KEY CONSIDERATIONS AND CHALLENGES OF EDC IN THE IMPLEMENTATION AND STATISTICS OF CLINICAL TRIALS

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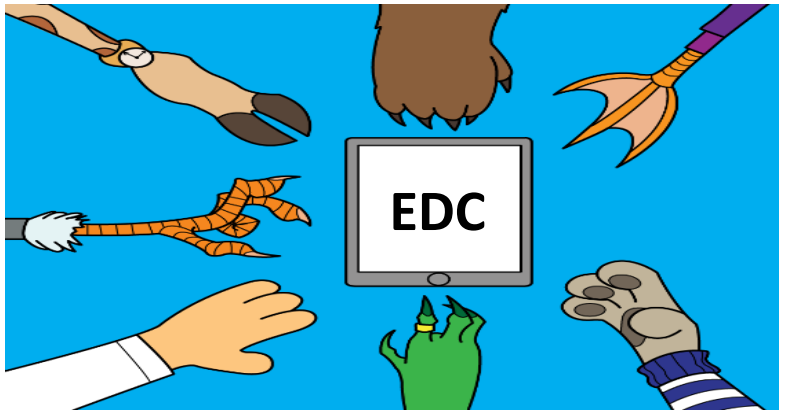
Omrix Biopharmaceuticals, Johnson & Johnson

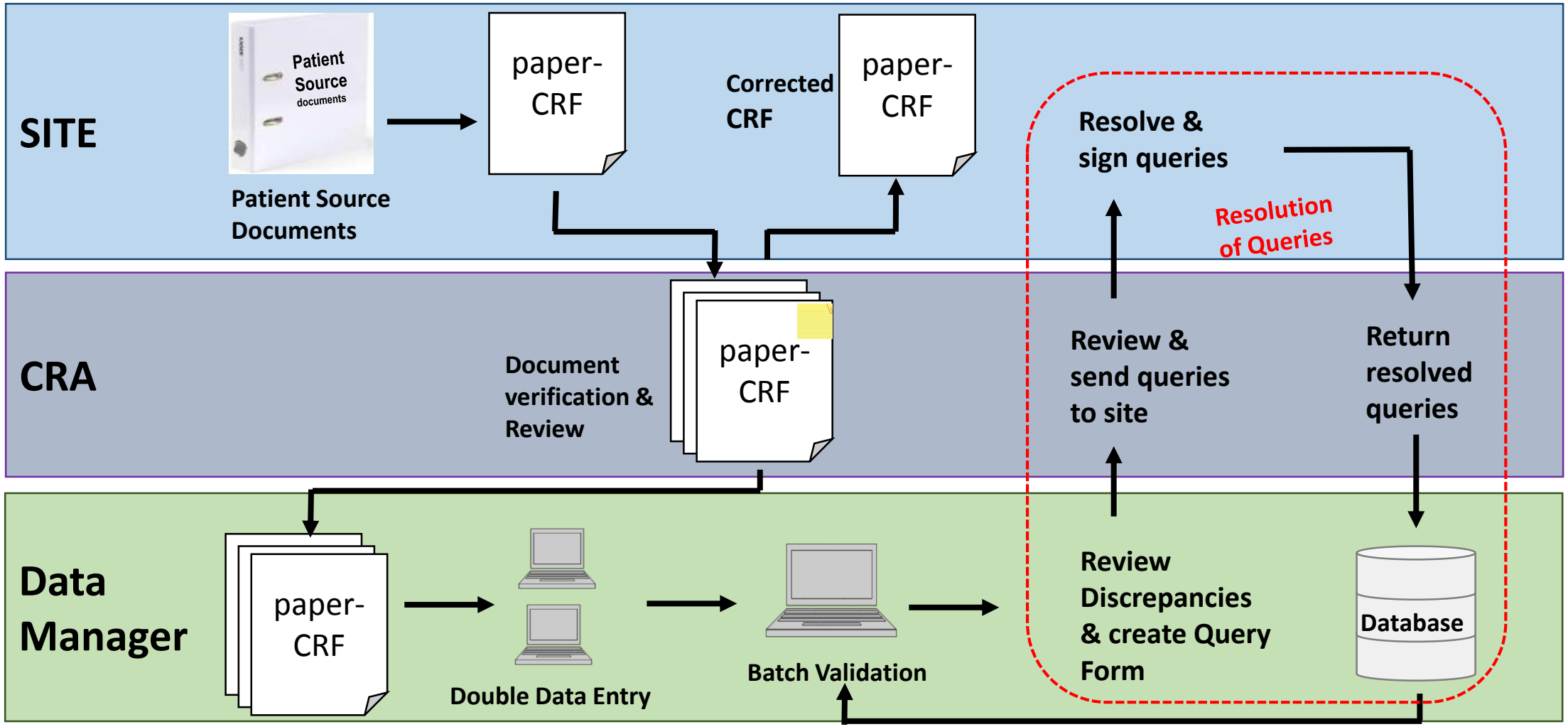


A Brief Survey:

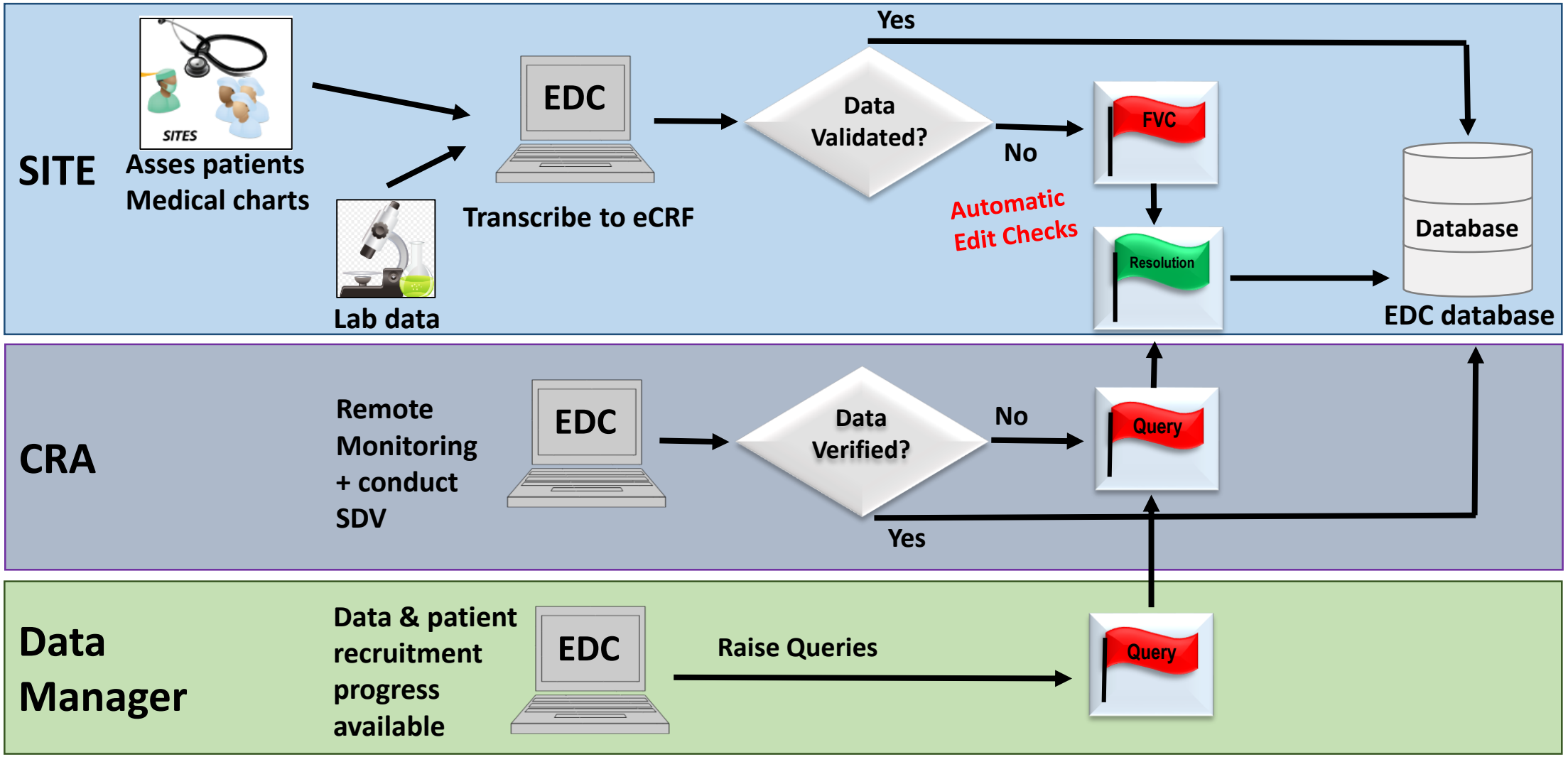
Which of the following describes your organization's Data Management?

- Full **EDC** system
- **Hybrid** combination of **paper-CRF** and **EDC**
- **Paper-CRF**

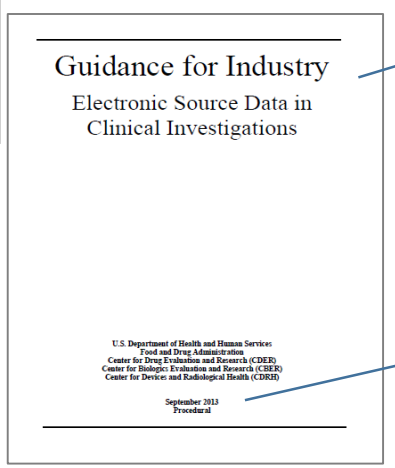
Data collection using paper-CRF



Data collection using eCRF



FDA 2013: Promoting eSource


Guidance for Industry
Electronic Source Data in Clinical Investigations

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

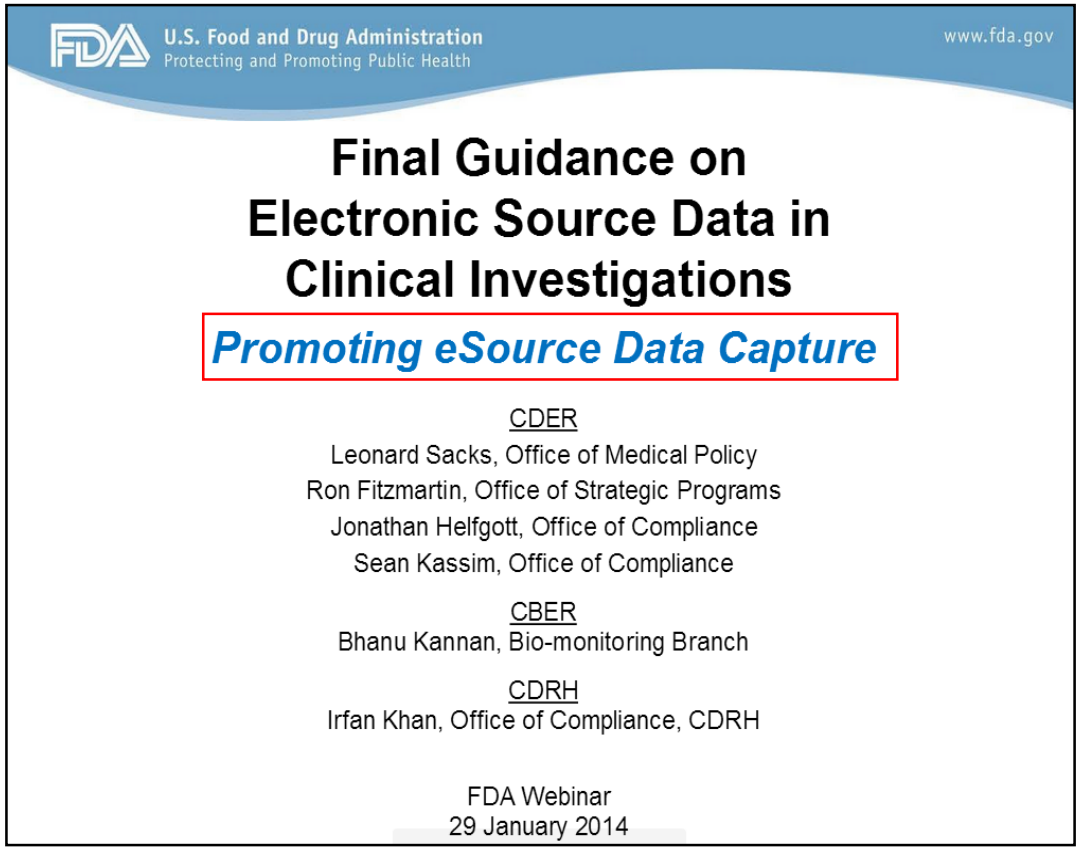
September 2013
Procedural

Guidance for Industry
Electronic Source Data in Clinical Investigations

September 2013

Why eSource?

- "…**promotes** capturing source data in electronic form…,"
- [assists] "in **ensuring** the **reliability, quality, integrity**, and **traceability** of electronic source data."


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Final Guidance on Electronic Source Data in Clinical Investigations

Promoting eSource Data Capture

CDER
Leonard Sacks, Office of Medical Policy
Ron Fitzmartin, Office of Strategic Programs
Jonathan Helfgott, Office of Compliance
Sean Kassim, Office of Compliance

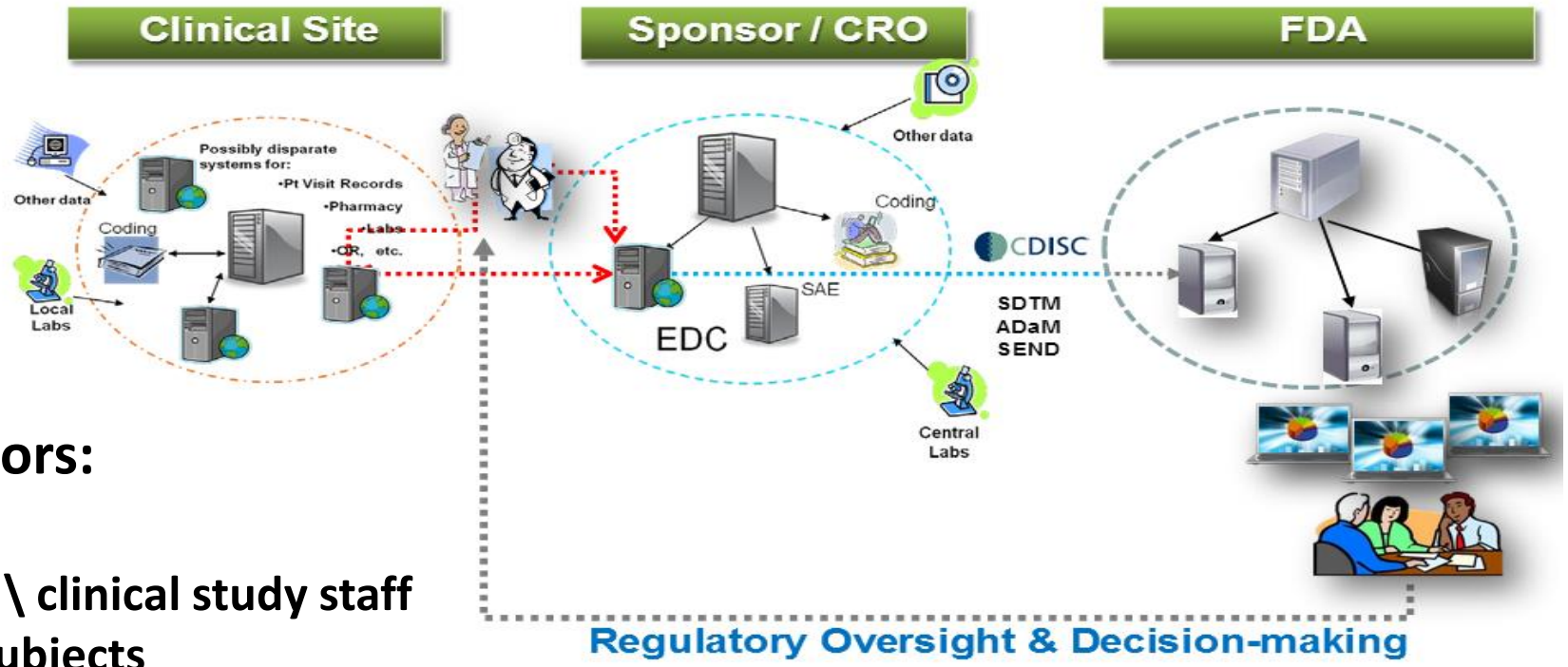
CBER
Bhanu Kannan, Bio-monitoring Branch

CDRH
Irfan Khan, Office of Compliance, CDRH

FDA Webinar
29 January 2014

Source: 2014 FDA "Promoting eSource Data Capture"

Data initially recorded in electronic format – no intermediary



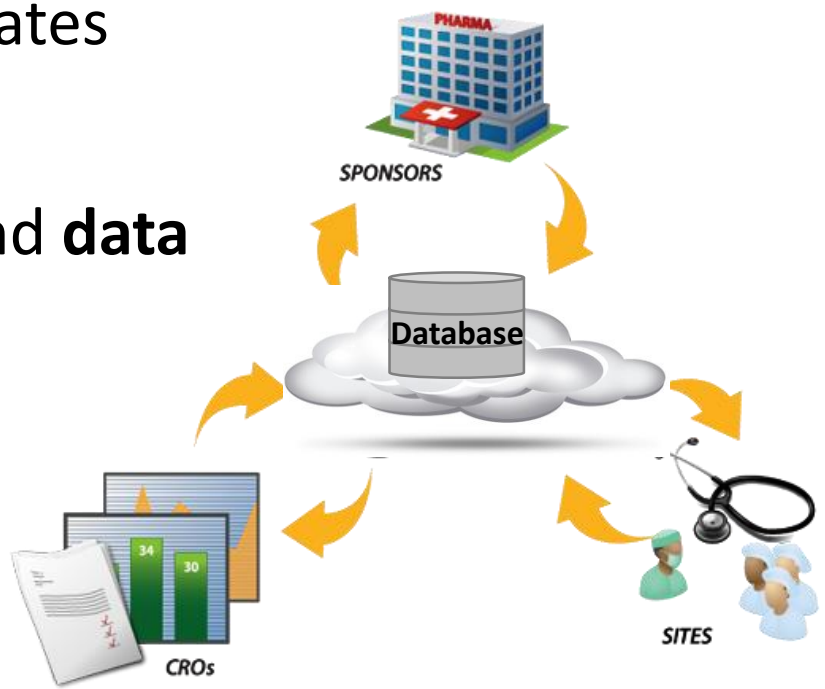
eSource data originators:

- **Clinical investigator(s) \ clinical study staff**
- **Clinical investigation subjects**
- **Consulting services** (e.g., a radiologist reporting on a CT scan)
- **Medical devices**
- **Electronic health records** (EHRs)
- **Automated laboratory reporting systems**

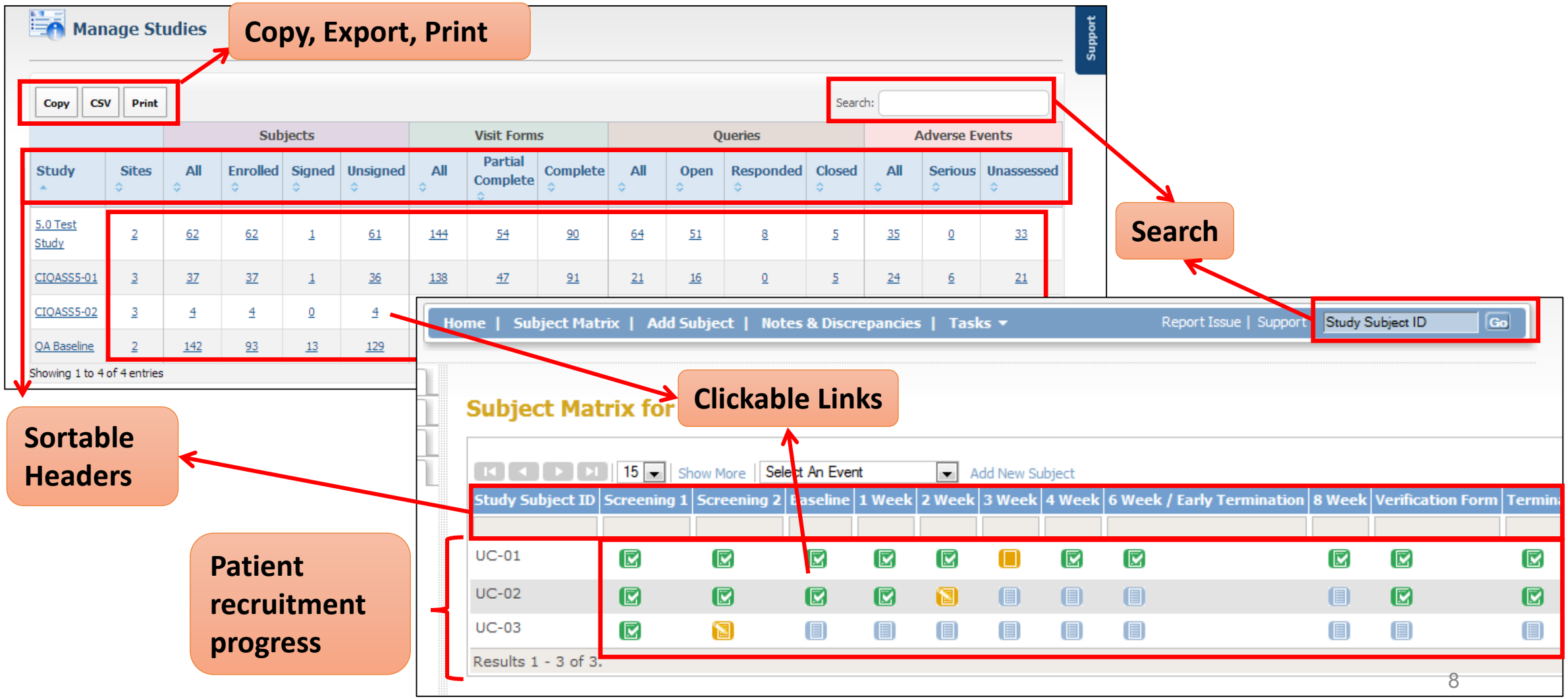
Source: 2014 FDA "Promoting eSource Data Capture"

Benefits of EDC deployment

- **REAL TIME Automatic Edit Checks**
- **Worldwide Connectivity** - Real Time Data Accumulation
- **REAL TIME Recruitment progress and status** updates automatically on **EDC dashboard**
- Ability to control both **hierarchical data access** and **data transparency**
- **Higher data quality – increased statistical power**
- **Mid-term reports** easily accomplished



EDC Applications Dashboards

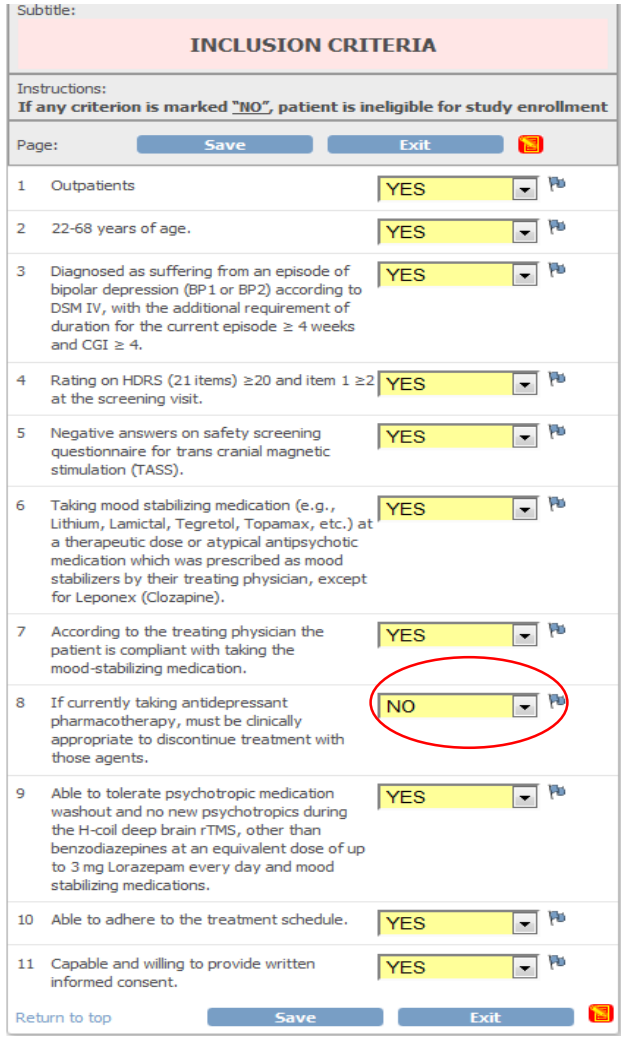


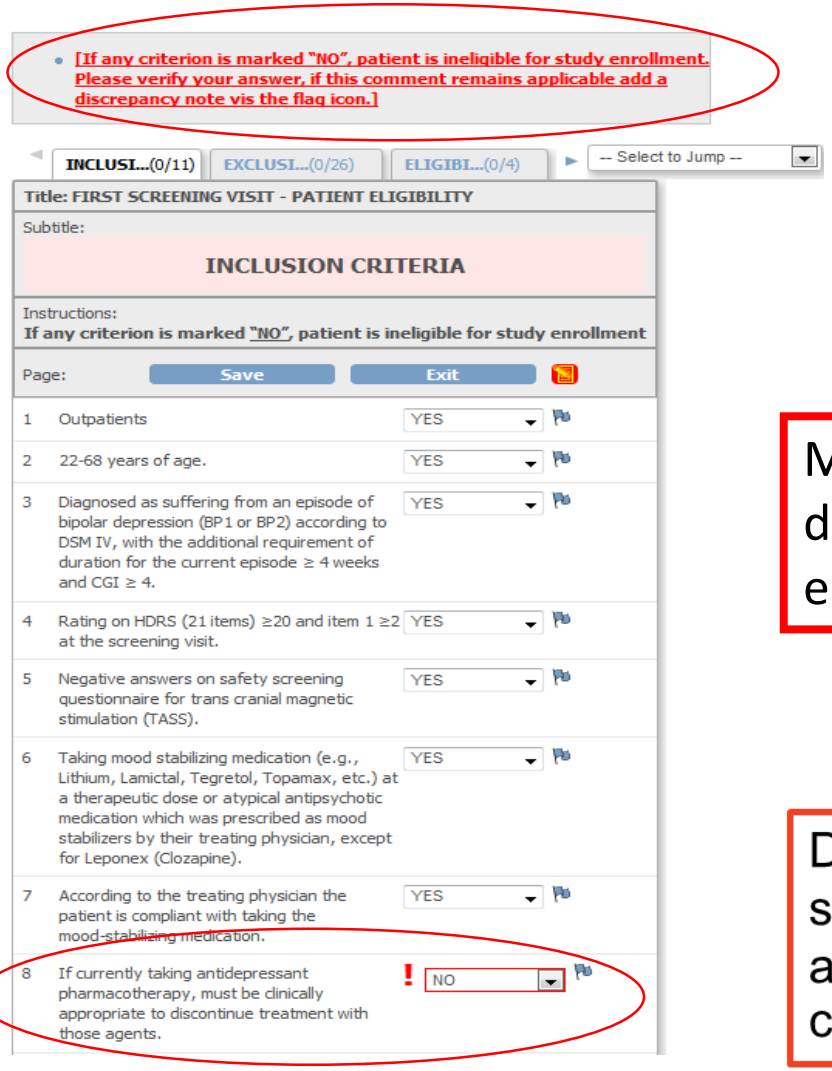
REAL TIME Edit Checks

- **Predefined** in the EDC system, **usually by the data manager**.
- **Prevent** the end-user from entering **mistaken invalidated data**.
- **Simplify monitoring** activities

Edit Check type	Example
Patient Eligibility	If any **Exclusion Criteria** are **yes**, then error message that **Subject should not participate**.
Comment availability	If a body system is selected as **Abnormal**, a **reason must be provided**.
Chronologic dating	**End date** is **not before Start Date**
Range checks	**Age is between 18 and 85**

Example for a Failed Validation Check (1):





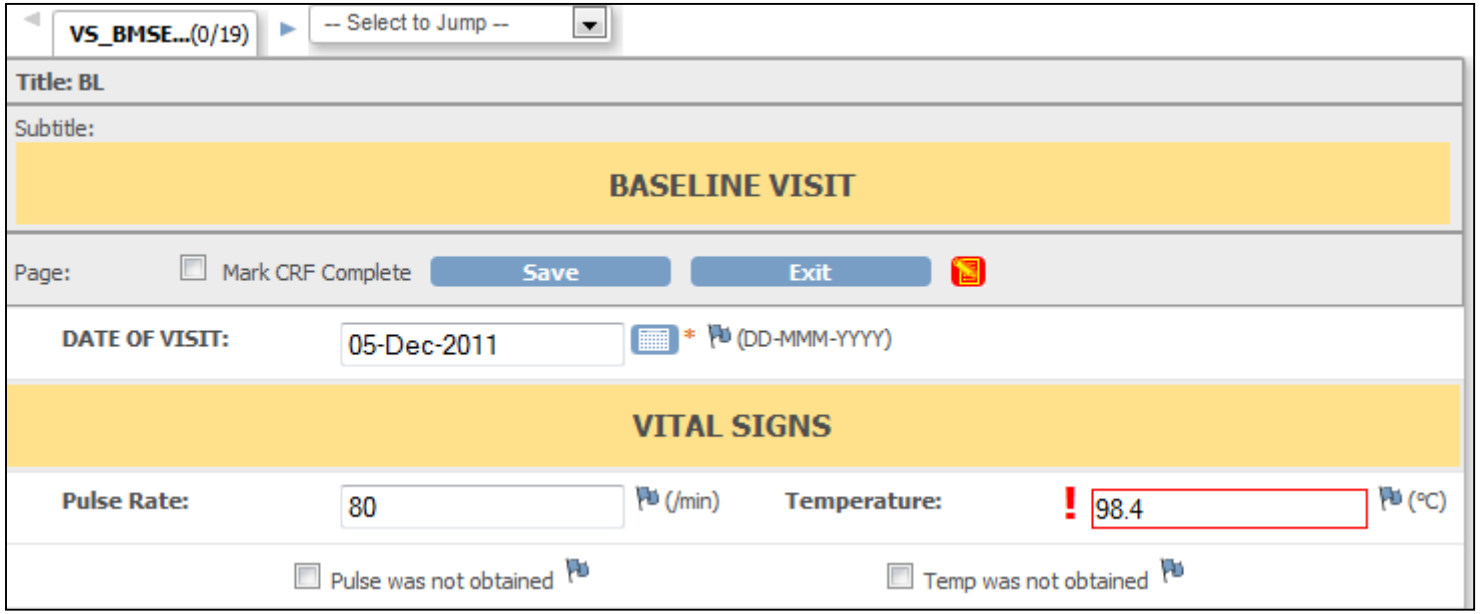
Mistake during data entry

Data is submitted after correction.

Example for a Failed Validation Check (2):

- [Make sure you convert the Temperature from ℉ to ℃! If the temperature was entered in Celsius and is still out of range: 35.5-41℃, please add a discrepancy note via the flag icon.]

System Alert!



Temperature entered in ℉ instead of ˚C.

Data is submitted after correction.

Data Element Identifiers (DEIs) enable Audit Trail

- The eCRF should include the capability to record **Audit Trail**:
  - **Who entered / transmitted** and **When**?
  - **What changes were made**? **When**? **Why**?

FDA 21 CFR Part 11

- DEIs should be attached to each data element:
  - **Originators of the data element**
  - **Date and time of data entry into the eCRF**
  - **Subjects to which the data element belongs**

- Allowing sponsors, FDA, and other authorized parties to **examine the audit trail of the eCRF data**.
- **Allowing FDA to reconstruct and evaluate the clinical investigation**.

Possible EDC implementation obstacles

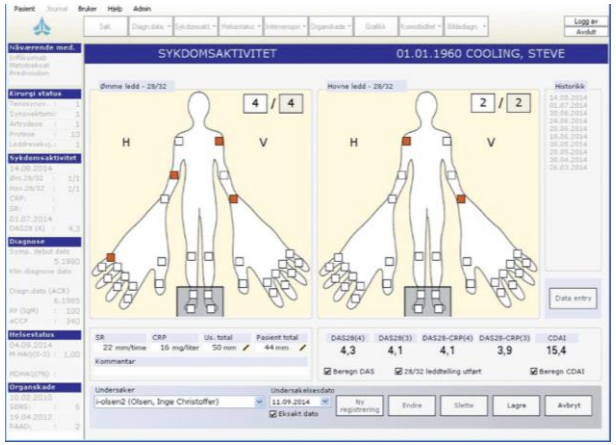
- High upfront cost
- Inability to work offline
- Need to invest in technical knowledge
- Resistance to change
- Restrictive Data Entry
- Loss of flexibility

Pros or Cons?

Let’s have a closer look

NOR-DMARD Case Study (1):
Transition from paper-CRF to EDC system

- **2000 ->** the **NOR**wegian **D**isease **M**odifying **A**nti-**R**heumatic **D**rugs (NOR-DMARD) **registry started recording disease activity, quality of life measures and adverse events during DMARD treatment** in 5 different rheumatology departments.
- **2011 -> new protocol** with focus on **biologic DMARD** treatment
- In addition **Electronic Health Record system** was implemented to enhances disease monitoring, e.g. providing a graphic and numeric display of data.



EHR system limitations:

1. The study tool was quite **rigid** and **limited to pre-specified modules**;
2. **Adverse Events** and other protocol-specific information **couldn't be adequately captured**;
3. **No Audit Trail** or **query handling**;
4. The **data were stored locally** without a central database.

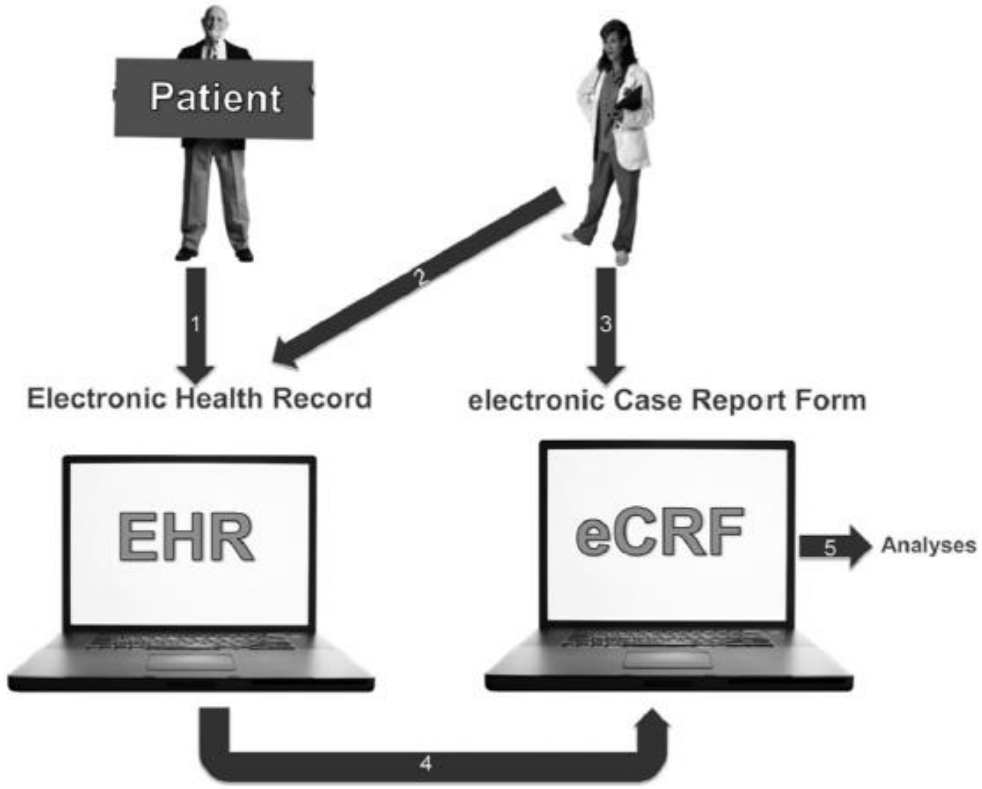
EDC system was added

Source: *"NOR-DMARD data management: implementation of data capture from electronic health records"* © Copyright Clinical and Experimental Rheumatology 2014

NOR-DMARD Case Study (2):
Transition from paper-CRF to EDC system

Data flow in the NOR-DMARD registry:

1. The **Patient records** his patient registered outcomes (**PROs**) **into the EHR system**;
2. The **treating nurse/physician** also **records clinical information into the EHR system**;
3. **Adverse Events** are **registered directly to the EDC system**.
4. **The EDC system generates a unique patient number,** which is then **registered in the EHR.** Enabling **transfer from one system to the other.**
5. **Data** in the eCRF is **available for analyses at any time.**



***Source**: "NOR-DMARD data management: implementation of data capture from electronic health records"* © Copyright Clinical and Experimental Rheumatology 2014

NOR-DMARD Case Study (3):
Transition from paper-CRF to EDC system

Previous paper-CRF vs. current EDC system **costs comparison**:

	paper-CRF
CRO Costs	14 EUR per visit\CRF
Total	**~88,000 EUR**

	EDC
Initial set-up costs (+ licensing fees)	18,000 EUR
Yearly licensing fees	1,800 EUR
Total	**24,000 EUR***

*Exclude the costs of the EHR system and some internal data management costs.

This illustration is based on data from almost **6400 visits** in **3400 patients** included in the EDC system between May 2012 and August 2014.

Source: *"NOR-DMARD data management: implementation of data capture from electronic health records"* © Copyright Clinical and Experimental Rheumatology 2014

NOR-DMARD Case Study (4):
Transition from paper-CRF to EDC system

EDC Advantages:

- **Data feasibility**,
- **Lower cost,**
- **Data quality**, and
- Routine **data extraction within minutes**

Problems and challenges:

- **Export/Import routine is complex and relies on SAS programming expertise:** only one person within the study management had the necessary knowledge to import from the EHR into the EDC system.
- The **export/import routine** is quite time consuming ~ **10 hours per transfer**.

Source: *"NOR-DMARD data management: implementation of data capture from electronic health records"*

EDC available at the market

	Commercial EDC	**Open-Source EDC**
Developer:	For-profit company or developer group	A single or group of developers, often as a voluntary effort.
Charges:	User licenses with or without annual support contracts	Free of charge *requires personnel training
Source Code:	Not published	Published online and can be **downloaded for free**
Some examples include:	Oracle® Clinical (Oracle, USA) Clinsys® (Jubilant Organosys, USA) InForm™ (Phase forward, USA) DATATRAK EDC (DATATRAK, USA) Medidata Rave® (Medidata Solutions)	OpenClinica® (Akaza Research, USA) DADOS P (Research group, Duke University, USA) Redcap (Vanderbilt University, USA) TrialDB (Yale University, USA)

Data Track Technology · medidata · MACRO · OpenClinica · REDCap Research Electronic Data Capture · clinovo Clinical Data Solutions · ORACLE · BIOCLINICA SEE MORE CLEARLY

***Source**: "Electronic Data Capture for Registries and Clinical Trials in Orthopaedic Surgery"* Open Source versus Commercial Systems

Considerations when comparing systems available at the market

- Availability of relevant personnel to support the system?
- Multi -central / single site?
- Payment **per study** ? Or **monthly fee** to run all your studies?
- Payment **per system user**? **per site**?
- **Training** site personnel? **Support number**?

- There are no clear rules!

Biostatistician involvement in EDC system design

Principal Investigator
- **Study purpose** and objectives
- Define **tests** and **evaluations**
- Operational aspects

Protocol

Statistical Analysis Plan

Biostatistician
- Study endpoints
- **Sample size** calculation
- Interim analysis planning
- Statistical methods

CRF review and approval

Case Report Form

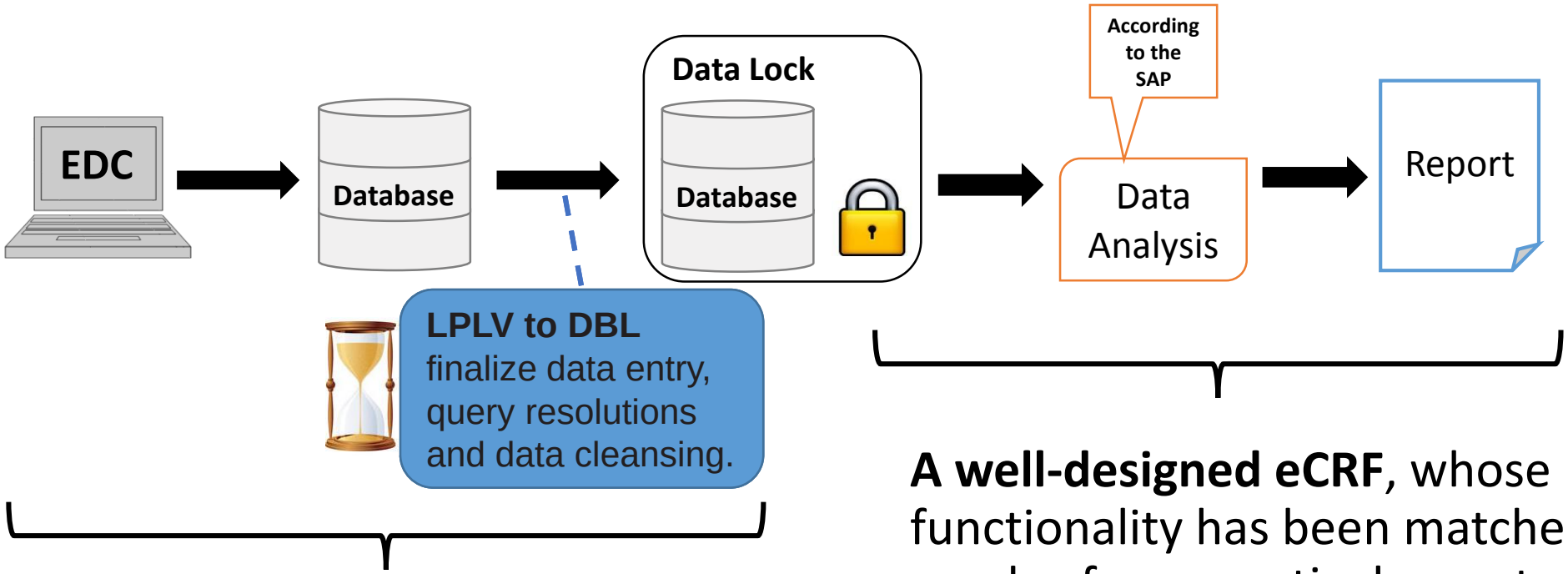
Biostatistician
- Ensure data requested will answer the aims of the study
- Review edit checks

Data Management Plan

Data Manager
- Develop electronic database

EDC

The clock is ticking -> Data analysis



Efficient database- less time to review /clean data

A well-designed eCRF, whose functionality has been matched to the needs of your particular protocol brings huge **benefits in data quality** –> **increases statistical power**.

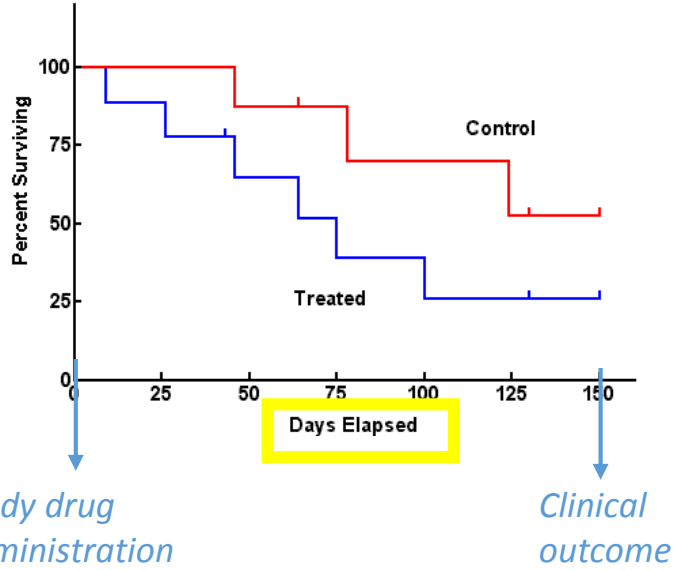
Source: *"*A Statistician Shows How to Save Time and Money through Data Management " By Katherine L. Monti

When statisticians review CRFs, they can be useful with:

- Making sure that **only essential information** is collected
- **Consistent coding** of variables -to avoid data loss or late detection.
- **Identifying relevant data checks -** used to **find errors early** —in order to gain greater efficiencies
- **Risk based monitoring -** helping decide **which questionable data values are worth querying**

Data error example:
Missing times - the most common missing variables in CRFs

- **Survival analysis:** is an analysis of the expected duration of time from a certain event to the other.



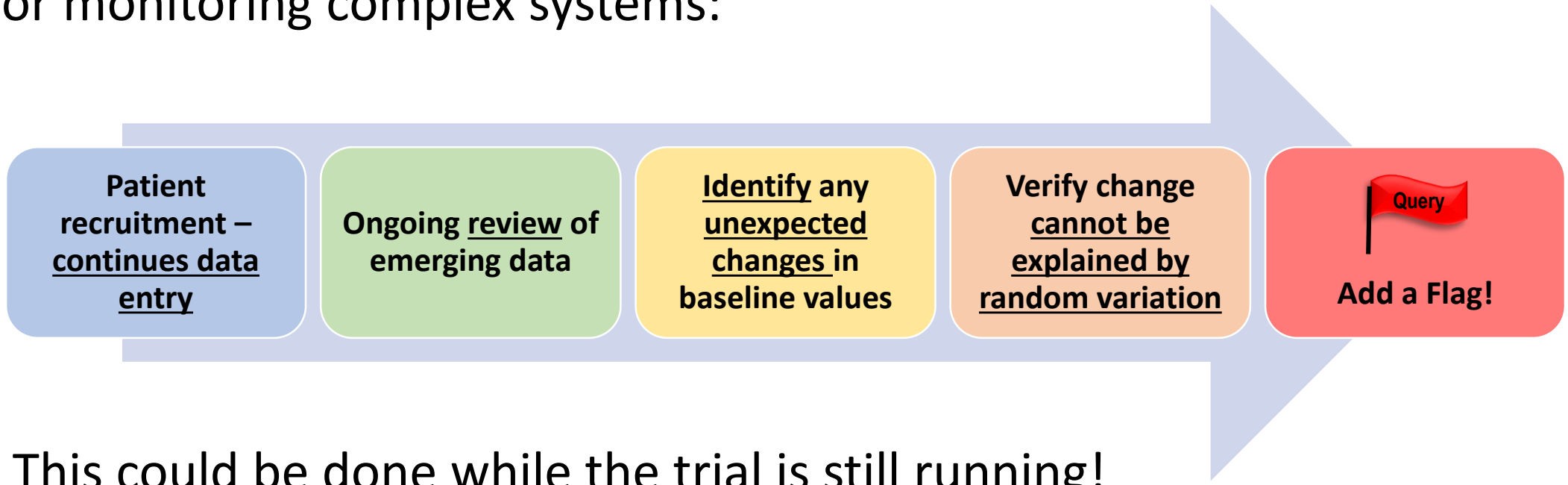
Expected survival Times	Required units
Long-term survival times	Calendar dates
Shorter-term survival times	Calendar dates+ clock times (sometimes even seconds!)

- In case the CRF design **fails to capture time with sufficient accuracy**, we will **loss statistical power**.

The future holds:

Implementation of statistical process control into the eCRF

For monitoring complex systems:



- This could be done while the trial is still running!
- In a **conventional locked clinical database** such artefacts are **identified only during data analysis**, it is then **lowering the trial power**.

Thanks for listening!!!