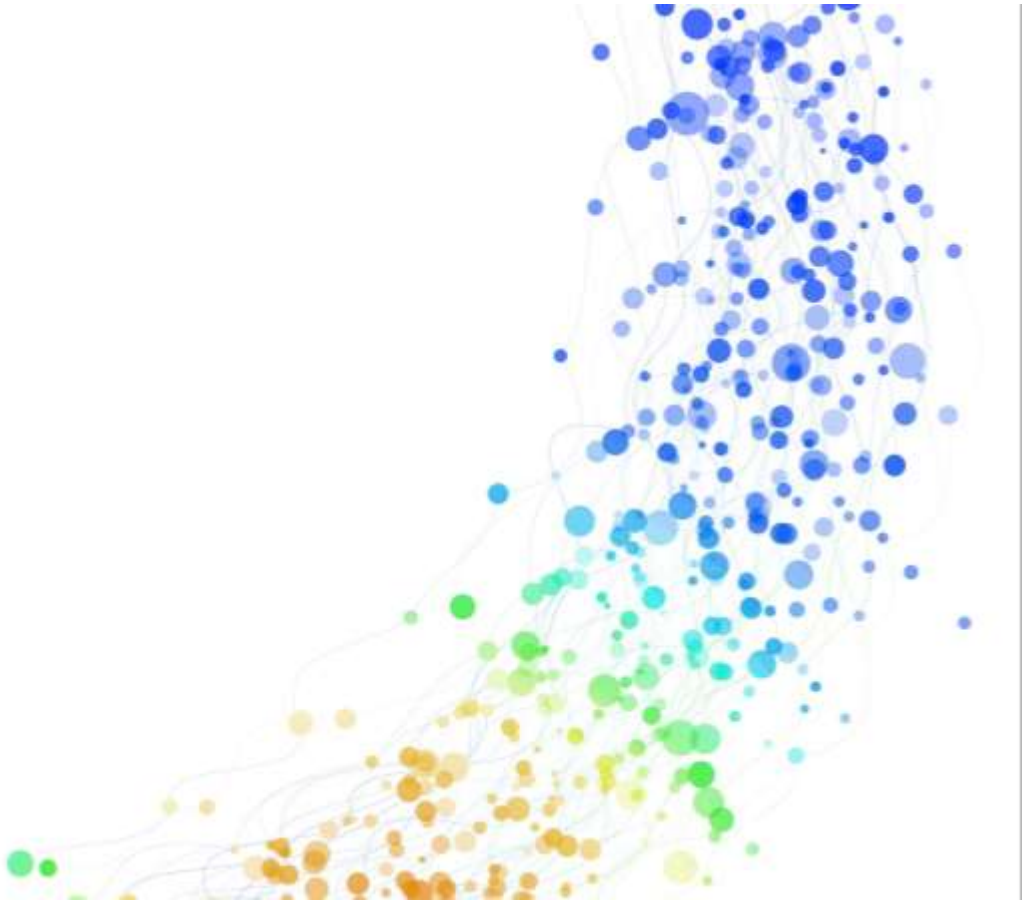
Stuart J. Pocock, The combination of randomized and historical controls in clinical trials, Journal of Chronic Diseases, Volume 29, Issue 3, 1976, Pages 175-188, ISSN 0021-9681, https://doi.org/10.1016/0021-9681(76)90044-8.

Type I error and bias

- Regulatory agencies require control of Type I error rate:

  The risk of concluding the new drug is effective, when it is not

- Non-randomised comparisons may introduce bias
- Methods such as Propensity Score matching may inflate the Type I error rate



Subset of slides presented at
Nordic Congress of Mathematicians, 2023

Increasing the power in randomised clinical trials using digital twins

Emilie Højbjerre-Frandsen

Digital twin

Artificial patient with **same baseline characteristics** as each RCT patients

Patient number	X_1	X_2	X_3	...	X_p
1	M	48	175		75
2	M	34	189		68
3	K	18	165		51
...					

Receives the **control group medication**

Patient number	X_1	X_2	X_3	...	X_p	W
1	M	48	175		75	1
2	M	34	189		68	0
3	K	18	165		51	0
...						

Has a **clinical record,** including the RCT outcome

Patient number	X_1	X_2	X_3	...	X_p	W	Y
1	M	48	175		75	1	4
2	M	34	189		68	0	3
3	K	18	165		51	0	?
...							

Create **prognostic model** *m*

Use **historical data** similar to the current control group to train the model

Patient number	X_1	X_2	X_3	...	X_p	W	Y
1	M	48	175		75	1	4
2	M	34	189		68	0	3
3	K	18	165		51	0	?
...							

The prognostic model predicts outcomes $m(X)$ of digital twins

**Randomised control trial (RCT)*

How the method works

Step 1

- Curate historical data from different sources

Step 2

- Train a prognostic model based on machine learning methods

Step 3

- Evaluate the performance of the prognostic model; **correlation between outcomes and predicted outcomes**

Step 4

- Perform a sample size estimation for the current RCT to estimate

$$ATE = \mathbb{E}[Y(1)] - \mathbb{E}[Y(0)]$$

where $Y(W)$ is the potential outcome under treatment W

- Use the estimated correlation between the outcomes and predicted outcomes on an independent test data set

Step 5

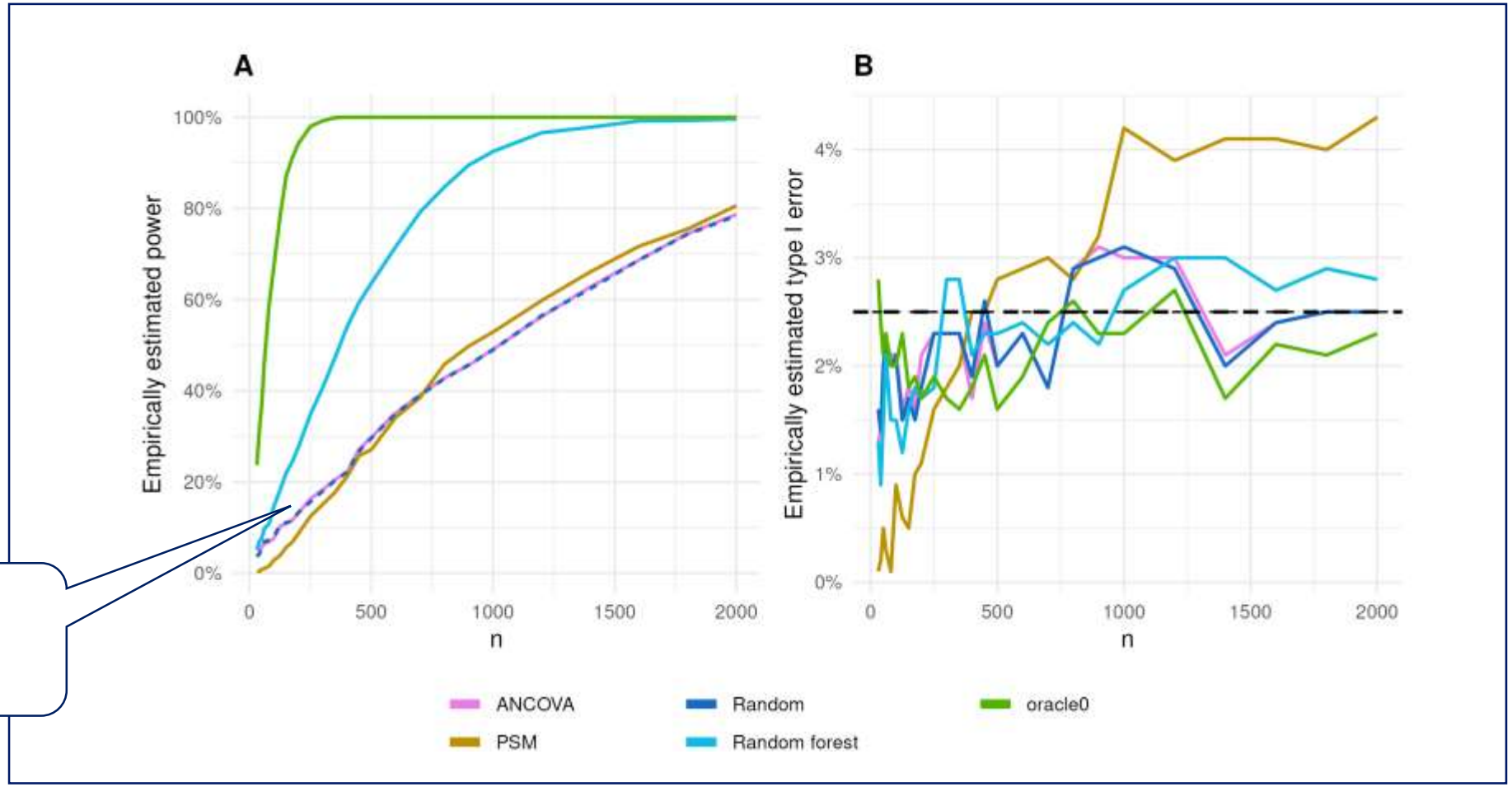
- Use predicted outcome in ANCOVA model

$$Y = ATE \times [treatment] + \beta \times [baseline\ covariates\ ] + \alpha \times [predicted\ outcome] + error$$

- Type I error control
- Under specific requirements $\widehat{ATE_{DT}}$ has the lowest possible assymptotic variance among RAL estimators

**Regular and assymptotically linear (RAL); ATE: Average Treatment Effect; RCT: Randomised Clinical Trial*

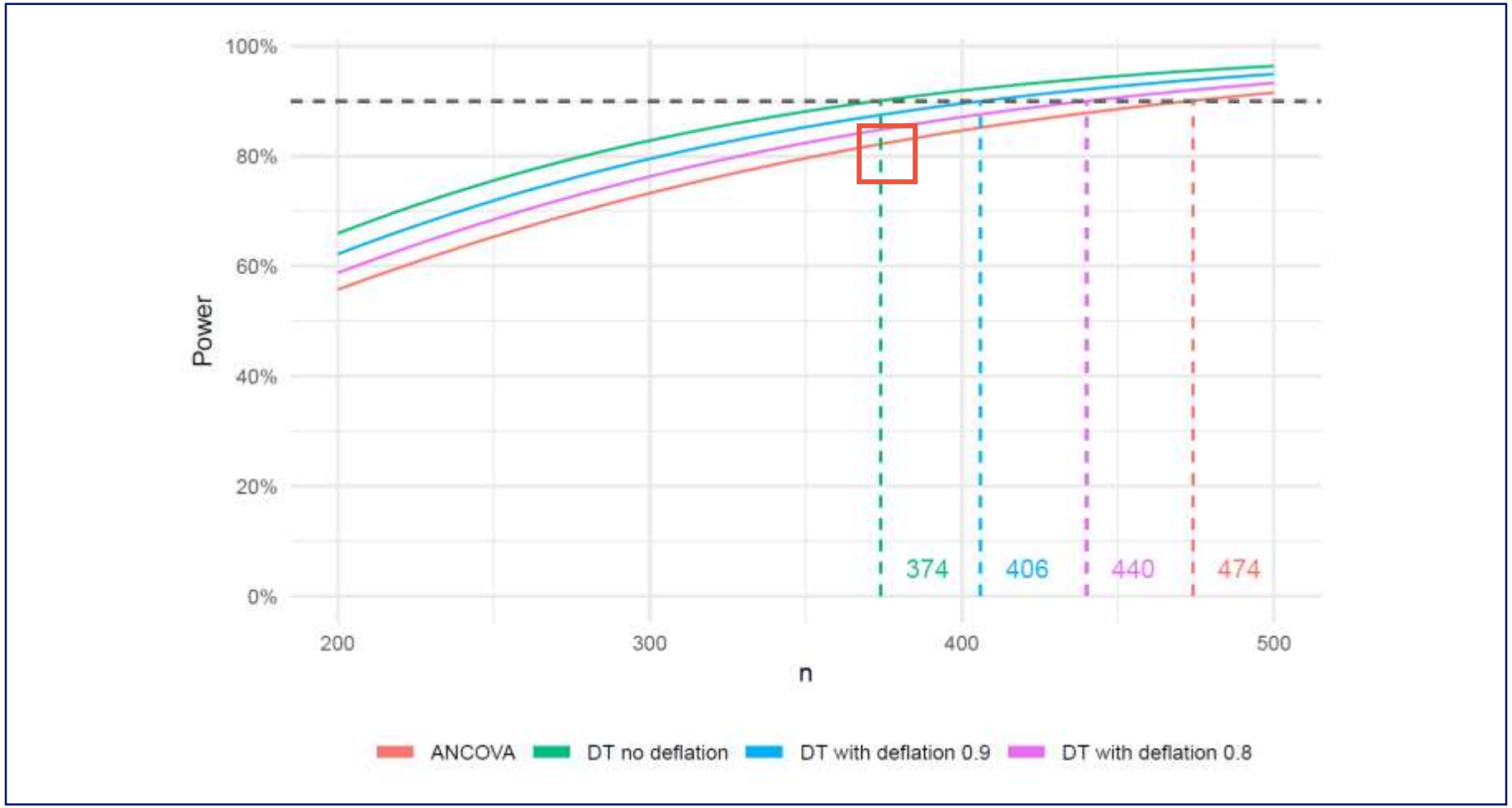
Power and type I error



Robustness property

*Propensity score matching (PSM)
** n is the sample size of the current RCT data, with the historical data amount being n'=5*n
*** Random and Random forest refers two the prognostic model being used to determine the predicted outcomes for each participant and afterwards adjusted for

Required sample size



References

- Schuler A et al. *Increasing the efficiency of randomized trial estimates via linear adjustment for a prognostic score.* The International Journal of Biostatistics. 2021
- NNpackages/PostCard: Package for constructing digital twins (github.com)

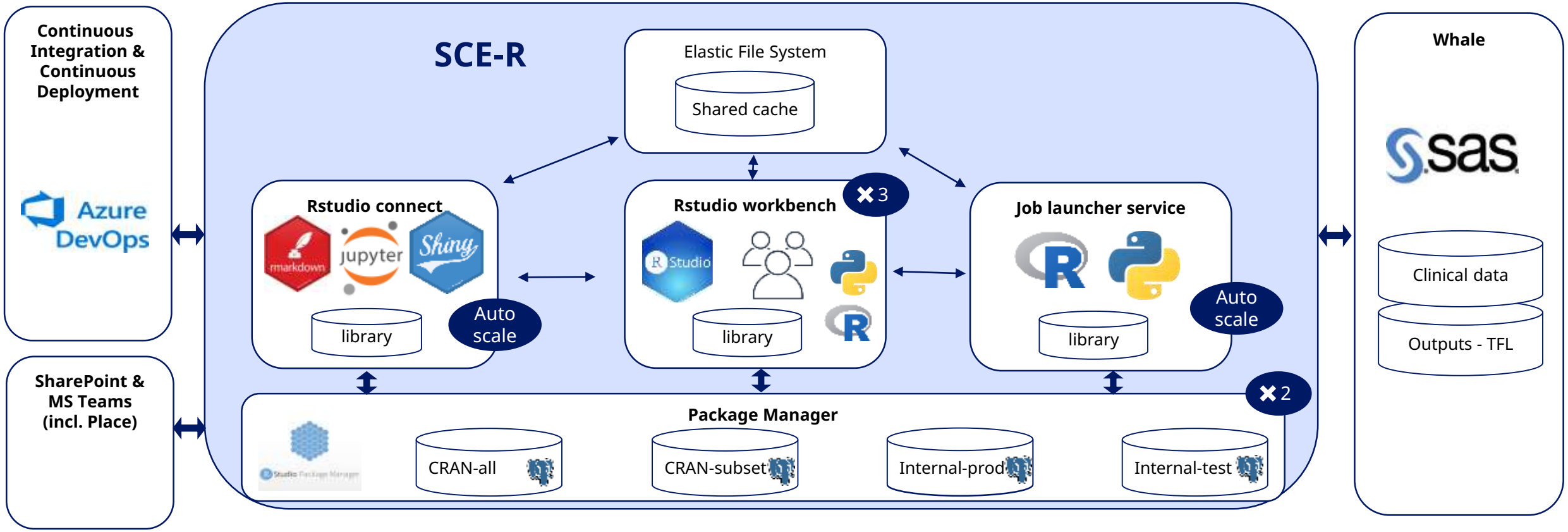
Using R in Novo Nordisk

Regulatory view on using R in pharma

- In 2015, the FDA released a Statistical Software Clarifying Statement. This document states that they do not require the use of any specific software for statistical analyses. But, the FDA requests that software package(s) be documented upon submission. This documentation must include version and build identification.
- In 2020, the European Medicines Agency published a Notice to sponsors on validation and qualification of computerised systems used in clinical trials and the associated Q&A.


My Laptop
RStudio
library
Whale
sas
Clinical data
Outputs - TFL

Current R environment in Novo Nordisk



Tables, Figures and Listings (TFLs)

- (redacted) Clinical study reports from Novo Nordisk available at novonordisk-trials.com

[redacted]
Trial ID: NN1218-3853
Clinical Trial Report
Report body

CONFIDENTIAL

Date: 30 September 2015
Version: 1.0
Status: Final
Page: 237 of 3653

Novo Nordisk

14.1.6 Demographics and baseline characteristics - summary - full analysis set

	[redacted] N	(%)	[redacted] N	(%)	Total N	(%)
Number of subjects	345		344		689	
Age group						
N	345	(100.0)	344	(100.0)	689	(100.0)
18-64 years	241	(69.9)	248	(72.1)	489	(71.0)
>= 65 years	104	(30.1)	96	(27.9)	200	(29.0)
BMI group						
N	345	(100.0)	344	(100.0)	689	(100.0)
18.5 - 24.9 kg/m2	32	(9.3)	36	(10.5)	68	(9.9)
25.0 - 29.9 kg/m2	109	(31.6)	108	(31.4)	217	(31.5)
>= 30.0 kg/m2	204	(59.1)	200	(58.1)	404	(58.6)
Sex						
N	345	(100.0)	344	(100.0)	689	(100.0)
Female	182	(52.8)	171	(49.7)	353	(51.2)
Male	163	(47.2)	173	(50.3)	336	(48.8)
Country of residence						
N	345	(100.0)	344	(100.0)	689	(100.0)
Canada	8	(2.3)	15	(4.4)	23	(3.3)
Croatia	7	(2.0)	9	(2.6)	16	(2.3)
India	36	(10.4)	38	(11.0)	74	(10.7)
Israel	14	(4.1)	20	(5.8)	34	(4.9)
Russia	50	(14.5)	57	(16.6)	107	(15.5)
Serbia	45	(13.0)	50	(14.5)	95	(13.8)
Slovakia	30	(8.7)	24	(7.0)	54	(7.8)
United Kingdom	11	(3.2)	13	(3.8)	24	(3.5)
United States	144	(41.7)	118	(34.3)	262	(38.0)
Ethnicity						
N	345	(100.0)	344	(100.0)	689	(100.0)
Hispanic or latino	26	(7.5)	18	(5.2)	44	(6.4)
Not hispanic or latino	319	(92.5)	326	(94.8)	645	(93.6)
Race						
N	345	(100.0)	344	(100.0)	689	(100.0)
White	277	(80.3)	281	(81.7)	558	(81.0)
Asian	45	(13.0)	42	(12.2)	87	(12.6)
Black or african american	22	(6.4)	18	(5.2)	40	(5.8)
American indian or alaska native	3	(0.9)	0		3	(0.4)
Native hawaiian or other pacific islander	2	(0.6)	0		2	(0.3)
Other	1	(0.3)	3	(0.9)	4	(0.6)
Smoking						
N	345	(100.0)	344	(100.0)	689	(100.0)
Current smoker	37	(10.7)	48	(14.0)	85	(12.3)
Never smoked	224	(64.9)	226	(65.7)	450	(65.3)
Previous smoker	83	(24.1)	70	(20.3)	153	(22.2)
Missing	1	(0.3)	0		1	(0.1)

N: Number of subjects, %: Percentage of subjects, BMI: Body mass index
Baseline is at randomisation (Visit 10 - Week 0).

nn1218/nn1218-3853/er_20150831_ctr_er
05SEP2015:13:48:30 - t_demo_fas.sas/t_demog_Researcher_fas.txt

[redacted]
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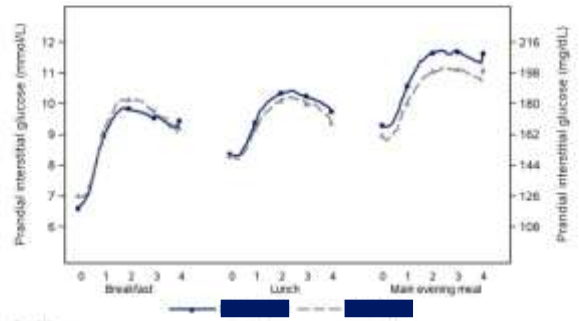

14.2.192 Prandial interstitial glucose profile at treatment week 0 - mean plot - full analysis set

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2022

Ari Siggaard Knoph • 1.
International Lead Programmer | Statistical Programming Specialist hos Nov...
4md. •

This week has been very special for my team at Novo Nordisk!

For the first time ever in NN we were able to present results from a trial where all tables, listings and figures were developed using R. To take it one step further we also were able to render nice looking slides for presentation of results from our R output objects without the error-prone CTRL+C/CTRL+V of tables and figures.

So proud of this achievement which has been years in the making requiring the expertise of many people.

Next step: The moon! 🚀

#rstats #rpharma #rforclinicalreporting #pharma

Se oversættelse

308 33 kommentarer

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Journey to an R-based FDA Submission

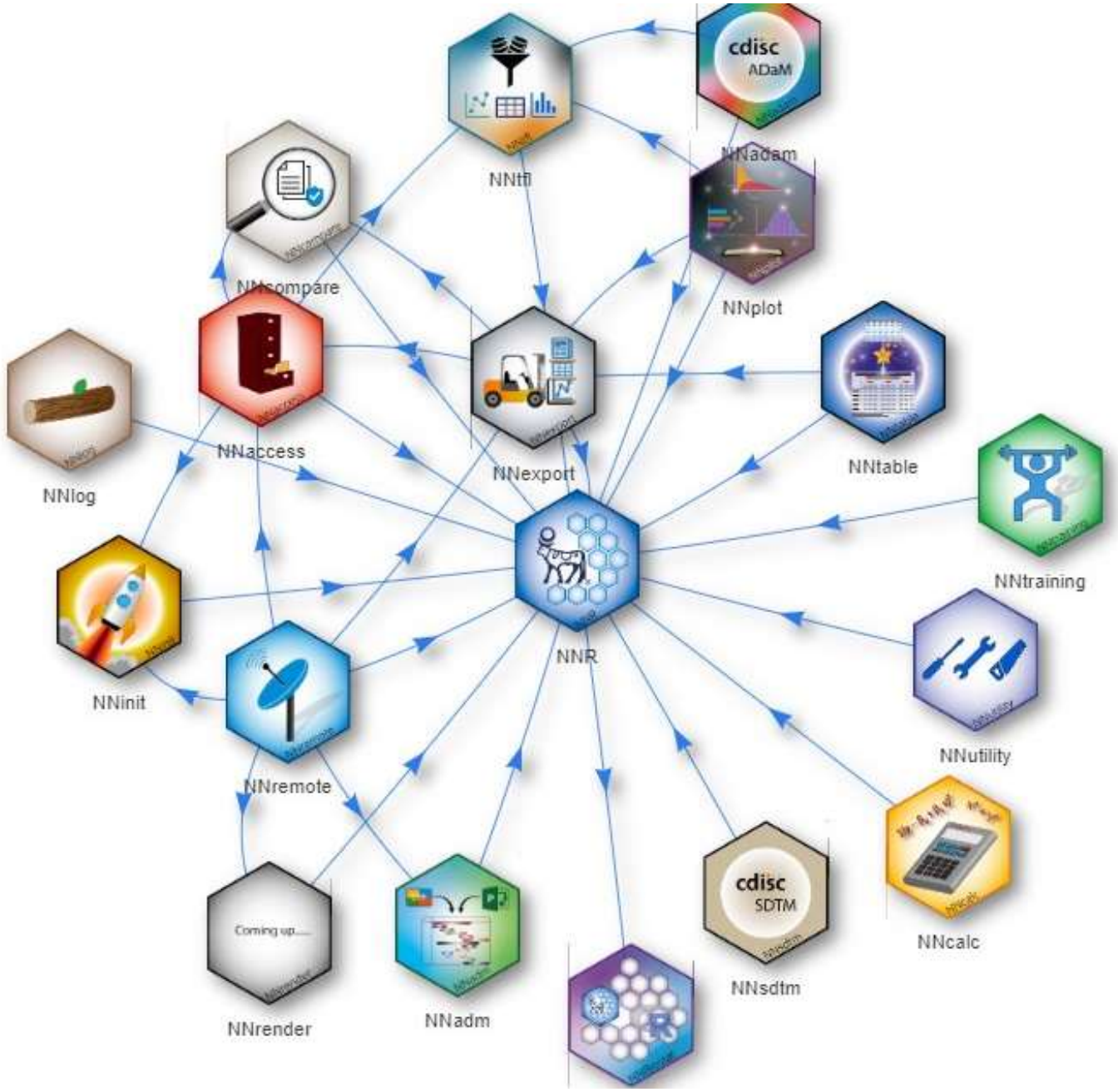
Available on youtube

>8000 views

Recent interaction with FDA

Question 5: Does the Agency accept that the software package R is used for programming of all statistical analyses and outputs?

FDA Response to Question 5:
This proposal is acceptable. Please submit the R code for the analysis.



Internally developed R packages

- Modular
- Github (MIT licence)
  - Integrate into pharmaverse
- Quality checks
- R package developers team

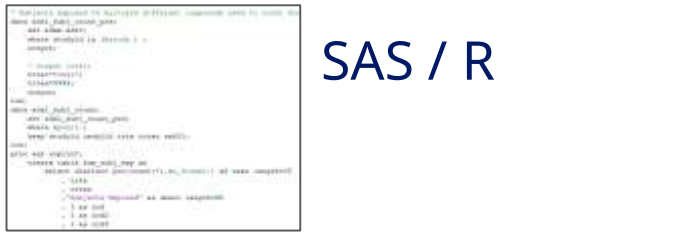
- `riskmetric` package for assessing ”package quality”
- R validation hub (www.pharmar.org/)

The peer programming process at Novo Nordisk

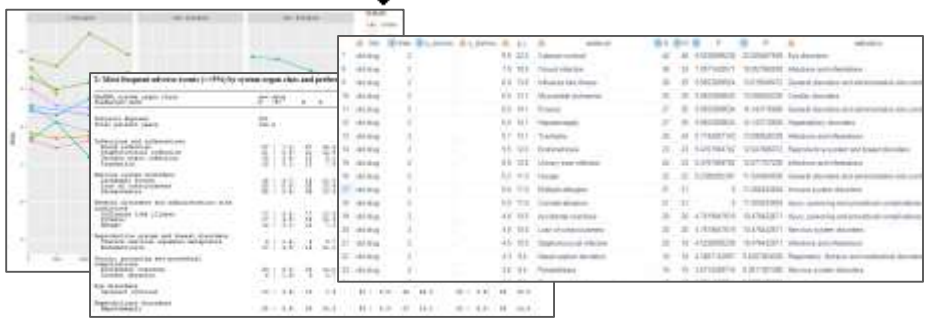
Programmer

Task

Reviewer

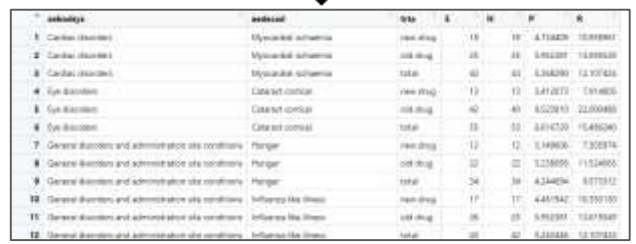


SAS / R



Compare the results by e.g. using NNcompare

SAS / R



NNcompare: An R package supporting the peer programming process in clinical studies
M.Bendtsen,S. Falgreen Larsen, F. Heinen, C. Dethlefsen, useR-2021

Future

- Co-existence of SAS, R and other languages
- Enable user to pick the ‘right tool for the job’
- Training and knowledge sharing through self-learning platform
- Dynamic and interactive tables, figures and listings

Discrepancies SAS / R

```
#Example code
> my_number <-c(2.2,3.99,1.2345,7.876,13.8739)
> round(my_number, digits=3);
[1]  2.200  3.990  1.234  7.876 13.874
```

my_number	r_3_dec
2.2	2.2
3.99	3.99
1.2345	**1.235**
7.876	7.876
13.8739	13.874

CAMIS pr

- CAMIS - A PHU
- Map discrepan
- Understand th

Methods		R	SAS	Python	Comparison
Summary Statistics	Rounding	R	SAS	Python	R vs SAS
	Summary statistics	R	SAS	Python	R vs SAS
	Skewness/Kurtosis	R	SAS		R vs SAS
General Linear Models	One Sample t-test	R	SAS	Python	R vs SAS
	Paired t-test	R	SAS	Python	R vs SAS
	Two Sample t-test	R	SAS	Python	R vs SAS
	ANOVA	R	SAS		R vs SAS
	ANCOVA	R	SAS		R vs SAS
	MANOVA	R	SAS		R vs SAS
	Linear Regression	R	SAS		R vs SAS
Generalized Linear Models	Logistic Regression	R	SAS		
	Poisson/Negative Binomial Regression	R			
	Categorical Repeated Measures				
	Categorical Multiple Imputation				
Non-parametric Analysis	Wilcoxon signed rank				
	Mann-Whitney U/Wilcoxon rank sum	R			
	Kolmogorov-Smirnov test				
	Kruskall-Wallis test	R	SAS		R vs SAS
	Friedman test				
	Jonckheere test				

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Learn more

about working in Novo Nordisk Biostatistics

CHRISTINE BENNETT, LINE QUIST BENDTSEN,
HANI YASSIN & LISA OLSEN
Clinical Drug Development
Development
Denmark