Non-Interventional Studies

building and broadening the value story

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iba Institute of Biostatistics and Analyses

SPARK Europe Webinar Series FALL 2022 | 7th September 2022 | 4 – 5 pm (CET) | Online Webinar

Who we are?

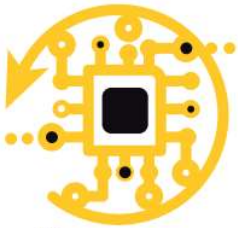
..::Masaryk University spin-off

Who we are?

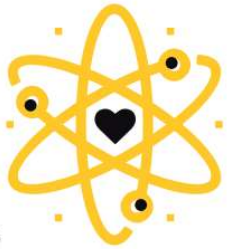
..::Masaryk University spin-off

data management

data analysis



information technologies



project management

Why should you be bothered with NIS?

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

improve drug development
&
clarify the value of new therapies.

Outline

- NIS within the scheme of clinical research phases
- Lifecycle of NIS
- Tools & people behind NIS
- EDC system and how it can facilitate a clinical research project

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- NIS criteria and rules
- Regulatory issues
- System validation
- System must-haves and nice-to-haves

- Recap: advantages of NIS against other types of studies
- Q/A session

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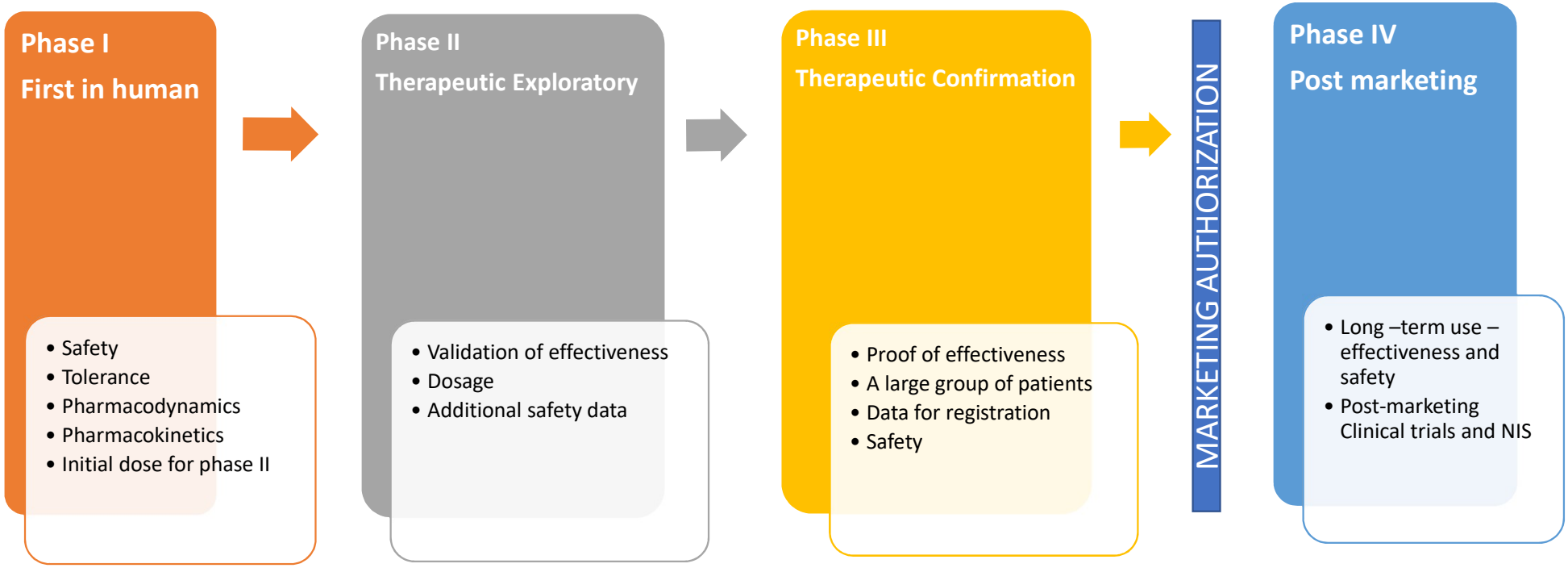
NIS

…and its position in the sequence of clinical research phases

NIS within the scheme of clinical research phases



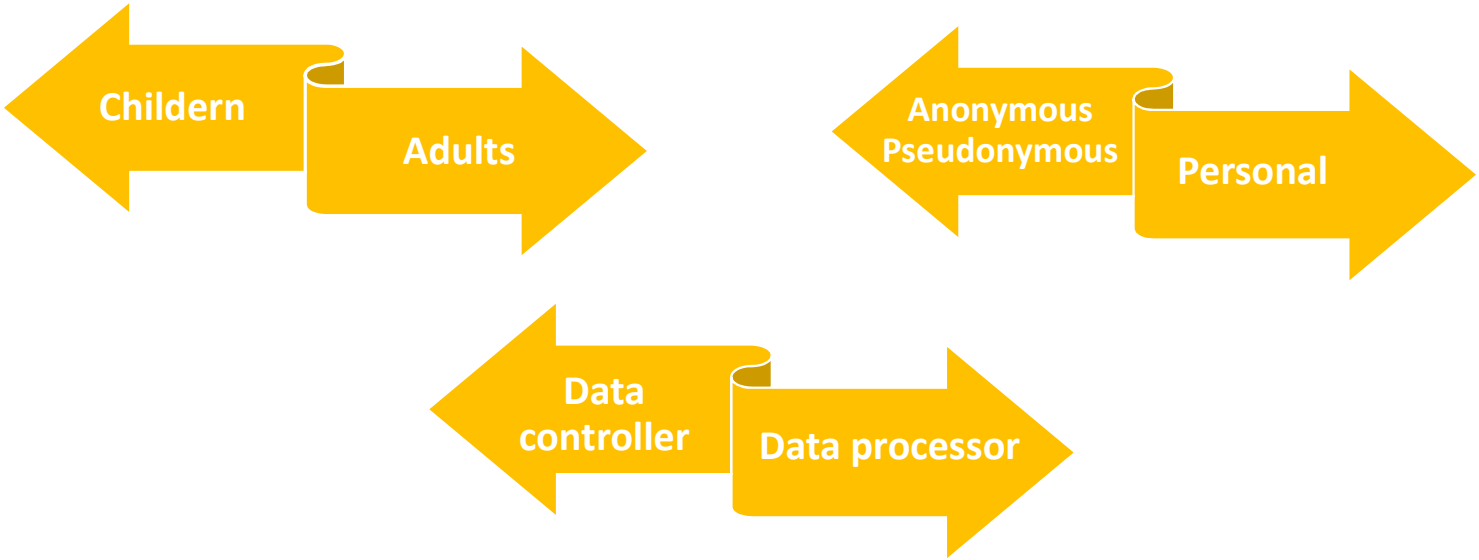
Lifecycle of NIS: purpose, design, criteria…

- Why should we perform a NIS or a secondary data analysis? What is their **purpose**?
- What **design** should we choose for NIS or secondary data analysis?
- What are the **criteria** qualifying a research project as a NIS?
- Can be effectiveness and safety of a product derived from a NIS?

Lifecycle of NIS: Initiation – patients enrolment

ICF – Informed consent form

- Ethical rules, Declaration of Helsinki and GCP ICH E6
- Consent with data protection rules



Course of the study

- ✓ Application of GCP rules
- ✓ Good Documentation practice
- ✓ Data quality
- ✓ EDC system

Study termination and out comes

- Final study report
- Publication
- Results disemination
- Change of SmPC, guidelines, market access, reimbursement,….

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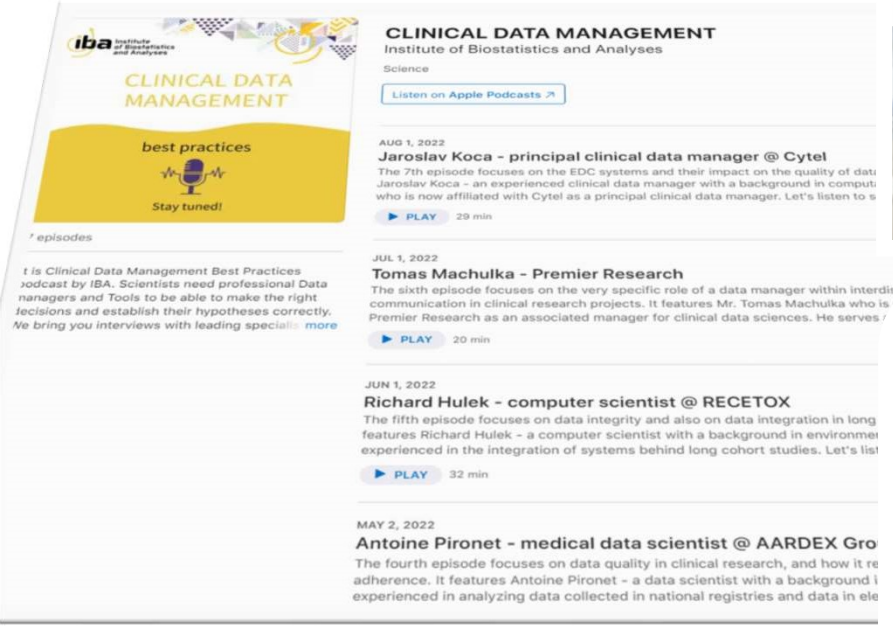
Tools vs. people

What is more important?

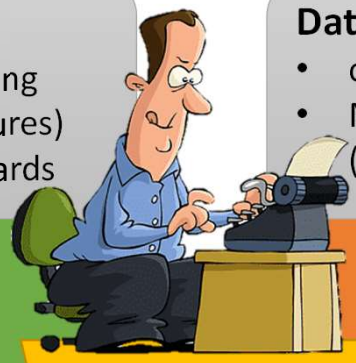
Tools vs. people ::: what is more important?



PEOPLE behind data-driven clinical research

Business Intelligence
- data collection (eCRF development including validation, calculation & skip logic procedures)
- data analysis through reports and dashboards

Data Mining
- correlation, prediction
- ML/AI techniques (classification, detection, text mining)



Data Management
- data collection settings
- transformation of structured data into scalable data warehouse

Data Science
- modeling (pattern recognition)
- causality (cause-and-effect)
- validation (goodness of fit)

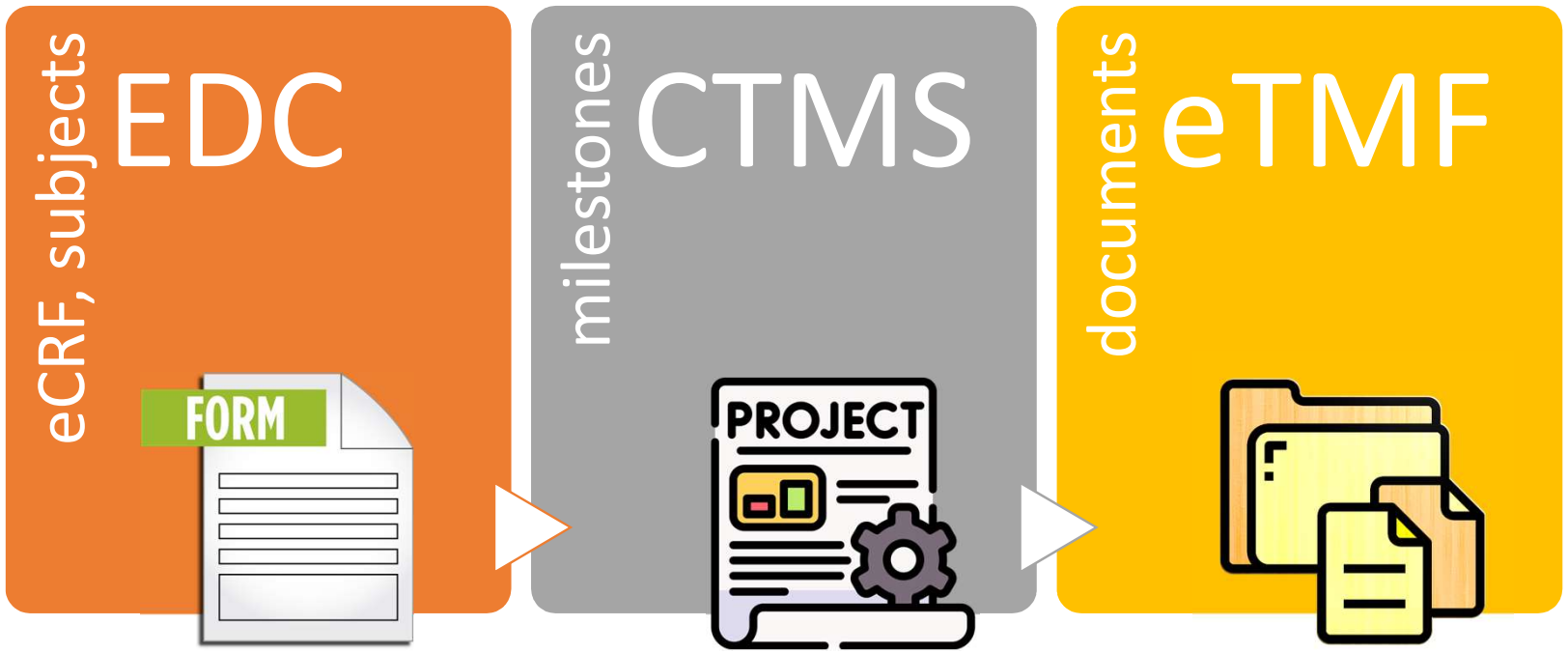
Data Quality

Data Integrity

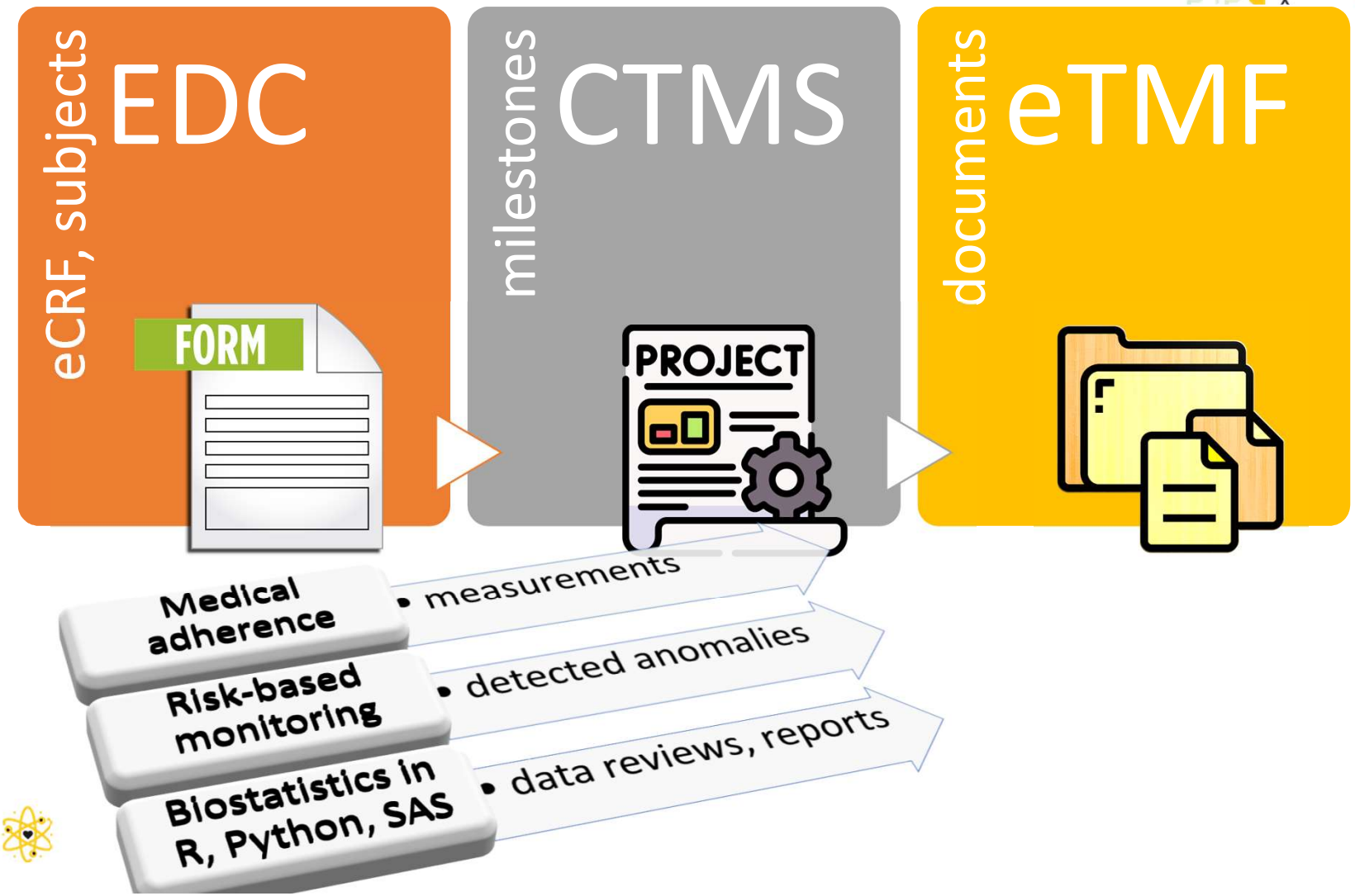
Data Insights

Data & SW Engineering
- EDC system
- Data warehouse

TOOLS for achieving good quality of data



Additional TOOLS for achieving good quality of data



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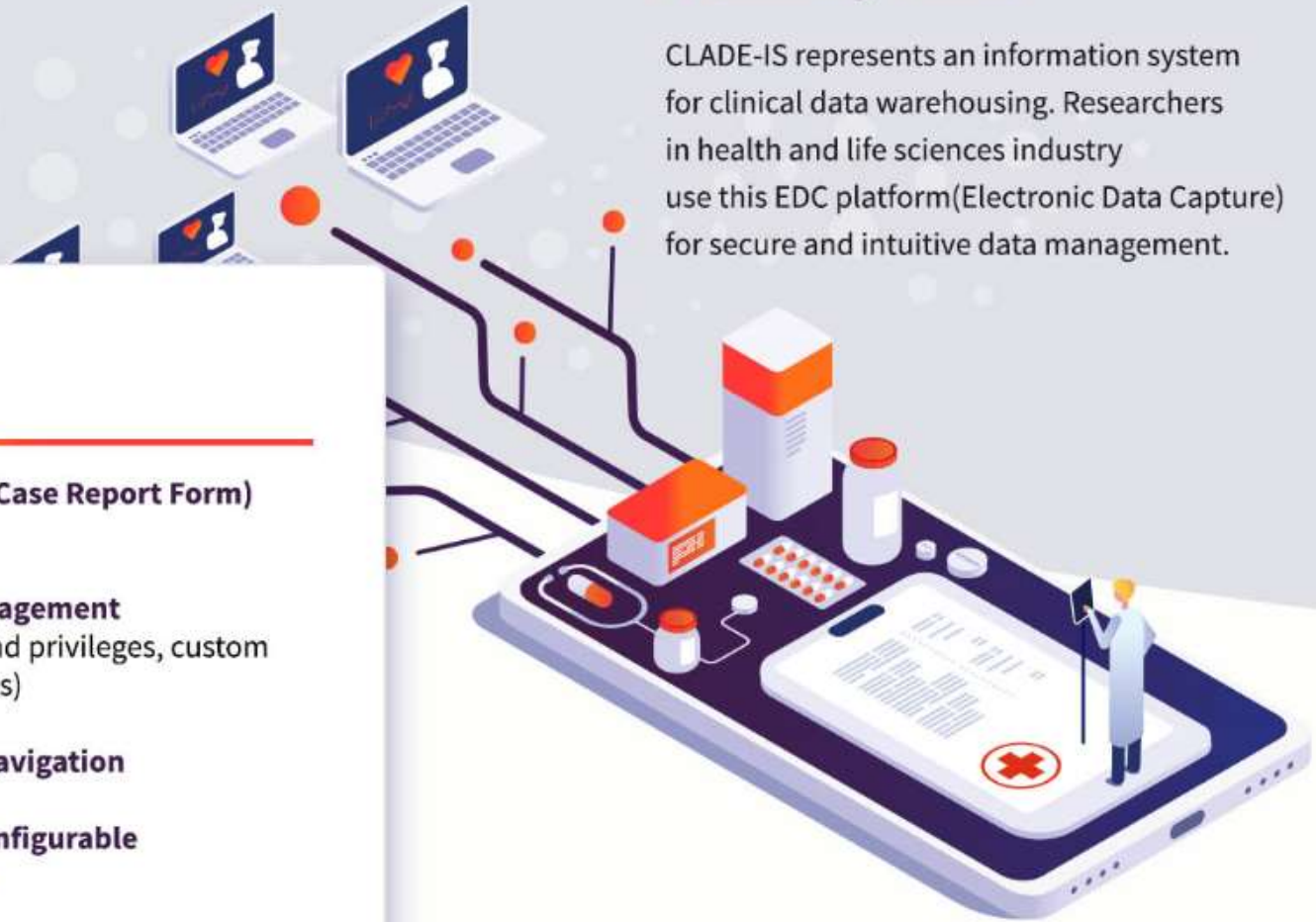
Electronic Data Capture

How can a good EDC system facilitate a clinical research project?

CLADE-IS
CLINICAL DATAWAREHOUSE

Healthy data

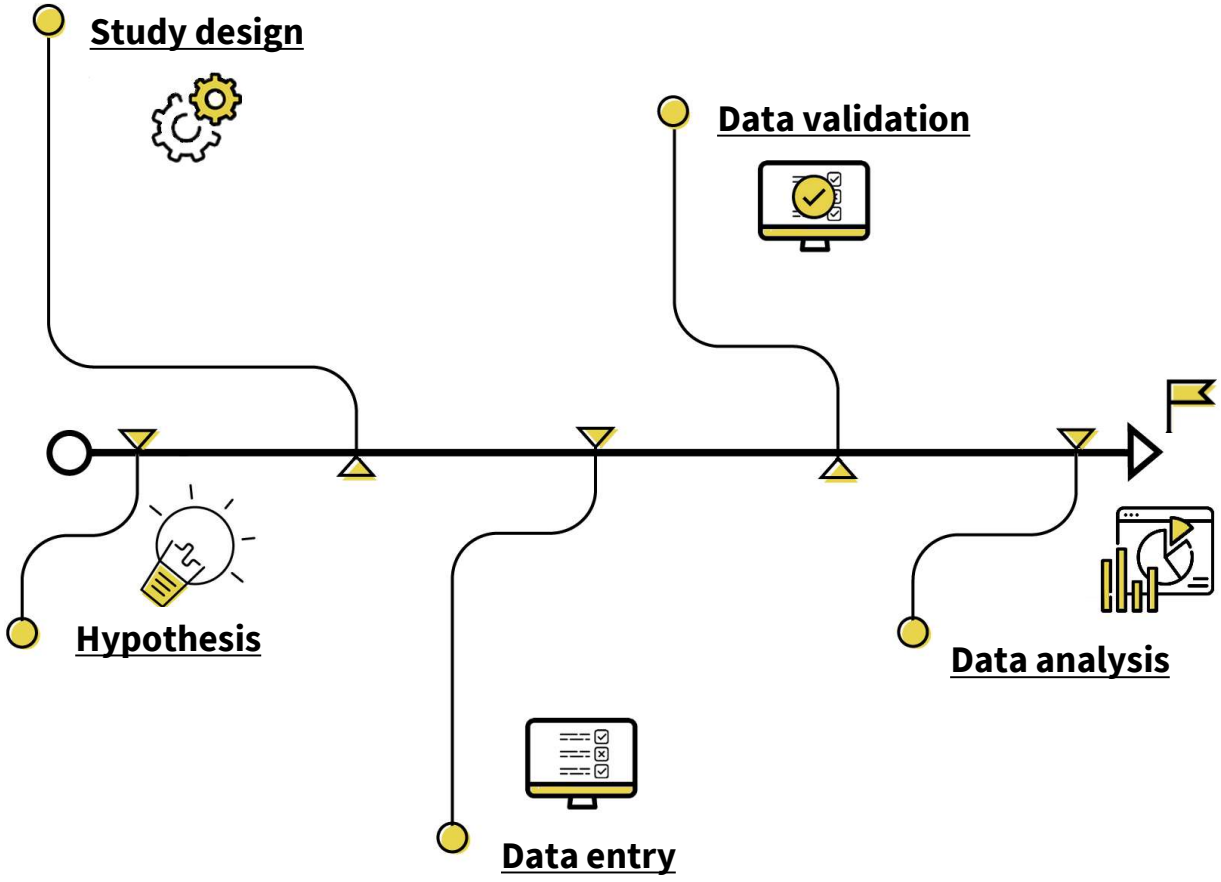
CLADE-IS represents an information system for clinical data warehousing. Researchers in health and life sciences industry use this EDC platform(Electronic Data Capture) for secure and intuitive data management.



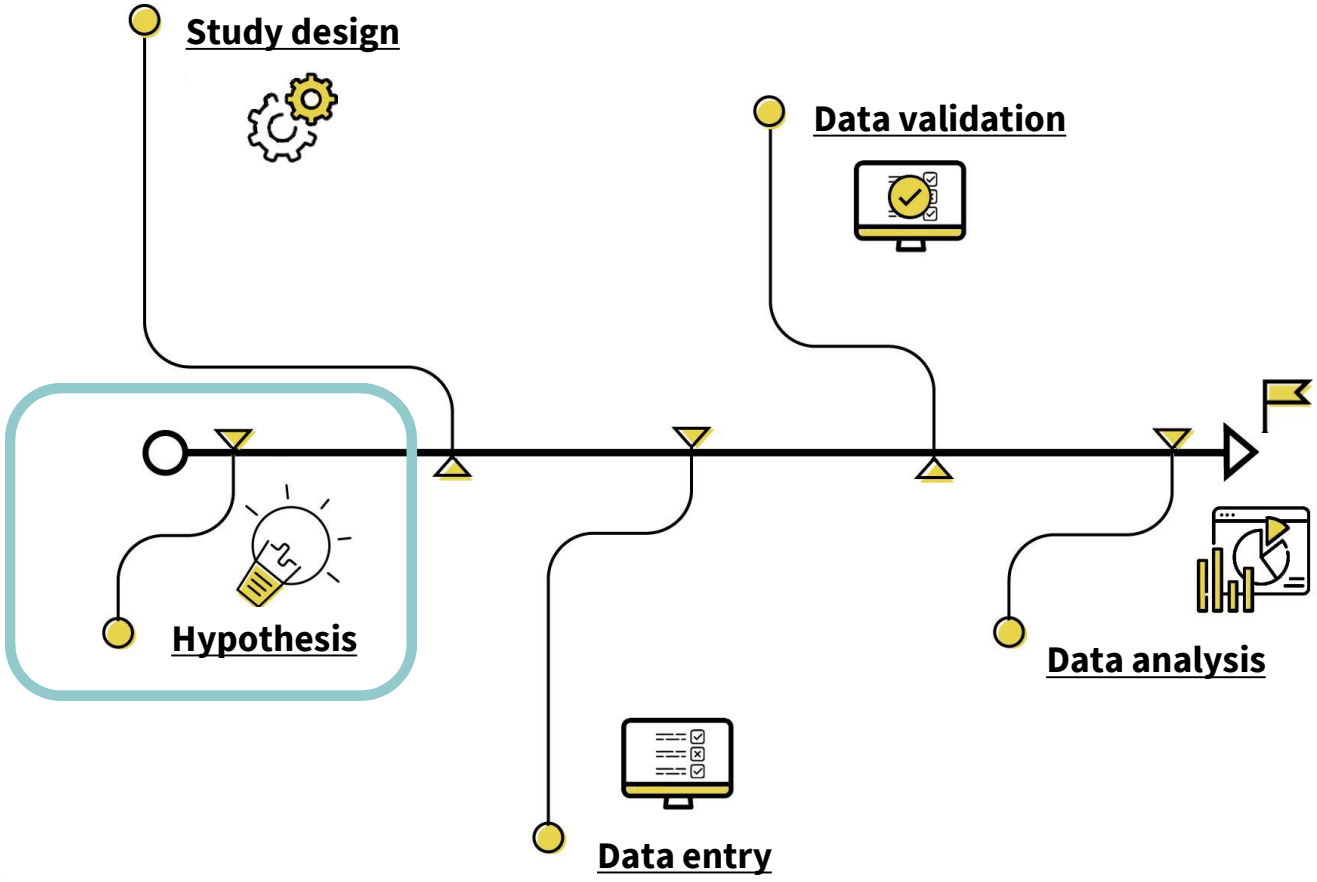
Features

- **Robust eCRF (electronic Case Report Form) design**
- **Flexible data access management** (configurable user roles and privileges, custom definitions of form statuses)
- **Easy & ergonomic user navigation**
- **Data insights through configurable dashboards and reports**

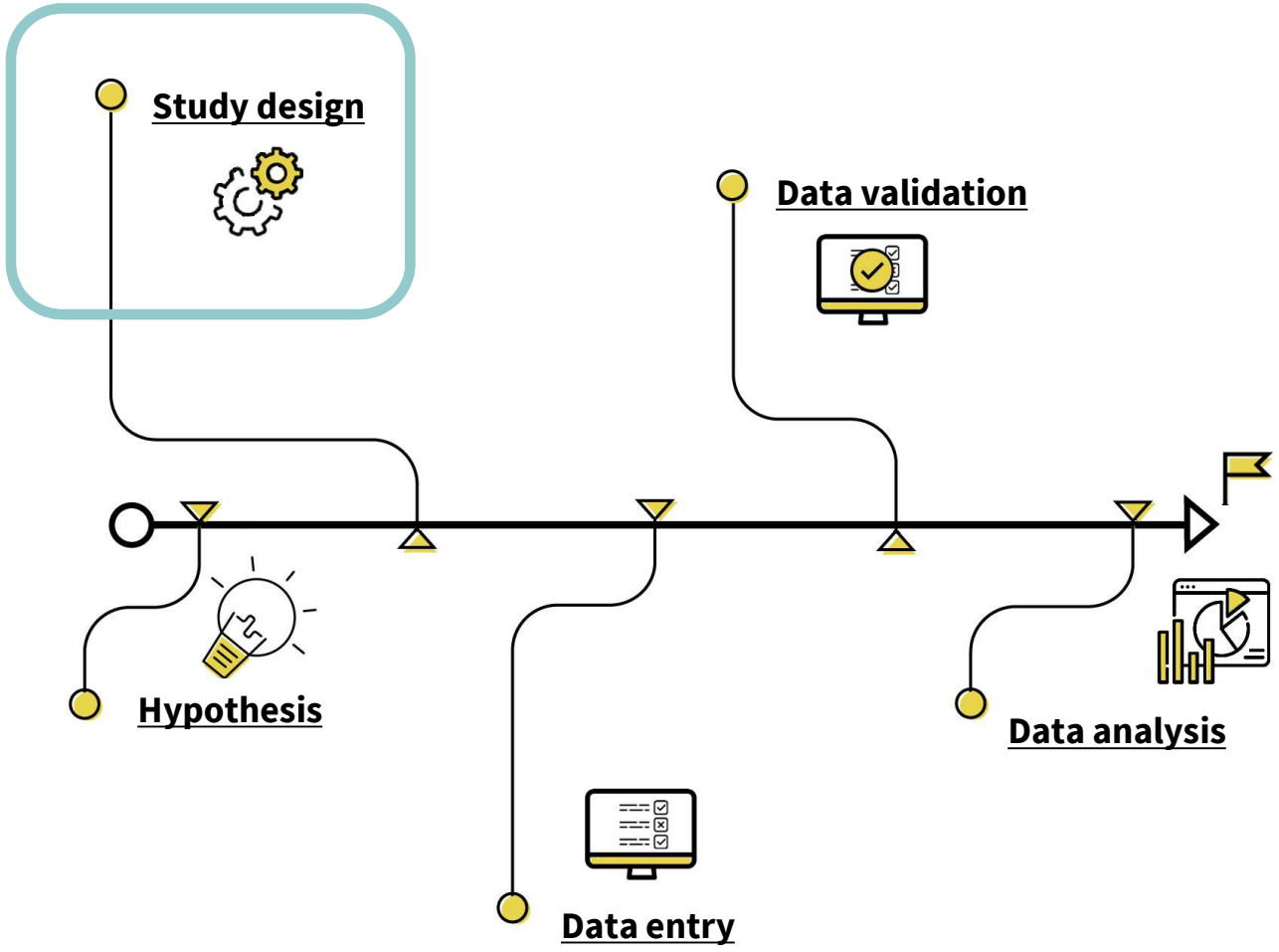
From a hypothesis to an outcome



From a hypothesis to an outcome

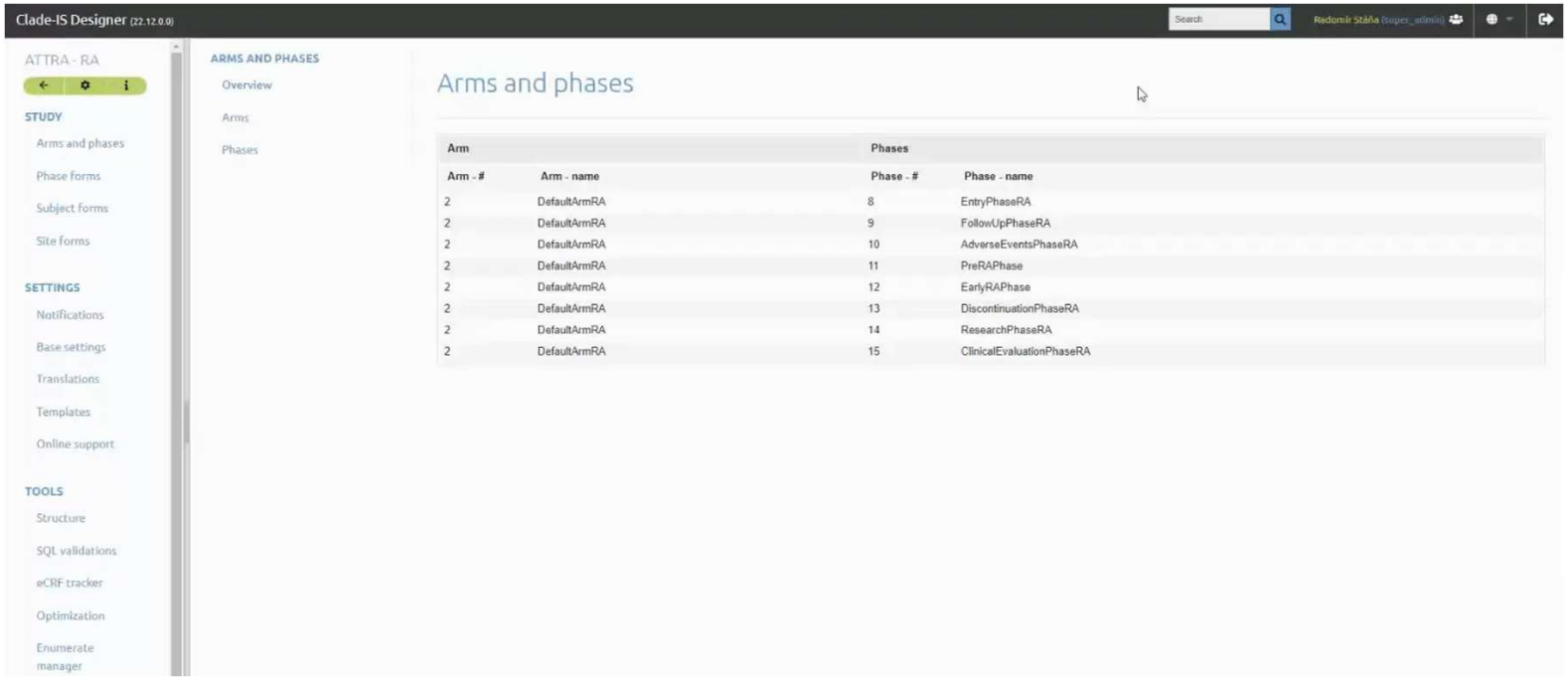


From a hypothesis to an outcome



Study design

Robust structure entities

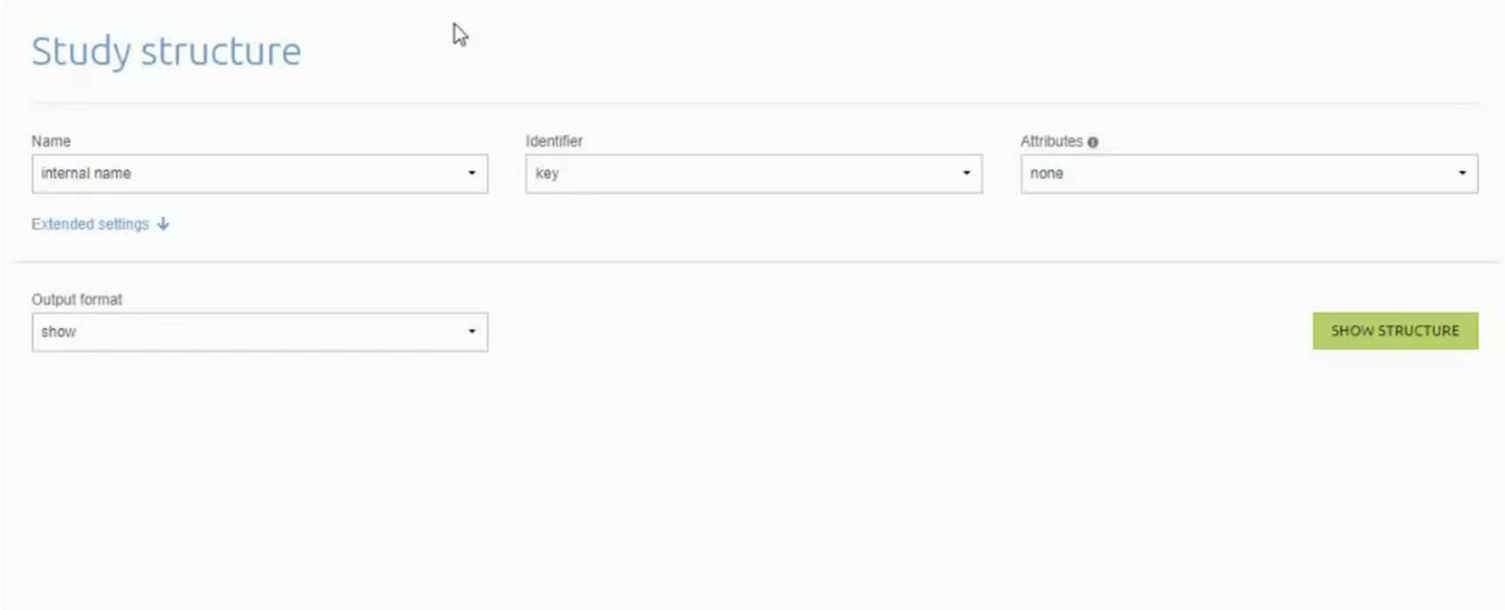


Who: Data manager

Where: Designer

Study design

Study structure export



Study structure

DEMO

Study structure generated: 2022-09-06

Structure of patient form

- PatientFormRA | **[16]**

  [max. instancies count - 1]
  - PatientDetails | **[116]**

    []
    - InformedConsentGDPR | [2687]

      Discrete value - select box [mandatory]
      - Yes | [710]
      - NoButWillBeObtained | [711]
      - NoPatientDead | [712]
      - NoPatientLostFromFollowUp | [713]
    - DateOfInformedConsentGDPR | [2688]

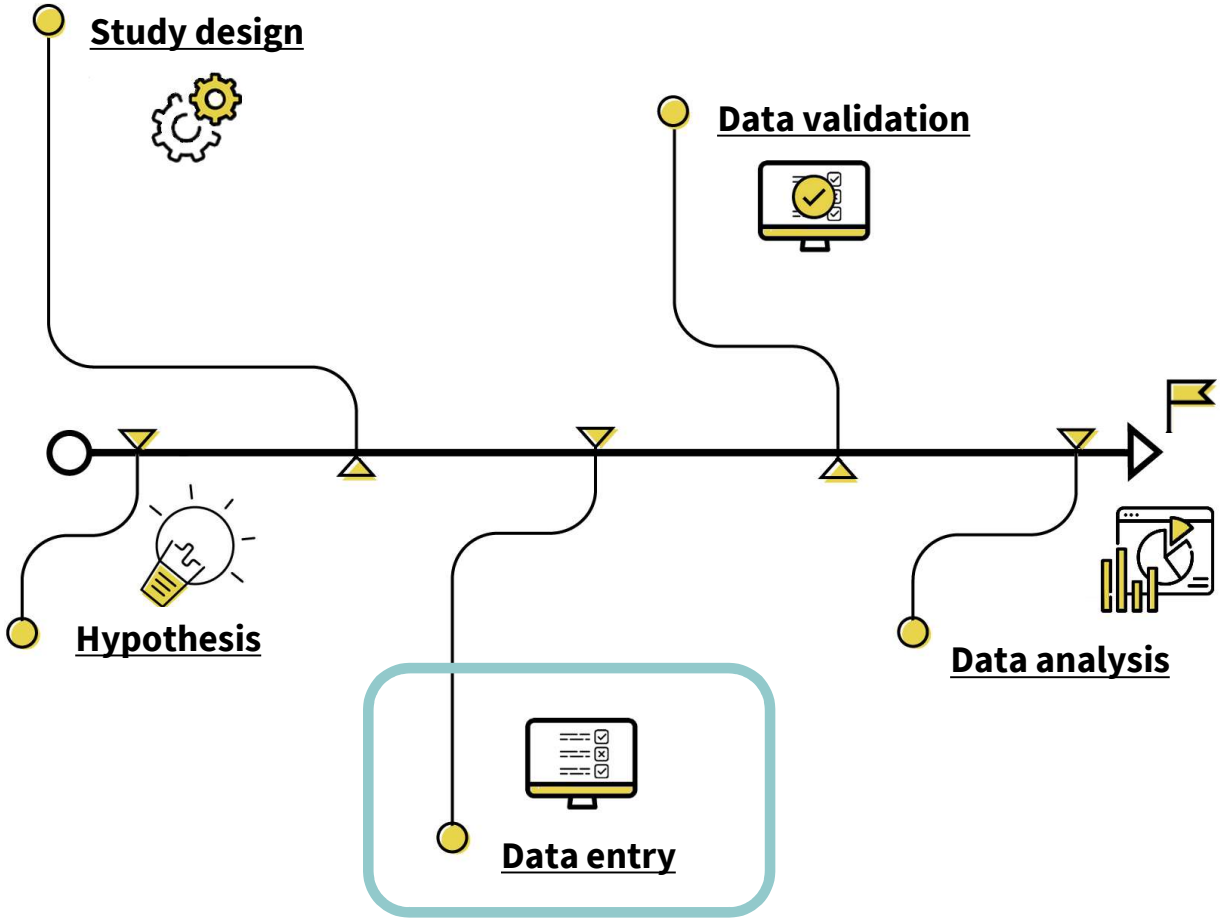
      Date - calendar
    - DateOfBirth | [799]

      Date - calendar [mandatory]
    - Sex | [800]

      Discrete value - select box [mandatory]
      - Male | [9]
      - Female | [10]
    - Initials | [801]

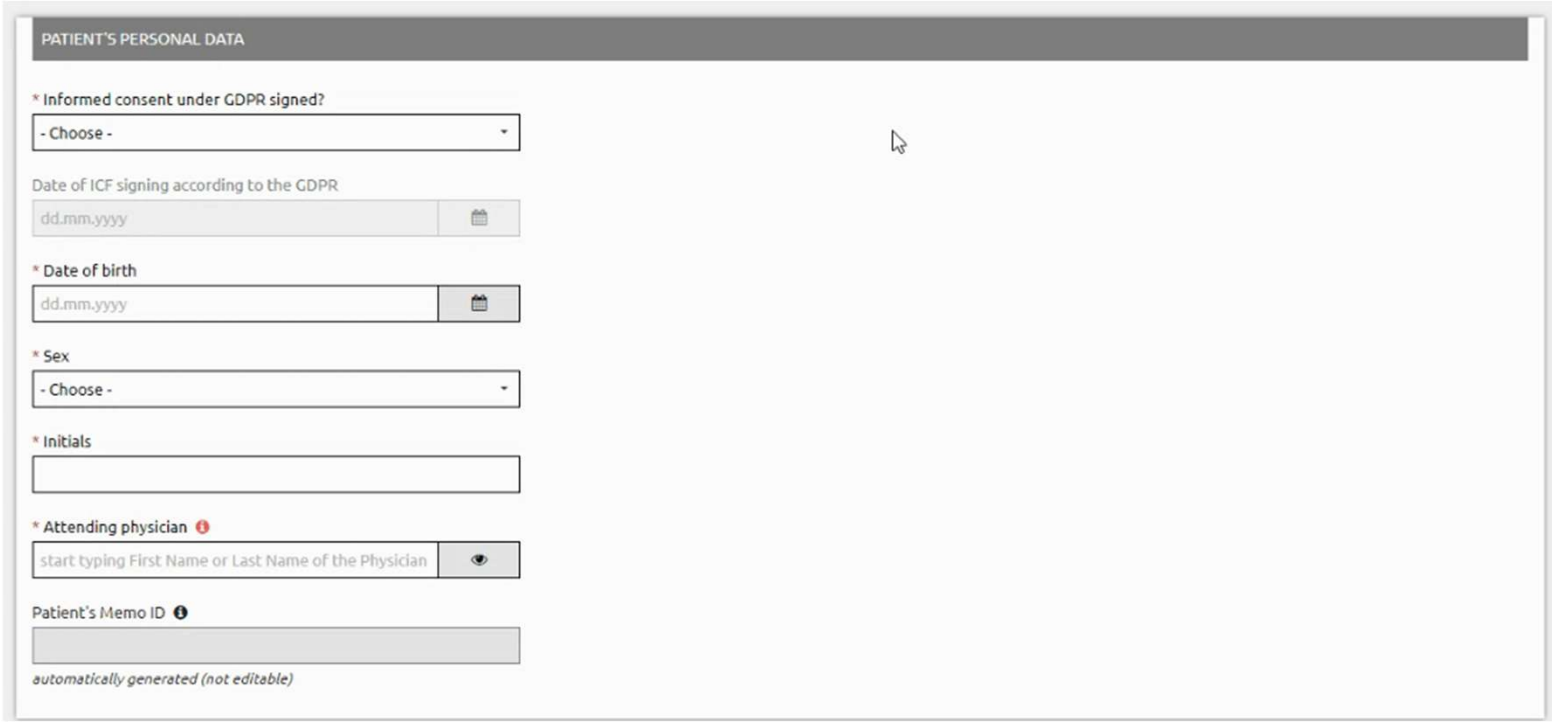
      Short text - long text [mandatory]
    - ResponsiblePhysician | [1317]

From a hypothesis to an outcome



Data entry

Create and edit forms



Who: Healthcare professional

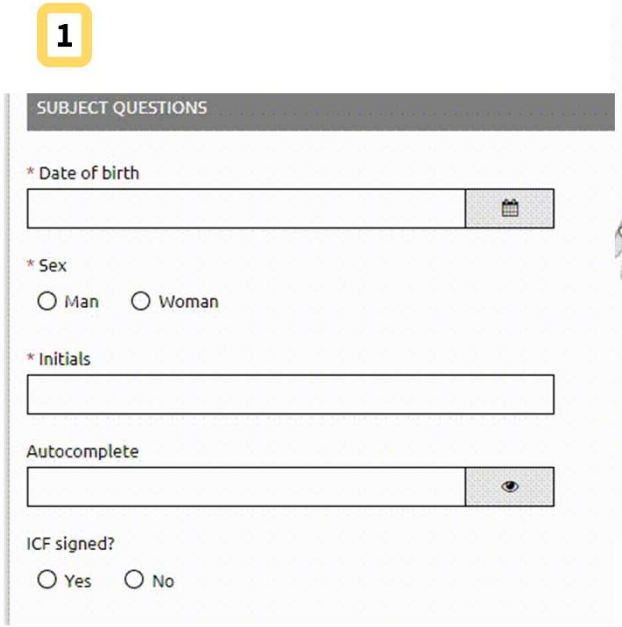
Where: Study

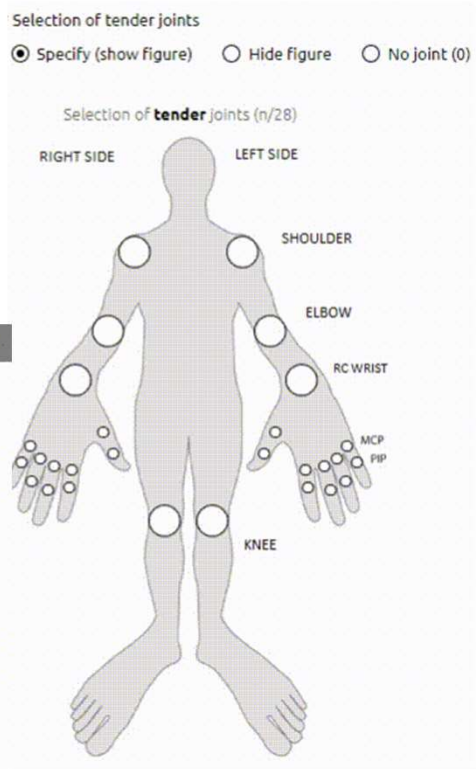
Data entry

Data entry – UX features

Wide range of data types and question settings

- text - short text, long text
- date – date and time, date, time
- selectbox – enumerate, codebook
- number - integer, real
- yes / no
- file
- button
- heading text
- json
- … other (custom)





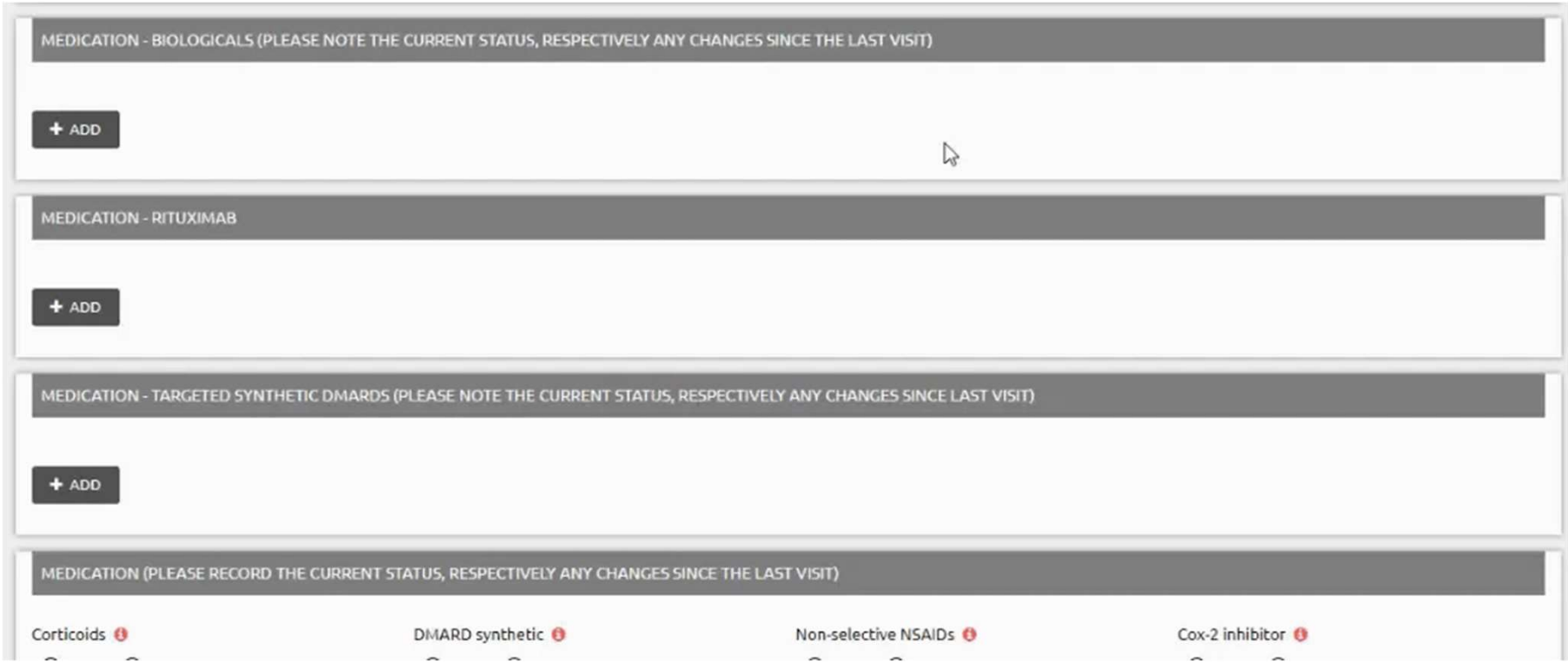
Who: Data manager

Where: Designer

Study design

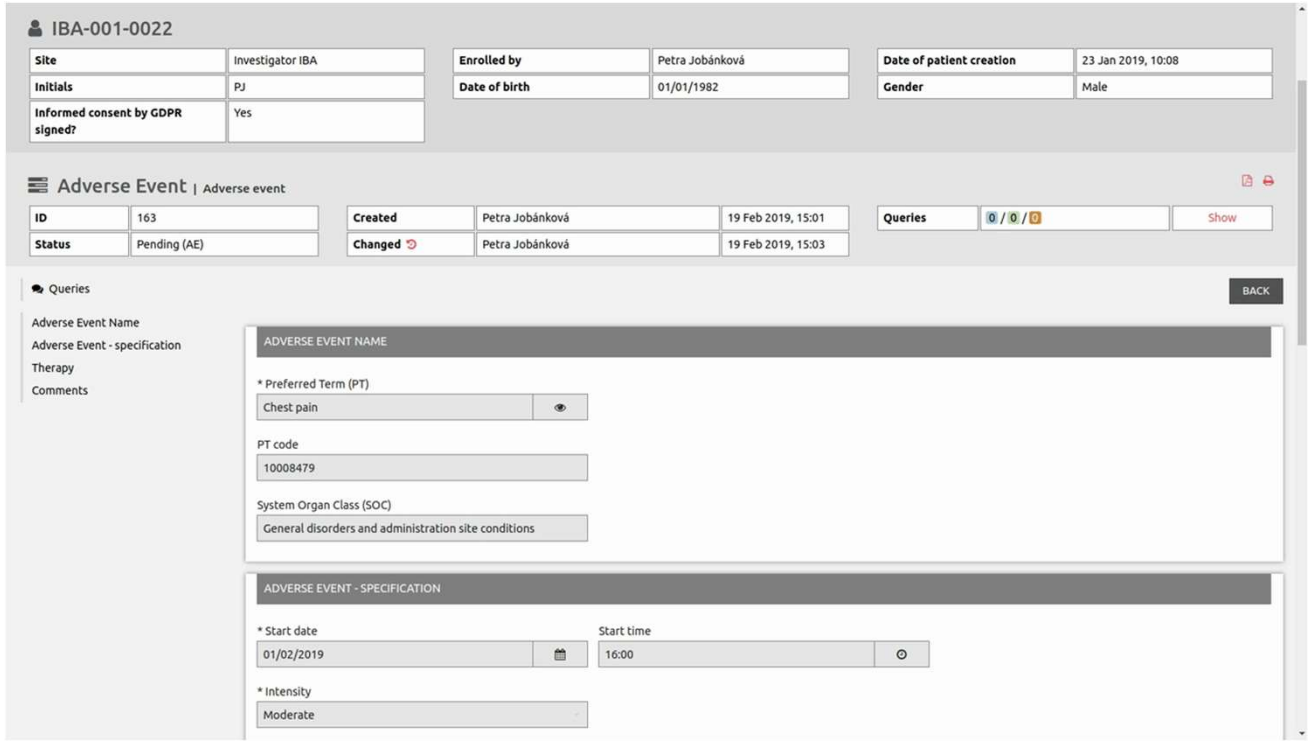
Data entry - UX features

Edit checks & instant validation



Data entry

Responsivity



Who: Healthcare professional

Where: Study

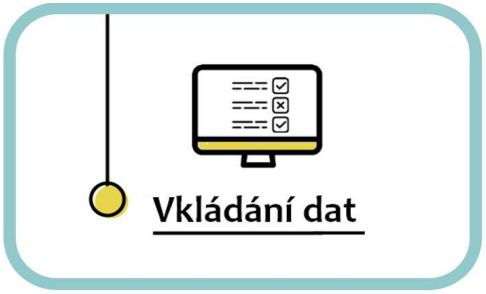
Data entry

UX features

Skip logic

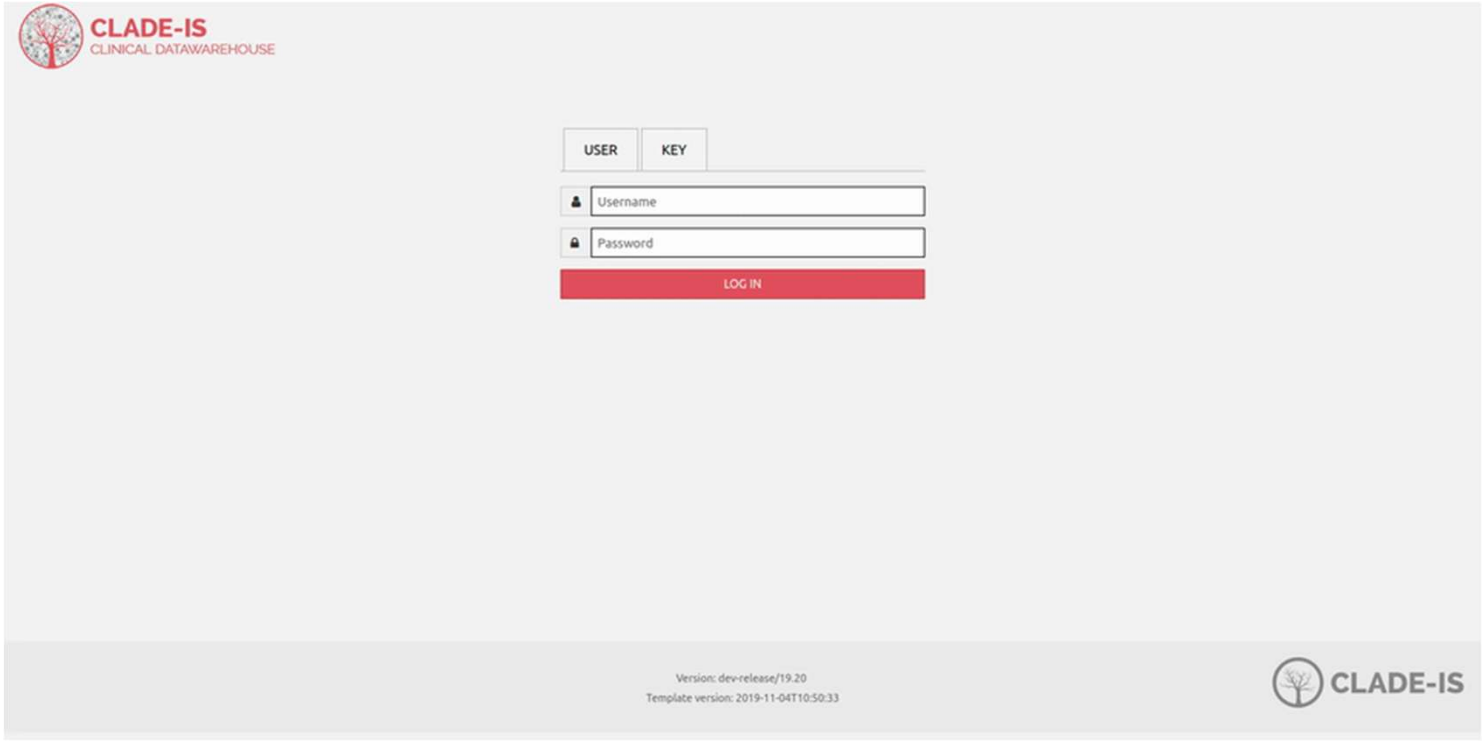
Who: Healthcare professional

Where: Study



Data entry

Single Form Mode – authentication through a hash code

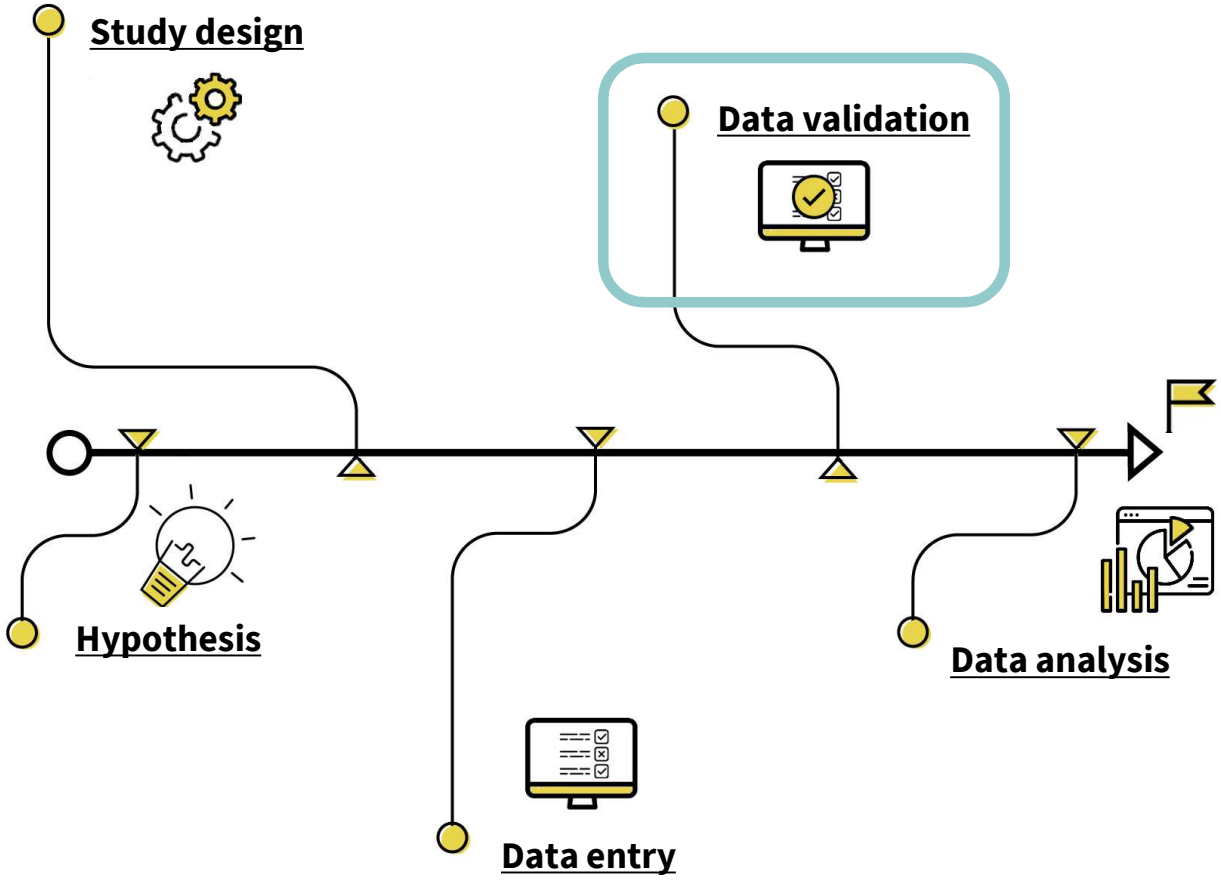


Who: Healthcare professional

Where: Study

Data entry

From a hypothesis to an outcome



Data Quality Checks

Queries

Query ID	Patient ID	Form name	Created the form	Message	Status	Action
4771	ATTRA-02790	Follow-up		Two Follow-up forms have the same Date.	new	Open
9310	RA_3321_RB	Adverse event		The Adverse Events form cannot be established with a date of origination of adverse event that follows the date on which the patient follow-up was terminated.	new	Open
575	RA_2773_V5	Follow-up		There is no Quality of life with SF36 filed for the entry visit or the visit after 1 year, 2 years, etc., or the date	new	
4770	ATTRA-02790	Quality of life		Two Quality of li Quality of Life fo		
3180	RA_3007_LH	Termination of monitoring		The patient show indicate in the se		
4248	ATTRA-2090	Termination of monitoring		The patient show indicate in the se		
6300	ATTRA-02773	Follow-up		The first Follow-u register at all. Pl or add missing e patient started t form (Evaluation		

Who: Monitor

Where: Study

Chemotherapy dose reduction indicated, but no dose reduction in clinical database. Please correct data.

[redacted], 22 Jul 2021, 13:43 closed RESPONSES (5) / UNREAD (5)

[redacted], 23 Jul 2021, 08:13
Total dose of each chemotherapy regimen was reduced, not available info here

[redacted], 23 Jul 2021, 08:16
Carboplatin AUC5 total dose 400mg instead of 550mg Pemetrexed 500mg/m2 total dose 750mg instead of 980mg

[redacted], 19 Oct 2021, 14:40
V0 values: Carboplatin AUC5 and Pemetrexed 500mg/m2 V2 values: Carboplatin AUC5 and Pemetrexed 500mg/m2 V3 values: Carboplatin AUC5 and Pemetrexed 500mg/m2 AND Chemotherapy dose reduction is answered YES. Dosage is reported the same an all visits, please explain the reduction or correct answer.

[redacted], 21 Oct 2021, 10:00
Change was done for Pemetrexed, not such availability for Carboplatin units

[redacted], 2 Nov 2021, 11:40
OK

Data lineage

Audit trail

QUESTIONS BY CONTENT | QUESTIONS BY TIME | FORM STATUS

Forms questions

INFORMED CONSENT

Informed consent

Change		Status		Value	
Date	**Author**	**Original**	**New**	**Original**	**New**
30/05/2018 09:26:18	Petra Jobankova	-	Empty		
30/05/2018 16:42:53	Petra Jobankova	Empty	Invalid		
30/05/2018 16:44:02	Petra Jobankova	Invalid	Done		Yes

Date of informed consent

Change		Status		Value	
Date	**Author**	**Original**	**New**	**Original**	**New**
30/05/2018 09:26:18	Petra Jobankova	-	Empty		
30/05/2018 09:26:35	Petra Jobankova	Empty	Skipped		
30/05/2018 16:44:02	Petra Jobankova	Skipped	Empty		

CML TREATMENT OVERVIEW

Treatment type (main)

27	132120	30/05/2018 09:26:	23628	INF-0001	INF-8201	Yes	Change to question		Q125	Data con	Data control			empty
28	132120	30/05/2018 09:26:	23628	INF-0001	INF-8201	Yes	Change to question		Q126	Note	Data control			empty
29	132121	30/05/20	Petra Joba	23628	INF-0001	INF-8201	Yes	Change to question		Q673	Date of in	Informed	empty	skipped
30	132121	30/05/20	Petra Joba	23628	INF-0001	INF-8201	Yes	Change to question		Q620	Date of la	Survival	empty	skipped
31	132121	30/05/20	Petra Joba	23628	INF-0001	INF-8201	Yes	Change to question		Q627	Date of d	Survival	empty	skipped
32	132121	30/05/20	Petra Joba	23628	INF-0001	INF-8201	Yes	Change to question		Q628	Phase of	Survival	empty	skipped

O
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empty

Who: QA manager
Where: Study

Data entry

Data insights

Dashboard

Number of patients	Total number of forms
13 / 1 total / newly added *(new for last 30 days, testing and shared pacients are not included)*	**64 / 7 / 41** total / valid / pending *(testing and shared pacients are not included)*
Total number of queries	**Number of new queries**
13 / 6 / 7 total / opened / closed *(testing and shared pacients are not included)*	**4 / 1 / 3** total / opened / closed *(last 30 days, testing and shared pacients are not included)*

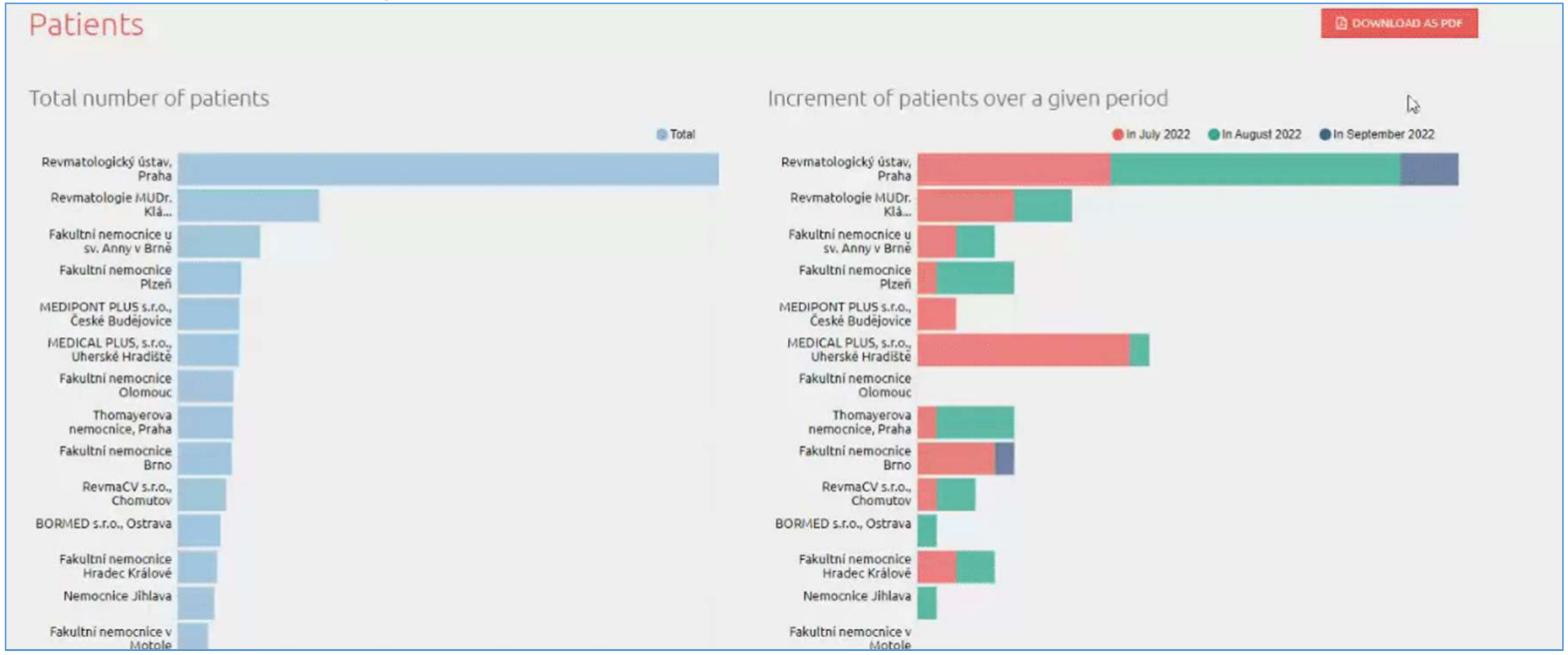
Who: Coordinator

Where: Study

Data validation

Data insights

Interactive reports



Who: Coordinator

Where: Study

Data validation

Anomaly d ing

Effic

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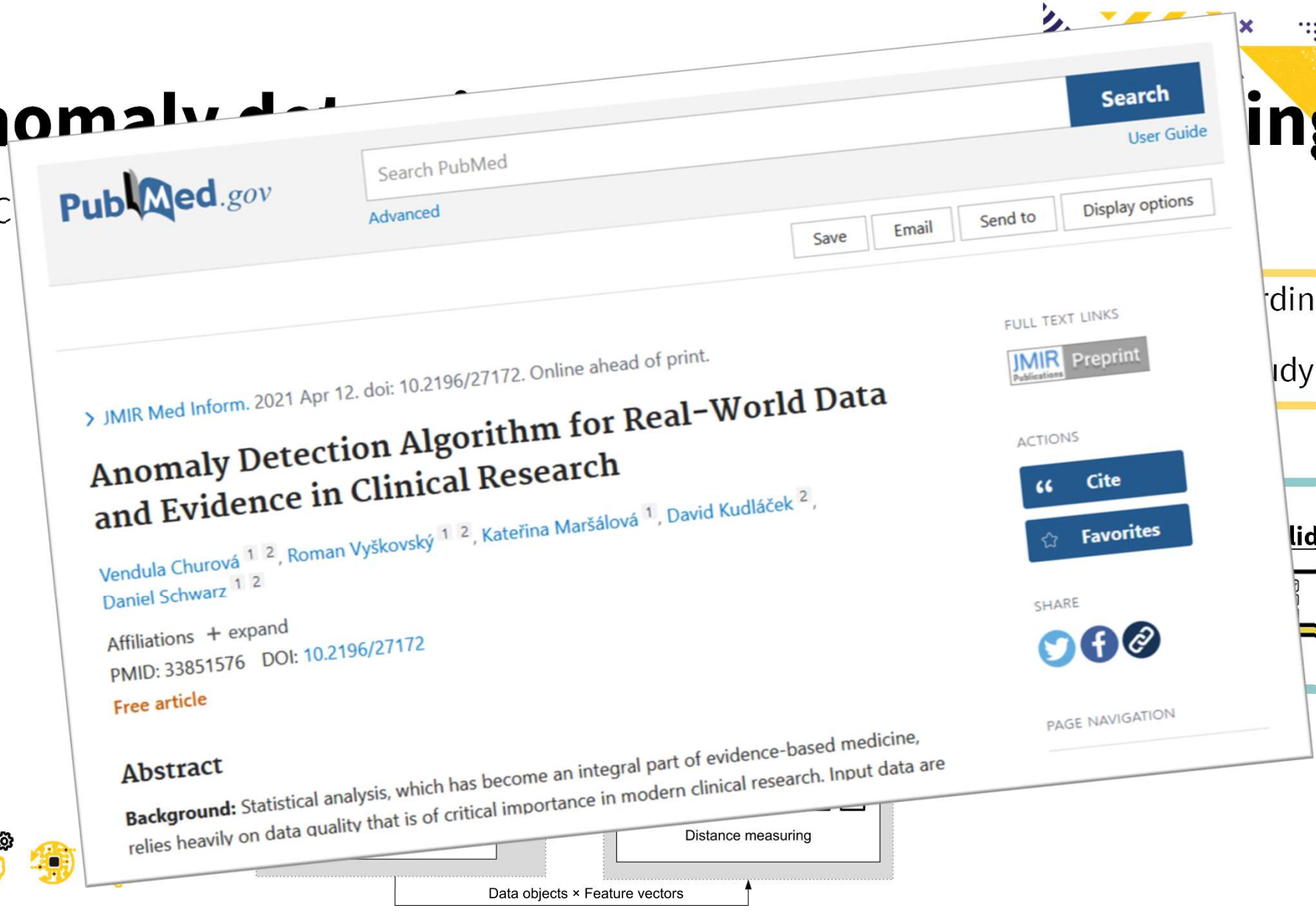
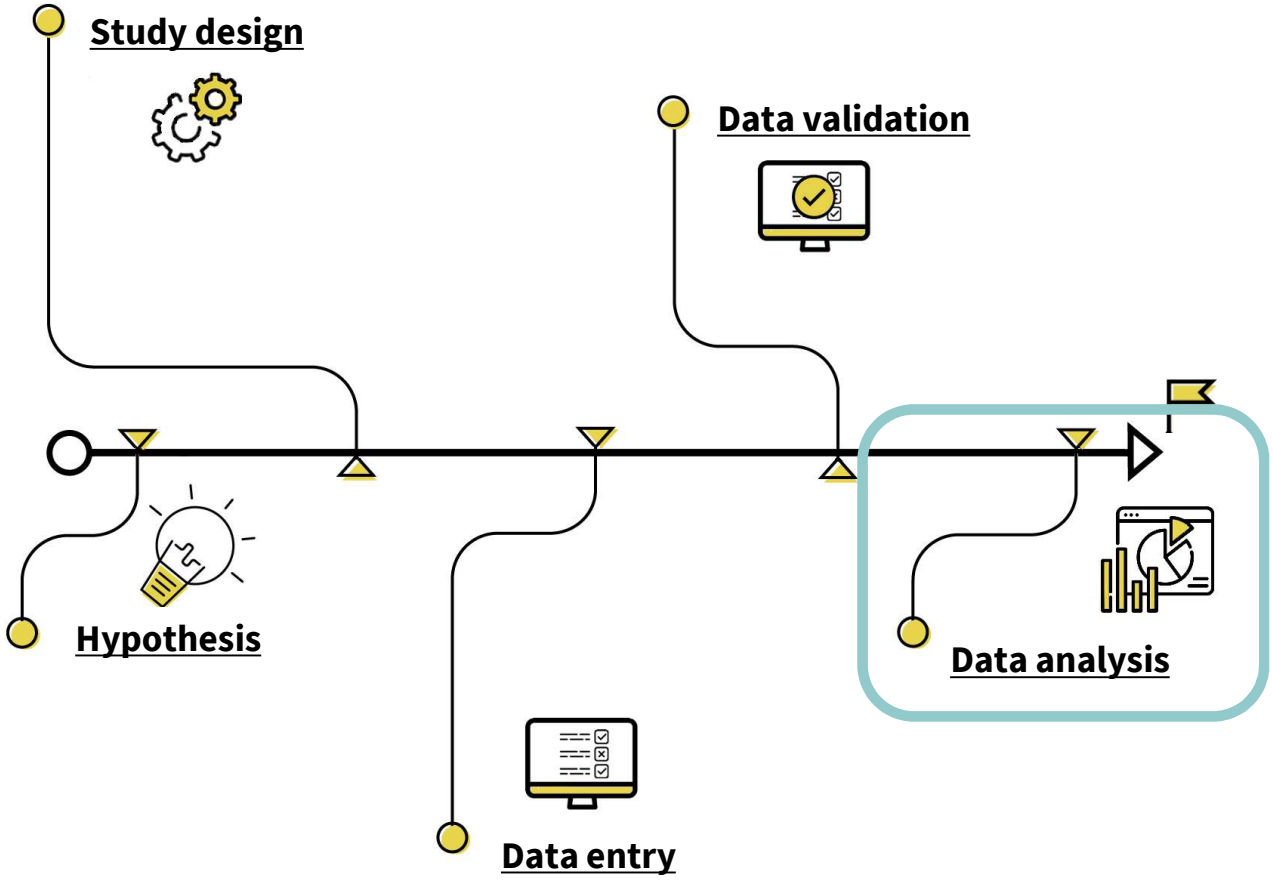
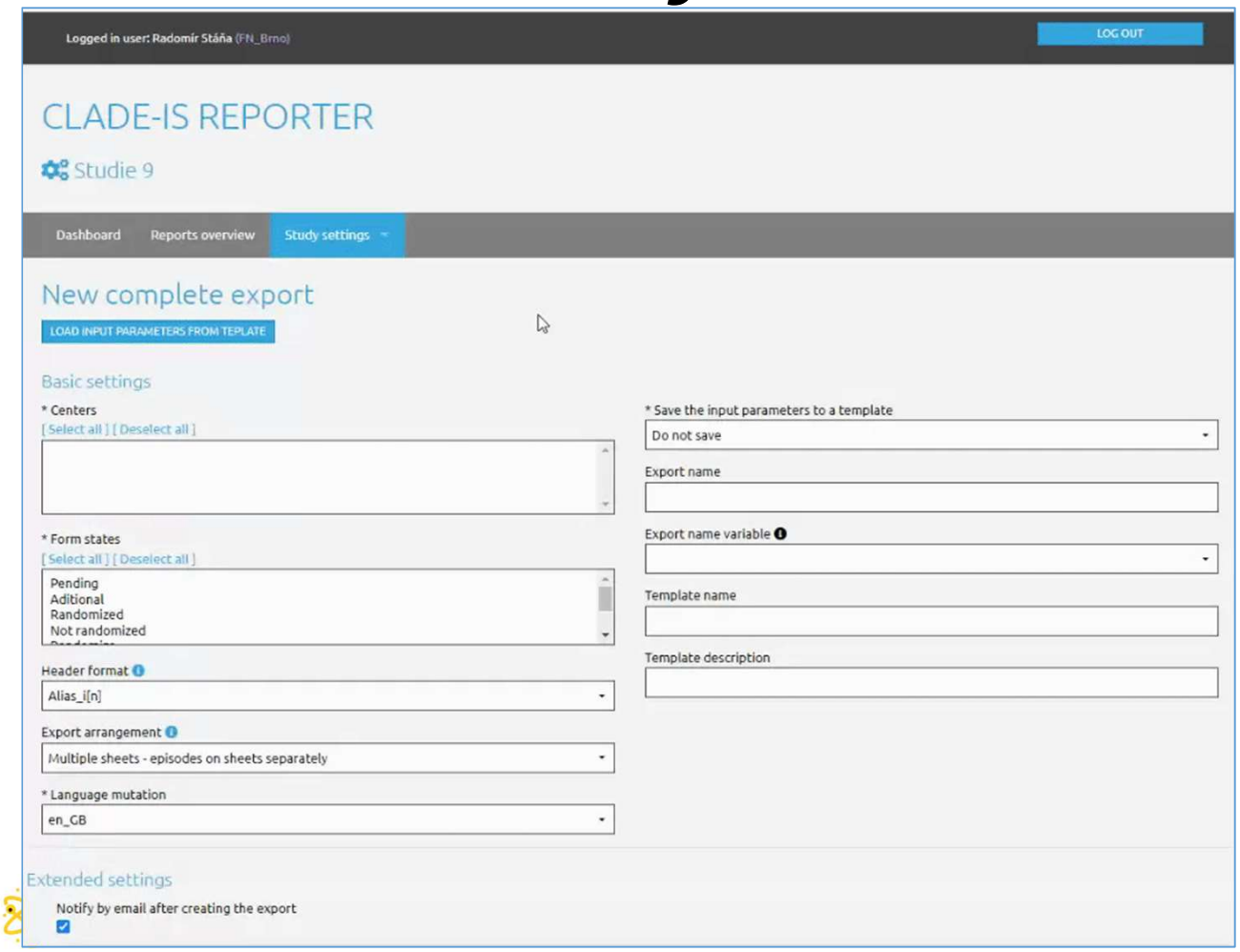


From a hypothesis to an outcome



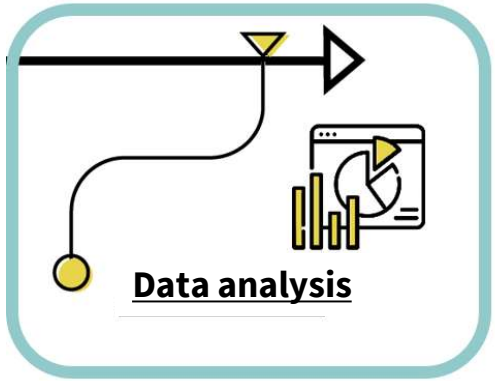
Toolkit for data analysis

Export



Who: Analyst

Where: Reporter



Toolkit for data analysis

Report

Institut biostatistiky a analýz, s.r.o.

Poštovská 68/3, 602 00 Brno
http://www.biostatistika.cz helpdesk@biostatistika.cz

Stav k datu: 04.11.2019 08:01

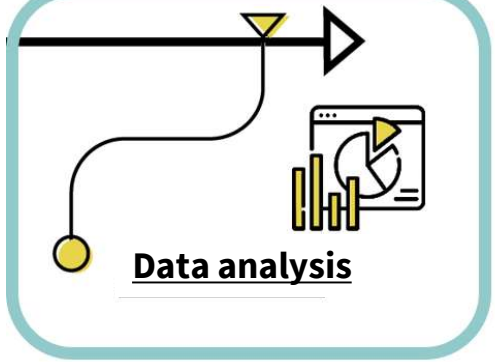
Registr HARM - [redacted]

Aktuální přehled pacientů v registru

Centrum	Pacienti			Léčba (probíhající a ukončená)			Léčba (ukončená)					
				Terapeutický postup			Terapeutický postup			SVR		
	Celkem	Léčení	Neléčení	Dasabuvir + Ombitasvir + Paritaprevir / Ritonavir	Dasabuvir + Ombitasvir + Paritaprevir / Ritonavir + RBV	Glecaprevir + Pibrentasvir	Dasabuvir + Ombitasvir + Paritaprevir / Ritonavir	Dasabuvir + Ombitasvir + Paritaprevir / Ritonavir + RBV	Glecaprevir + Pibrentasvir	SVR	Relaps	Nelze hodnotit
[redacted]	124	124	0	33	15	13	33	15	11	55	1	3
[redacted]	328	328	0	64	27	80	64	27	44	121	1	13
[redacted]	46	46	0	4	2	5	4	2	5	11	0	0
[redacted]	100	88	12	13	3	13	12	3	7	19	1	2
[redacted]	101	101	0	24	1	26	22	0	26	41	0	7
[redacted]	73	73	0	4	5	19	4	5	13	21	0	1
[redacted]	211	211	0	30	2	25	30	2	8	38	1	1
[redacted]	264	264	0	37	18	32	37	18	32	83	3	1
[redacted]	24	24	0	6	0	0	6	0	0	5	0	1
[redacted]	52	52	0	29	2	0	28	2	0	30	0	0
[redacted]	299	268	31	49	12	68	48	10	52	104	1	5
[redacted]	0	0	0	0	0	0	0	0	0	0	0	0
[redacted]	167	156	11	6	0	35	6	0	18	23	1	0
[redacted]	19	19	0	2	0	9	1	0	6	4	0	3
[redacted]	0	0	0	0	0	0	0	0	0	0	0	0
[redacted]	132	132	0	22	1	8	22	1	8	31	0	0
[redacted]	9	9	0	0	0	3	0	0	3	3	0	0
[redacted]	74	74	0	7	2	12	7	1	8	13	2	1
[redacted]	63	63	0	1	19	0	1	17	0	15	0	3
[redacted]	50	50	0	6	5	11	5	4	10	19	0	0
[redacted]	60	60	0	29	11	1	4	1	0	5	0	0
Celkem	**2196**	**2142**	**54**	**366**	**125**	**360**	**334**	**108**	**251**	**641**	**11**	**41**

Who: Analytik

Where: Reporter



Toolkit for data analysis

On-line vizualization

DEVELOPMENT OF THE DISEASE

TABLE | GRAPH

Follow-up date	HAQ	DAS 28 - FW
12/05/2022	1.5	5.7325
24/11/2021	1.88	6.7709
24/08/2022	1.88	4.833
09/06/2022	2	6.0125
12/05/2022	1.5	5.7325
03/02/2022	1.88	7.1353
24/11/2021	1.88	6.7709

FORM STATUS

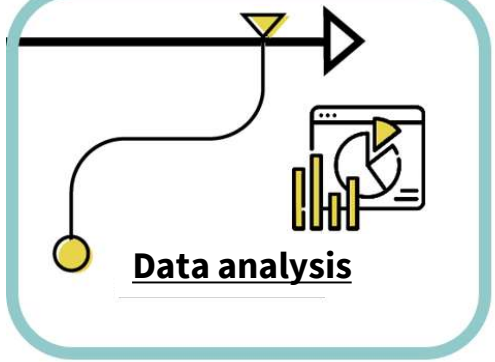
Form status

Valid

BACK

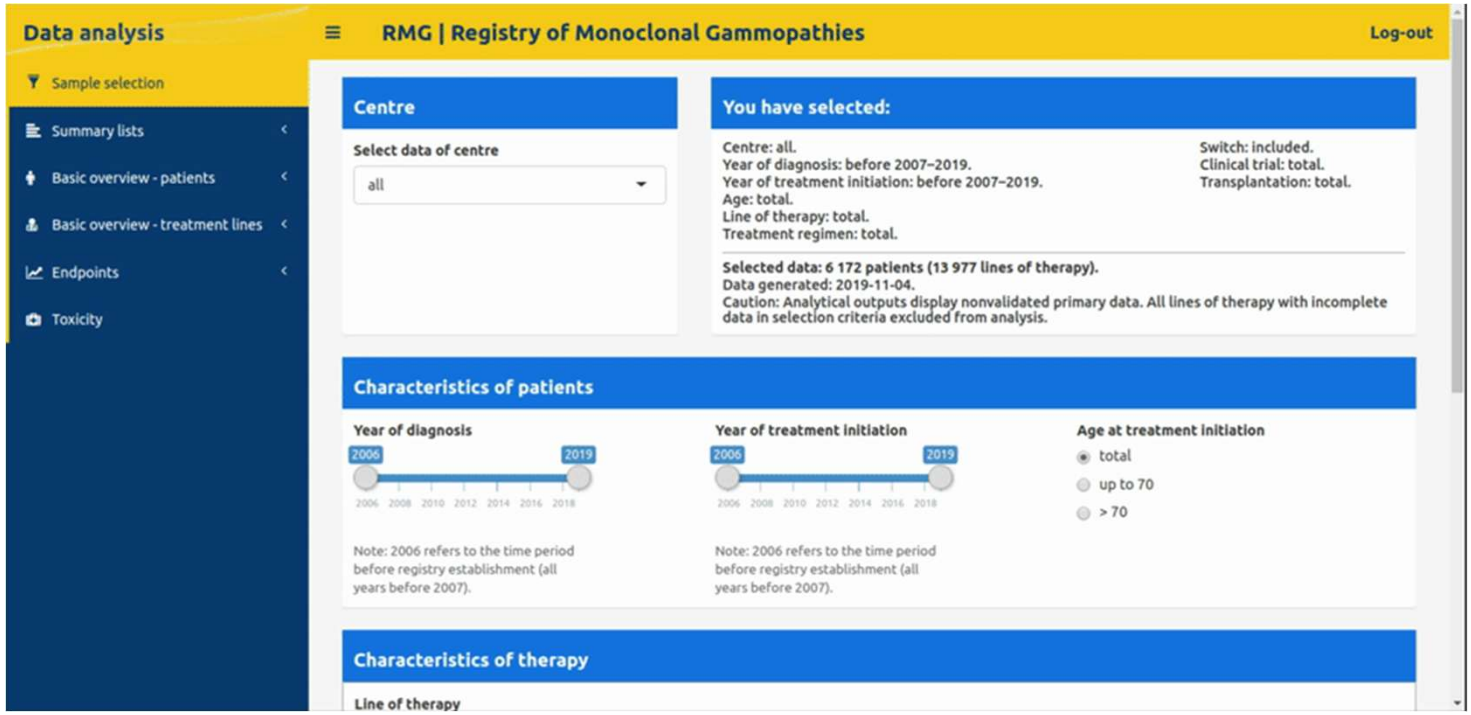
Who: Healthcare professional

Where: Study



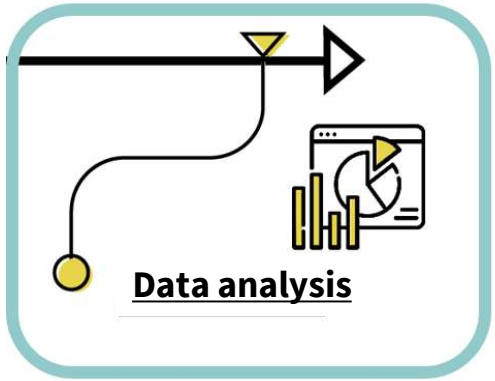
Toolkit for data analysis

Visual analytics on a project website

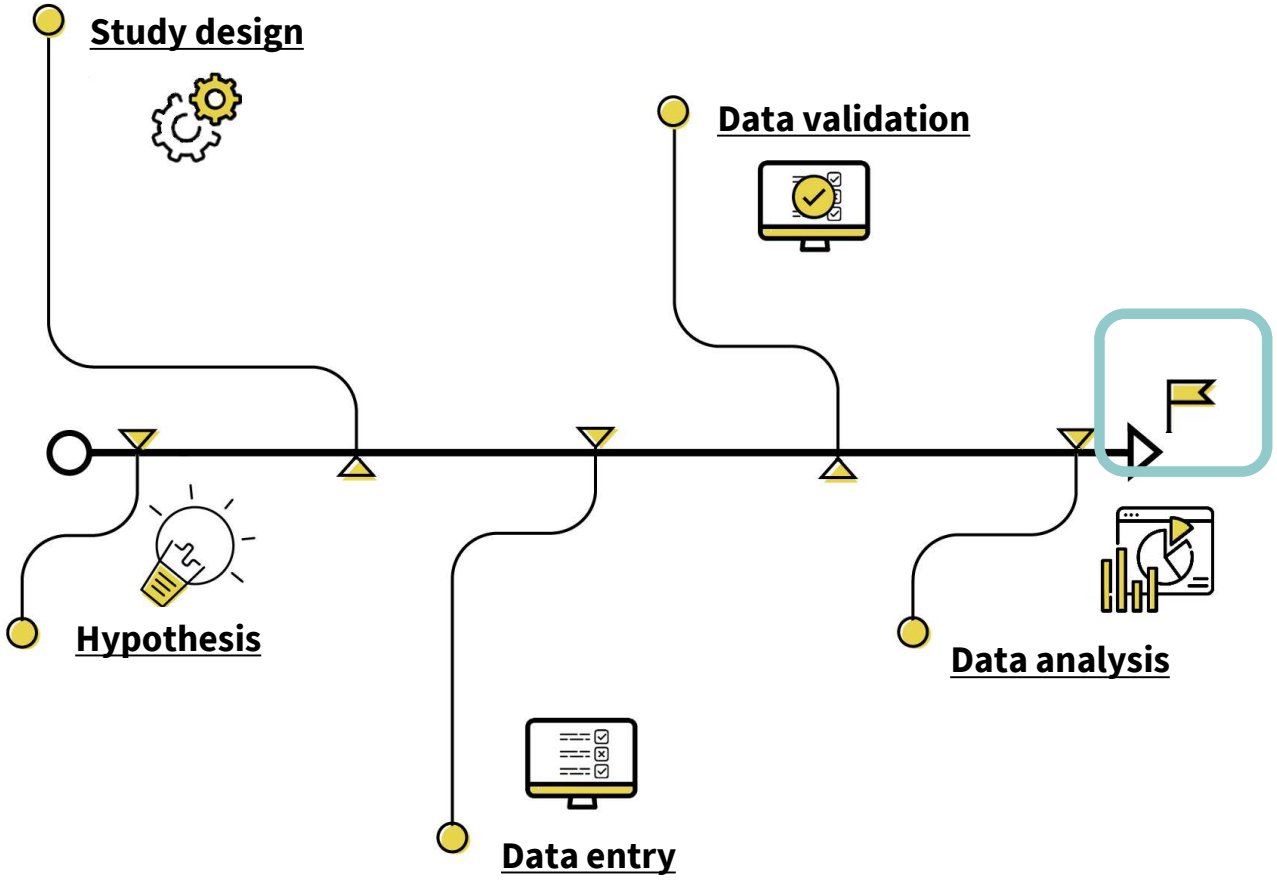


Who: Biostatistician

Where: Ext. website



From a hypothesis to an outcome



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NIS

criteria and regulatory issues

NIS criteria and rules: medicinal product

Use of medicinal product with marketing authorization only

- is used in accordance with SmPC

- registered in the country when the data collection is planned

- available in the distribution network

- is prescribed and dispensed in the usual manner

- must not be provided for free: promotional samples cannot be used

NIS criteria and rules: other

Study must NOT be promoted

Marketing Authorization Holder may not provide financial compensation in excess of compensation for time and expenses

No additional diagnostic or monitoring procedures are applied

Patient selection must not be pre-influenced

Regulatory: NIS from the legislation point of view

- 2001/20/ES: Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

- 536/2014/EU: REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Differences between intervention and non-intervention

Medical product

- Medical product without MA = INTERVENTION
- Medical product with MA = NON-INTERVENTION

Study Subject

- Healthy volunteers = early phases of clinical research, cohort studies
- Patients = late phases of clinical research (phase III, IV, NIS)

Intervention

- Whatever additional to common clinical proctice
- Randomization; placebo; other than approved dossage, other than approved way of administration, additional examinations, sampling for research purposes

Completing the questionnaire by the patient is not an intervention

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System validation

self-assessment, certifications,
& penetration tests

Information Security Policy & ISMS certification

ZERTIFIKAT ◆ CERTIFICATE ◆ 認證證書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

TÜV SÜD Czech

CERTIFICATE

Certification Body Management System No. 3053
TÜV SÜD Czech s.r.o.

certifies that

iba Institute of Biostatistics and Analyses

Institut biostatistiky a analýz, s.r.o.
Poštovská 68/3
CZ – 602 00 Brno
Ident. No.: 02784114

has established and applies
an Information Security Management System for

- **management of research projects in health and life sciences**
- **clinical data management, analysis and interpretation**
- **development and provision of CLADE-IS information system services for data registration, storage and processing**

An audit was performed, Report No. **14.617.593**
Proof has been furnished that the requirements according to

EN ISO/IEC 27001:2017

are fulfilled.

The certificate is valid from **22.07.2022** until **21.07.2025**
Certificate Registration No. **14.598.255**
Statement of applicability dated 08.06.2022.

TÜV SÜD Czech s.r.o. • Novodvorská

Prague, 24.06.2022

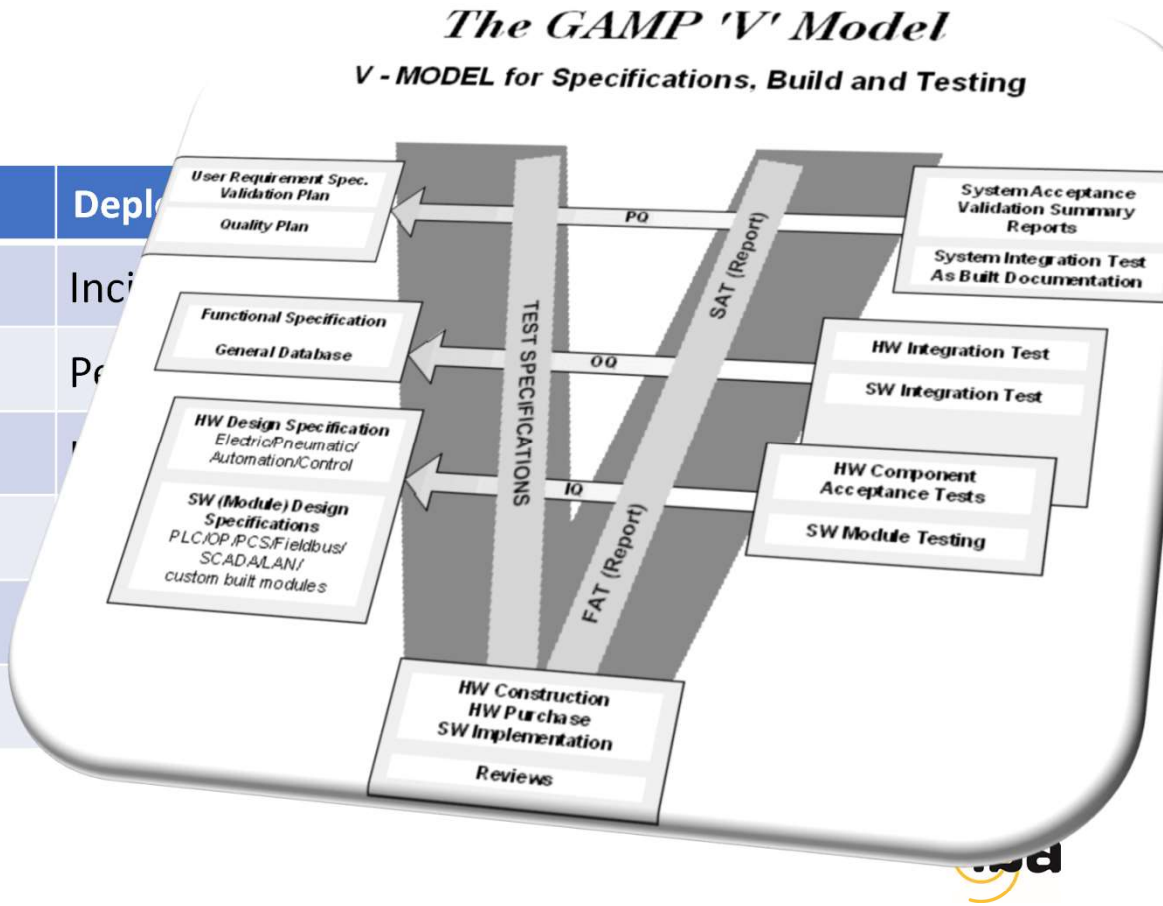
S 3053

Relevant documentation

What should an organization that develops and/or operates an EDC system have documented?

- SOPs – Standard Operation Procedures,
- WIs – Working Instructions

Development & testing	Depl
Release management	Inci
Software Development	Pe
Testing and verification	
Software documentation	
Management of changes in SW source code	
Safety of software development	



Security measures

- ✓ Logins,
- ✓ Storage space,
- ✓ Backups,
- ✓ Data reach,
- ✓ Failover,
- ✓ Data privacy,
- ✓ Permanent support & maintenance,
- ✓ GDPR compliance,
- ✓ and Security of facilities

Precautions…

= 3-D penetration tests:

- system/application
- IT infrastructure
- people

Compliance

- the EC Directive 2003/94/EC Annex 11
- USA (FDA) 21 CFR part 11

Stability…

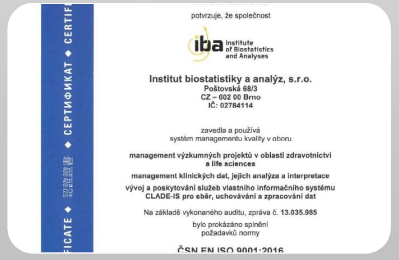
= release management:

- separated Dev/Test/Prod environments
- Dev, Test1, Test2 cycles

How to prove or verify that a system is valid?

Self-assessment

- Documentation using SOPs and WIs
- Internal audits



Certification

- Documentation and the processes are compliant with a standard and/or recommendation(
- ISO 27k, GAMP, HIPAA,…

Additional tests

- Penetration tests
- IT infrastructure, System/Application, People (social engineering)

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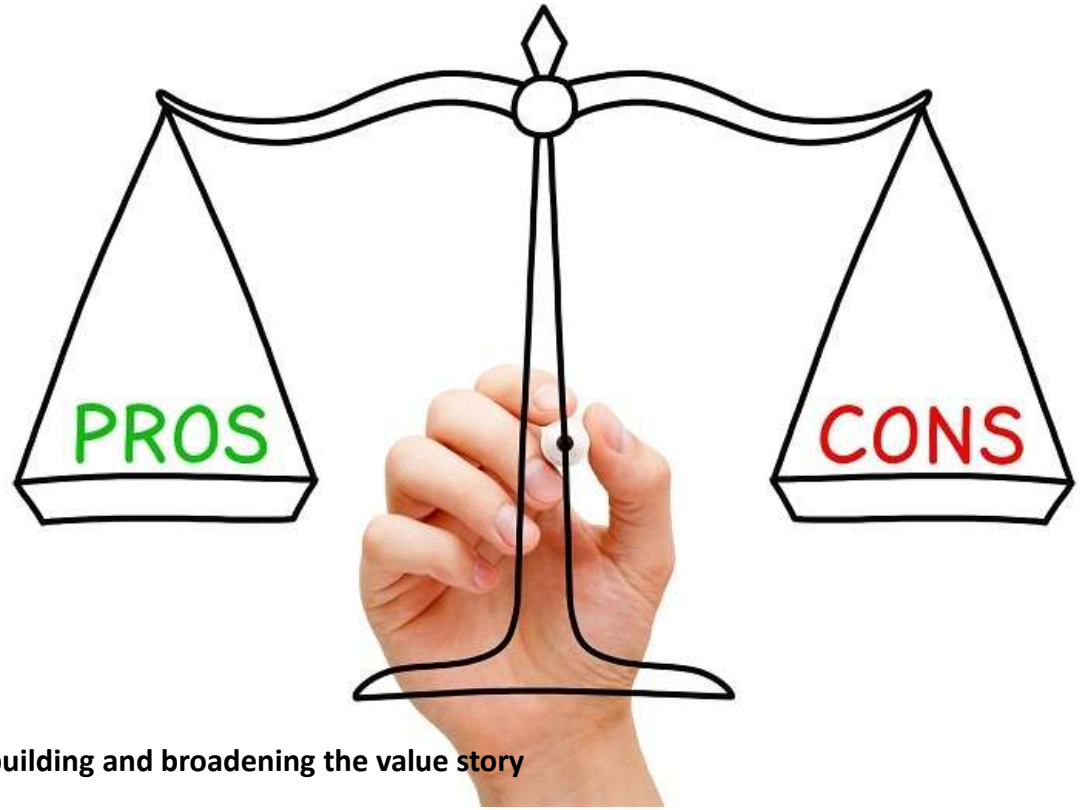
NIS: Let's recap!

pros & cons



Advantages of NIS against other types of studies

Aspect	NIS & RWD/RWE projects	Clinical trials (RCTs)
COSTS	low costs	very high costs
SUCCESS	high success rate	low certainty
ABILITY TO ANSWER RESEARCH QUESTION(S)	can answer	answers only the product-related questions, fails in answering more general research questions
ROLE IN DRUG DEVELOPMENT	significant	significant
REGULATORY ISSUES	easy procedures	complex and tedious procedures
RECRUITMENT OD SUBJECTS	easy and fast	difficult, long-term, multiple challenges
EVIDENCE OF CLINICAL VALUE	very helpful	limited

Conclusion(s)

NIS and RWE projects collect valuable data which have a potential:

- to inform clinical practice
- to develop and/or update new guidelines in health care
- to clarify the value of new therapies
- to improve drug development cycle

Pharma, biotech companies, and other R&D organizations including academics should value their data resources…

- …and use them, among other things, in their future development(s).

Multiple data sources may create a space for errors, but you can avoid them…

- by employing well educated and experienced clinical data managers,
- and by using solid and validated tools and systems.

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CLADE-IS
CLINICAL DATAWAREHOUSE

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