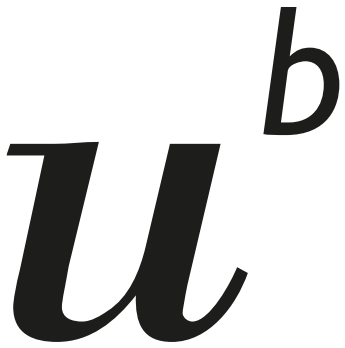

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UNIVERSITÄT
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Central Data Monitoring (CDM)

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CTU Lecture

22.03.2023

Lecture Overview

1. Background

- What is CDM
- CDM in the context of Risk based monitoring
- Databases

2. Procedure of CDM

- Data cleaning (queries)
- Data monitoring (reports)

Central data monitoring CDM

Definition: Monitoring NOT done on-site but done **centrally** or **remotely**, e.g.

- Phone calls with study sites
  - to follow up on action items, discuss study procedures, etc
- Verify some source documents centrally/electronically
  - site delegation logs, IMP accountability logs, IMP storage temperature logs, etc.
- Review the data collected in the electronic study database (eCRF) and post queries to clarify, confirm or correct (implausible) data and typo errors
- According to **Central Data Monitoring Plan**, which can be very extensive or only minimal.

Recommendations

2013 - Food and Drug Administration (FDA)

"FDA encourages greater use of centralized monitoring practices, where appropriate, than has been the case historically, with correspondingly less emphasis on on-site monitoring"

Ref: Guidance for Industry – Oversight of Clinical Investigations- A Risk-Based Approach to Monitoring (August 2013)

2016 – ICH E6 (R2) Good Clinical Practice (GCP)

"The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring."

Ref: ICH-GCP E6 (R2) section 5.18.3

Gist of these recommendations

Risk based monitoring approach with a **combination and a right balance** of on-site and central monitoring methods required to achieve good data quality.

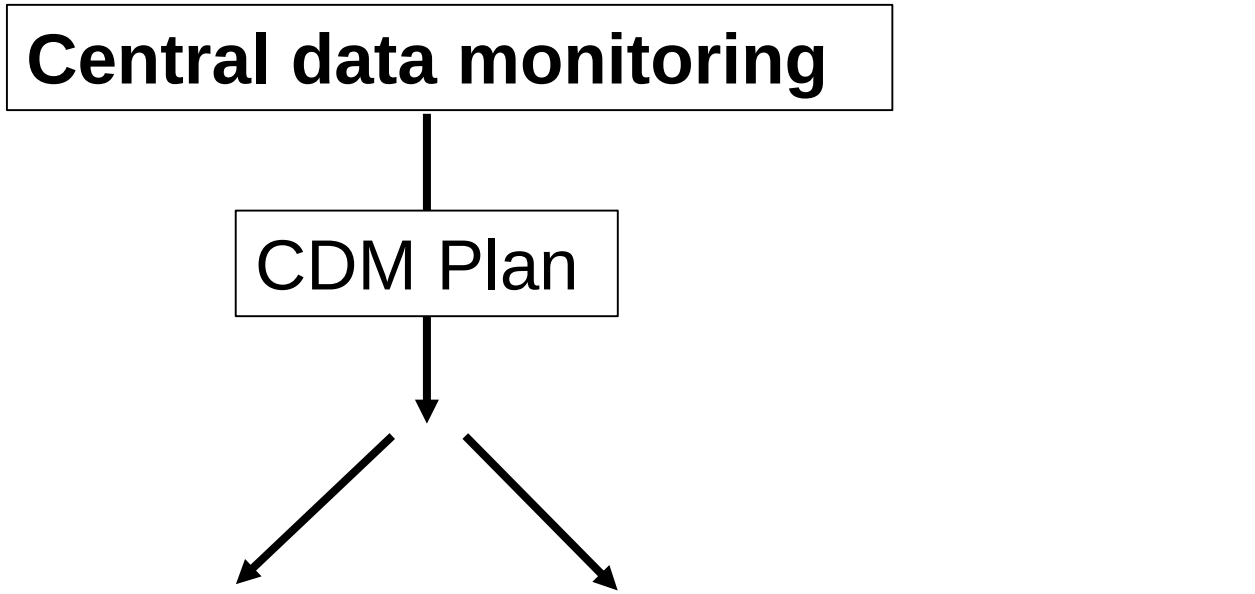
General aims of CDM

- To enhance the overall **quality** of the trial data – *accurate, reliable, and collected according to the study protocol, GCP rules and other governing regulations.*
- To identify **study related risks and issues** in a timely manner - *ensure the integrity and validity of the trial*
- Extend of CDM depends on **risk assessment of the trial** - *defined inside a Central Data Monitoring Plan*

Minimal aims of CDM at CTU Bern

- To enhance the overall **quality** of the primary endpoint and most important secondary endpoints assessments
- To ensure data entry of mandatory data is **complete** (e.g. to describe the population adequately, randomization, adherence, cross-overs, per-protocol population, safety)
- Minimal aims are usually extended according to the risk assessment of the trial and defined inside a **Central Data Monitoring Plan**.

Conduct of CDM



Data cleaning (queries)

Identify and correct incomplete, incorrect, inaccurate data

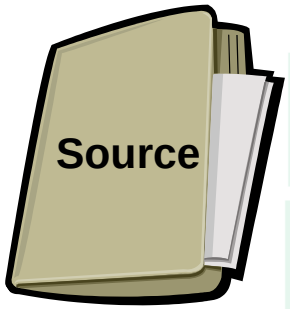
Daily, weekly, monthly, using targets or risk based

Data monitoring (reports)

Overseeing the conduct of the clinical trial

Monthly, quarterly, using targets or risk based

Data cleaning



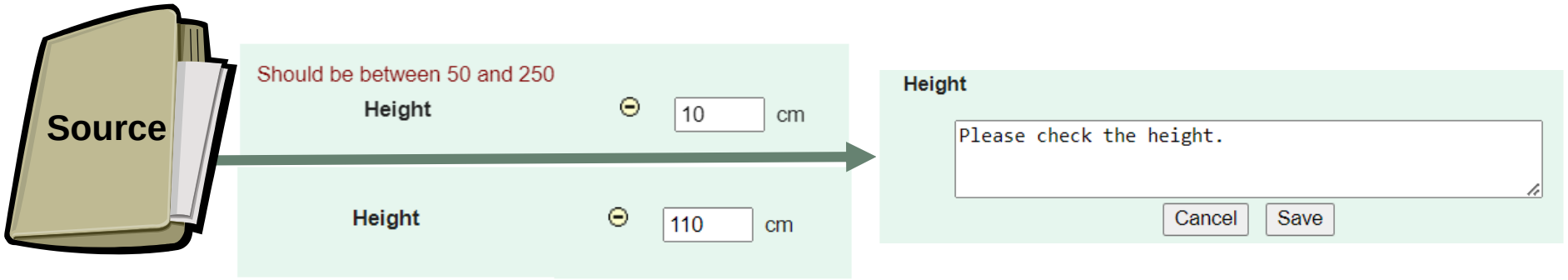
Real time checks in the database (**edit checks**)

- Outliers (extreme values)
- Missing data
- Transcription errors
- Source check

1st level of data cleaning

Study nurse checks/corrects the data

Data cleaning



Real time checks in the database (**edit checks**)

- Outliers (extreme values)
- Missing data
- Transcription errors
- Source check

Clarification from study sites (**queries**, email, phone)

- Data completeness
- Plausibility, Typo errors
- Consistency, Accuracy
- Protocol compliance
- Patient safety assessed

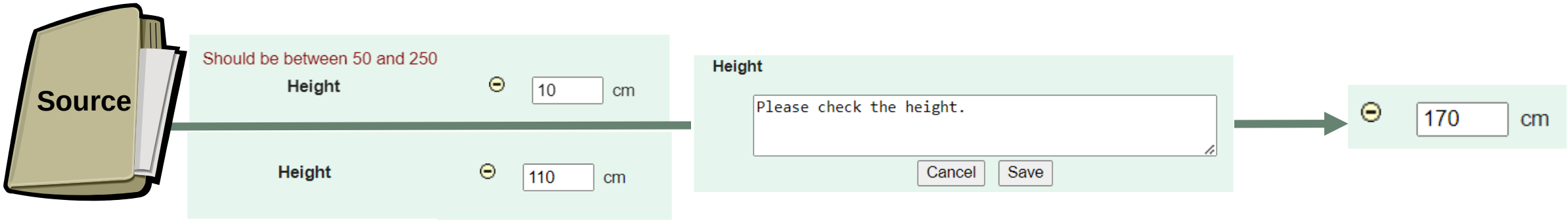
1st level of data cleaning

Study nurse checks/corrects the data

2nd level of data cleaning

Central data monitor checks/queries the data

Data cleaning



Real time checks in the database (**edit checks**)

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Clarification from study sites (**queries**, email, phone)

- Data completeness
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- Consistency, Accuracy
- Protocol compliance
- Patient safety assessed

Statistical analysis trial result/outcome

Final data check (contact CDM, study sites directly)

Quality

1st level of data cleaning

Study nurse checks/corrects the data

2nd level of data cleaning

Central data monitor checks/queries the data

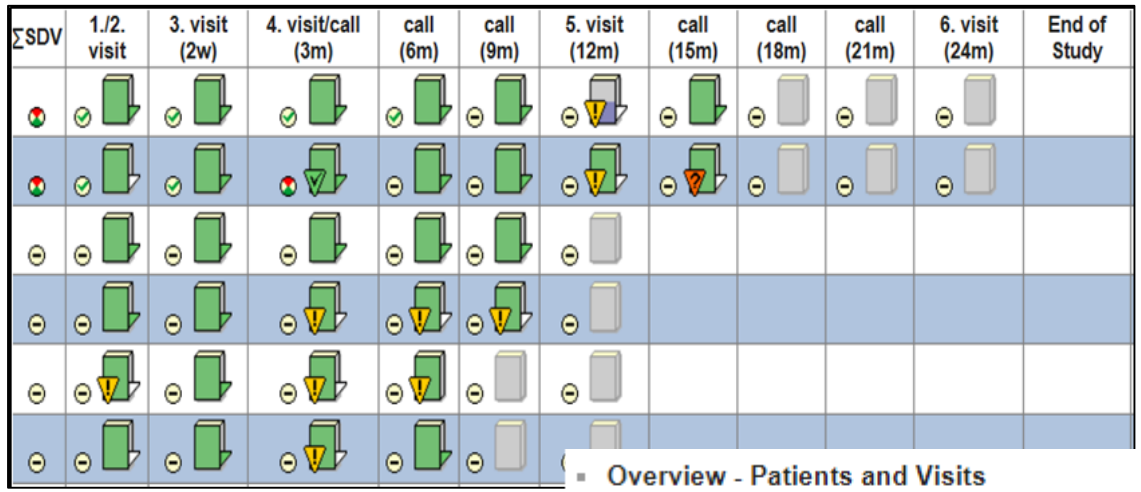
3rd level of data cleaning

Statistician checks

Clinical Data Management Systems (CDMS)

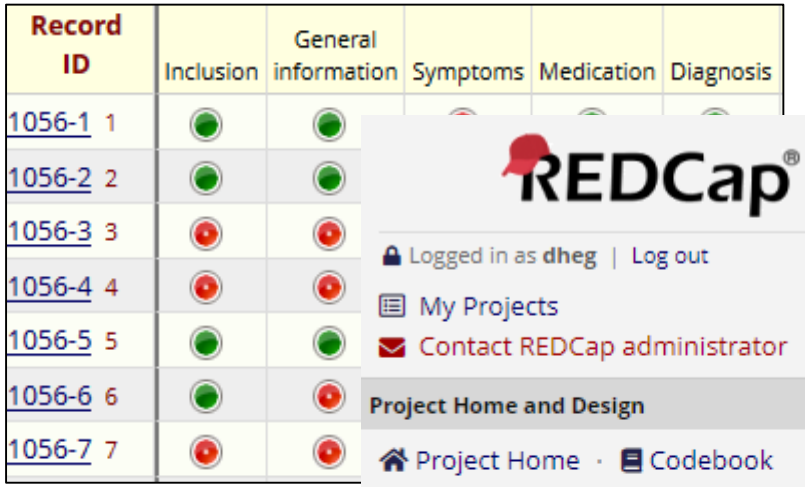
Database, eCRF, queries

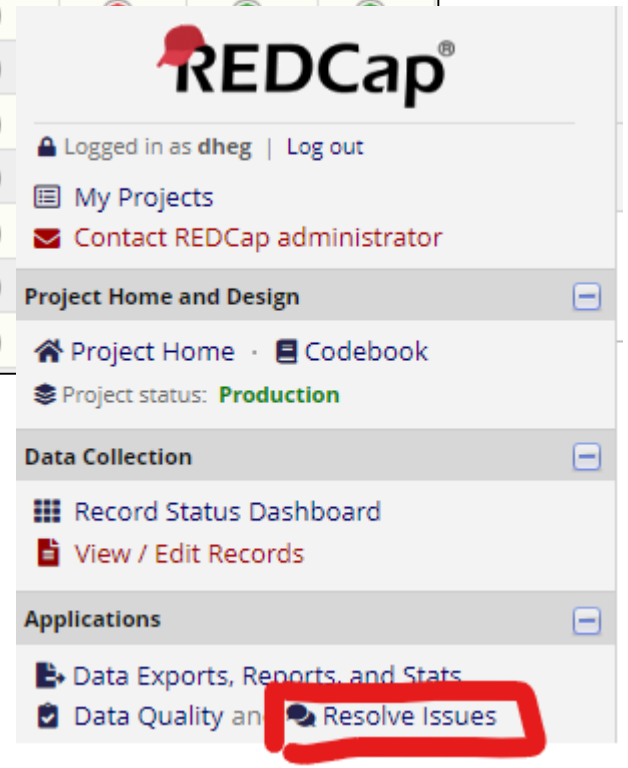
secuTrial®
web-based data capture in clinical trials



- Overview - Patients and Visits
- Overview - Completion status
- Overview - Query status
- Overview - Missings, warnings and errors
- Query details
- Serious Adverse Events (SAEs)
- Random overview
- Protocol Deviation
- CEAC
- CEAC w/procedure date

REDCap
Research Electronic Data Capture





Data **cleaning** by central data monitor

- **Data completeness -** Are all study visits conducted; are all required assessments and questionings done and is the corresponding data properly recorded in the database?

- **Data consistency -** Are there any inconsistencies or errors in data entry? e.g., if the question “did any new adverse event occur since the last visit?” is answered with “yes”, is there a corresponding event and/or concomitant medication recorded in the database?

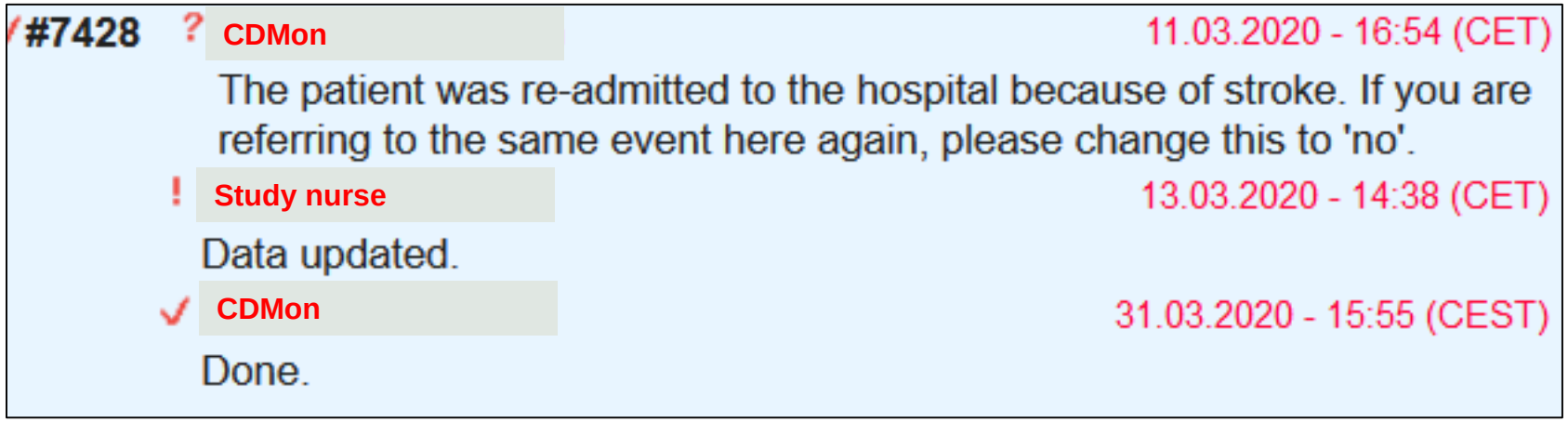
- **Data plausibility -** Is the entered data plausible? Pregnant male???

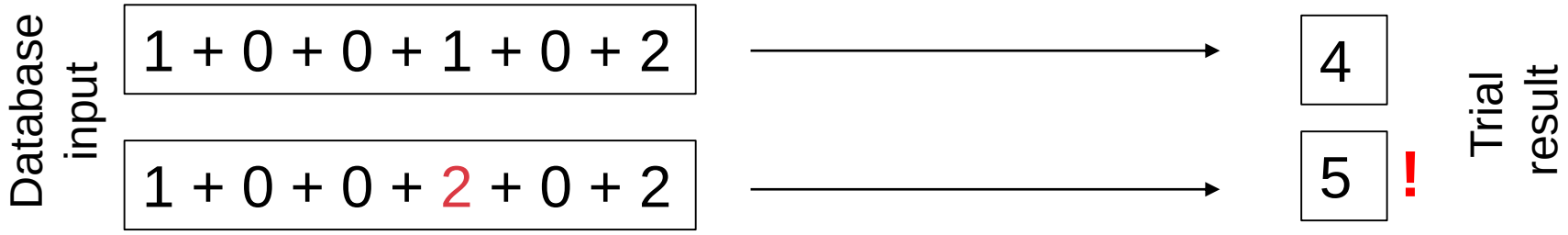
Data **cleaning** by central data monitor

- **Protocol and GCP compliance -** Are the required lab values recorded and do the participants fulfill the eligibility criteria; are study-specific visits performed in the correct time window, etc.?
- **Primary and secondary outcomes -** Is data required for the outcomes collected and properly recorded in the database?
- **Participant safety -** Is the informed consent obtained? Are (Serious) Adverse Events recorded and reported in time to the sponsor? Are withdrawal criteria adhered to, etc.? Are safety assessments performed?

Data **cleaning** - examples

Incorrect reporting of outcome: e.g. primary outcome (stroke) is reported twice or reporting the same event in 2 different visits

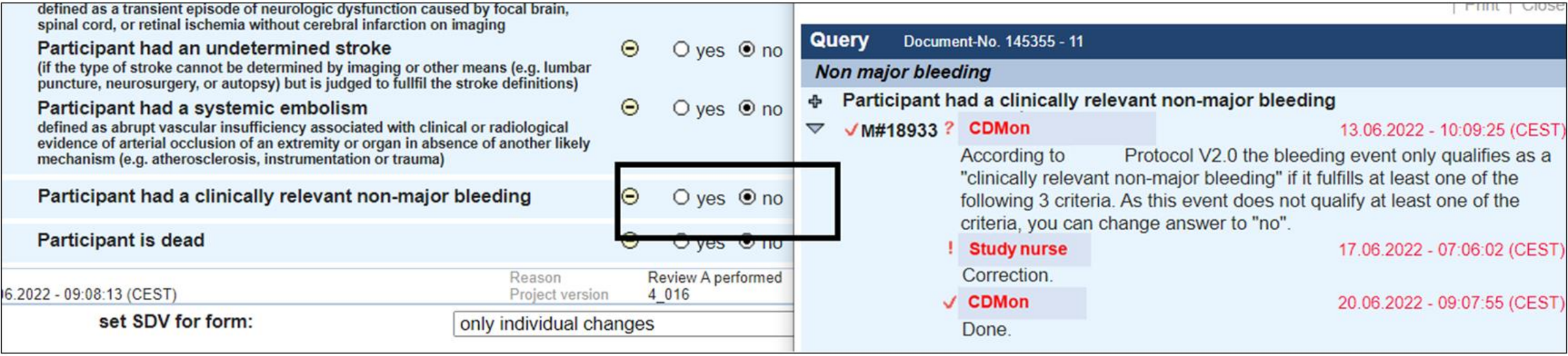




Mistakes can have a direct impact on the trial outcome!

Data **cleaning** - examples

Incorrect reporting of outcome: e.g. event does not qualify as a study outcome.



Database input

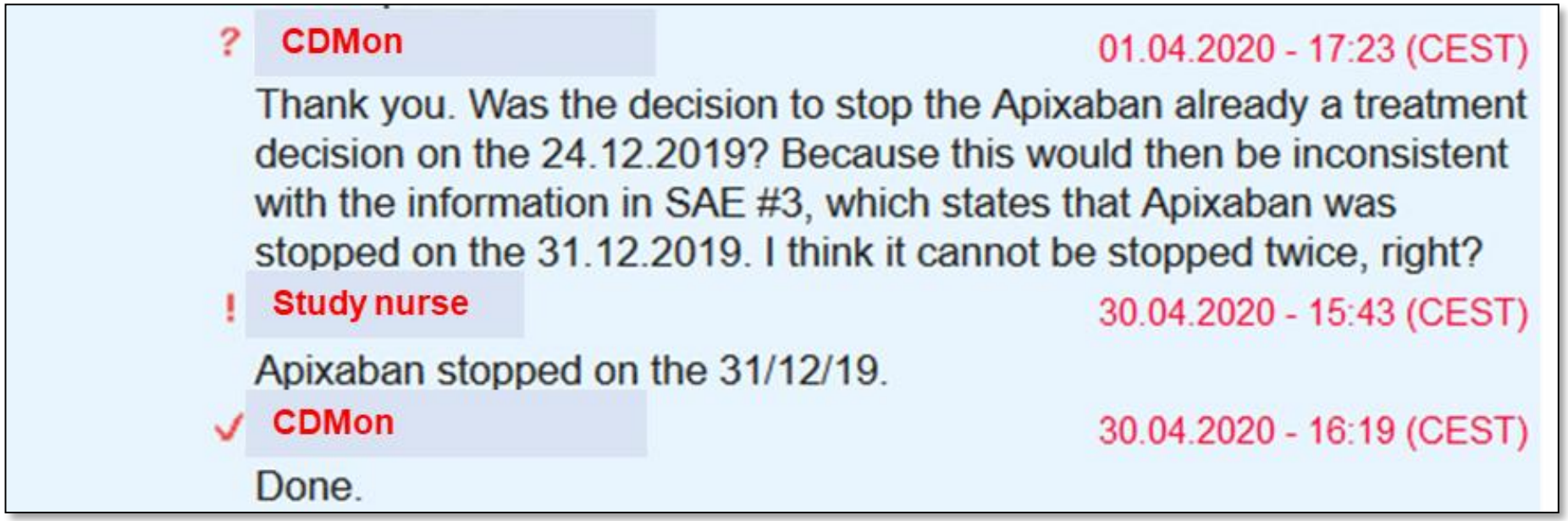
1 + 0 + 0 + 1 + 0 + 2 → 4

1 + 0 + 0 + 0 + 0 + 2 → 3 !

Trial result

Data **cleaning** - examples

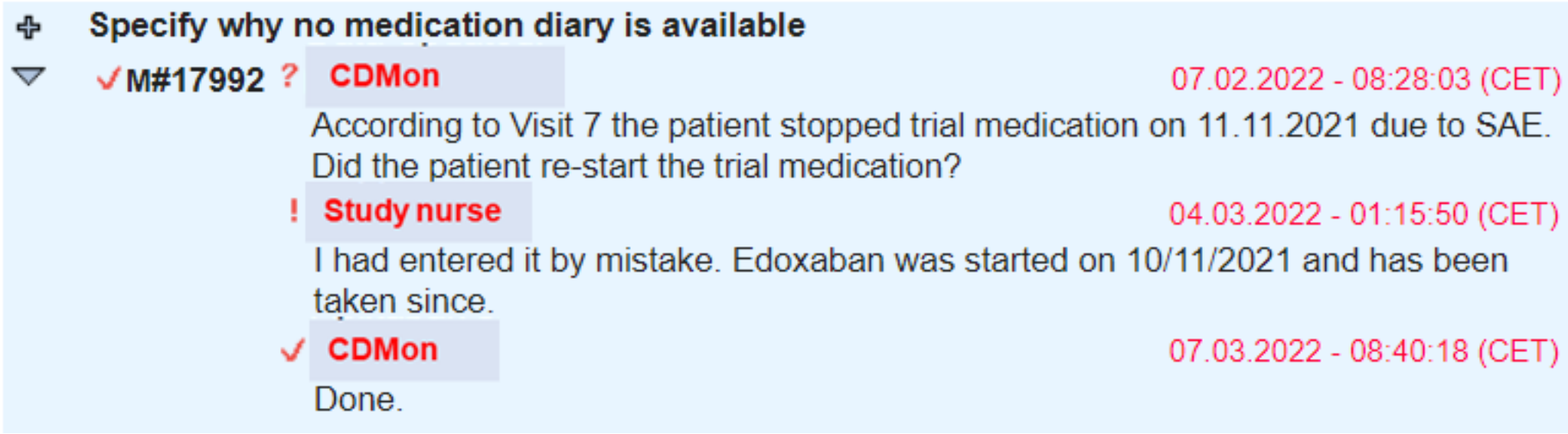
Treatment start/stop: e.g. Treatment stop reported on two different dates



Dates are important! **If not checked by EDC system during data entry can have up to 5% typo errors**

Data **cleaning** - examples

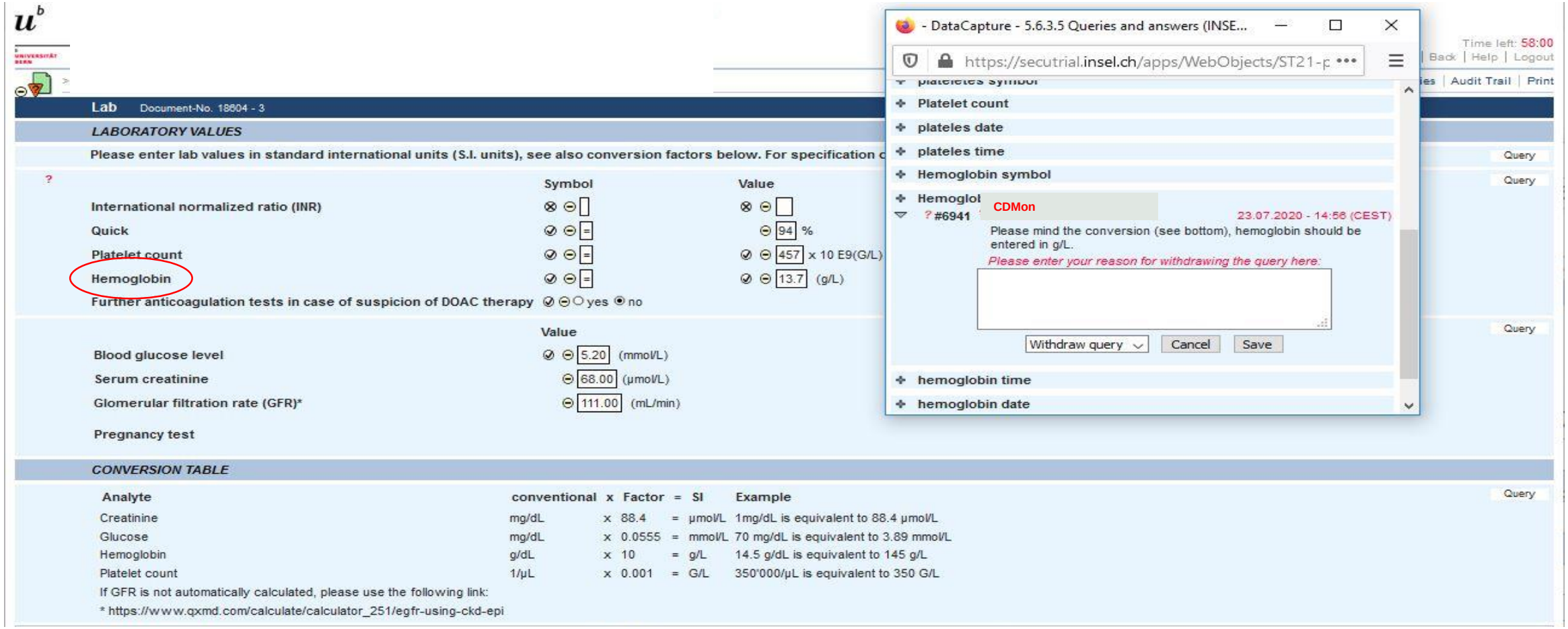
Changes in medication: e.g. trial medication stop was incorrectly entered in database even though medication was continued



Changes in Medication must be documented accurately

Data **cleaning** - examples

Measurement units: incorrect units or no/incorrect conversion



Hemoglobin 137 g/L = 13.7 g/dL

Double check the correctness of the values that are entered

(additional units needed?)

Data **cleaning** - examples

Serious adverse event (SAE) reporting:

SAE AND INVESTIGATOR INFORMATION	
Date of initial report	25.07.2021 dd.mm.yyyy
Start date of SAE	15.02.2021 dd.mm.yyyy
Date of awareness of the SAE by the trial site	10.03.2021 dd.mm.yyyy

SAE not reported to the Sponsor within 24 hours of awareness e.g. in a drug trial

Adhere strictly to SAE reporting timelines!

Data **cleaning** - examples

Language must be English – especially for safety reporting

	Specify AE		Need for medical/surgical intervention		
1.	V.a. chronisch-fistelnde Os		◉ yes	○ no	
2.	hypovolämischer Schock		◉ yes	○ no	
3.	Hypertension		◉ yes	○ no	
4.	Plusbilanz Niere		◉ yes	○ no	
5.			○ yes	○ no	

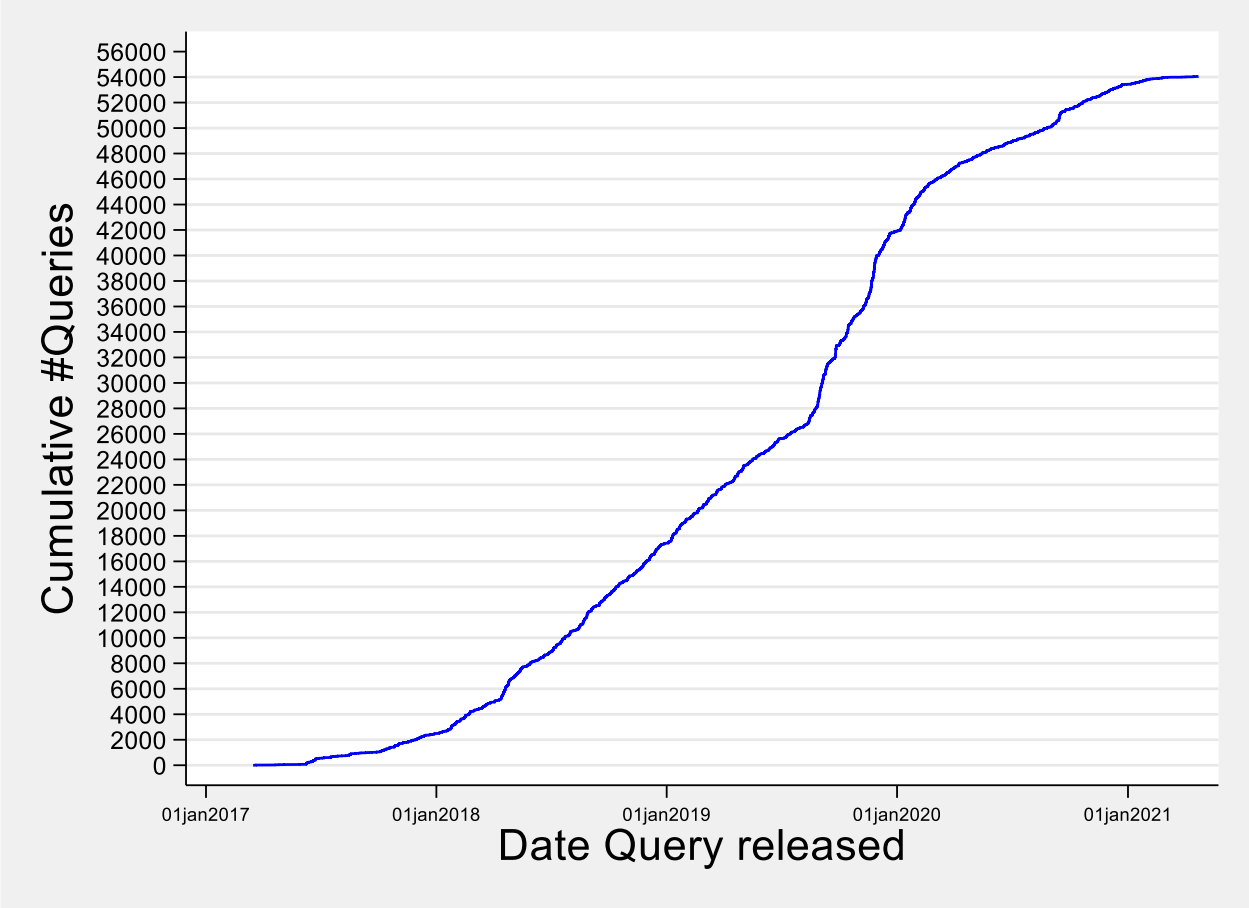
Nr of queries

Trial	Nr of patients	Nr of visits	Nr of queries	Queries/patient
SERVE	100	4	983	9.8
CLEVER ACS	150	2	2048	13.7
PACMAN	300	9	2187	7.3
EVOPACS	308	3	1722	5.6
SCOPE	739	4	10242	13.9
BIOSTEMI	1300	3	2395	1.8
MASTER DAPT	5204*	6	54048	10.4

Nr of visits: only counting baseline and all mandatory follow-up visits
*includes n=625 consented but non-randomized patients with only 2 visits

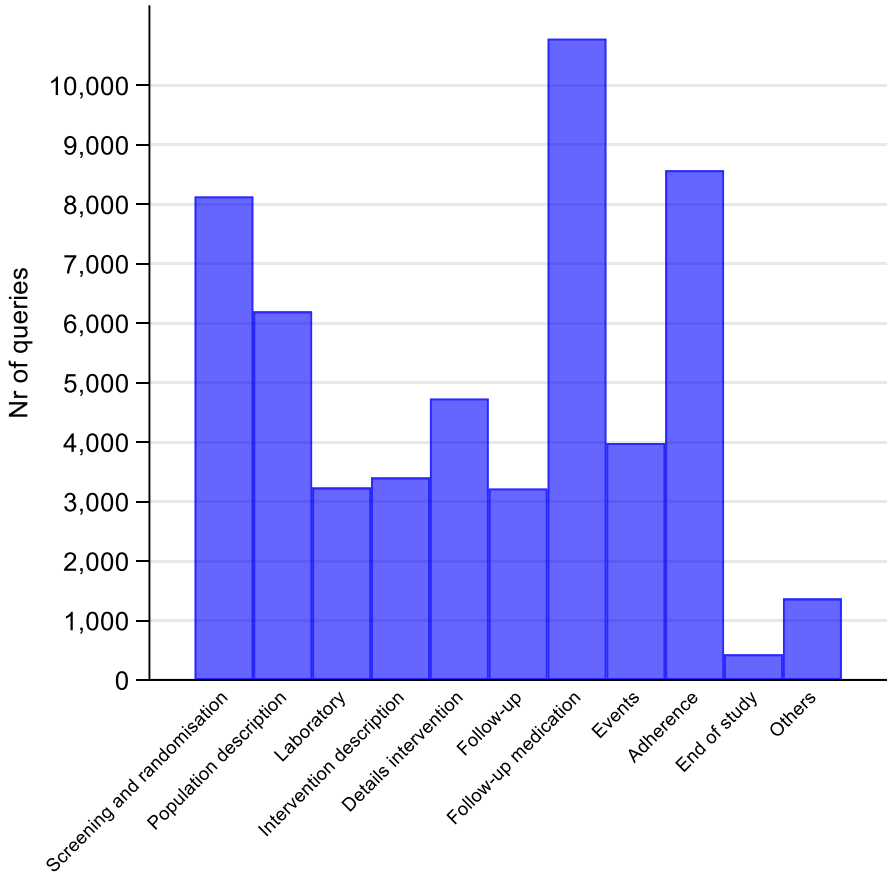
Includes **avoidable queries** due to changes/change of interpretation in the eCRF which need to be queried to complete/amend!

Nr of queries



Unanswered queries and **delayed data entry** are often a problem to close the trial… phone calls, emails…

Nr of queries



e.g. daily Adherence checked with cross-sectional Follow-up medication = **majority of queries**

Data **monitoring**

Perspective

Closer view

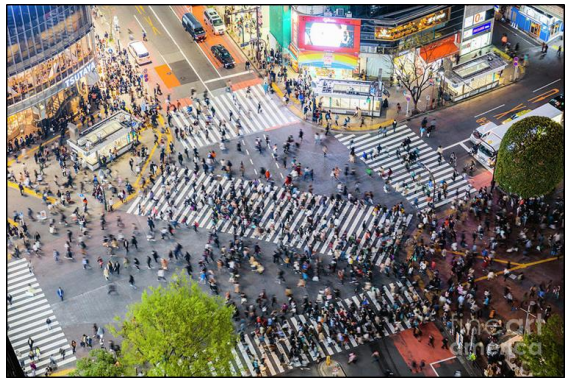
On-site monitoring

Bird’s eye view

Central data monitoring

Patterns or trends can be identified only if data is seen as a whole

VS.



On-site monitoring	Central data monitoring
Visits to the trial site	Data centrally monitored
Source data verification – Review documentation of informed consent, eligibility criteria; ISF/TMF; **medical records** to assess AEs, SAEs, protocol deviations; Investigational product accountability, storage, etc.	No access to source documents
Personal contact with the site staff – assess site's familiarity with protocol, involvement of the investigators and PI in the study; **verification of proper study conduct**, safety of the study participants, etc.	Contact through queries, emails, phone

VS.

On-site monitoring	Central data monitoring
Study Data	
Scattered view of the data • Data of one site at a time • Few patients at a time (1-5) • Data at the time point of monitoring is checked	**Overall view of data – data export** • **all trial sites** from the study • **all patients** included in the study • **all visits** – FPFV to LPLV
Cross-site trends Difficult to compare across sites	**Identify cross-site trends**, inconsistencies, and differences between study sites **in real time** – • Site performance • Participant safety • Adherence to ethical principles and participant rights • Possible data fabrication

Cross-site trends

Site performance:

Sites with

1. a high number of screening failures, withdrawals, or discontinuations
2. too many or too few protocol deviations
3. a large amount of missing data, missing visits
4. a high number of queries or queries remaining unanswered for a long time, or answers are unclear.
5. Not completing the eCRF in a timely manner
6. Other protocol specific indicators

Patient safety:

1. sites reporting an unusual number of (S)AEs, i.e. considerably more or fewer (S)AEs than the average site
2. many subjects enrolled though all eligibility criteria are not met, or enrolling patients before confirming all eligibility criteria (e.g., patient randomized before checking a blood value that is important for eligibility)

Cross-site trends

Adherence to ethical principles and participant rights:

1. Study-specific examinations or interventions are performed before informed consent was obtained.

Possible data fabrication:

1. Lack of variability or preference of digits in the recorded data across visits of a single subject or across multiple subjects.
2. Data too perfect

- ✓ Export of data form the database into simple tools like Microsoft Excel can be sufficient
- ✓ Assessment of more complex issues might require statistical methods, e.g. KPI reports (critical performance indicators)

Data **monitoring** – spot the difference

3m	6m	9m	12m	15m	18m	21m
yes, call performed						
yes, visit performed						
yes, visit performed	yes, call performed	yes, call performed	yes, visit performed	yes, call performed	yes, call performed	yes, call performed
yes, visit performed	yes, call performed	yes, call performed	yes, visit performed	yes, call performed	yes, call performed	no
yes, visit performed	yes, call performed	yes, call performed	yes, visit performed	yes, call performed	yes, call performed	no
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yes, call performed	yes, call performed					
yes, call performed	yes, call performed	yes, call performed				
yes, call performed	yes, call performed					
yes, call performed						
yes, call performed	yes, call performed	yes, call performed	yes, visit performed			
no	no	no	yes, visit performed			
yes, call performed	yes, call performed	yes, call performed				
yes, call performed	yes, call performed	yes, call performed	yes, visit performed			
yes, call performed	yes, call performed	yes, call performed				
yes, call performed	yes, call performed	no				
yes, call performed	yes, call performed	yes, call performed				
yes, call performed	no	no				
yes, call performed	yes, call performed	yes, call performed				
yes, call performed	no	no				
yes, call performed	yes, call performed	yes, call performed				
yes, call performed	yes, call performed	yes, call performed				

Missing visits

Data **monitoring** – spot the difference

Study XYZ

Universitätsspital XYZ

Recruitment Report

2.2 Number of samples

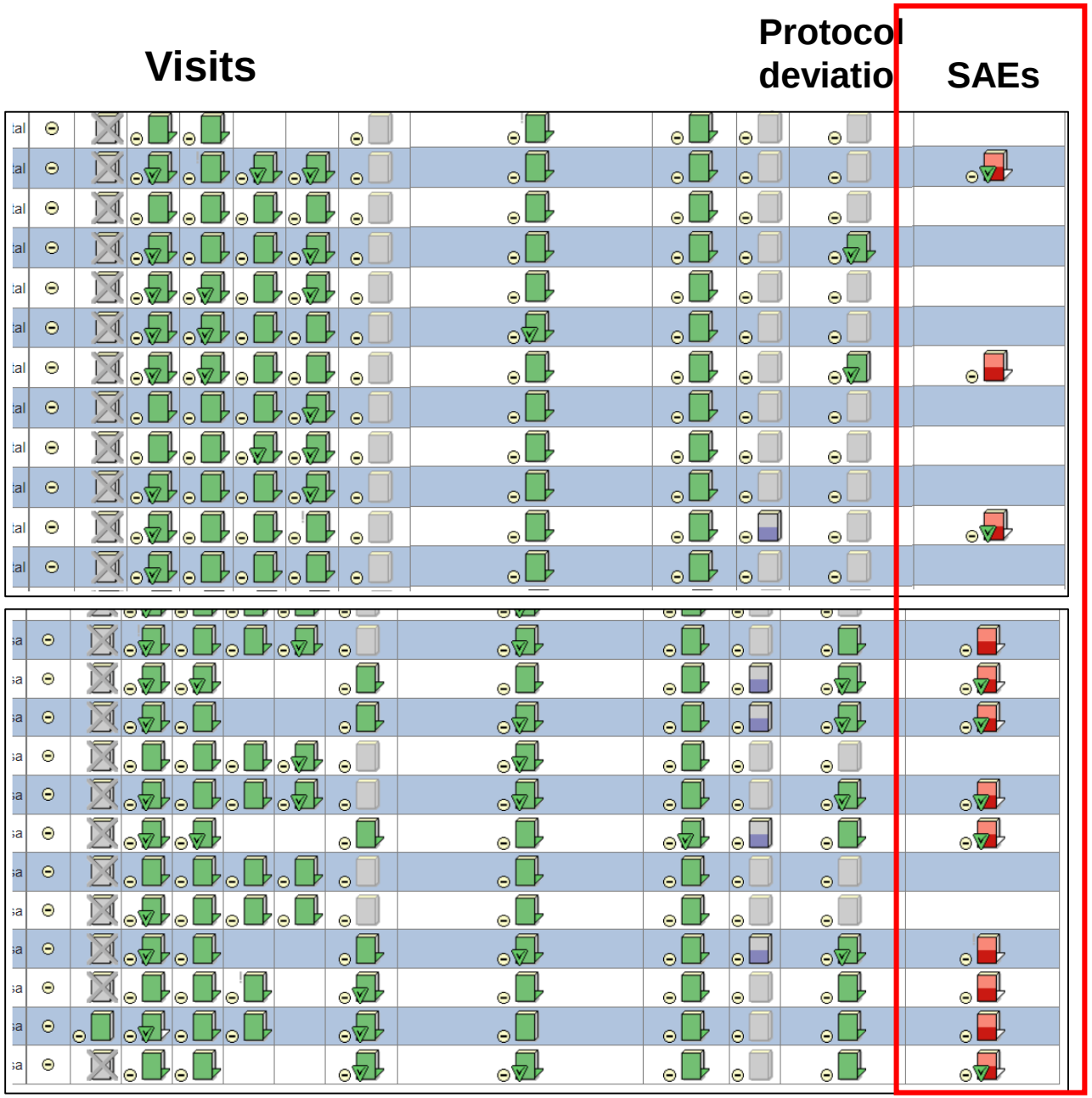
Samples from patients with pending definitive consent or which are screening failures or refused to participate are not shown in this table

	Total no. of EVD and LD samples	Total no. of EVD samples	Total no. of LD samples	Total no. of CSF infections*	% of CSF infections
Site 1	336	293	43	0	**0.00%**
Site 2	160	132	28	3	**0.02%**
Site 3	27	27	0	1	**0.04%**
Site 4	5	5	0	0	**0.00%**
Site 5	21	21	0	5	**0.20%**
Total	**549**	**478**	**71**	**9**	

**Positive CSF culture without clinical symptoms is not counted as infection in this table.*

Compare the occurrence of endpoints across sites:

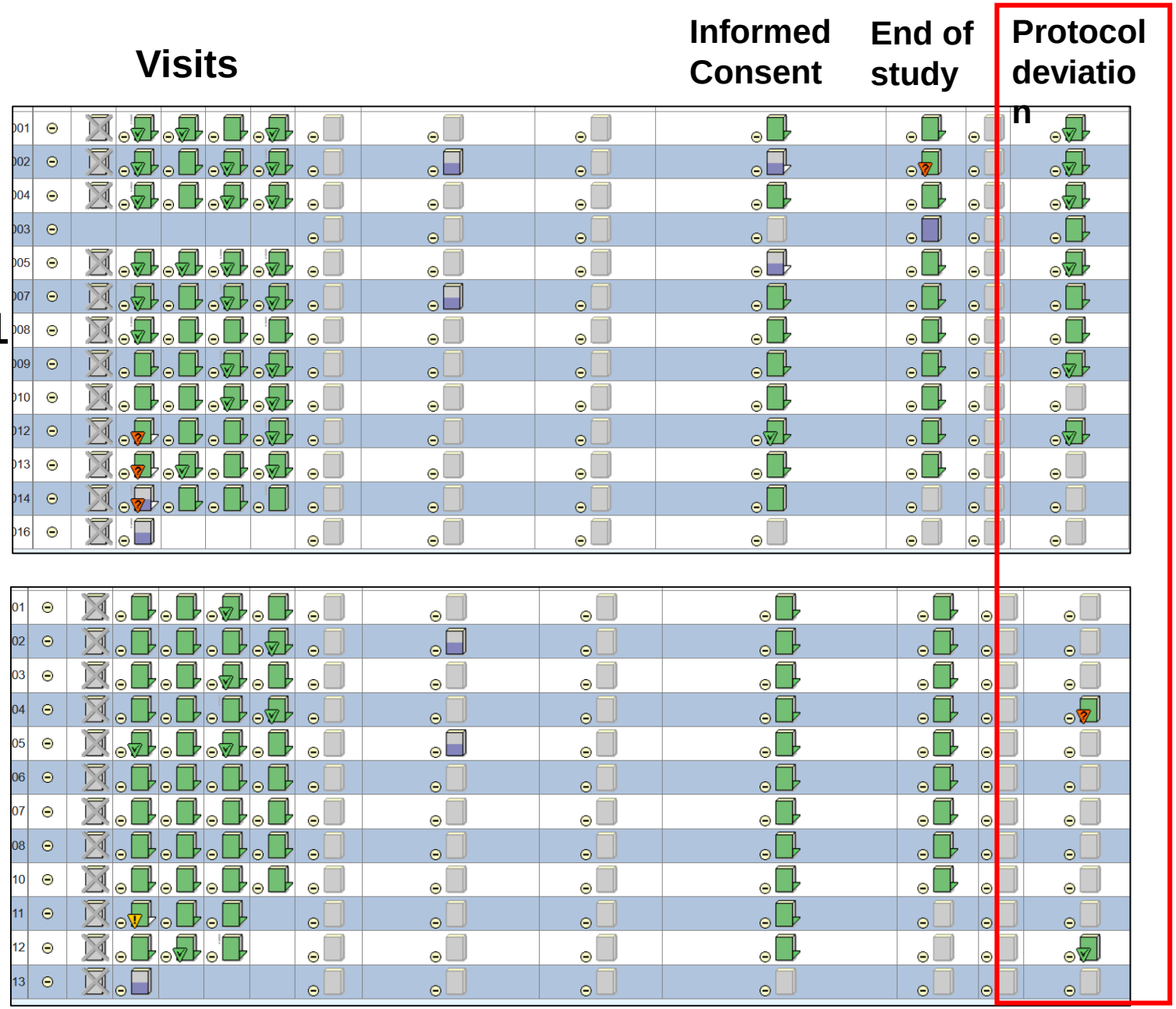
Data **monitoring** – spot the difference



~1% of patients

Many SAEs
45.0% of patients

Data **monitoring** – spot the difference



Too many protocol deviations

78.5% patients

20.0% patients

Data monitoring report

Central Data Monitoring Progress Report

Study acronym or No.:	
Sponsor:	
Date of report:	
Database:	Choose an item.

Status of central data monitoring (CDM)

No. of subjects planned: No. of subjects <enrolled/randomized, recruited etc., based on the study> so far: % of planned subjects <enrolled/randomized, recruited etc., based on the study> so far:	 %
No. of CRF pages planned to be monitored (total in the study): (Excluding repetitive pages such as <insert repetitive pages i.e., forms that need not be filled in for all participants e.g., (Serious) adverse event, protocol violation forms, etc.>) Note that numbers only refer to CRF pages that need to be monitored according to the monitoring plan.	
Total no. of CRF pages filled in so far (planned and repetitive pages) No. of CRF pages with CDM completed (<locked / review A performed / checked>) % of CRF pages with CDM completed (<locked / review A performed / checked>) No. of CRF pages with queries (and **not** <locked / review A performed / checked>) % of CRF pages with queries (and **not** <locked / review A performed / checked>) Note that numbers only refer to CRF pages that need to be monitored according to the monitoring plan.	 % %
Total no. of queries raised so far: No. of queries resolved so far: No. of queries still open:	
Remarks: <e.g. if any additional forms are checked; if any fields or pages other than mentioned in the monitoring plan were reviewed, etc.>	

Central data monitoring observations

1. General issues
<report here any issues that concern the study as a whole, such as: - Inconsistencies in the study protocol - Any patterns or trends observed in data - Delay in filling in the data in the database - Difficulties in communication with the sites in general, etc.>
2. Database issues
<report here any major issues related to the database i.e., issues with the database itself, and not issues related to the recorded data: E.g. issues that have a major impact on data quality, such as inconsistencies in forms related to end point data, safety reporting forms, implementation of new forms or fields based on CDM findings etc., or any other issues considered important by the CDMonitor.

Questions?