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

Denis Lacombe, MD, MSc
EORTC, Director General
Brussels, Belgium
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)

<table>
<thead>
<tr>
<th>A world-class network</th>
<th>An expert HQ</th>
<th>Unique output</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ± 5,000 collaborators</td>
<td>• 202 employees</td>
<td>• 12 new studies open to patient entry in 2016</td>
</tr>
<tr>
<td>• 870 institutions</td>
<td>• &gt; 195,000 patients in database</td>
<td>• 54 ongoing studies</td>
</tr>
<tr>
<td>• 35 countries</td>
<td>• 24,000 patients in follow-up</td>
<td>• 19 studies in protocol outline development</td>
</tr>
<tr>
<td>• 21 groups &amp; task-forces</td>
<td></td>
<td>• 15 studies in protocol development</td>
</tr>
<tr>
<td>• 111 collaborative groups</td>
<td></td>
<td>• 15 studies in regulatory activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Working on ≈ 193 studies</td>
</tr>
</tbody>
</table>
Tools for clinical trials management

- ORTA (IWRS)
- VISTA RDC (eCRF)
- PRISMA (CTMS)
- SharePoint
- Monitoring & Regulatory
- eTMF
- Vista (CDMS)
- VISTA Stat
- sTrack
- SAfE
- CDISC
- ssas
- IMAGYS & RT

Compliance with FDA 21CFR part 11 & EU Annex 11
EORTC infrastructure to support new generation clinical trials

- Translational Research
- Biobank

Sample tool

KEOSYS platform

RTQA
VODCA platform

ORTA, VISTA, Safe, PRISMA

- Imaging

Clinical infrastructure

The future of cancer therapy
Consent
Consent

Suggested reading: the changing face of clinical trials


• 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

ECs(/CAs)
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

Informed consent?
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

Data bundle

Remote Data Capture (e CRF)
RTQA webform
DICOM-RT data

Data integrity QA
EORTC RTQA platform (data review-VODCA)

DICOM-RT viewer interface
EORTC RTQA platform

Data collection

Data coordination (HQ)

Data review
EORTC RTQA platform (data collection)

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

**Digital data transfer**

**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:

1. Facility Questionnaire (FQ) Beam Output Audit (BOA)
   - Admin data
   - External QA

2. Benchmark Case (BC) or Dummy Run without delineation exercise (DR)
   - “Dummy” patient and/or “connectivity” check

3. Limited Individual Case Review (L-ICR)
   - Review for protocol compliance

4. Extensive Individual Case Review (E-ICR)

5. Complex Dosimetry Check (CDC) or Virtual Phantom Procedure (VPP)
   - IMRT

The future of cancer therapy
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)
Easy imaging uploading
direct information export from DICOM header
Local site case report from
Online quality control
Easy to measure
central review form
Automatic email contact to the sites and the manager team

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
2. Daily QC performed
3. Were all clocks properly synchronized
4. Radiopharmaceutical dose administered [MBq] or Unknown
5. Date of radiopharmaceutical administration [th mm] or Unknown
6. Exact uptake time
7. Date of last quarterly maintenance

PET QC form
1. Is this a PET/CT Dummy run scan
2. Assessor's name & de-identification compliance
3. Comments
4. Visual quality assessment
5. Comments
6. Acquisition parameters compliance
7. Comments

PET review form
1. Site of ROI/PET scan
2. Name of reviewer
3. Transport of PET scans
4. Other fields

Measurements

Dear [Name],
We have the pleasure to inform you that the FDG-PET scans & local PET CRF you have submitted are now being processed for QC and central review of response.

Protocol: [Protocol]
Patient: [Patient]
Visit: [Visit]

Kindest regards

The future of cancer therapy
Risk management for imaging biomarker-driven studies

1. Trial development
   - 2a. Obtain the approvals of regulatory bodies
   - 2b. Obtain the accreditations before site activation

2. Recruit and treat patients
   - 3. Enrollment
   - 4a. Report including safety data
   - 4b. Imaging upload to the platform
   - 5. Feedback to sites

3. Imaging agent production
   - Scan calibration

4. Imaging analysis
   - Central review
   - Reader 1
   - Reader 2
   - Adjudicator

5. Quality Assurance & Quality Control
   - Certified

6. Imaging data
   - INVESTIGOR

7. Trial monitoring and management
   - Send data to sponsor

Trial related documents

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 (ΔSUVmax ≥ 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

<table>
<thead>
<tr>
<th></th>
<th>required</th>
<th>% compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>60 ±5 min</td>
<td>39% (15/35)</td>
</tr>
<tr>
<td>FU</td>
<td>60 ±5 min</td>
<td>51% (18/35)</td>
</tr>
<tr>
<td>BL+FU</td>
<td>60 ±5 min</td>
<td>31% (11/35)</td>
</tr>
<tr>
<td>FU±10 min from actual BL</td>
<td>60 ±5 min</td>
<td>66% (23/35)</td>
</tr>
</tbody>
</table>

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

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Lessons learnt (II)

- 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)

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**‘Chain of custody of HBM’**

- Acquisition
- Handling Processing
- Storage
- Distribution
- Analysis
- Re-shipping

**EORTC: Coordinator of the chain of custody**

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*The future of cancer therapy*
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

- On-site monitoring
  - Site visits
- Central monitoring
  - Data Cleaning + Form Tracking
  - Medical Review + Safety Review
  - Statistical analysis

- Remote monitoring - Communications with sites (e-mails, TC, Phone calls, WebEx)

- Study protocol
- Source Data Hospitals
- Database cleaning VISTA
- Clinical and Safety Data Assessment
- Study report
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)
On-site Monitoring tasks
What can be supported by e-monitoring?

- Checking PIS/IC
- Visiting the pharmacy
- Source data verification
- Protocol & GCP compliance
- Biological samples
- Checking the ISF
- Meeting the investigator
- Tracking pending issues
- Site training
- Support in queries resolution
- Handling of major observations

The future of cancer therapy
## E-research at EORTC: impact of “remote monitoring”: a few examples

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