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

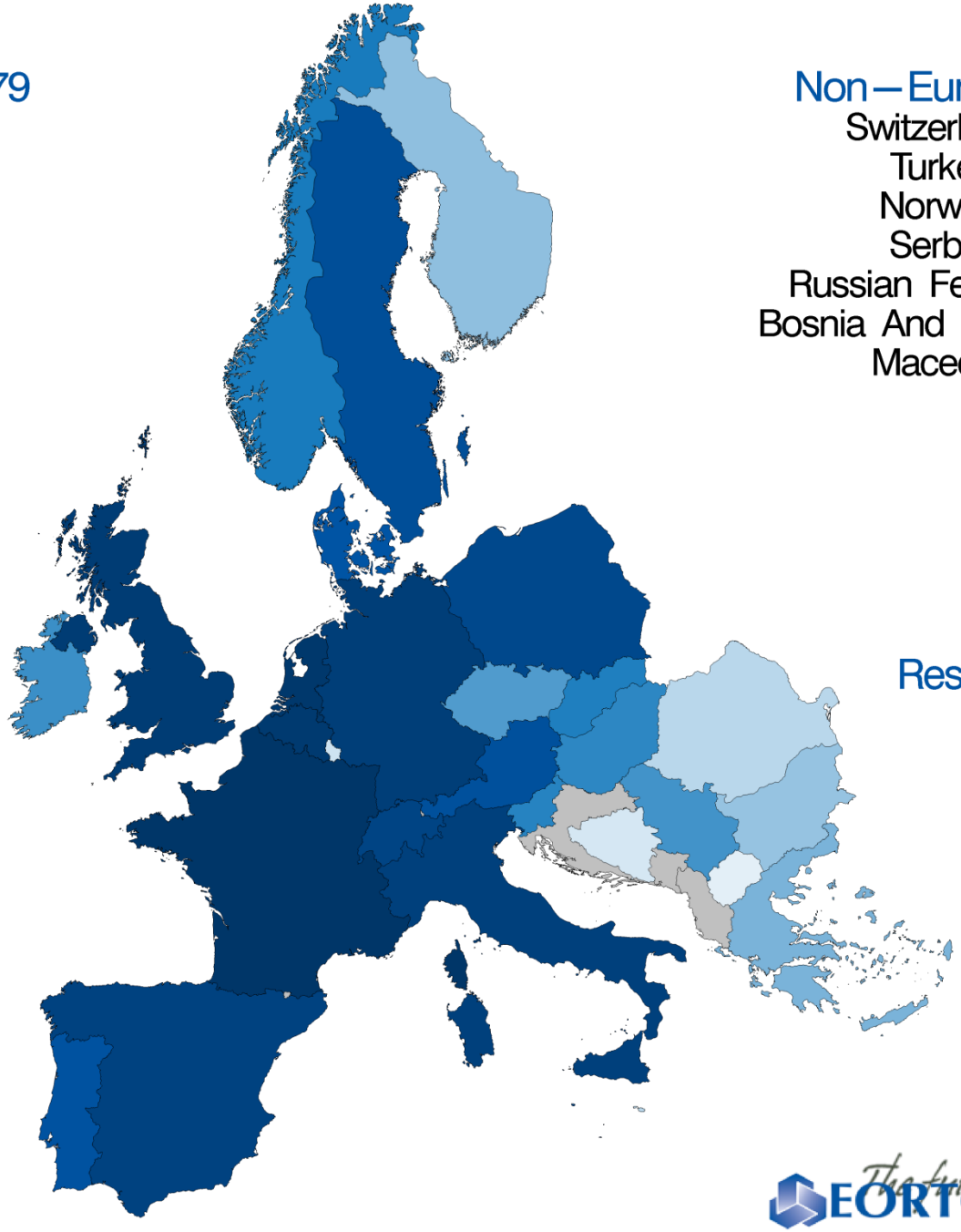
Accrual of screened patients in EORTC clinical studies from 2000 to 2016: 89095 patients

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

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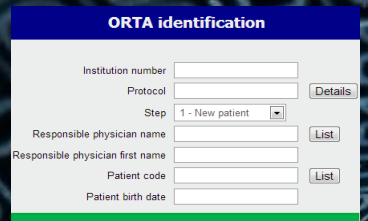
The future of cancer therapy

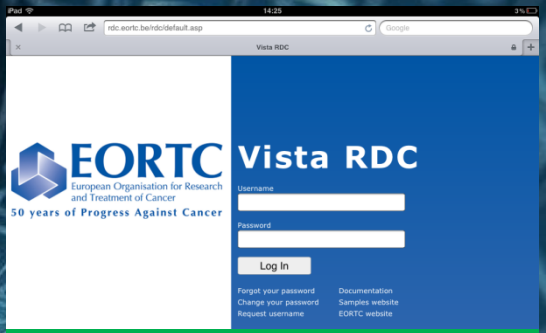
EORTC by the numbers (2016)

A world-class network	An expert HQ	Unique output
• ± 5,000 collaborators • 870 institutions • 35 countries • 21 groups & task-forces • 111 collaborative groups	• 202 employees • > 195,000 patients in database • 24,000 patients in follow-up	• **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**

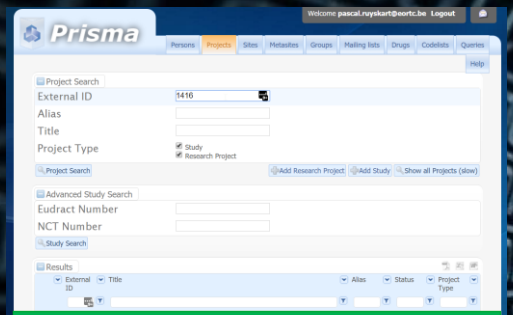
Tools for clinical trials management



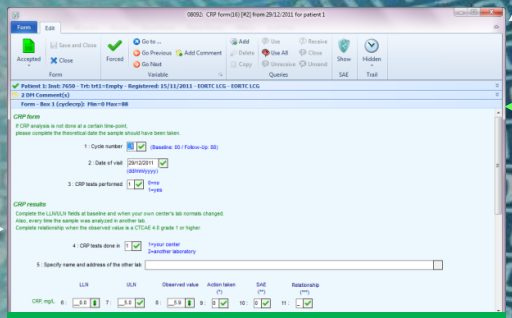
ORTA (IWRS)



VISTA RDC (eCRF)



PRISMA (CTMS)



VISTA (CDMS)

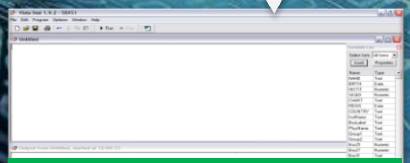
sTrack

SAfE

SharePoint

eTMF

Monitoring & Regulatory



VISTA Stat

IMAGYS & RT

Compliance with FDA 21CFR part 11 & EU Annex 11

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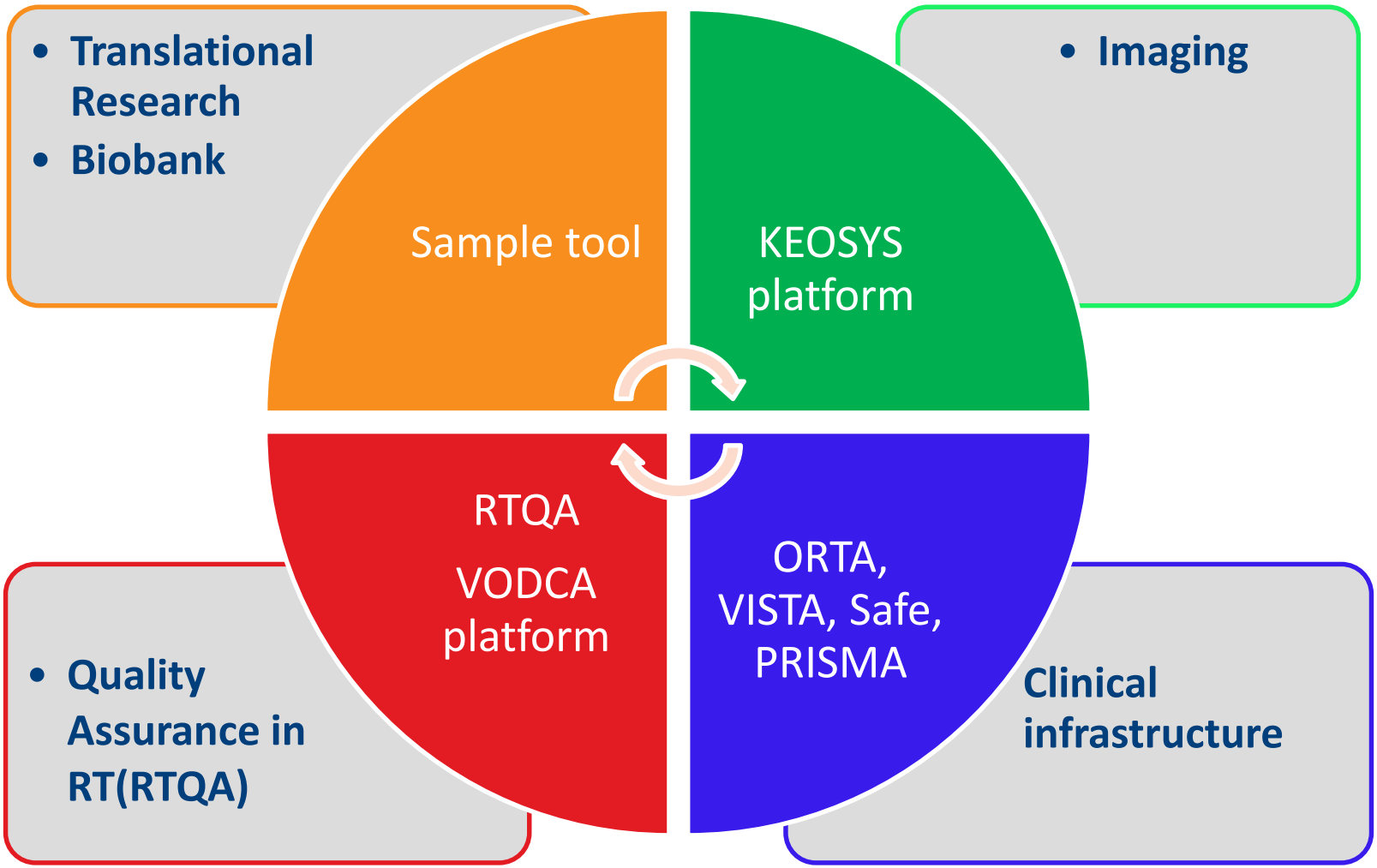
EORTC infrastructure to support new generation clinical trials



Consent

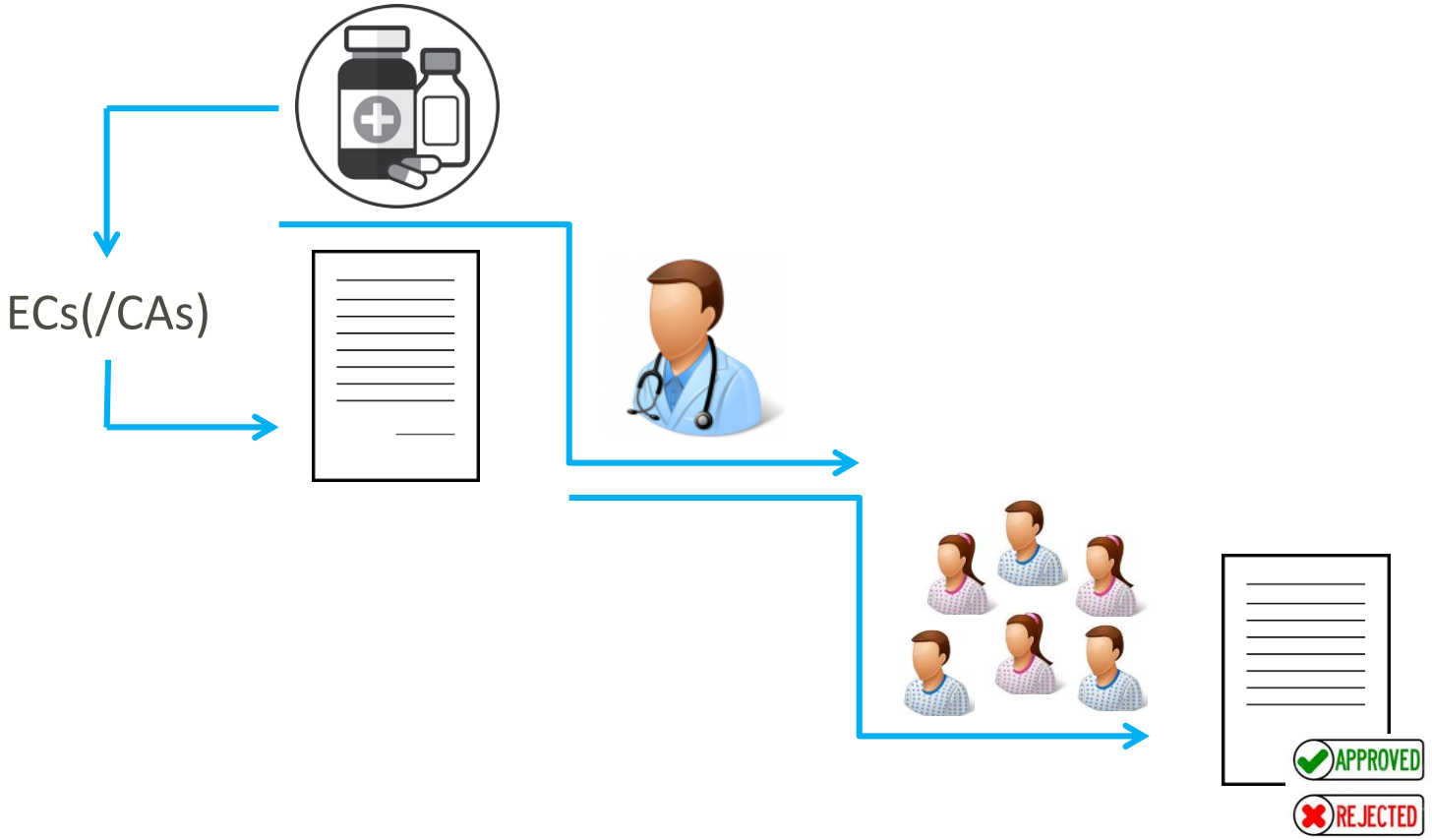
Consent

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?

Informed consent?

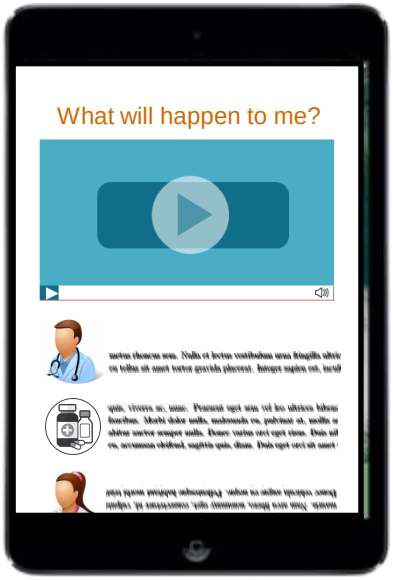
- Difficulty to go back to patients
  - Complicates sharing of research results
  - Limits re-use of patient data and samples
  - Safety updates during trials

- "Take it or leave it" approach: difficult to incorportate 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…

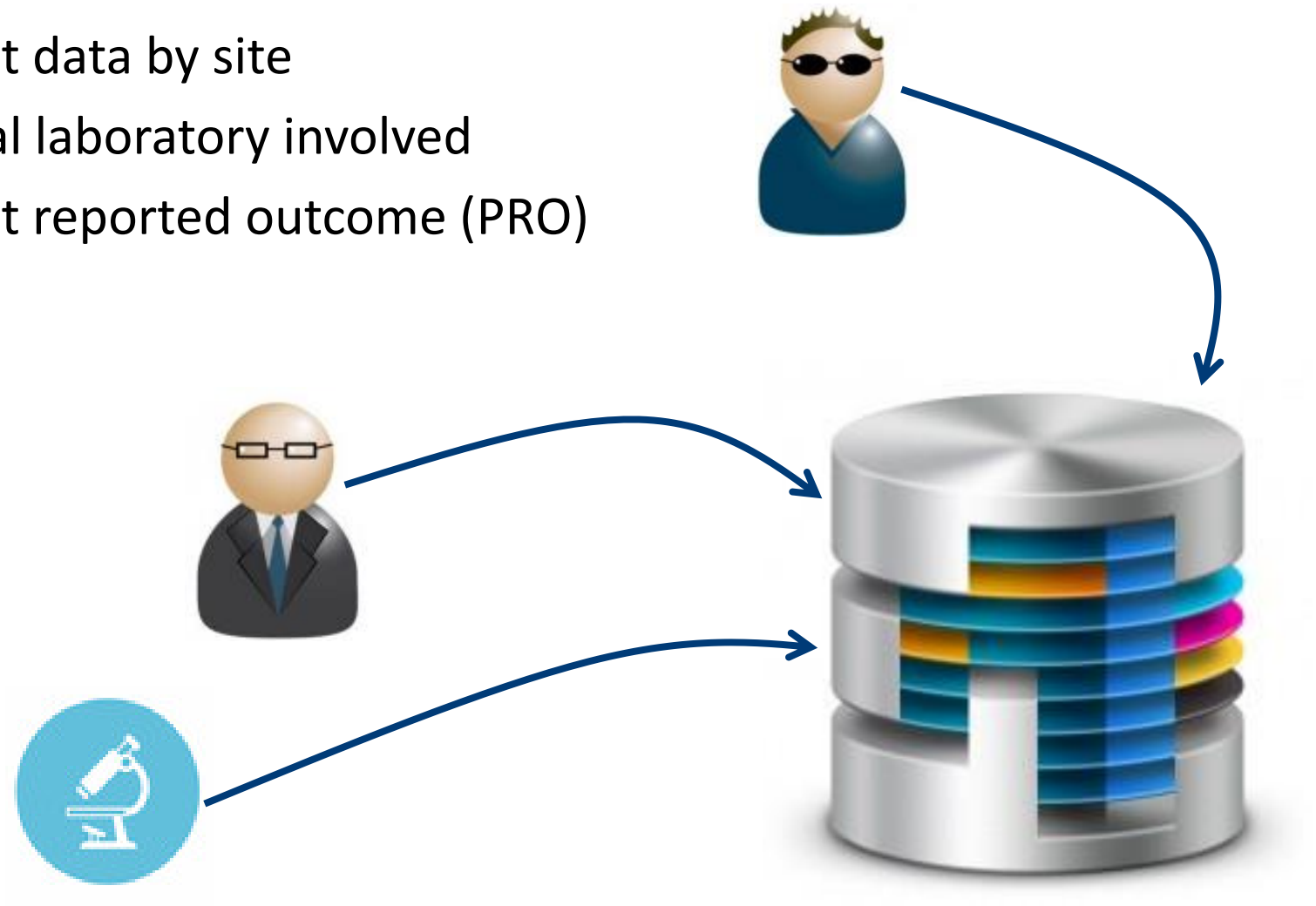


Data Collection

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)

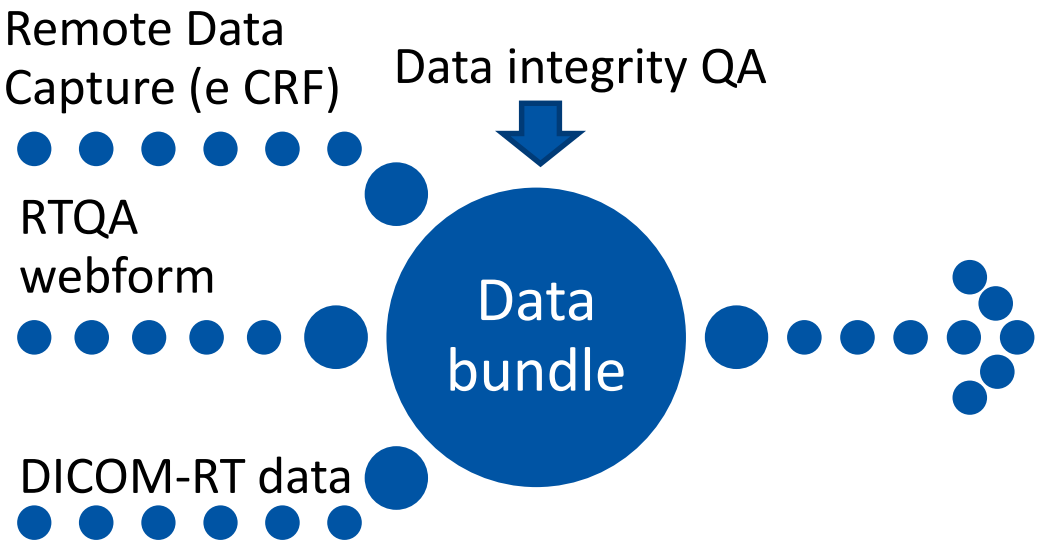
- Setting up the database creates the eCRF at the same time
- Time saved collecting data -> no more (double) data entry by sponsor and makes data available in real time. This insight enables faster decision making, and can support adaptive trial designs
- If CRFs needs new version, just publish it, no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

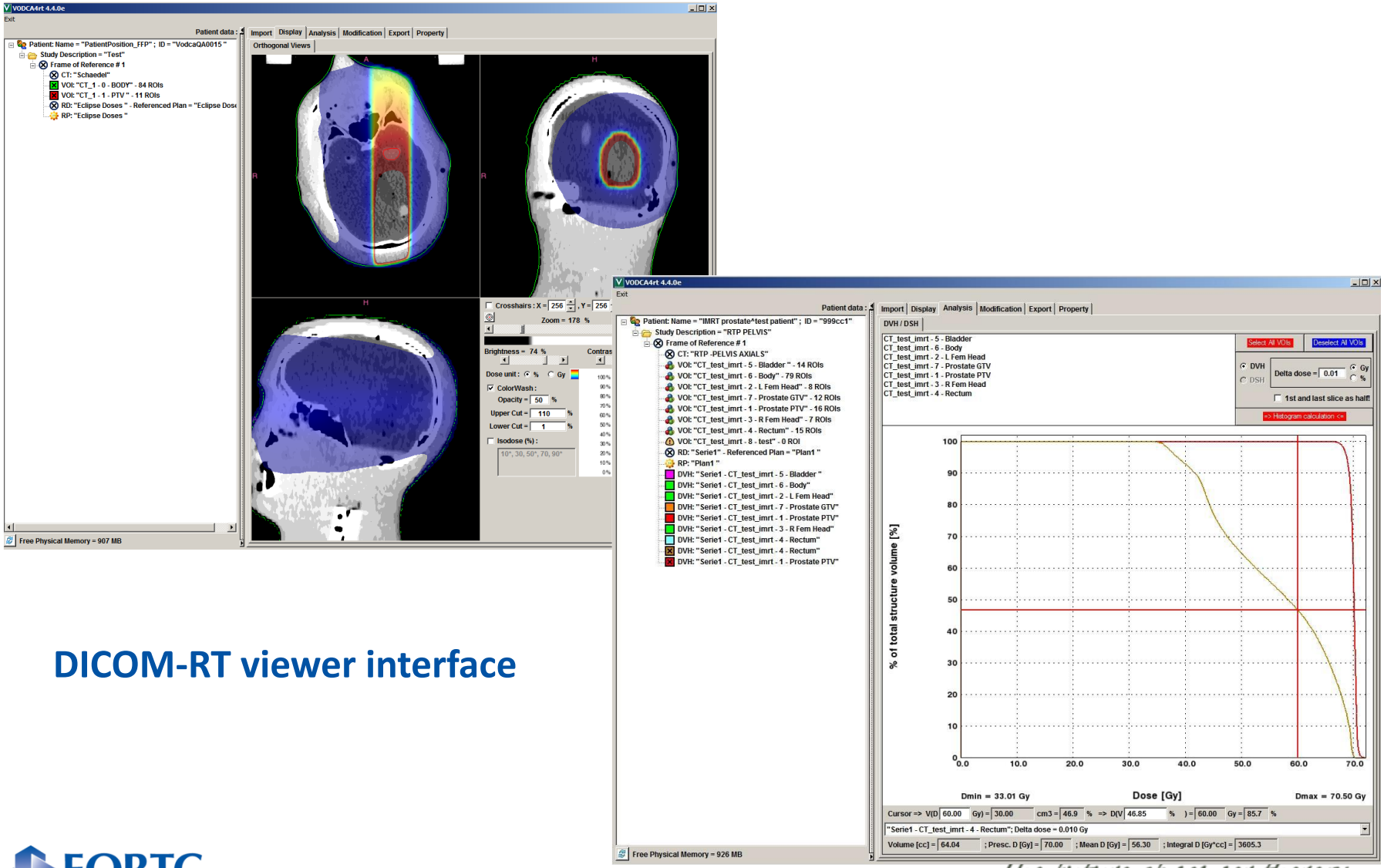
EORTC RTQA platform (data integrity QA)



Integrated submission

- Data consistency
- Formatting
- Completeness
- anonymisation

EORTC RTQA platform (data review-VODCA)



DICOM-RT viewer interface

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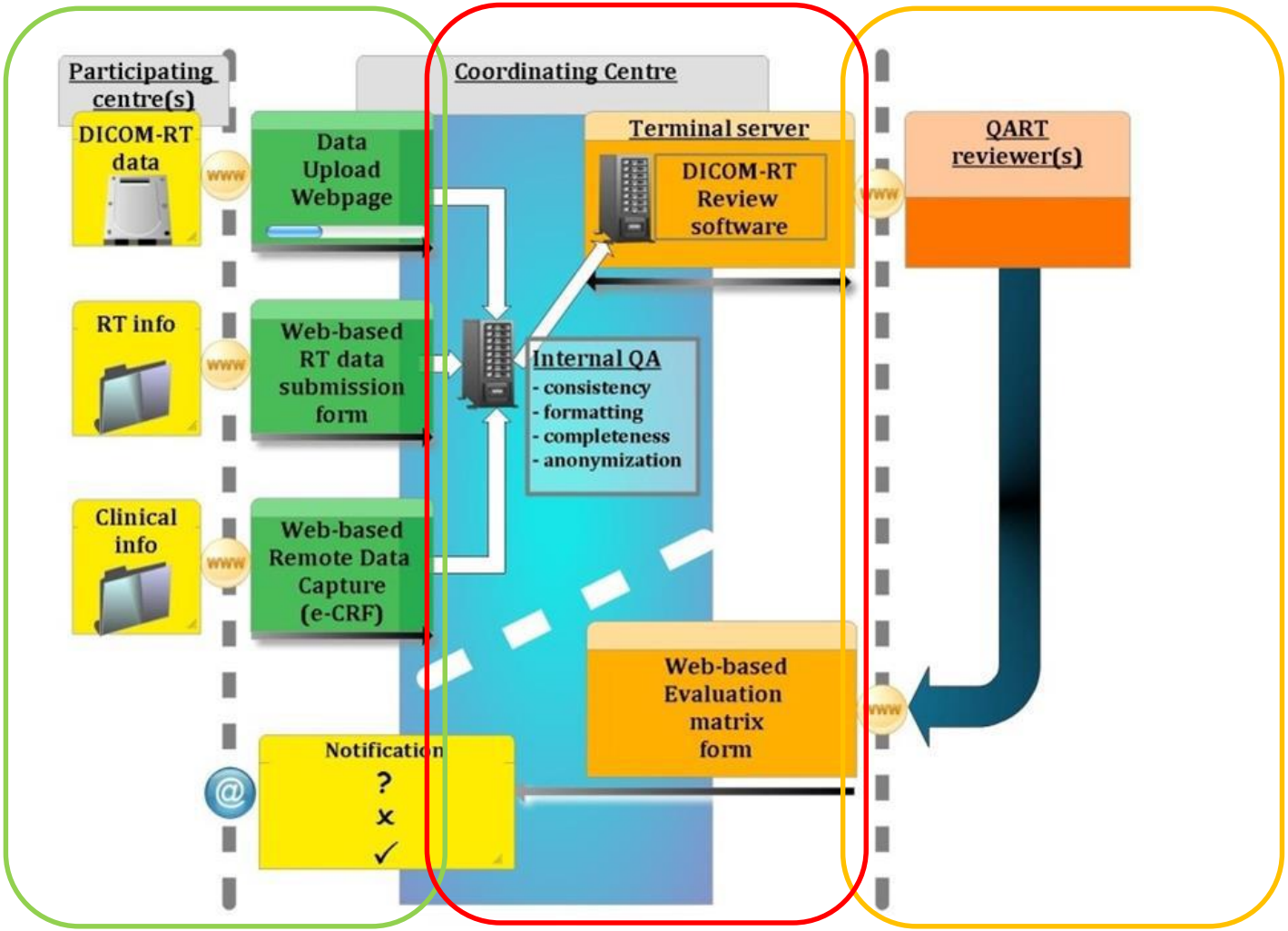
EORTC RTQA platform

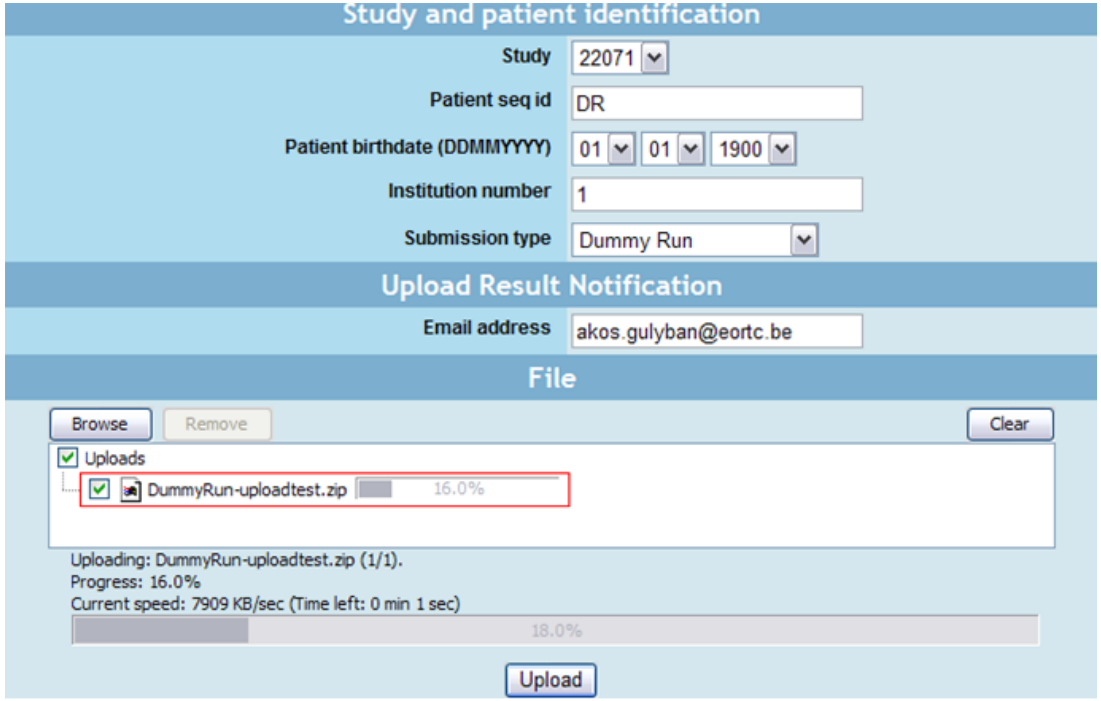


EORTC RTQA platform (data collection)

Digital data transfer

Advantages:

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



Web based uploader:

- Java (platform independent)
- Automatic email notification

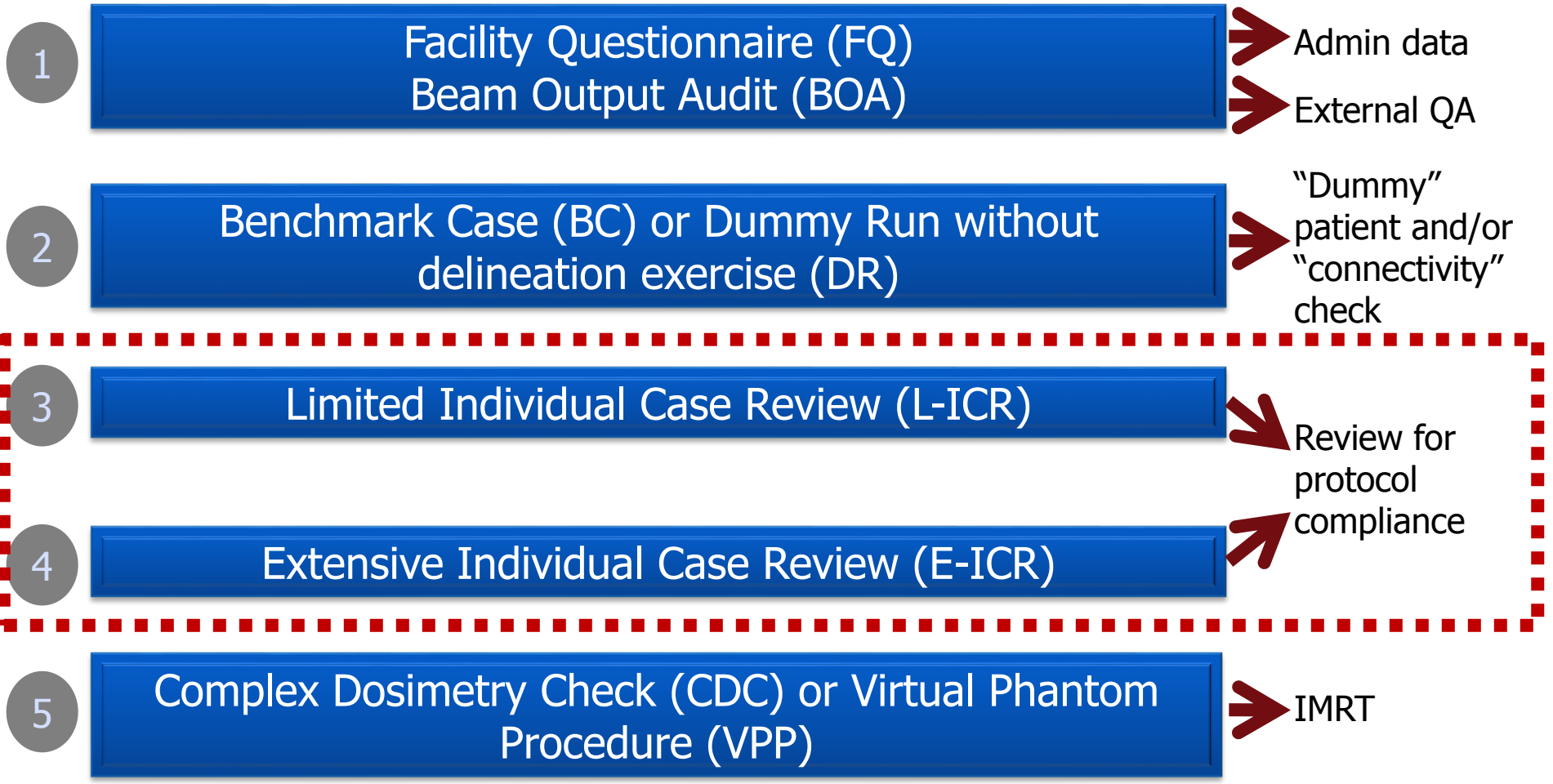
EORTC RTQA programme (I)

Achievements:

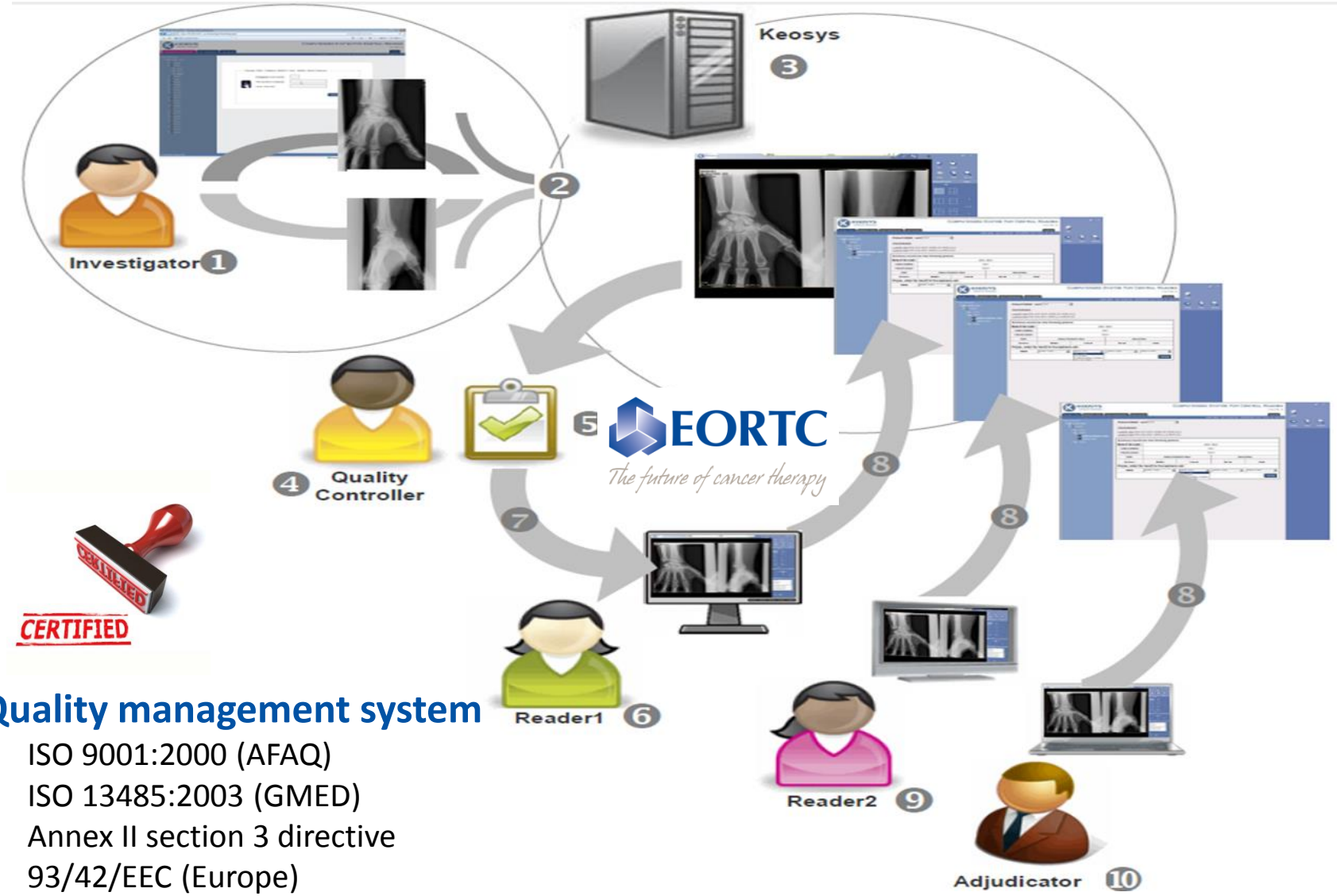
- > 40 manuscripts led by RTQA since 1982
- Real time individual case review for 4 ongoing trials, with turnaround time of 2-3 calendar days
- >300 institutions/hospitals at EORTC facility questionnaire database
- >400 Beam Output Audit-report received since 2005 (from >200 centers, >700 treatment machines, 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:

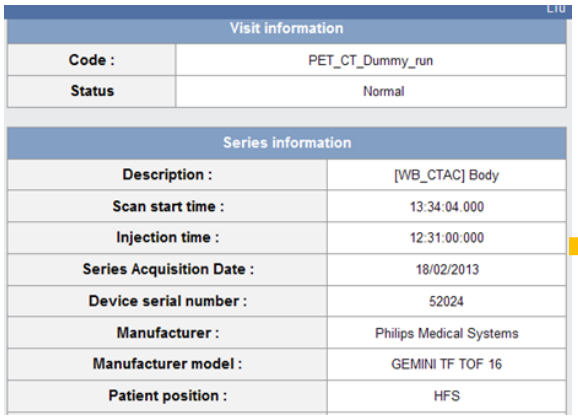


Imaging QA



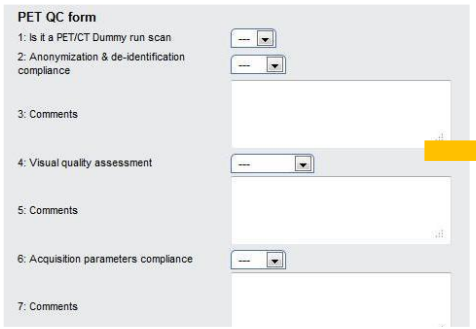
Quality management system

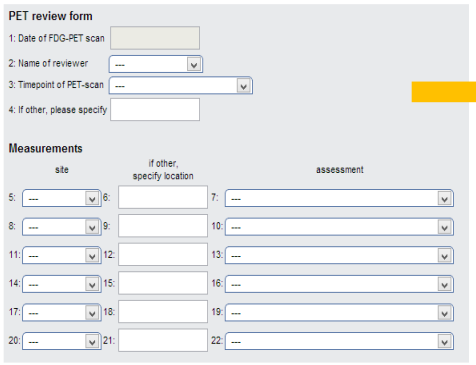
- ISO 9001:2000 (AFAQ)
- ISO 13485:2003 (GMED)
- Annex II section 3 directive 93/42/EEC (Europe)
- CMDCAS SQ (Canada)
- 510 (k) and the 21 CFR part 11 (US)



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





Easy imaging uploading

direct information export from DICOM hea

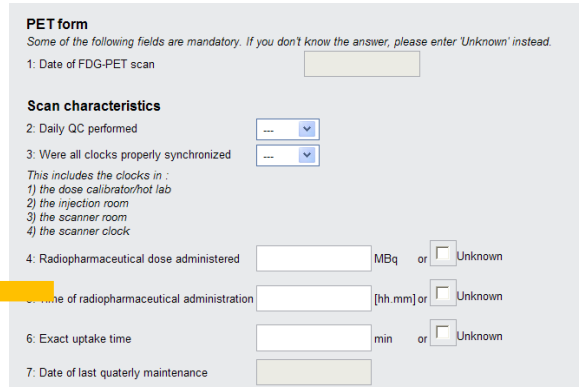
Local site case report from

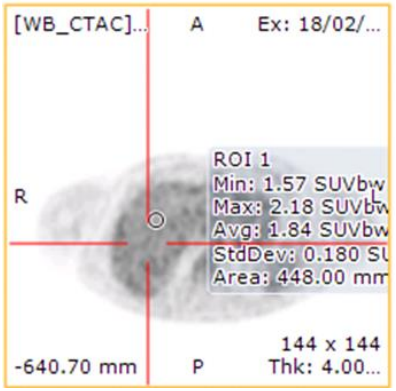
Online quality control

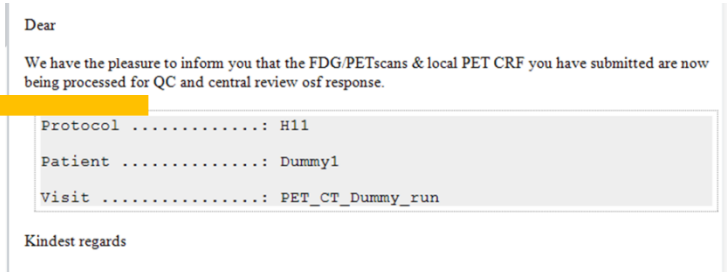
Easy to measure

central review form

Automatic email contact to the sites and the manager team







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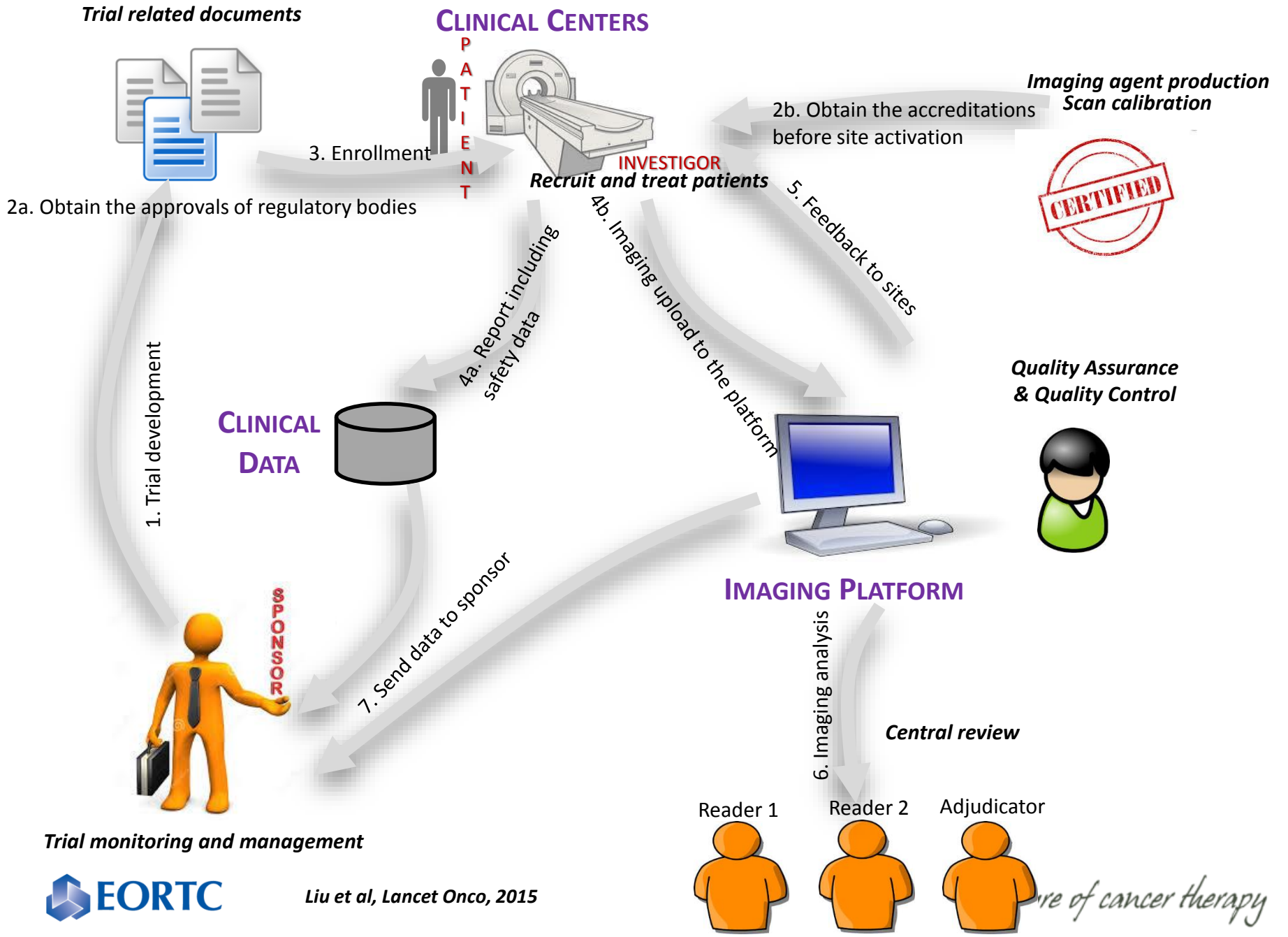
Risk management for imaging biomarker-driven studies



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

Lancet Oncol 2015; 16: e622–28

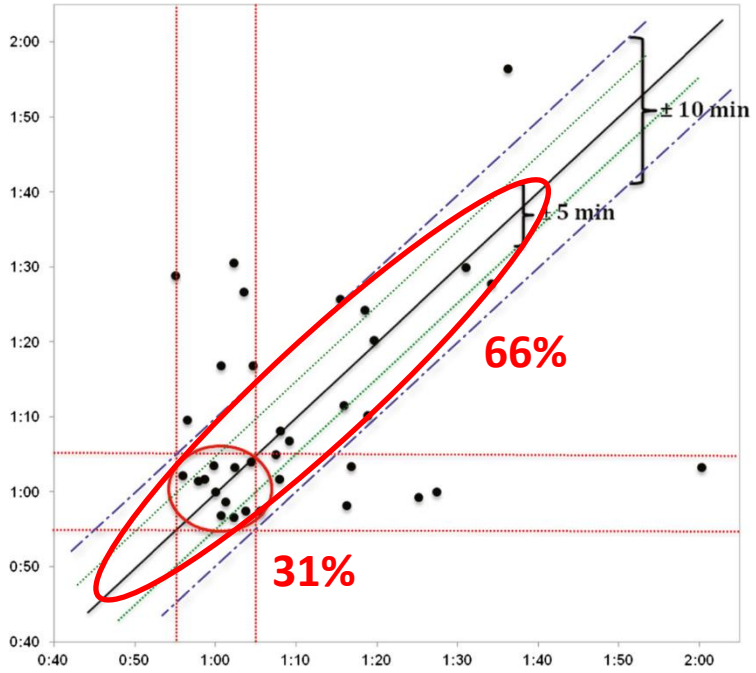
European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium (Y Liu MD, S Collette MSci); Cancer Research UK Cancer Imaging Centre, MRI Unit, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK (Prof N M deSouza MD); Clinical Trial Branch, Cancer Imaging

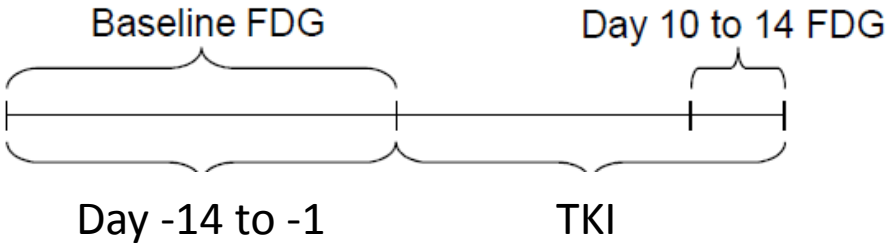
Imaging has steadily evolved in clinical cancer research as a result of improved conventional imaging methods and the innovation of new functional and molecular imaging techniques. Despite this evolution, the design and data quality derived from imaging within clinical trials are not ideal and gaps exist 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.

Lessons learnt (I)

Example

Hypothesis: patients with FDG-PET response ($\Delta SUVmax \geq 25\%$), the PFS is 12 weeks longer than in patients without PET response





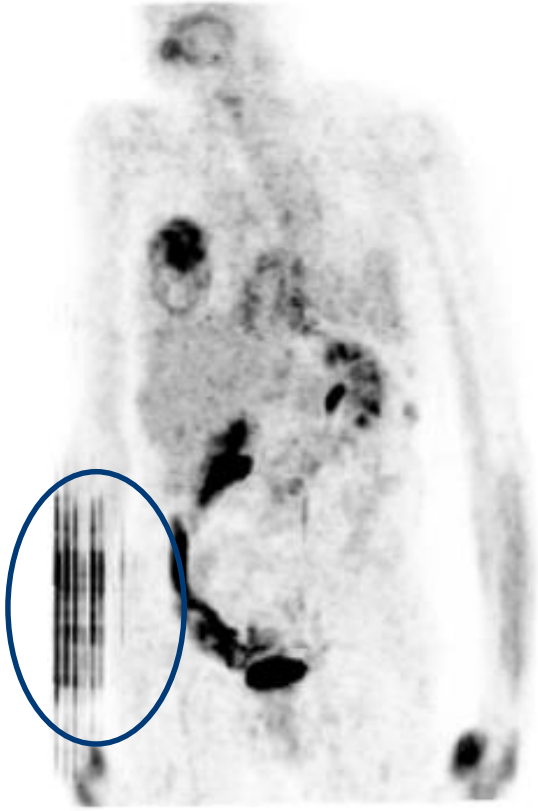
- 44 patients enrolled (81 scans received)
- 35 patients have both scans with good visual quality
- Low compliance to the imaging guidelines

	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)

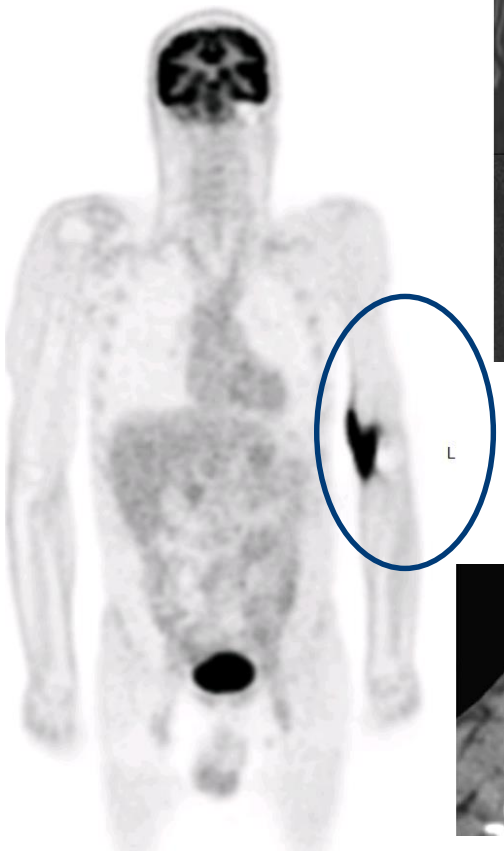
Finally, less than half of pts could be used for quantitative assessment. No conclusion could be drawn due to inadequate sample size

Hristova at al, EJNMMI 2015

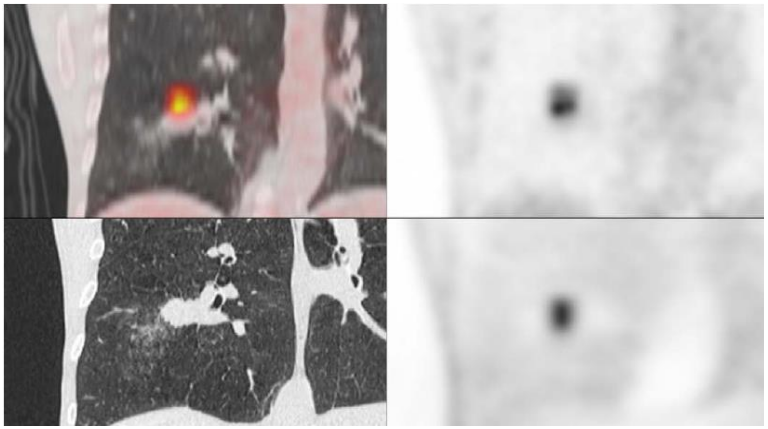
Lessons learnt (II)



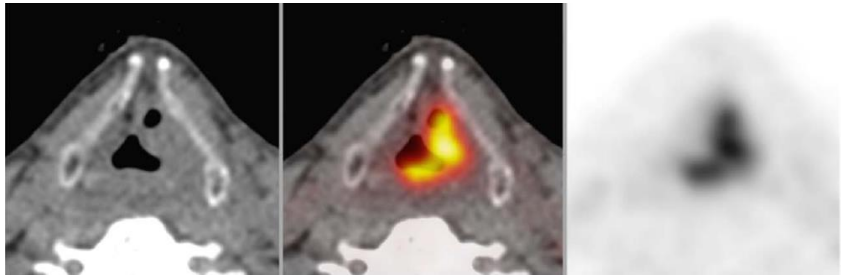
artifacts



extravasation



breathing



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

What is the truth?

Collection of HBM

The origin of HBM

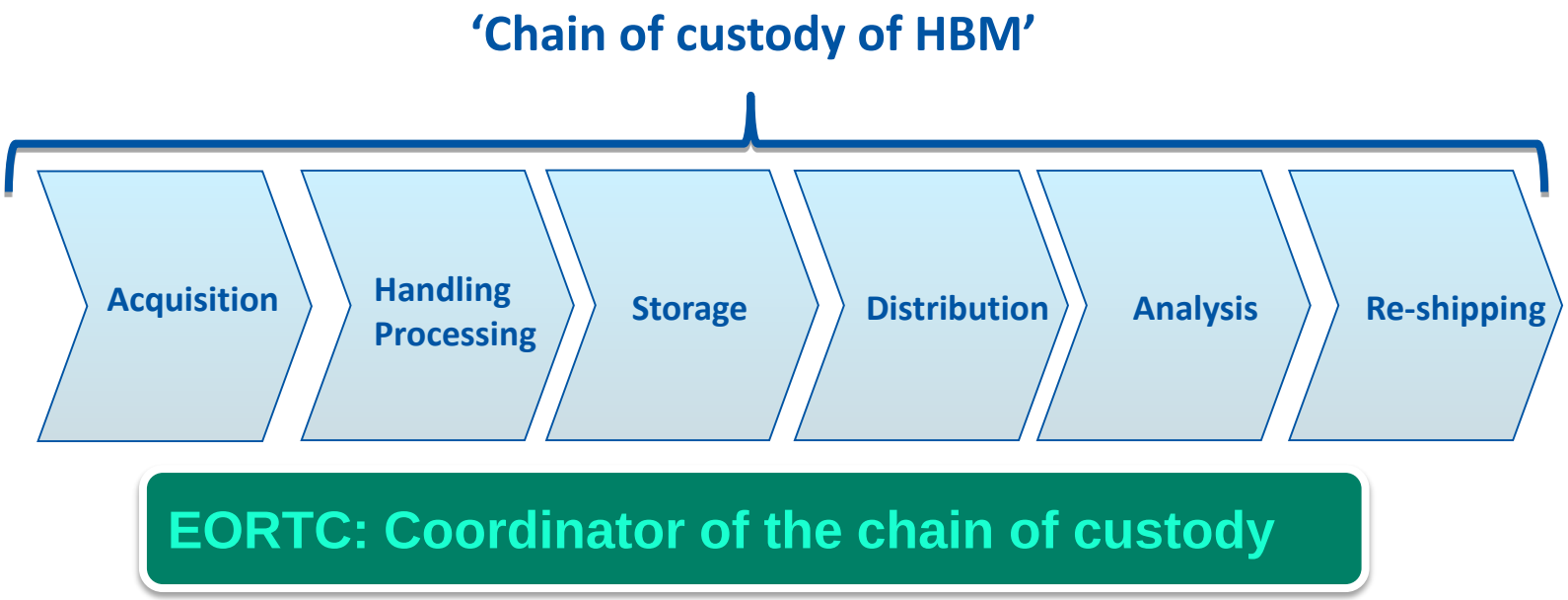
3 types of HBM

- 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

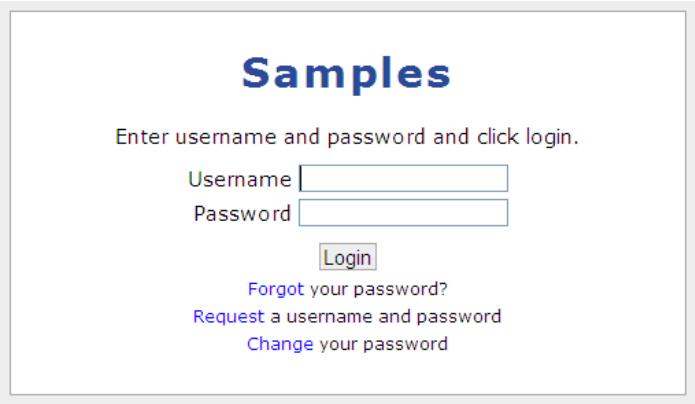
Institutes can remain custodian *even if* HBM is offsite in an EORTC storage facility (the contributing institute still decides future use)



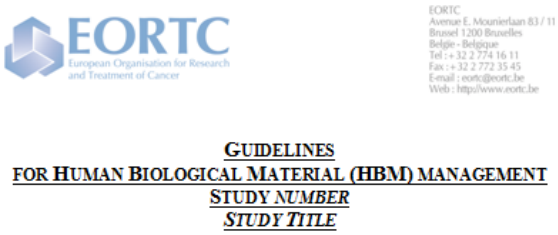
Logistics for HBM collection

➢ HBM traceability

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



➢ HBM handling procedures/guidelines

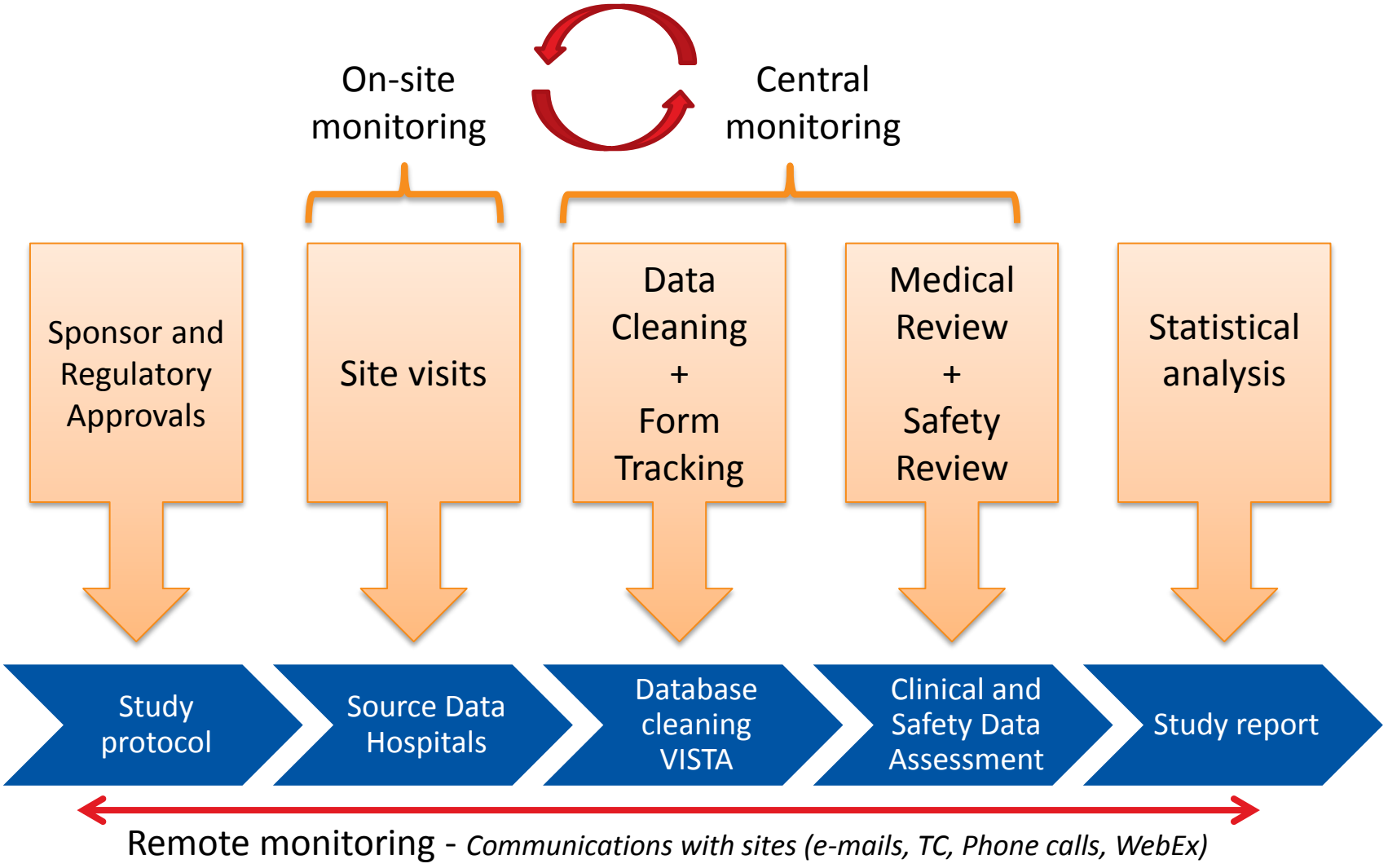


- optimize quality of samples
- must be developed prospectively
- based on international standards

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

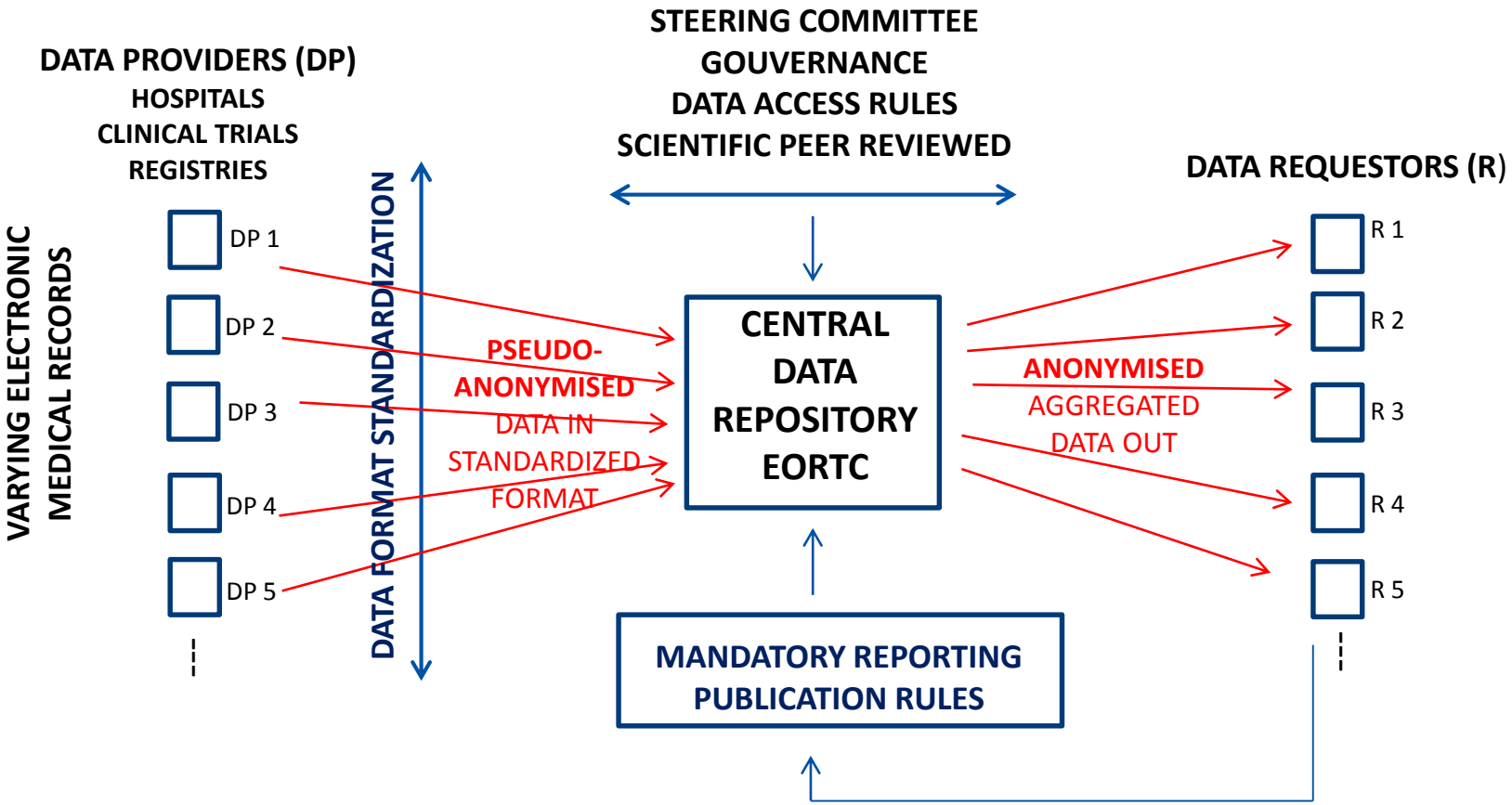
Meeting the investigator

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