

Challenges and opportunities related to the use electronic data capture for cancer clinical trials

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Contents

- Short introduction to EORTC
- EORTC e-landscape
- E-consent
- E-data management
- Specific e-QA programs
- E-monitoring
- Some future perspectives
- Conclusions

Accrual of screened patients in EORTC clinical studies from 2000 to 2016: 89095 patients

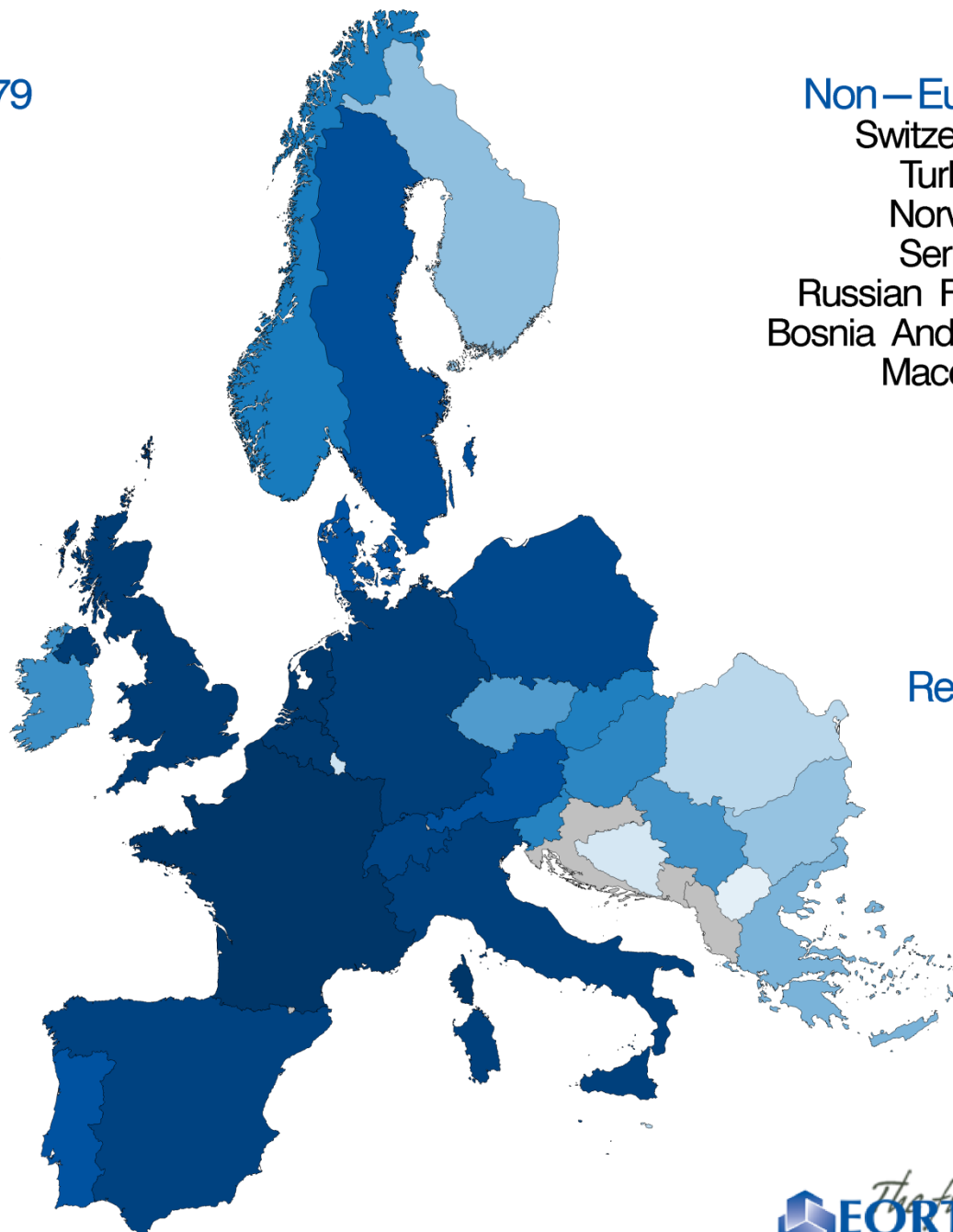
European Union: 79479

France: 17779
Netherlands: 17350
Belgium: 9472
United Kingdom: 8604
Germany: 8174
Italy: 7479
Spain: 3823
Poland: 1296
Sweden: 977
Austria: 960
Portugal: 725
Denmark: 642
Slovakia: 480
Slovenia: 414
Hungary: 364
Ireland: 286
Czech Republic: 209
Cyprus: 101
Greece: 96
Finland: 64
Bulgaria: 51
Estonia: 39
Latvia: 34
Malta: 20
Romania: 20
Lithuania: 11
Luxembourg: 9

Non—European Union: 3649

Switzerland: 2011
Turkey: 631
Norway: 489
Serbia: 283
Russian Federation: 221
Bosnia And Herzegovina: 8
Macedonia: 6

Rest of the world: 5967



EORTC by the numbers (2016)

| A world-class network | An expert HQ | Unique output |
|---|--|--|
| <ul style="list-style-type: none">• $\pm 5,000$ collaborators• 870 institutions• 35 countries• 21 groups & task-forces• 111 collaborative groups | <ul style="list-style-type: none">• 202 employees• > 195,000 patients in database• 24,000 patients in follow-up | <ul style="list-style-type: none">• 12 new studies open to patient entry in 2016• 54 ongoing studies• 19 studies in protocol outline development• 15 studies in protocol development• 15 studies in regulatory activation• Working on ≈ 193 studies |

Tools for clinical trials management

ORTA identification

| | | |
|----------------------------------|---|--|
| Institution number | <input style="width: 90%;" type="text"/> | |
| Protocol | <input style="width: 90%;" type="text"/> | Details |
| Step | <div style="border: 1px solid #000; padding: 2px; display: inline-block;"> 1 - New patient </div> | |
| Responsible physician name | <input style="width: 90%;" type="text"/> | List |
| Responsible physician first name | <input style="width: 90%;" type="text"/> | |
| Patient code | <input style="width: 90%;" type="text"/> | List |
| Patient birth date | <input style="width: 90%;" type="text"/> | |

ORTA (IWRS)

rdc.eortc.be/rdc/default.asp

Vista RDC

EORTC
European Organisation for Research
and Treatment of Cancer
50 years of Progress Against Cancer

Vista RDC

Username

Password

Log in

[Forgot your password](#)
[Change your password](#)
[Request username](#)

[Documentation](#)
[Samples website](#)
[EORTC website](#)

VISTA RDC (eCRF)

Welcome pascal.nuyk@ortec.be Logout

Persons Projects Sites Metafiles Groups Paging lists Drugs Codefiles Queries

Project Search

| External ID | Alias | Title | Study | Research Project |
|-------------|-------|-------|-------------------------------------|-------------------------------------|
| 1410 | | | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |

Project Search

Add Research Project Add Study Show all Projects (slow)

Advanced Study Search

| Eudrad Number | NCT Number | Study Search |
|---------------|------------|--------------|
| | | |

Study Search

Results

| External ID | Alias | Status | Project Type |
|-------------|-------|--------|--------------|
| 1410 | Study | Study | Study |

PRISMA (CTMS)

[illegible]

VISTA Stat 1.0.0 - 12/15/11

File Project Window Macro Help Run

Open Save Print Run

Variable List

| Select | View | Type |
|--------|------------|------------|
| Age | Continuous | Continuous |
| Age2 | Continuous | Continuous |
| Age3 | Continuous | Continuous |
| Age4 | Continuous | Continuous |
| Age5 | Continuous | Continuous |
| Age6 | Continuous | Continuous |
| Age7 | Continuous | Continuous |
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| Age97 | Continuous | Continuous |
| Age98 | Continuous | Continuous |
| Age99 | Continuous | Continuous |
| Age100 | Continuous | Continuous |

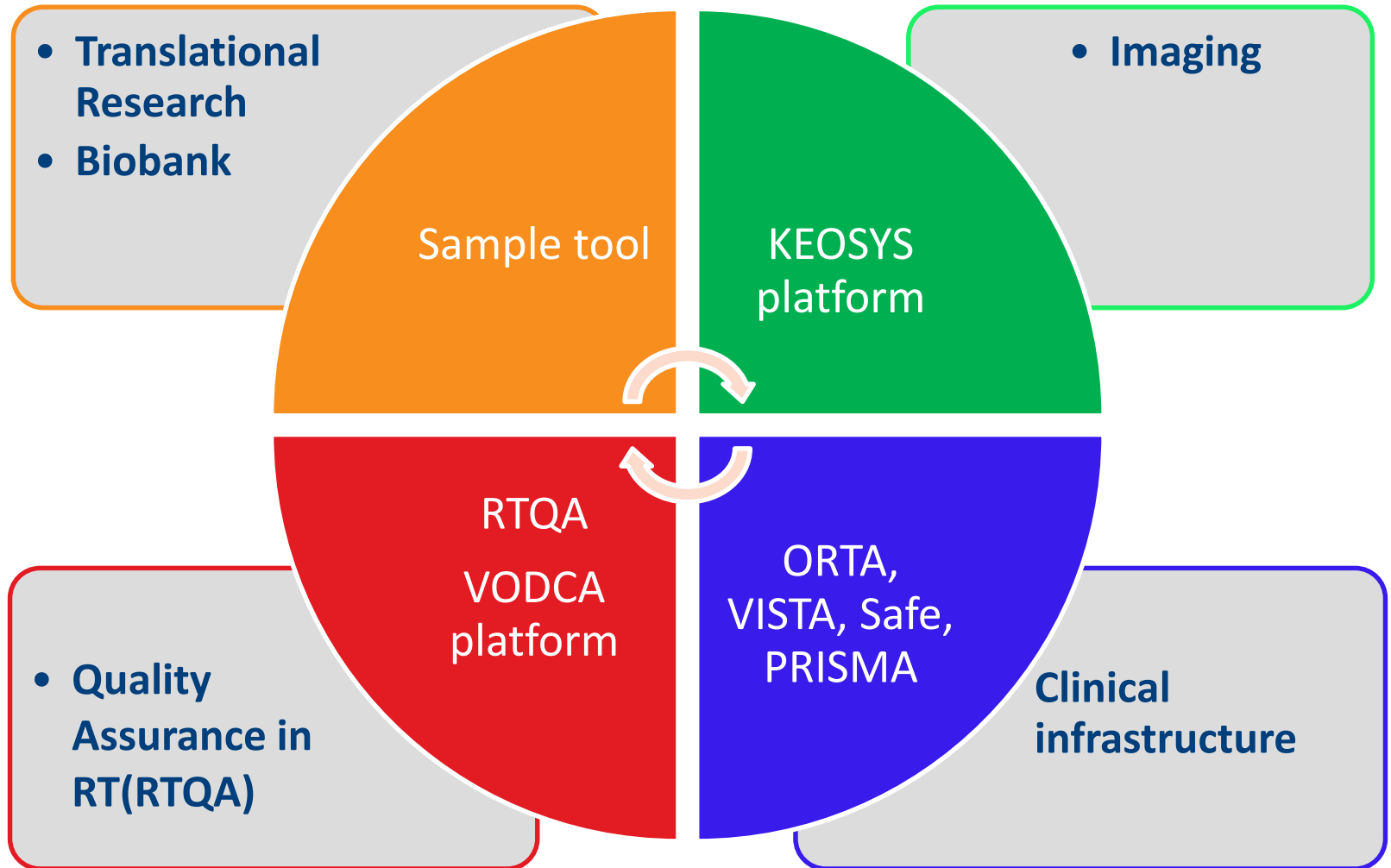
VISTA Stat: Home Worksheet - Worksheet 01 (12/15/11)

VISTA Stat



Compliance with FDA 21CFR part 11 & EU Annex 11

EORTC infrastructure to support new generation clinical trials



Consent

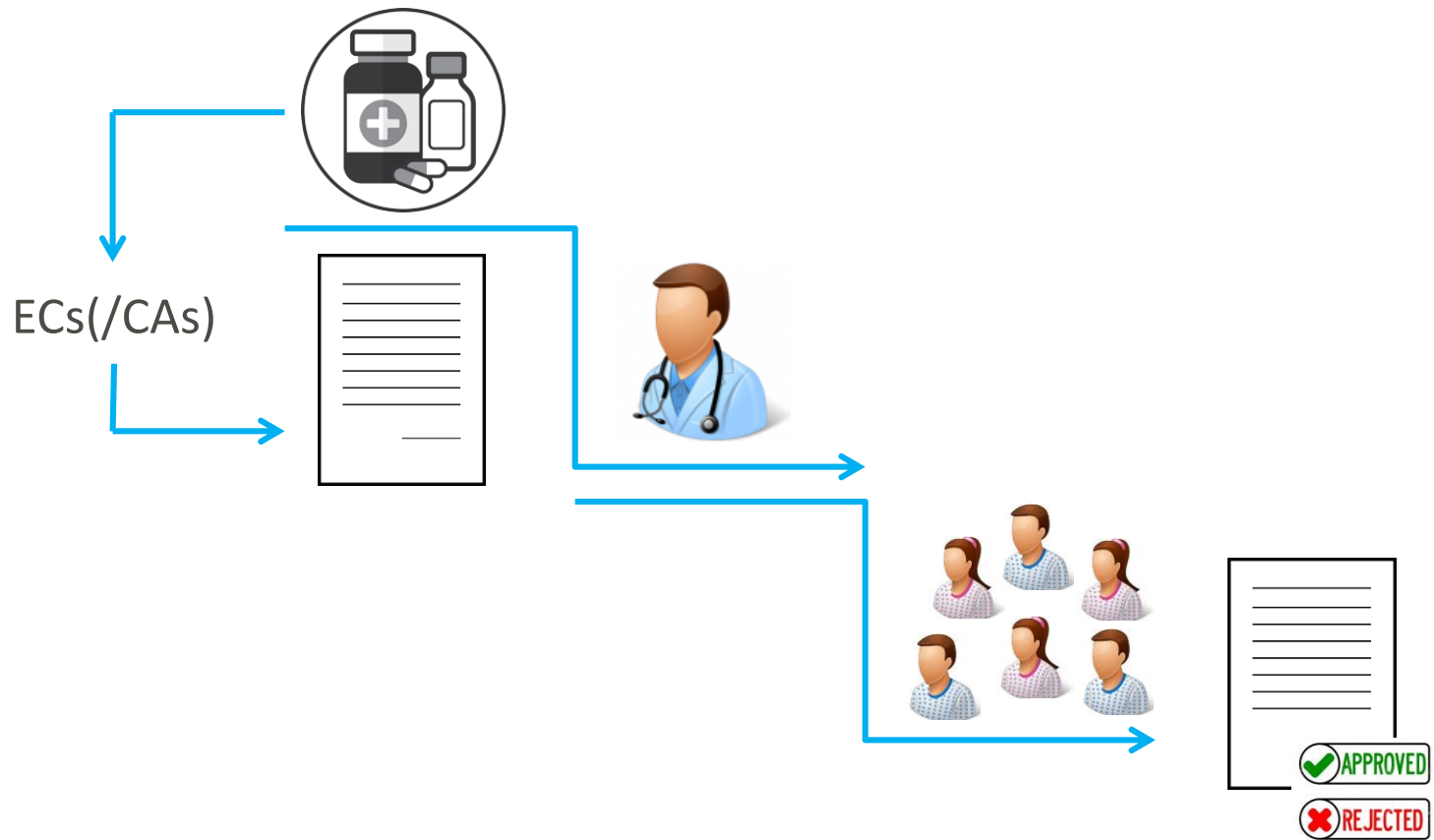
Consent

Suggested reading: the changing face of clinical trials

N. Engl. J. Med 376;9 March 2, 2017

- The changing face of informed consent
- Electronic informed consent and internet based trials
- Mobile health research: App-based trials and informed consent
- Video Informed Consent

Consent practices today



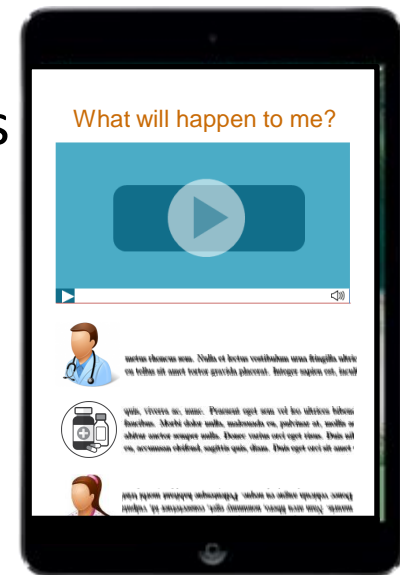
Concerns

- 20/30 pages
 - Information overload
 - Scientific/legal language
 - Comprehensibility?
- Difficulty to go back to patients
 - Complicates sharing of research results
 - Limits re-use of patient data and samples
 - Safety updates during trials
- “Take it or leave it” approach: difficult to incorporate individual’s preferences
 - Patients’ control over data and samples is limited



E-consent

- Use of multimedia increasing patients' level of understanding
 - Indirect impact on enrollment rates and fewer drop outs
- Interactivity and more fine-grained consents
- Possibility for off-site recruitment
- Legal compliance, auditability
- Decrease workload
- Efficiency gains can reduce clinical trial costs
- However, adoption is slow
 - High start-up costs, privacy concerns, unfamiliar sponsors IRBs and RECs, time...



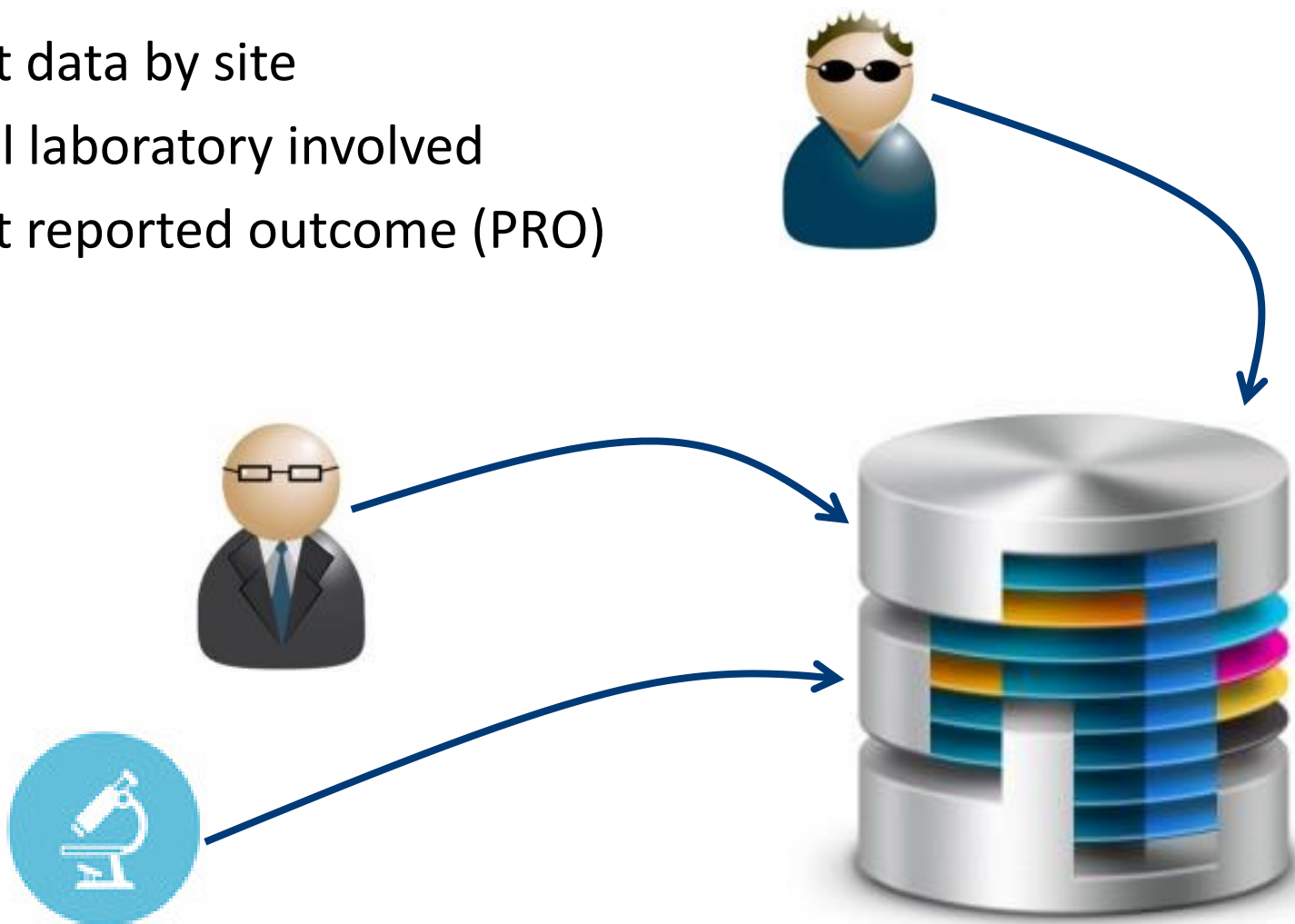
Data Collection

Data collection through EDC system



Data providers

- Patient data by site
- Central laboratory involved
- Patient reported outcome (PRO)
- →



EDC advantages (I)

- Dynamic, more intelligent data collection
- Keep users engaged at all levels of the clinical research process
Bridge the gap between site staff, monitors, data managers and sponsors
- On-line user guides with general guidance on the EDC system itself. Useful to remind centers for e.g. protocol criteria. Guidelines are visible/shown at time of relevance
- Improved data quality by automated edit checks during data entry. Edit checks programmed into the software can make sure data meets certain required formats, ranges, etc. before the data is accepted into the trial database

EDC advantages (II)

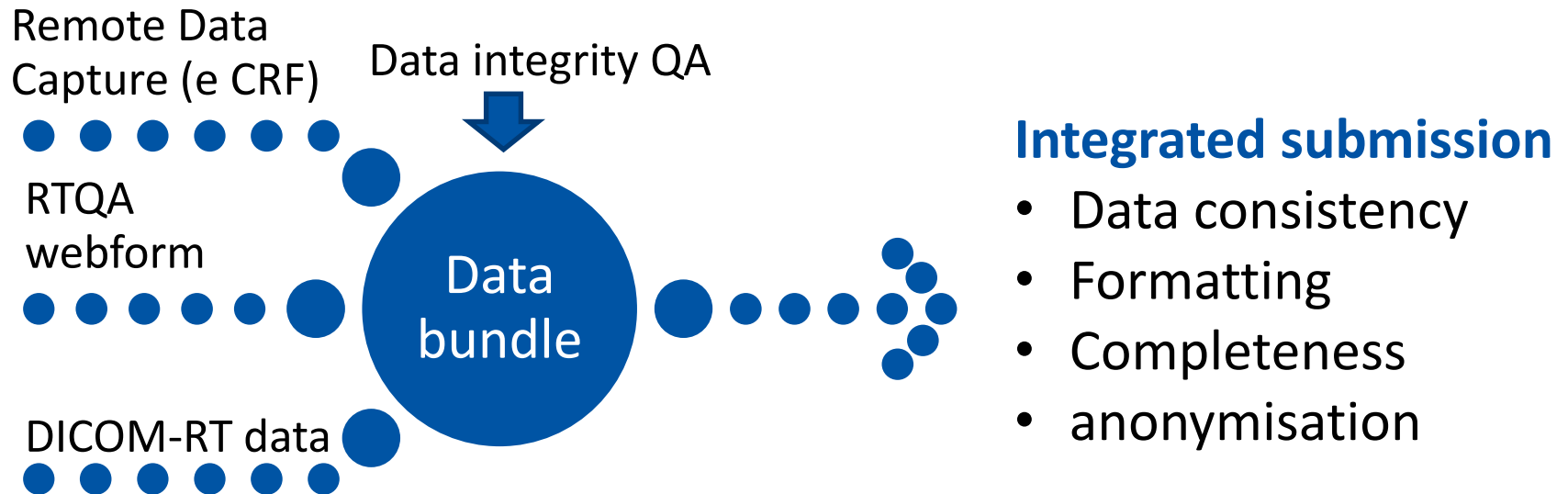
- Setting up the database creates the eCRF at the same time
- Time saved collecting data -> no more (double) data entry by sponsor and makes data available in real time. This insight enables faster decision making, and can support adaptive trial designs
- If CRFs needs new version, just publish it, no more printing and distribution
- Uses less space and has a higher security

EDC advantages (III)

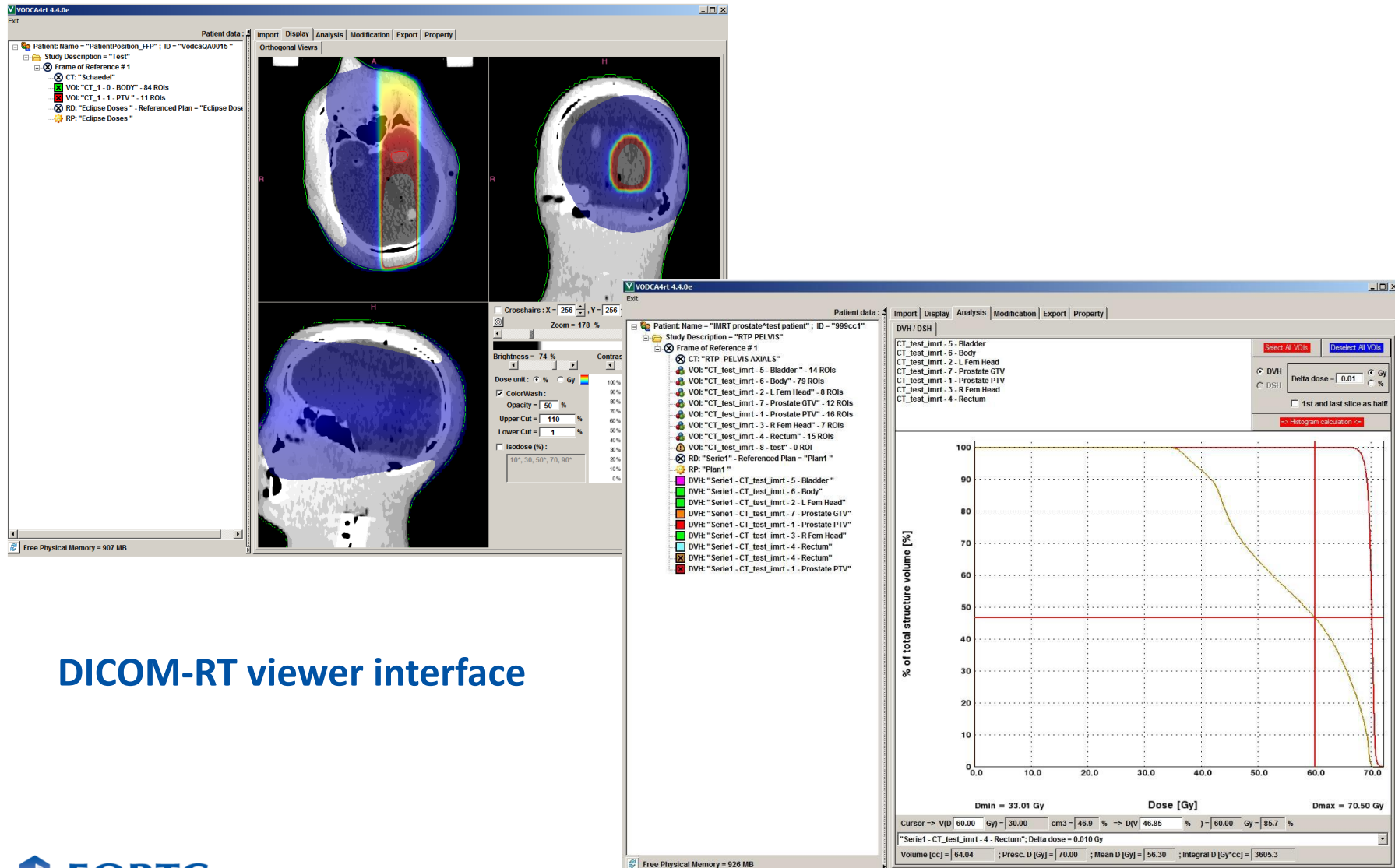
- More Efficient Processes through dynamic triggering of CRFs – EDC software can help guide the site through the series of study events
- requesting only the data needed for the particular patient's circumstance at a particular time. It facilitates the process of clarifying data discrepancies with tools for identifying and resolving data issues with sites, and can help reduce the number of in-person site visits required during a trial
- Possible integration of the EDC system with other software

Radiotherapy Quality Assurance Program

EORTC RTQA platform (data integrity QA)

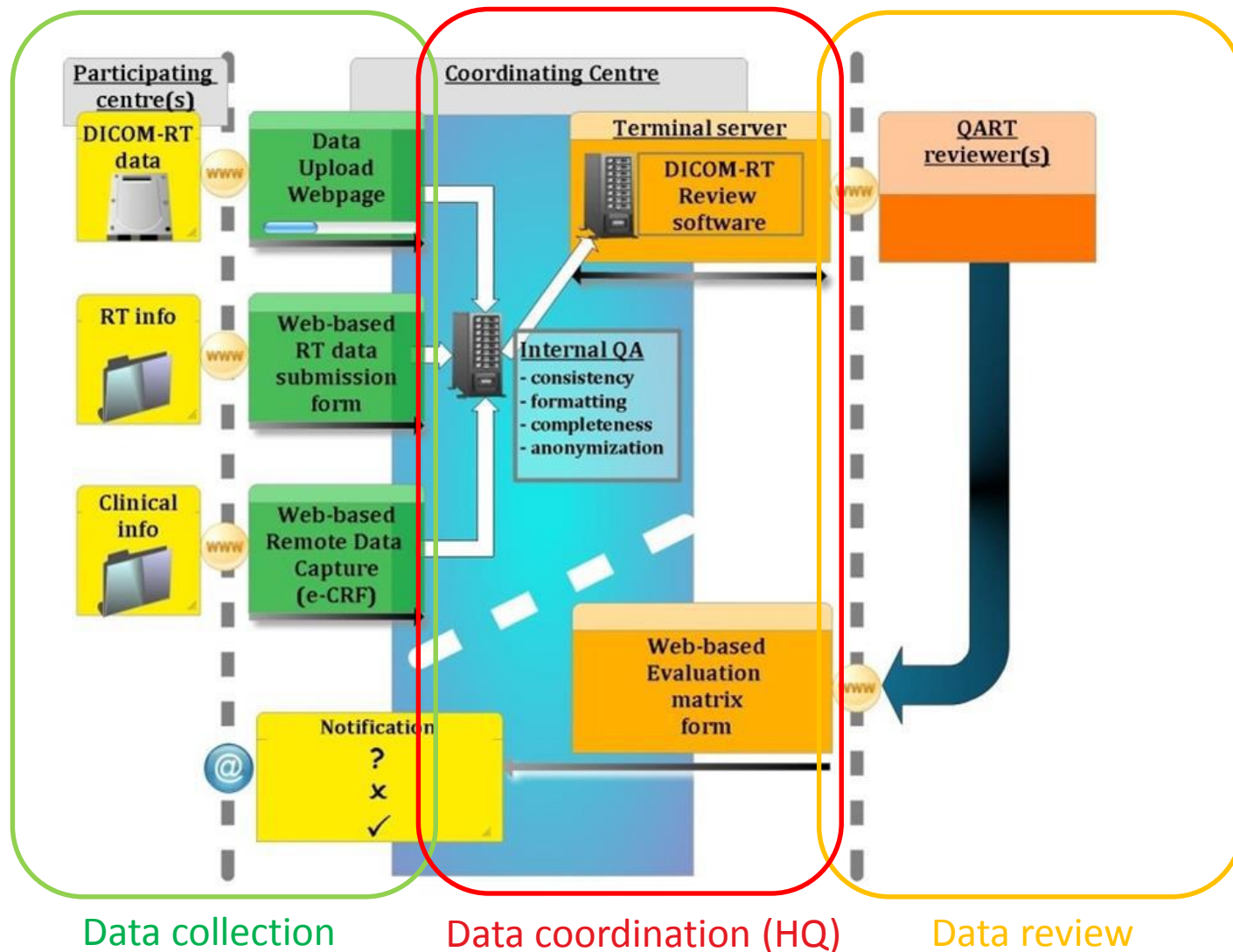


EORTC RTQA platform (data review-VODCA)



DICOM-RT viewer interface

EORTC RTQA platform



EORTC RTQA platform (data collection)

Digital data transfer

Advantages:

- More efficient
- No local installation required
- Large data transfer
- Proper security
- Trial independent

The screenshot displays the EORTC RTQA platform interface, organized into three main sections:

- Study and patient identification:** This section contains several input fields:
 - Study:** A dropdown menu with the value "22071".
 - Patient seq id:** A text input field containing "DR".
 - Patient birthdate (DDMMYYYY):** Three dropdown menus showing "01", "01", and "1900".
 - Institution number:** A text input field containing "1".
 - Submission type:** A dropdown menu with the value "Dummy Run".
- Upload Result Notification:** This section includes an **Email address** input field containing "akos.gulyban@eortc.be".
- File:** This section features a file upload interface:
 - Buttons for "Browse", "Remove", and "Clear".
 - An "Uploads" list showing a file named "DummyRun-uploadtest.zip" with a progress bar at 16.0%.
 - Text indicating the upload status: "Uploading: DummyRun-uploadtest.zip (1/1). Progress: 16.0% Current speed: 7909 KB/sec (Time left: 0 min 1 sec)".
 - A large progress bar at the bottom showing 18.0% completion.
 - An "Upload" button at the bottom right.

Web based uploader:

- Java (platform independent)
- Automatic email notification

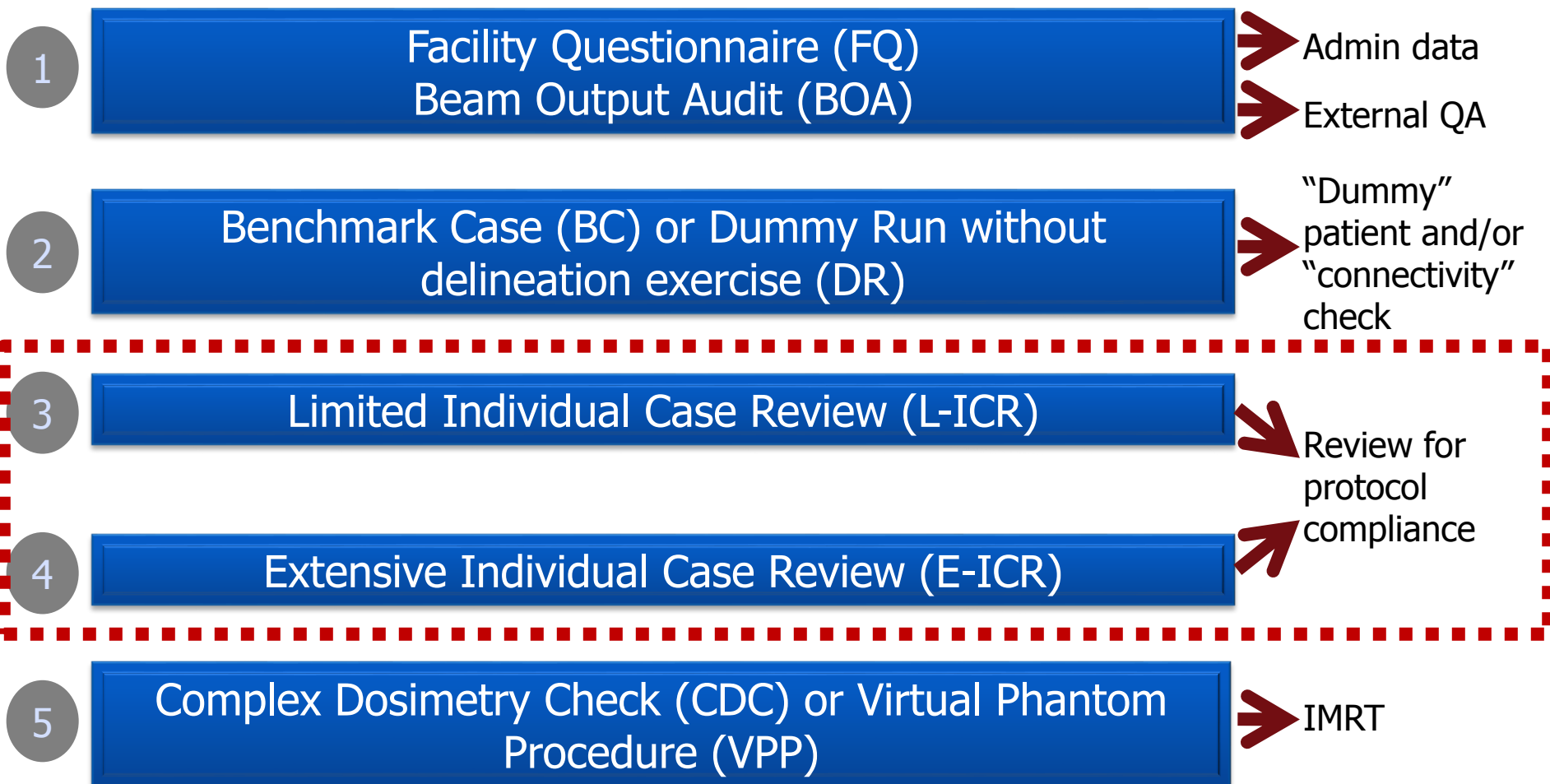
EORTC RTQA programme (I)

Achievements:

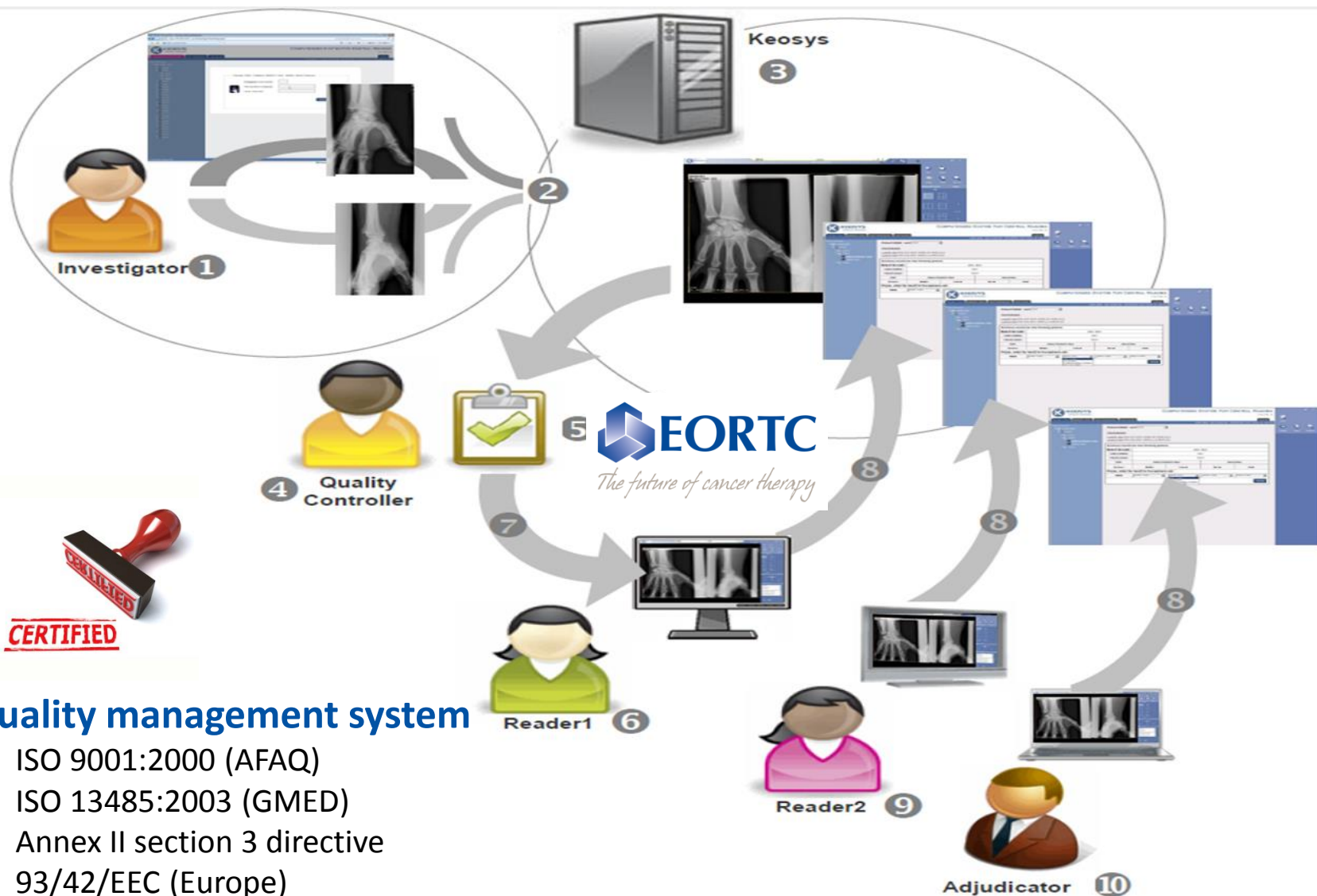
- > 40 manuscripts led by RTQA since 1982
- Real time individual case review for 4 ongoing trials, with turnaround time of 2-3 calendar days
- >300 institutions/hospitals at EORTC facility questionnaire database
- >400 Beam Output Audit-report received since 2005 (from >200 centers, >700 treatment machines, and 33 countries)
- >80 sites with Complex Dosimetry Checks credentialing
- Virtual phantom procedures are also used for IMRT and other novel techniques

EORTC RTQA programme (II)

Procedures:



Imaging QA



Quality management system

- ISO 9001:2000 (AFAQ)
- ISO 13485:2003 (GMED)
- Annex II section 3 directive 93/42/EEC (Europe)
- CMDCAS SQ (Canada)
- 510 (k) and the 21 CFR part 11 (US)

| Visit information | |
|-------------------|------------------|
| Code : | PET_CT_Dummy_run |
| Status | Normal |

| Series information | |
|---------------------------|-------------------------|
| Description : | [WB_CTAC] Body |
| Scan start time : | 13:34:04.000 |
| Injection time : | 12:31:00.000 |
| Series Acquisition Date : | 18/02/2013 |
| Device serial number : | 52024 |
| Manufacturer : | Philips Medical Systems |
| Manufacturer model : | GEMINI TF TOF 16 |
| Patient position : | HFS |

PET QC form

1: Is it a PET/CT Dummy run scan ☐

2: Anonymization & de-identification compliance ☐

3: Comments

4: Visual quality assessment

5: Comments

6: Acquisition parameters compliance ☐

7: Comments

PET review form

1: Date of FDG-PET scan

2: Name of reviewer

3: Timepoint of PET-scan

4: If other, please specify

Measurements

| site | If other, specify location | assessment |
|--------------------------|----------------------------|--------------------------|
| 5: <input type="text"/> | 6: <input type="text"/> | 7: <input type="text"/> |
| 8: <input type="text"/> | 9: <input type="text"/> | 10: <input type="text"/> |
| 11: <input type="text"/> | 12: <input type="text"/> | 13: <input type="text"/> |
| 14: <input type="text"/> | 15: <input type="text"/> | 16: <input type="text"/> |
| 17: <input type="text"/> | 18: <input type="text"/> | 19: <input type="text"/> |
| 20: <input type="text"/> | 21: <input type="text"/> | 22: <input type="text"/> |



PET form
Some of the following fields are mandatory. If you don't know the answer, please enter 'Unknown' instead.

1: Date of FDG-PET scan

Scan characteristics

2: Daily QC performed

3: Were all clocks properly synchronized

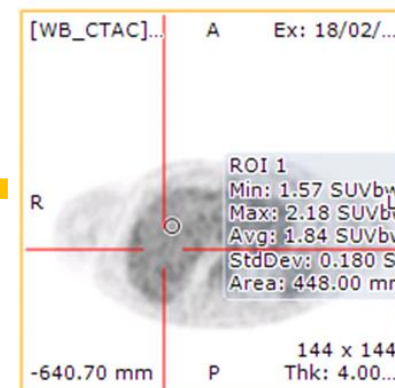
This includes the clocks in :
 1) the dose calibrator/hot lab
 2) the injection room
 3) the scanner room
 4) the scanner clock

4: Radiopharmaceutical dose administered MBq or ☐ Unknown

5: Time of radiopharmaceutical administration [hh.mm] or ☐ Unknown

6: Exact uptake time min or ☐ Unknown

7: Date of last quarterly maintenance



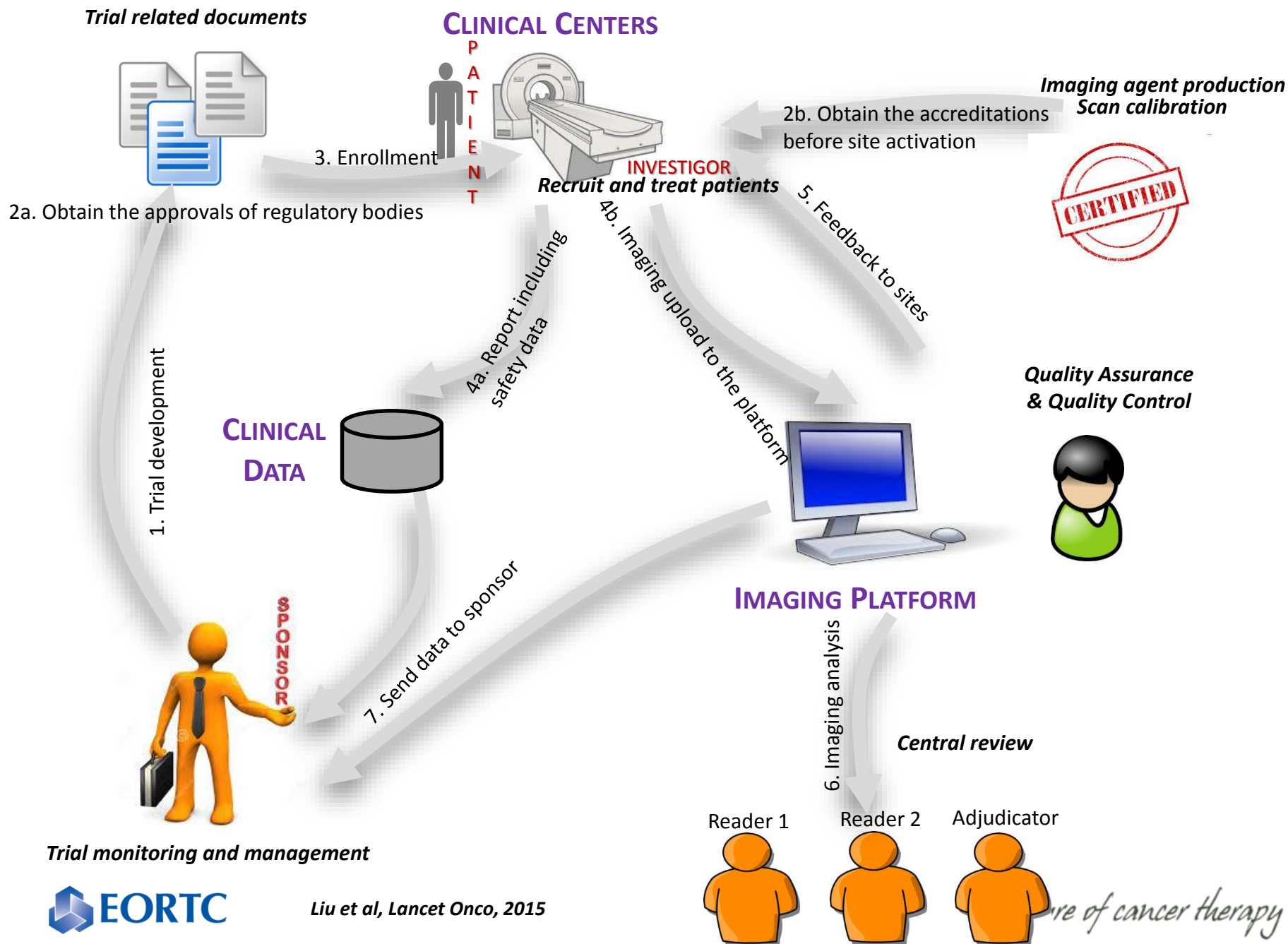
Dear

We have the pleasure to inform you that the FDG/PETscans & local PET CRF you have submitted are now being processed for QC and central review osf response.

Protocol: H11
 Patient: Dummy1
 Visit: PET_CT_Dummy_run

Kindest regards

Risk management for imaging biomarker-driven studies



Imaging risk assessment

A risk management approach for imaging biomarker-driven clinical trials in oncology

Yan Liu, Nandita M deSouza, Lalitha K Shankar, Hans-Ulrich Kauczor, Siegfried Trattnig, Sandra Collette, Arturo Chiti

Imaging has steadily evolved in clinical cancer research as a result of improved conventional imaging methods and the innovation of new functional and molecular imaging techniques. Despite this evolution, the design and data quality derived from imaging within clinical trials are not ideal and gaps exist with paucity of optimised methods, constraints of trial operational support, and scarce resources. Difficulties associated with integrating imaging biomarkers into trials have been neglected compared with inclusion of tissue and blood biomarkers, largely because of inherent challenges in the complexity of imaging technologies, safety issues related to new imaging contrast media, standardisation of image acquisition across multivendor platforms, and various postprocessing options available with advanced software. Ignorance of these pitfalls directly affects the quality of the imaging read-out, leading to trial failure, particularly when imaging is a primary endpoint. Therefore, we propose a practical risk-based framework and recommendations for trials driven by imaging biomarkers, which allow identification of risks at trial initiation to better allocate resources and prioritise key tasks.



Lancet Oncol 2015; 16: e622-28

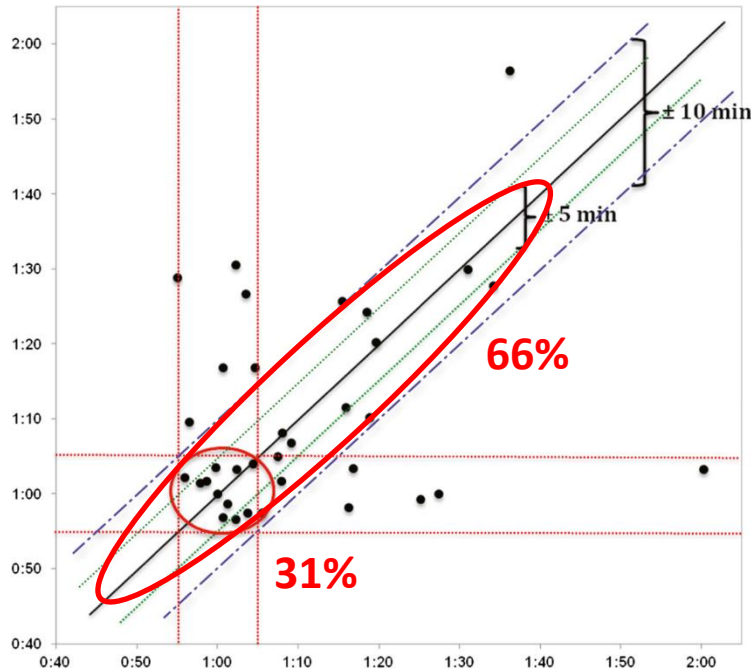
European Organisation for
Research and Treatment of
Cancer Headquarters, Brussels,
Belgium

(Y Liu MD, S Collette MSc);
Cancer Research UK Cancer
Imaging Centre, MRI Unit, The
Institute of Cancer Research
and Royal Marsden NHS
Foundation Trust, Sutton,
Surrey, UK
(Prof N M deSouza MD); Clinical
Trial Branch, Cancer Imaging

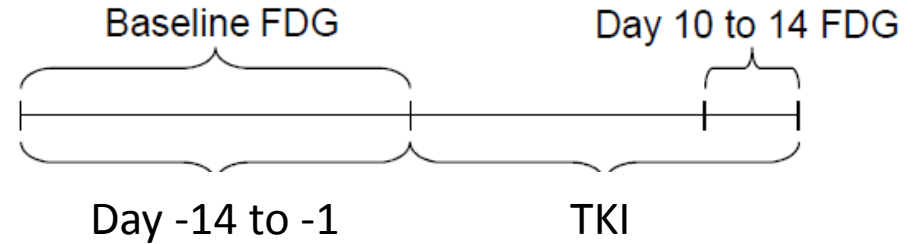
Lessons learnt (I)

Example

Hypothesis: patients with FDG-PET response ($\Delta\text{SUV}_{\text{max}} \geq 25\%$), the PFS is 12 weeks longer than in patients without PET response



Finally, less than half of pts could be used for quantitative assessment. No conclusion could be drawn due to inadequate sample size



- 44 patients enrolled (81 scans received)
- 35 patients have both scans with good visual quality
- Low compliance to the imaging guidelines

| | required | %compliance |
|--------------------------|-----------|-------------|
| BL | 60 ±5 min | 39% (15/35) |
| FU | 60 ±5 min | 51% (18/35) |
| BL+FU | 60 ±5 min | 31% (11/35) |
| FU±10 min from actual BL | | 66% (23/35) |

Hristova et al, EJNMMI 2015

The future of cancer therapy

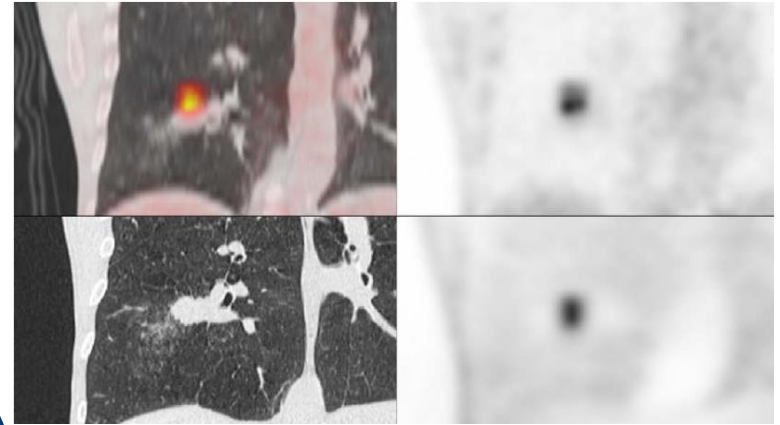
Lessons learnt (II)



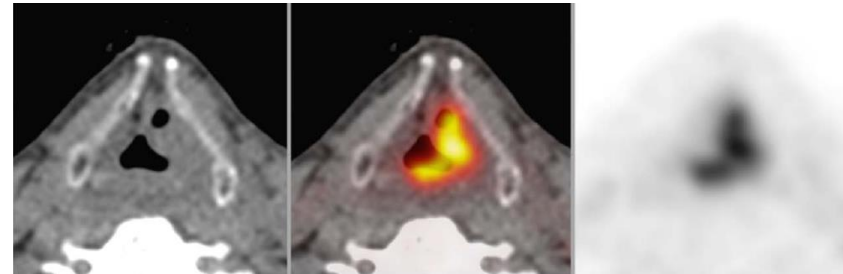
artifacts



extravasation



breathing



What is the truth?

- Imaging resolution, partial volume effects, blurring
- Involuntary patient motion, swallowing

Collection of HBM

The origin of HBM

3 types of HBM

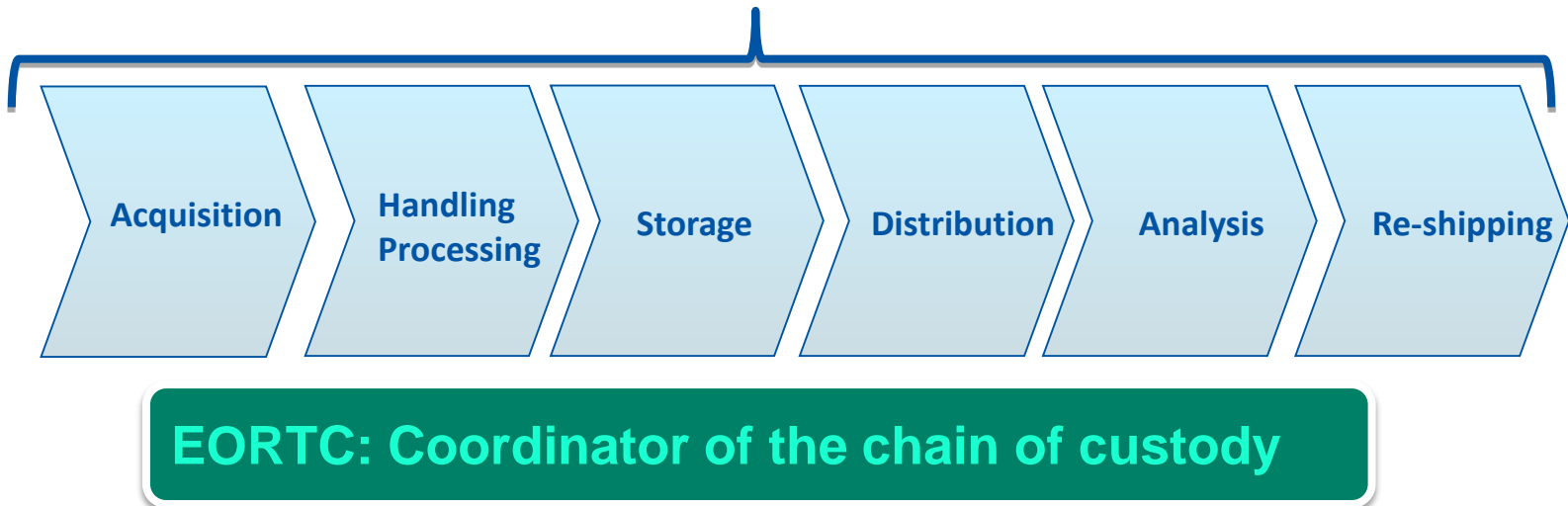
- **Additional HBM**: collected expressly for research within the clinical trial
 - e.g. blood samples for correlative TR
- HBM **pre-existing** to the trial without diagnostic value
 - e.g. banked frozen tissue from an institutional biobank
- HBM **pre-existing** to the trial with diagnostic value
 - e.g. diagnostic FFPE block

HBM custodianship

Custodian: legal entity responsible for safeguarding HBM and oversight of its use

Institutes can remain custodian *even if* HBM is offsite in an EORTC storage facility (the contributing institute still decides future use)

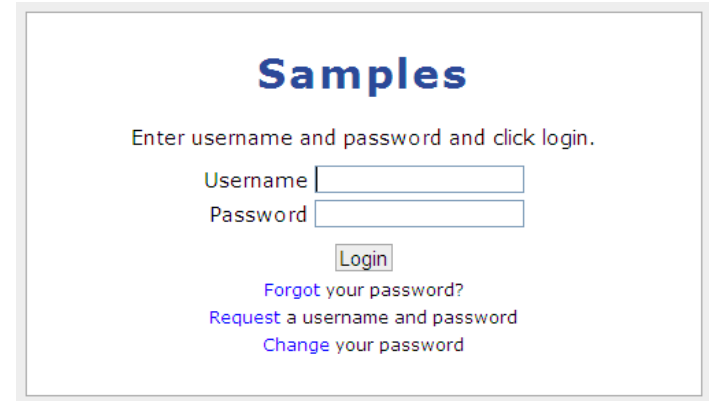
'Chain of custody of HBM'



Logistics for HBM collection

➤ HBM traceability

- EORTC web-based tracking tool
<https://samples.eortc.be/>
- Restricted access
- 24h/24h, 7d/7d



Samples

Enter username and password and click login.

Username

Password

[Forgot your password?](#)

[Request a username and password](#)

[Change your password](#)

➤ HBM handling procedures/guidelines



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Fax : + 32 2 772 35 45
E-mail : eortc@eortc.be
Web : http://www.eortc.be

GUIDELINES
FOR HUMAN BIOLOGICAL MATERIAL (HBM) MANAGEMENT
STUDY NUMBER
STUDY TITLE

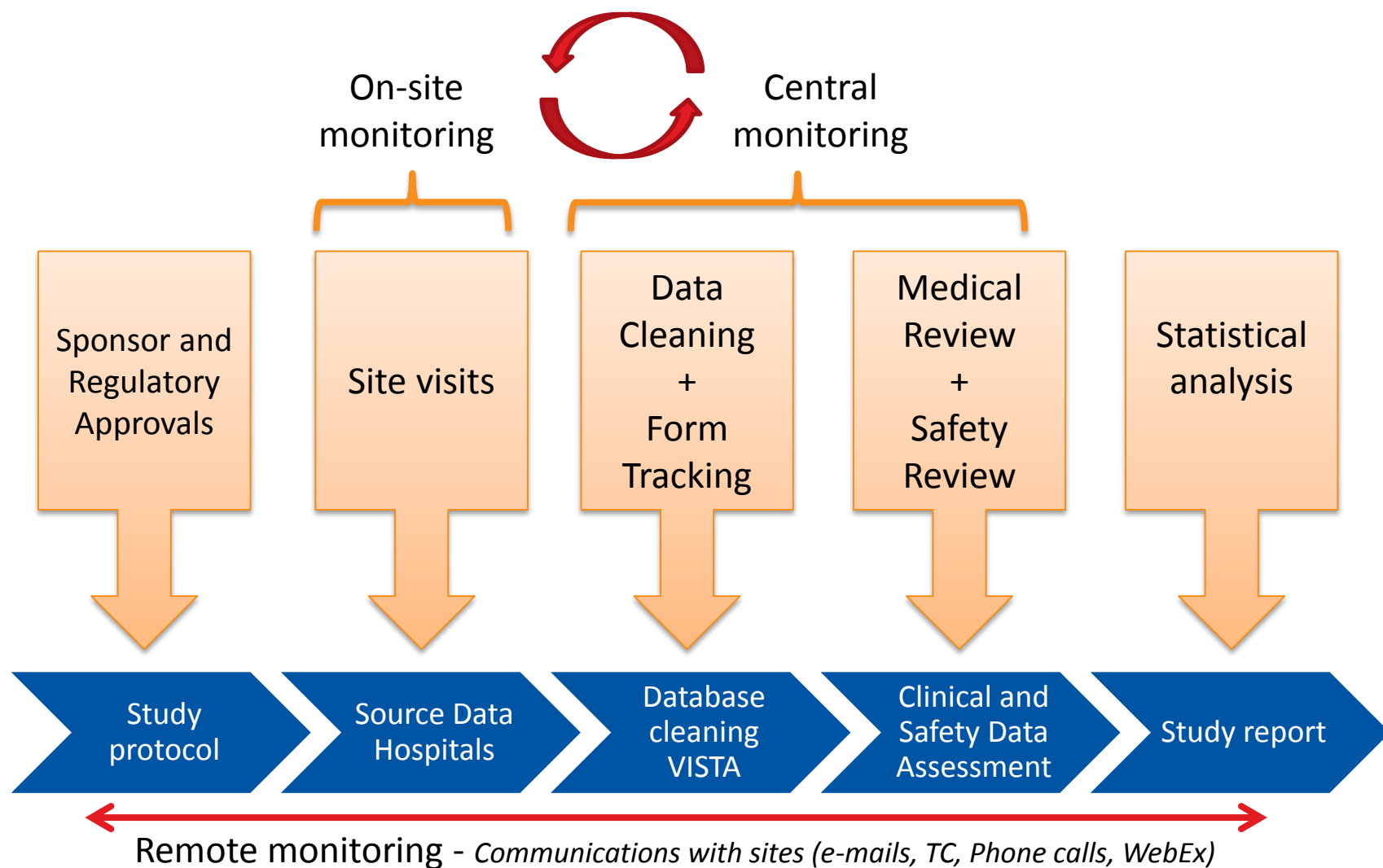
- optimize quality of samples
- must be developed prospectively
- based on international standards

E- research

QA and Monitoring

C. de Balincourt

Types of “monitoring” in clinical trials



Central monitoring

- **Accrual** assessment
- **CRFs** tracking & cleaning
- **Medical & Safety** review



On-site monitoring

- **Patient's protection** (PISIC)
- **Protocol & GCP compliance** (source documents)
- **Data reliability** (SDV, CRF versus source documents)

QUALITY

On-site Monitoring tasks

What can be supported by e-monitoring?



Checking PIS/IC



Source data verification
Protocol & GCP compliance



Support in queries
resolution



Tracking pending issues



Visiting the pharmacy



Biological samples



Checking the ISF



Site training



Meeting the investigator

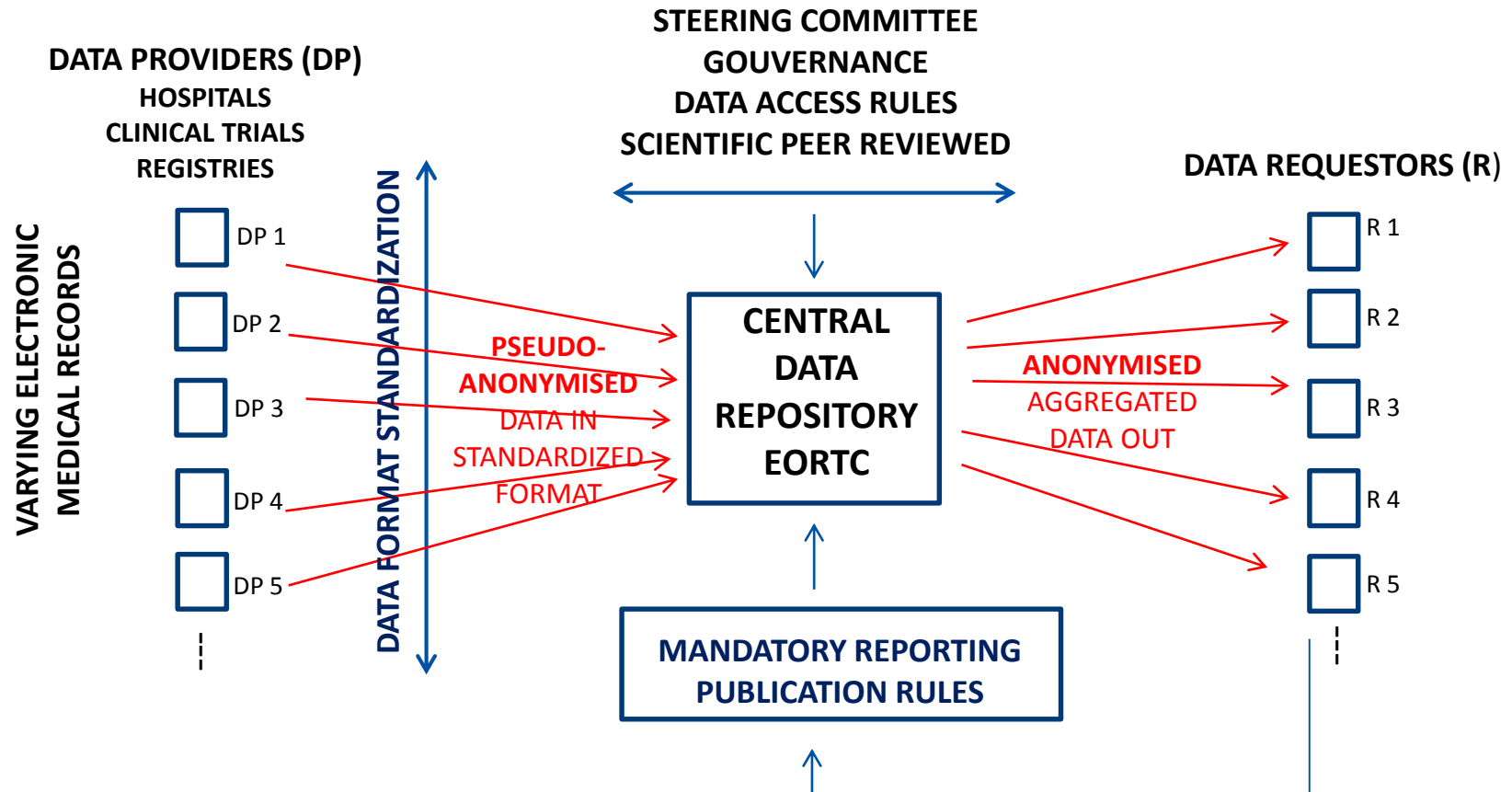


Handling of
major observations

E-research at EORTC: impact of “remote monitoring”: a few examples

| Research activity | Conventionally | Now | Advantage |
|-------------------------|--|---|---|
| Sites feasibility | Pre-study visit | Questionnaire on – line to check site’ capacities | Cost-effectiveness Time-saving |
| Sites training | On-site initiation visit by a CRA | E-training: Web-based training material - WebEx | Cost-effectiveness Time -saving |
| Investigator Study File | Paper binders prepared and sent to sites | Web-based study essential documents (restricted access) | Availability for site at any time Up-to-date Maintenance by sponsor |

Can EMR push our standards a step further?



Conclusion

- Patient centered clinical research can benefit from e-solutions
- PRO and other activities directly involving patients can be made easier
- Efficient and timely QA programs at all levels are made easier
- Opening to new possibilities:
 - Real life studies
 - Long term outcome and survivorship
- Lack of data regarding effectiveness and cost efficiency