Anhang

Datenqualität in klinischen Studien
Einzelauswertung der eingeschlossenen Untersuchungen

Nr.	**01**
Title	Quality assurance experience with the randomized neuropathic bone pain trial (Trans-Tasman Radiation Oncology Group, 96.05)
Author/Years/ Journal	Roos et al., Radiother Oncol 67 (2003) 207-212
Setting	Radiation oncology clinical research organization (TROG) with QA measures (evolving in parallel with the audits)
Clinical trial	Prospective randomized trial comparing 2 regimes of radiotherapy for neuropathic pain due to bone metastases (1999-2002)
Outcome criteria	• Eligibility infringement rate • Violation of radiotherapy
Methods	• Independent eligibility/quality assurance audits (n = 5) • Source data verfication for all radiotherapy prescription and treatment documentation using copies of source data
Audit	Yes (according to authors)
results	• Eligibility infringement rate = 18/225 (8%) • Violation of radiotherapy = 52/232 (22%) - per protocol ± 5%) = 22/232 (9%) - minor variation (between ± 10%) = 15/232 (6%) - Unacceptable variation (more than ± 10%) = 15/232 (6%) • Inaccurate recording of radiotherapy = 3/232 (3%) • Improvement after first audit
consequences	• QA auditing essential and should commence soon after study activation

Nr.	**02**
Title	Quality control of validity of data collected in clinical trials
Author/Years/ Journal	Vantongelen et al., Eur J Cancer Clin Oncol 25 (1989) 1241-1247
Setting	EORTC Study Group on Data Management
Clinical trial	• Phase III breast cancer trial for adjuvant therapy • Phase III breast cancer trial for advanced disease • Phase III ramdomised trial in advanced soft tissue carcinoma
Outcome criteria	• Correct/missing/incorrect data/not in file
Methods	• Site visits with source data verification • 15 centres visited • Analysis according to centres with and without administrative trial structure
Audit	Unsure
Results	• Correct data: 78% - 98% Missing data: 0.3% - 2.9% incorrect data: 0.5% - 7% Not in file: 0.4% - 14.5% (verification not possible)
Consequences	• Data quality influenced by internal organization and local data monitoring • Importance of the design of CRF

Nr.	**03**
Title	Quality control in multicentre clinical trials. An experience of the EORTC Gynaecological Cancer Cooperative Group
Author/Years/ Journal	Favalli et al., Eur J Cancer 36 (2000) 1125-1133
Setting	EORTC Study Group on Data Management
Clinical trial	Randomized phase III trial of chemotherapy in disseminated squamous cell carcinoma of the uterine cervix (1986-?)
Outcome criteria	• Adherence to protocol chemotherapy • Incorrect/correct/missing data/not in file • Documentation of side effects
Methods	• Source data verification • Written informed consent not compulsory
Audit	Unsure
Results	• Altered treatment intervals = 54/176 (31%) intervals - avoidable = 19/176 (11%) • Incorrect data = 7% of data items • Correct data = 81.8% missing on form = 3.6% not in file = 7.6% • Side effects missing = 19/125 (15%) cycles incorrectly graded = 59/125 (47%)
Consequences	• Simple protocols and CRFs • Trained data managers should be present in all institutions • Standardized treatment toxicity reporting • Necessity of quality control activities

Nr.	**04**
Title	Participation of community hospitals in clinical trials. Analysis of five years of experience in the Eastern Cooperative Oncology Group
Author/Years/ Journal	Begg et al., NEJM 306 (1982) : 1076-1080
Setting	Eastern Cooperative Oncology Group (ECOG)
Clinical trial	97 Cancer therapy protocols (1976-1981)
Outcome criteria	• Inegilibility rate • Protocol-violation rate • Inadequate-data-submission rate
Methods	• Quality control by data managers at the ECOG Statistical Center • Review by person not-involved with the institution from which patients data were collected • matched pair analysis (protocol, treatment, data of registration)
Audit	No
Results	• Inegilibility rate = 7.2%, 5.7% (affiliates, member institutions) • Protocol-violation rate = 6.2%, 4.5% (affiliates, member institutions) • Inadequate-data-submission rate = 5.0%, 5.7% (affiliates, member institutions)
Consequences	• Inegilibility and protocol-violation rate steadily improving • Quality of participation between member institutions and affiliates similar

Nr.	**05**
Title	A successful system of scientific audits for clinical trials. A report from the cancer and leukemia Group B
Author/Years/ Journal	Weiss et al., JAMA 270 (1993) 459-464
Setting	Cancer and Leukemia Group B (CALBG) Data Audit Committee (NCI)
Clinical trial	• Clinical trials representing a cross section of malignancies and stages
Outcome criteria	• IRB compiance • Informed consent • Eligibility rate • Protocol compliance • Data submission
Methods	• On-site audits with source data verification (1982-1992)
Audit	Unsure
Results	• Institutions with major IRB deviations = 13.3, 28.2 (main, affiliate, 4th cycle) • Rate of consent from deficiences = 18.5%, 10.2%, 3.8%, 3.9% (1st, 2nd, 3rd, 4th cycle) • Eligibility rate = 90.0%, 91.6%, 93.5%, 94.5% (1st, 2nd, 3rd, 4th cycle) • Major protocol deviations in drug dosing = 12.2%, 10.1%, 10.8% (2nd, 3rd, 4th, cycle) • Data submission forms delinquent = 7.7%, 6.9% (main, affiliate, 4th cycle)
Consequences	• Scientific improprieties rarely occurred • Protocol compliance high • Improvement with respect to IRB, consent forms and data submission due to audits

Nr.	**06**
Title	Quality of institutional participation in multicentre clinical trials
Author/Years/ Journal	Sylvester et al., NEJM 305 (1981) 852-855
Setting	EORTC Data Center
Clinical trial	• Clinical trial in metastatic soft-tissue sarcoma (EORTC Soft Tissue and Bone/Sarcoma-Group)
Outcome criteria	• Protocol violation rate • Incomplete data rate • Ineligible rate
Methods	• Criteria of the EORTC data center, no source data verification
Audit	No
Results	• Protocol violation: 4%, 7% (major, minor participants) • Incomplete data: 1%, 22% (major, minor participants) • Ineligible: 13%, 25% (major, minor participants)
Consequences	• More valid patients for major participants

Nr.	**07**
Title	The Use of a Systemic Therapy Checklist Improves the Quality of Data Acquisition and Recording in Multicentre Trials. A Study of the EORTC Soft Tissue and Bone Sarcoma Group
Author/Years/ Journal	Verweij et al Eur J. Cancer 1997 ; 33 : 1045 - 1049
Setting	EORTC Soft Tissue and Bone Sarcoma Group (STBSG)
Clinical trial	Randomized trial for soft tissue sarcoma (EORTC 62903) performance according to GCP
Outcome criteria	• Data quality (correct, incorrect missing, only on CRFs) • Side-effects (correct, incorrect missing, only on CRFs)
Methods	• Site visits with source data verification by monitors from the EORTC-STBSG • Assessment of EORTC systemic therapy checklist (retrospective comparison, results dependent on the use of the checklist)
Audit	Unsure
Results	• Data quality: correct = 91%, incorrect = 2% missing = 1%, only on CRF = 6% • Side-effects: correct = 87%, incorrect = 4%, missing 1%, only on CRF = 8%
Consequences	• Use of systemic therapy checklist improves quality of data acquisition

Nr.	**08**
Title	Response assesment errors for all Southwest Oncology Group (SWOG) clinical trials are more likely overestimates of response
Author/Years/ Journal	Weiss et al, Proceedings of ASCO (1987) 6: 227 (abstract)
Setting	Southwest Oncology Group (SWOG) QA programm
Clinical trial	Different trial protocols
Outcome criteria	Incorrect response assessment
Methods	Site visits with source data verification
Audit	Yes (according to authors)
Results	Incorrect response assessment: 7%
Consequences	Correct response assessment in 93%

Nr.	**09**
Title	Compliance with protocol: quality assurance (QA) data from the Southwest Oncology Group (SWOG)
Author/Years/ Journal	Sunderland et al., Proc Am Soc Clin Oncol 1990 : 9/60 (Abstract)
Setting	Southwest Oncology Group (SWOG) QA program with periodic site-visits
Clinical trial	Different trial protocols
Outcome criteria	• Ineligibility • Inaccurate toxicity reporting • Treatment not per protocol • Inaccurate response assessment
Methods	• Site visits with source data verification
Audit	Yes (according to authors)
Results	• Ineligibility: 5.2% inaccurate toxicity reporting: 5% • Treatment not per protocol: 21.5% inaccurate response assessment: 5%
Consequences	• Eligibility, toxicity recording and response assessment correct in 95% • Recommendations for therapy adherence

Nr.	**10**
Title	Site visit monitoring program of the clinical cooperative groups: results of the first 3 years
Author/Years/ Journal	Mauer et al., Cancer Treatment Reports 1985 ; 69 ; 1177- 1187
Setting	Cooperative Groups Site Visit Monitoring Program of the Eastern Oncology Group
Clinical trial	17 groups, 812 institutions, 2814 protocols, 5988 patient cases
Outcome criteria	• Ineligibility • Treatment inconsistercy • Response assessment deficiency • Toxicity assessment deficiency • Data verification deficiency • Informed consent deficiency • Drug accountability
Methods	• On-site audits with data verification • Comparison of members and affiliates
Audit	Yes (according to authors)
Results	• Ineligibility: 7% (by case) • Treatment in consistency: 12% (by case) • Response assessment deficiency: 6% (by case) • Toxicity reporting deficiency: 4% (by case) • Data verification deficiency: 5% (by case) • IRB deficiency: 6% (per protocol) • Informed consent deficiency : 9% (per case) • Drug accountability deficiency: 14% (by institution)
Consequences	• Cooperative clinical trial networks conduct research according to high standards • Site visiting monitoring program useful for tracing performance of individual institutions and groups

Nr.	**11**
Title	Chemotherapy administration and data collection in an EORTC collaborative group - can we trust the results?
Author/Years/ Journal	Steward et al., Eur J Cancer 1993 ; 29A : 943-947
Setting	EORTC Quality Control Group/ EORTC Data Centre
Clinical trial	Phase II trial for treatment of patients with advanced soft tissue carcinoma
Outcome criteria	• Missing/ incorrect/ not verifiable data • Delivery of chemotherapy
Methods	• Site visits with source data verification • 15 centre visited • Randomly selected patients
Author	Unsure
Results	• Missing data: 0.2% • Incorrect data: 3.4% • Not verifiable data: 30% • Delayed cycles of chemotherapy: 21%
Consequences	• Propagation of a systematic quality control programme with occassional visits to all centers and review of data quality for a small section of patients • Suggestion for a systematic checklist for recording toxicity and chemotherapy administration

Nr.	**12**
Title	The National Cancer Institute audit of the National Surgical Adjuvant Breast and Bowel Protocol B-06
Author/Years/ Journal	Christian et al. NEJM 1995 : 333 : 1469-1474
Setting	National Surgical Adjuvant Breast and Bowel Protocol B-06 (reanalysis because of fraud)
Clinical trial	Randomized controlled trial for breast cancer
Outcome criteria	• Signed informed consent(documented, not documented, status unable) • Eligibility (verified, not verified, discrepant) • Patient characteristics, treatment assignments, outcome (verified, not verified, discrepant)
Methods	• Site visits with source data verification by NCI personnel and professional auditors
Audit	Yes (according to authors)
Results	• Signed informed consent: documented = 92.9; not documented = 4.6%; status unable = 2.4% • Eligibility: verified = 94.8%, not verified = 5.1%, discrepant: 0.1% • Pat.char., treatment assignments, outcome: verified = 97.5%, not verified = 1.6%; discrepant = 0.9%
Consequences	The audit reconfirms adequacy of data

Nr.	**13**
Title	Application of quality improvement. Theory and process in a national multicenter HIV/AIDS Clinical Trials Network
Author/Years/ Journal	Rouff et al., Q Manage Health Care 2003 ; 12 :89-96
Setting	National Multicenter HIV/AIDS Clinical Trial Network (Community Programs for Clinical Research on AIDS (CPCRA) sponsored by Nat. Inst. of Allergy and Infections Diseases (NAID)
Clinical trial	Not specified
Outcome criteria	• Unreported AE • Unreported clinical event • Ineligibility
Methods	• Monitoring of performance measures quarterly through performance efforts by Quality Improvement Committee members (internal?) data from 1993-1998 • Technique, sample-size, trials not documented
Audit	No
Results	• Unreported AE: <0.1-2.9 • Unreported clinical event: 0-1.2 • Ineligibility: 0.5-5.5
Consequences	Analysis of selected performance measures reveals improvements that coincide with increased efforts on quality improvement

Nr.	**14**
Title	Postmarketing survillance of oral terbinafine in the UK: report of a large cohort study
Author/Years/ Journal	O`Sullivan et al., Br J Clin Pharmacol 1996; 42: 559-565
Setting	Guidelines for Post Marketing Surveillance studies (PMS) coordination by pharmcovigilance group of Sandoz Pharmaceuticals
Clinical trial	Prospective observational surveillance study of oral terbinafine in the UK (postmarketing)
Outcome criteria	• Patients with every item verified correctly • Data entry error rate • Patients with correctly verified demographic data • Data item discrepancy rate
Methods	• Source data verification in a random sample (13%) • Monitory of data capture at investigator sites • Regular reports to Medicine Control Agency • Accuracy check of completed record forms by Parexel
Audit	Unsure
Results	• Patients with every item verified correctly: 82% • Data entry error rate: 2% • Patients with correctly verified demographic data: 96% • Data item discrepancy rate: 0.9%
Consequences	Successful conclusion of study and apparent data quality attested by SDV, which is relatively unique in the post marketing setting

Nr.	**15**
Title	Quality assurance in the EORTC 22921 trial on preoperative radiotherapy with or without chemotherapy for resectable rectal cancer: evaluation of the individual case review procedure
Author/Years/ Journal	Kouloulias et al., Eur J Cancer 2002 : 38 : 1849-1856
Setting	EORTC radiotherapy group
Clinical trial	EORTC 2291 trial investigating a new combination of neoadjuvant and adjuvant treatment of rectal cancer with preoperative radiotherapy as integral part
Outcome criteria	• Ineligibility • Missing data • Protocol compliance (radiotherapy, chemotherapy)
Methods	• Individual case review for data consistency and protocol compliance • Sample of 5 patients per institution randomly selected by EORTC data center • Central evaluation of source data and comparison with CRF
Audit	No
Results	• Ineligibility: 1.7% • Missing data on CRF: 10%, 12% • Inconsistency between clinical and pathological strategy: 10% • Incorrect size of pathology specimen: 17% • Fractionation of radiotherapy not according to protocol: 22% • Variation in prescribed chemotherapy schedule: 13% • Major protocol violations for chemotherapy: 0%
Consequences	The individual case review as part of QA has revealed a number of protocol violations. Immediate feedback can reduce treatment variation and improve adherence to protocol.

Nr.	**16**
Title	Quality control reviews for radiotherapy of small breast cancer: analysis of 708 patients in the GBSG I trial
Author/Years/ Journal	Seegenschmiedt et al., Strahlenther. Onkol. 1993; 169: 339-350
Setting	German Breast Cancer Study Group (GBSG) (quality control review of radiotherapy and treatment routinely by four reference centers)
Clinical trial	GBSG I trial for breast carcinoma (initially randomized then prospective observational multicenter trial)
Outcome criteria	Protocol compliance of radiotherapy
Methods	• Quality control review of radiotherapy in 733 irradiated patients • Examination of radiotherapy records by radiotherapy reference center for completeness and quality of the data
Audit	No
Results	• Radiotherapy per protocol: 41.2% • Acceptable deviation of radiotherapy: 41.0% • Unacceptable deviation of radiotherapy: 17.8% (highest violation: treatment duration 9.5%)
Consequences	• Improvement of protocol compliance by time • Important differences of protocol compliance for accrual per hospital, institutional treatment performance and type of institution

Nr.	**17**
Title	The need for immediate monitoring of treatment parameters and uniform assessment of patient data in clinical trials
Author/Years/ Journal	Schaake-Koning et al., Eur J Cancer 1991; 27: 615-619
Setting	EORTC Radiotherapy and Lung Cancer Cooperative Groups
Clinical trial	EORTC trial 08844 (radiotherapy combined with low-dose cisplatin vs radiotherapy alone in inoperable non-small cell lung cancer
Outcome criteria	• Ineligibility • Protocol compliance for radiotherapy, chemotherapy • Agreement on outcome assessment
Methods	• Site visits by quality control committee in centers which had Randomized 10 patients or more • Source data verification by the committee
Audit	Unsure
Results	• Ineligibility: 7.3% • Incorrect radiotherapy radiation dose (first course): 7% • Insufficient field size: 15% • Tumor free margin less than 1 cm: 17% • Incorrect dose of cisplatin: 7% • Differences in response between review and CRF: 39% • Discrepancy concerning local progression: 8 patients • Discrepancy concerning time of local recurrence: 22 patients • Discrepancy concerning date of manifestation of metastases: 18 patients • Missing data on distant metastases: 8 patients • Discrepancy concerning date of death: 5 patients
Consequences	Imperative need for a direct quality control system to monitor performance of trials to avoid mistakes and to correct faults

Nr.	**18**
Title	Impact of initial quality control review on study outcome in lung and head/neck cancer studies – review of the radiation therapy oncology group experience
Author/Years/ Journal	Wallner et al., Int J Radiol Oncol Biol Phys 1989; 17 : 893-900
Setting	Radiation Therapy Oncology Group (RTOG) RTOG Quality Control program
Clinical trial	11 lung trials 9 head and neck trials
Outcome criteria	Protocol compliance for radiotherapy (treatment assignment, radiotherapy, dosis)
Methods	Review of protocol compliance for radiotherapy by radiological oncologist based on inspection of data (?)
Audit	No
Results	• Missing/delayed data for lung cases: 6.2% • Missing/delayed data for head/neck cases: 6.8% • Needing modification of radiotherapy for nodal borders, dose to the nodes, borders for the critical structures, dose to critical structures (data according to year and localization see original publication)
Consequences	• Sharply defined but long lasting learning experiences involved in clinical trial participation • Marked improvement of data by quality control program

Nr.	**19**
Title	A quality assurance audit; phase III trial of maximal androgen deprivation in prostate cancer (TROG 96.01)
Author/Years/ Journal	Steigler et al., Australasian Radiol 2000; 44: 65-71
Setting	Trans-Tasman Radiation Oncology Group (TROG)
Clinical trial	Phase III randomized trial to examine the effects of maximal androgen deprivation (MAD) using the drugs Goserelin and Flutamide prior and during definitive radiation therapy for locally advanced cancer of the prostate
Outcome criteria	• Protocol compliance concerning radiotherapy • Source data verification of clinical data (stratification variables)
Methods	• Audit sample composed of first 5 pat. randomized at each center • Centers paired to exchange and review each other´s data • Transferral of copies of source data to reviewers
Audit	Yes (according to authors)
Results	• Variation of radiotherapy for prescribed dose: minor: 0%, major: 0%, unacceptable: 0% • Variation of radiotherapy for fractionation: minor: 0%, major: 0%, unacceptable: 0% • Variation of radiotherapy for treatment time: minor: 30.4%, major: 7.1%, unacceptable: 1.8% • Variation of radiotherapy for field placement: minor: 23.6%, major: 0%, unacceptable: 1.8% • Source verification of clinical data: stage, non-compliance: 3.6%, missing: 3.5% • Source verification of clinical data: PSA, non-compliance: 0%, missing: 1.8% • Source verification of clinical data: grade, non-compliance: 0%, missing: 0% • Source verification of clinical data: treatment time, non-compliance: 3.6%, missing: 1.8%
Consequences	Overall improvements were detected in data quality and quantity, and in protocol compliance with a reduction in the rate of unacceptable protocol violations from 10% for 4%

Nr.	**20**
Title	Eligibility audits for randomized neuropathic bone paine trial (TROG 96.05)
Author/Years/ Journal	Roos et al., Australasian Radiol 2000 ; 44 : 303-307
Setting	Trans Tasman Radiation Oncology Group (TROG)
Clinical trial	Multicenter prospective randomized trial comparing two types of radiotherapy for neuropathic pain
Outcome criteria	Ineligibility rate
Methods	• Transferral of copied source data documents to the auditor (record, CRF´s etc.) • Examination of source data by auditor (audit1: n = 42) (audit2: n = 48)
Audit	Yes (according to authors)
Results	• Ineligibility rate for audit 1: 19% • Ineligibility rate for audit 2: 2%
Consequences	QA measure undertaken early in the trial led to significant improved clinical awareness and compliance with eligibility/exclusion criteria

Nr.	**21**
Title	Quality assurance audit in an Australasian phase III trial of accelerated radiotherapy for head and neck cancer (TROG 91.01)
Author/Years/ Journal	Hamilton et al., Australasian Radiol 1999 ; 43 : 227-232
Setting	Trans Tasman Radiation Oncology Group (TROG)
Clinical trial	Randomized trial company two types of radiotherapy for squamous cell carcinoma of the head and neck
Outcome criteria	Protocol compliance of radiotherapy
Methods	• Retrospective technical audit • Transferral of copies of source data to reviewers • Queries concerning missing data unclear information
Audit	Yes (according to authors)
Results	• Variation of radiotherapy for dose: minor: 1%, major: 0%, unacceptable: 3% • Variation of radiotherapy for field placement: minor: 22%, major: 5%, unacceptable: 3% • Variation of radiotherapy for fractionation: minor: 0%, major: 0%, unacceptable: 3% • Variation of radiotherapy for treatment time: minor: 34%, major: 11%, unacceptable: 7%
Consequences	The 91.01 trial has a satisfactory technical violation rate (but not optimal). The technical data quality was unsatisfactory across a few institutions