Data Quality in Investigator Initiated Trials: The EORTC Experience

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Principles of Monitoring

According to ICH-GCP, the purpose of trial monitoring is to verify that:

- **the rights and well-being of human subjects are protected**
- **the reported trial data are accurate, complete and verifiable from source documents**
- **the conduct of the trial is in compliance with currently approved protocol/amendments, with GCP and applicable regulatory requirements**

Definition of Monitoring

ICH-GCP 1.38

"The act of overseeing the progress of a clinical trial and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP and the applicable regulatory requirements"

Monitoring does not necessarily mean on-site visits

Possible alternative monitoring

ICH-GCP 5.18.3:

"the sponsor should determine the <u>appropriate</u> <u>extent and nature</u> of monitoring….. in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, extensive written guidance can assure appropriate conduct of trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified"

Accrual of patients in EORTC clinical studies in 2005: 4471 patients

European Union

Austria
Belgium
Cyprus
Czech Republic
Denmark
Finland
France
Germany
Hungary
Ireland
Italy
Latvia
Luxemburg
Poland
Portugal
Slovakia
Slovenia
Spain
Sweden
The Netherlands
United Kingdom

Rest of the World:

Australia
Egypt
Israel
Lebanon
Mexico
Peru
South Africa
U.A. Emirates
U.S.A.

Non-EU Countries:

Croatia
Norway
Russia
Serbia and Montenegro
Switzerland
Turkey

Quality assurance procedures at EORTC on-site activities

- **On-site Quality Assurance audits:**
  - **Academic activities/affiliated institutions/US Intergroup studies**
- **Protocol specific monitoring:**
  - **Early drug development/registration trials/Phase I**
- **Disease/modality oriented QA**
  - **Group oriented: i.e. sarcoma, neuro-oncology**
  - **Radiation oncology specific programmes**

Quality assurance procedures at EORTC Data Center/Central activities

- **Data management:**
  - **Standardized CRFs, Eligibility check lists, X-Checks, Patient profiles, data timeliness, pre-defined ranges**
- **Statistics:**
  - **yearly review of DB, data trends**
- **Internal audits**
- **Specific reviews/questionnaires:**
  - **Clinical validation of all cases, panel reviews, central pathology, RT facility questionnaire**
- **Pharmacovigilance issues**
  - **Pharmacovigilance Unit, RAU, DSMB, IDMC**

Central monitoring in Low risk IITs

- **Limited to no funding**
- **Usually large phase III trials/public health issues**
- **Well known network/peer review/affiliated institution network**
- **Track records of institutions in past trials**
- **For-cause audits by QA unit based on central monitoring**
- **Possibility for limited on site monitoring programme if funding available and reasonable trial size**

Monitoring programme in high risk IITs

- **Early drug development/Phase I/registration trials**
- **Funding usually available**
- **Protocol specific**
  - **EORTC/CRO/Company**
- **In addition but not to replace central QA procedures**
- **Alternatively trials placed in limited and high quality institutions (phase I)**

QA supported by fast adaptative environment

- **On going training of multidisciplinary centralized expertise of Data Center Staff**
- **Rapid adaptation to the changing regulatory framework**
- **Standardized EORTC group membership**
- **Communication and training of investigators**
- **Development of training activities: course, conferences, manual for investigators and patients…**

DATA CENTER MONITORING & QUALITY ASSURANCE IN EORTC TRIALS

	2003 - 2005		2005	
	Monitoring	QA	Monitoring	QA
• **Trials**	21	35	9	23
• **Research Groups**	10	13	5	10
• **Institutions**	216	54	98	19
• **Total n°. of site visits**	992	53	265	19

On-site monitoring activities 2001 - 2005

- **82 clinical trials**
- **16 clinical research groups**
- **3818 site visits**
  - **1193 EORTC**
  - **1077 Company**
  - **1548 CRO**

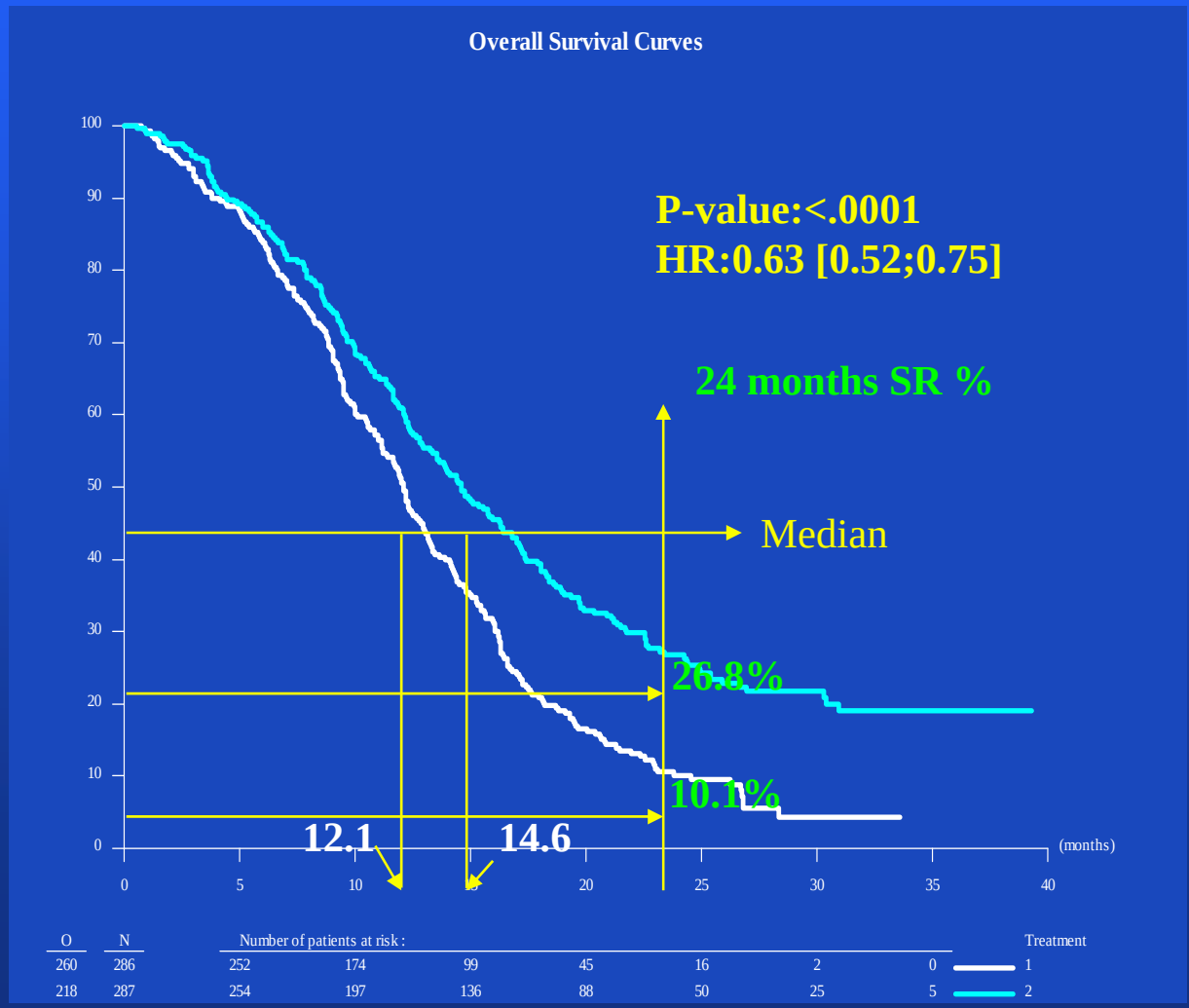
Concomitant and adjuvant TMZ in newly diagnosed high grade glioma (I)

- **Phase III trial in a relatively rare disease**
- **573 patients accrued in 16 months by 85 sites in 14 countries**
- **No prospective on site monitoring**
- **Retrospective monitoring at 18 sites accruing 49% of the patients**
- **Activity: 5 discrepancies in days in date of death**

Concomitant and adjuvant TMZ in newly diagnosed high grade glioma (II)

- **Safety summary analysis of data from 18 monitored sites vs 67 non monitored: no systematic difference found**
- **Tabulation of safety events found during site visits: only mild to moderate events not changing the safety information on TMZ**
- **27 SAEs found (no SADR/SUSARS)**
- **Readily submission of the EORTC DB to EMEA/FDA**
- **Estimated costs saved: Euros 2,000, 0000.**

EORTC 26981-22981: Overall Survival



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Future directions

- **Requiring systematic prospective on site monitoring for all trials in Europe would be a major strategical mistake for European research**
- **Procedures for ensuring data quality should not be limited to on site monitoring, complementary and varying methods do provide higher data output**
- **Industry does not necessarily provide higher quality data than IIT**
- **Tailored made programme should be discussed depending on end-points, environment...**
- **Pragmatic approach is key for Europe to remain competitive: comparative analysis of US NIH/NCI programmes should be performed by EU regulators**