Overview on data quality in clinical trials

- International Workshop -

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Prof. Dr. C. Ohmann
Wissenschaftlicher Leiter
Koordinierungszentrum für Klinische Studien Düsseldorf

Overview on data quality in clinical trials

- aim of the presentation -

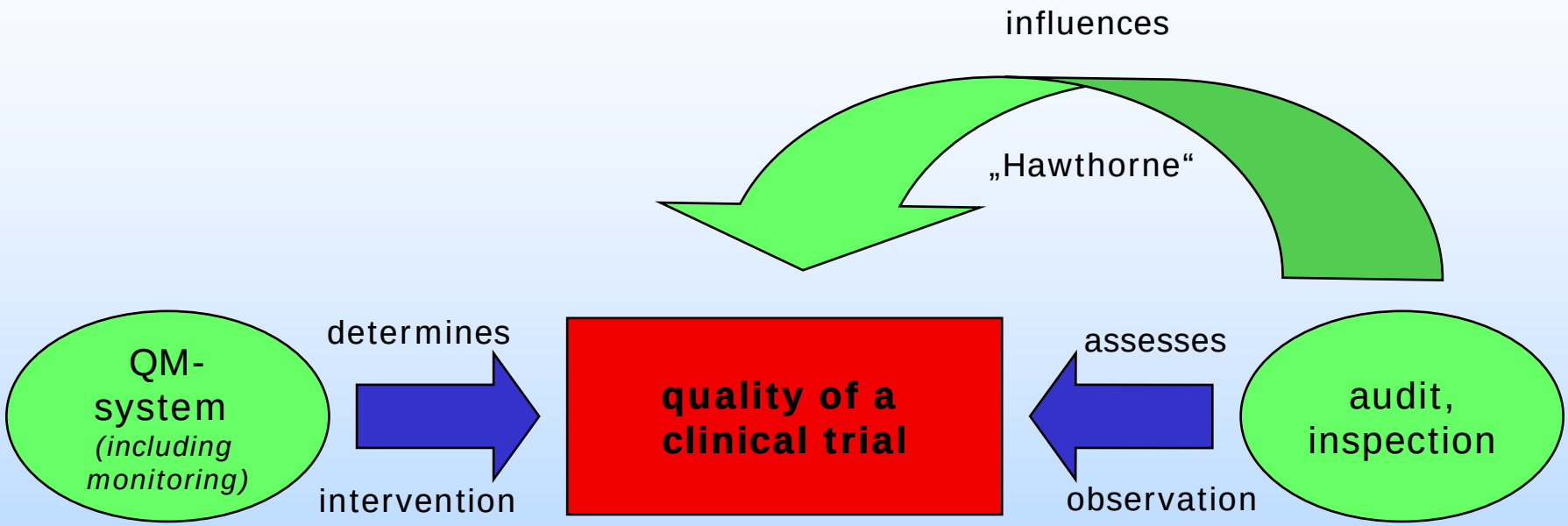
- introduction
- literature review on data quality and protocol compliance in clinical trials
- FDA-audits
- fraud
- conclusions

ICH-E6: Guideline for Good Clinical Practice

- definitions -

monitoring	*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, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requrement(s).*
audit	*A systematic and indepentent **examination of trial related activities and documents** to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor`s standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)*
inspection	*The act by a regulatory authority(ies) of conducting an **official review of documents, facilities, records**, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor´s and/or contract research organizationis (CROis) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).*

Roles of monitoring / audit in a clinical trial



Guidelines for quality assurance in multicenter trials*

- central monitoring of data
- site visits
- record auditing: central or on site
- performance-monitoring reports
- statistical investigations
- review of data from quality control programs
- checks on data analysis

**Knatterud et al., Controlled Clinical Trials 1998; 19: 477-493*

Auditing of clinical trials*

„Surprisingly little quantitative informations is available about methods for auditing clinical trials“

„More quantitative information is needed to set standards of monitoring and auditing.“

**Califf et al., Controlled Clinical Trials 1997; 18: 651-660*

literature review on data quality and protocol compliance in clinical trials

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Data quality in clinical trial groups
- methods -

- medline search *(Ovid, 1966 to March Week 2, 2006)*
- search pattern: *„quality assurance, quality control, medical audit, data quality, monitoring, site visit, source data verification, data accuracy“* restricted to *„clinical trials“ (with some further restrictions)*
- evaluation of titles ➟ abstracts ➟ full publications
- inclusion criteria:
  - investigation of data quality and protocol compliance in clinical trials by audits *(no restrictions with respect to type of monitoring)*
  - quantitative data *(rates, frequencies)*
  - information about quality management in the trial
- assessment of selected publications by standardized form

*

Data quality in clinical trial groups
- results -

21 publications fulfilling the inclusion criteria:

- EORTC Cooperative Groups/ Study Group on Data Management **(n = 7)**
  - ✓ Gynecological Cancer Cooperative Group (GCCG)
  - ✓ Soft Tissue and Bone Sarcoma Group (STBCG)
  - ✓ Radiotherapy and Lung Cancer Cooperative Groups

- National Cancer Institute (NCI) Cooperative Groups **(n = 7)**
  - ✓ Eastern Cooperative Oncology Group (ECOG)
  - ✓ Cancer and Leukemia Group B (CALGB)
  - ✓ North Central Cancer Treatment Group (NCCTG)
  - ✓ Southwest Oncology Group (SWOG)
  - ✓ National Surgical Adjuvant Breast and Bowel Project (NSABP)

- Trans- Tasman Radiation Oncology Group (TROG) **(n = 4)**

- other **(n = 3)**

Quality assurance by EORTC

- development and implementation of a quality control programme
  - ✓ first programme by radiotherapy group (1982)
  - ✓ programme for data quality control by EORTC Study Group on Data Management (1988)
  - ✓ chemotherapy quality programme (1990)

- site visits
  - ✓ source data verification
  - ✓ visiting panels including external persons *(data center, quality control group)*

Audits of the EORTC Groups

criterion (%)	Vantongelen 1989	Steward 1993	Verweij 1997	Schaake-Koning, 1997	Favalli 2000	Kouloulias 2002
methodological approach	site visit, SDV*	site visit, SDV	site visit, SDV	site visit, SDV	site visit, SDV	central monitoring, SDV
data quality - correct - missing - incorrect - not in file	**91.4** 0,3 – 2,9 3.0 / 2.3 4.5 / 4.6	**66.4** 0.2 3.4 30	**91** 1 2 6	**-** - - -	**81.8** 3.6 7 7.6	**-** 10,12 17 -
protocol compliance - non-aderence to chemotherapy - non-adherence to radiotherapy	- -	**21** -	- -	7 7,15,17	**27** -	13 22
reporting of side-effects - correct - missing - incorrect - not in file	- - - -	- - - -	**87** 1 4 8	- - - -	**-** 15 **47** -	- - - -
ineleigibility	-	-	-	**7.3**	-	**1.7**

*source data verification

Quality assurance levels of the NCI-CALGB*

person	task
investigators clinical research associates	data collection
central data management office	data receiption, review, queries, storage
study chairpersons	assessment for protocol eligibility and compliance
central reviewers	central reviews of pathology, surgical procedures, radiographic studies, etc.
auditors	on-site audits of patients

** National Cancer Institute*
Cancer And Leukemia Group B
Weiss, Cancer Chemother Pharmacol
1998: 42 (Suppl): 588-592

Audit procedure of the NCI-CALGB*

- audit team: 2-8 people *(physicians, CRAs from CALGB)*
- team leader: member of Data Audit Committee
- guidelines for on-site audits (NCI)
- audits at least once every 36 month
- notification to be audited 3-5 month in advance
- minimum of 10% of patients audited
  (at least one patient unannounced)
- all audit reports sent to the NCI

** National Cancer Institute*
Cancer And Leukemia Group B
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Audit results of the NCI-CALGB*

parameter	findings (%)	
	1982-1984	1990-1992
consent form deficiences	18.5	3.9
inegibility	10	5.5
major protocol violation in drug dosing	-	10.8
major data submission deficiencies	-	≈ 7

** National Cancer Institute*
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Audits of NCI Cooperative Groups

Criterion (%)	Begg 1982 ECOG	Mauer 1985 ECOG	Weiss 1987 SWOG	Sunderland 1990 SWOG	Weiss 1993 CALBG	Christian 1995 NSABP
IRB deficiency	-	6	-	-	13.3/28.2	-
informed consent deficiency	-	6	-	-	3.9	7.1
ineligibility	7.2/5.7	7	-	5.2	5.5	5.2
protocol violation	6.2/4.5	-	-	-	-	-
treatment inconsistency	-	12	-	22	-	1.5
protocol deviation in drug dosing	-	-	-	-	10.8	-
response accessment deficiency	-	6	7	5	-	5.3
toxicity accessment deficiency	-	4	-	5	-	-
inadequate data submission	5.0/5.7	-	-	-	7	-
data verification deficiency	-	5	-	-	-	-
drug accoountability problems	-	14	-	-	-	-

Conclusions of data audits in the NCI-CALGB*

„Scientific improperties have occound very rarely in clinical trials conducted by the CALGB. Protocol compliance in assessing patient eligibility and tumor responses has been high. Attention to administratic matters of consent forms, institution review board approval, and aucillary data submission has measurably improved in the CALGB, which is at least due to the pressure from this on-site peer review of investigator performance“

** National Cancer Institute*
Cancer And Leukemia Group B
Weiss, Cancer Chemother Pharmacol
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review on data quality and protocol compliance
- summary -

- acceptable protocol compliance and high data quality in clinical trial groups considered due to established quality assurance procedures *(e.g. EORTC, NCI)*
- no problems with informed consent, eligibility and data quality in 90 - 95 % of cases
- problems with protocol compliance in specific trials (10 – 20 %)
- detection of fraud only in very rare cases
- number and type of deficiencies dependent on study type, quality management and study group organisation
- improvement of quality due to audit procedures
- little information about data quality/protocol compliance outside study groups

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FDA-audits

FDA Bioresearch Monitoring Program*

A comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research.

**FDA Bioresearch Monitoring Program (BIMO)*
http://www.fda.gov/ora/compliance_ref/bimo/background.html

FDA Bioresearch Monitoring Program*

- protect the rights and welfare of research subjects
- assure quality and integrity of data submitted to the agency in support of new product proposals

**FDA Bioresearch Monitoring Program (BIMO)*
http://www.fda.gov/ora/compliance_ref/bimo/background.html

Routine audits by the FDA*

most common deficiencies	total (%)
problems with patient consent	37
inadequate drug accountability	33
protocol non-adherence	19
records inaccuracy	15
records non-availability	4
other deficiencies	11
no of investigators in full compliance	17

** 1977-1981, 549 investigations*
Lisook, Drug Information Journal, 1982; p97-p101

Routine audits by the FDA*

criterion	Total No. (%)
routine data audits	1955 (100)
serious deficiencies found	211 (11)
- written response required to demonstrate solution of problems	137 (7)
- for-cause investigation launched	74 (4)
specific deficiencies	
- problems with patient consent	1002 (51)
- inadequate drug accountability	504 (26)
- protocol nonadherence	507 (26)
- inaccurate records	403 (21)
- records not available	60 (3)
- miscellaneous deficiencies	473 (24)

** routine audits of investigators between 1977 und 1988*
Shapiro et al. JAMA 1989; 261: 2505-2511

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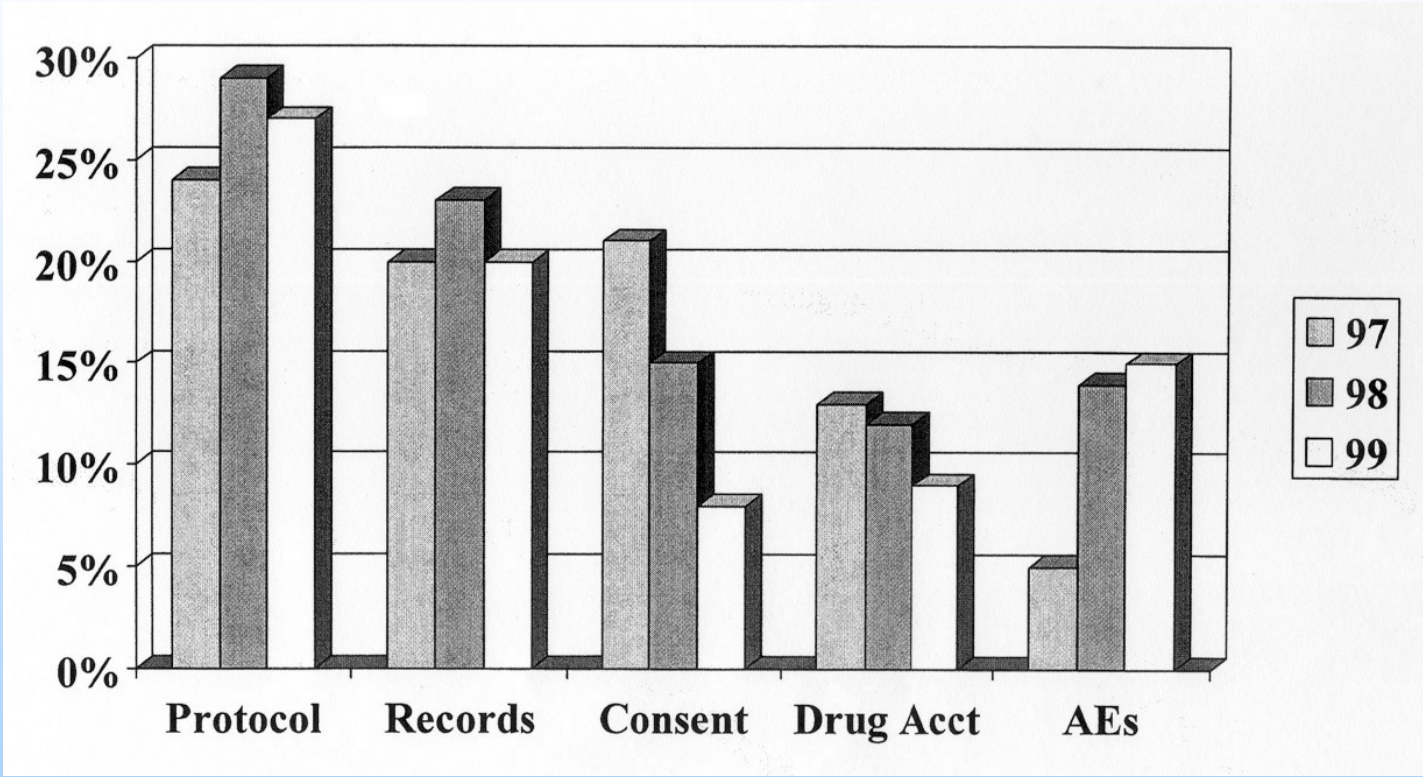
Clinical investigator deficiency categories*



**Wollen: Patient misuse and investigator fraud in clinical trials: what can be done? Part I*
Division of Scientific Investigations, Center for Drug Evaluation and Research, FDA, DIA Meeting, June 2000

Regulatory Actions*

- clinical investigators -

Year(s)	93-96	97	98	99
warning letters	22	0	7	8
disqualifications	2	0	0	2
consent agreements	7	1	4	5

**Wollen: Patient misuse and investigator fraud in clinical trials: what can be done? Part I*
Division of Scientific Investigations, Center for Drug Evaluation and Research, FDA, DIA Meeting, June 2000

Study of warning letters by the FDA*

violation theme	frequency (%)
deviation from investigational plan	88.9
flawed/nonexistent consent process	66.7
failure to report or late reporting of AE	47.2
study reporting	13.9
study supervision	5.6
IRB	25.0
misconduct	8.3

**36 FDA warning letters in 25 months*
Bramstedt, Clin Invest Med 2004; 27:129-134

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Routine audits by the FDA

- summary -

- regular investigator inspections performed
- many specific deficiencies
- relatively few serious deficiencies and rarely actions taken
- major deficiency categories: protocol compliance, records, informed consent, drug accountability and handling of adverse events‘
- continuous improvement of routine audit results with time

Fraud

Definition of fraud*

- research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results
- fabrication is making up results and recording or reporting them
- falsification is manipulationg research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record
- plagiarism is the appropriation of another person‘s ideas, processes, results, or words without giving appropriate credit, including those through confidential review of others‘ research proposals and manuscripts

*US Federal Research Misconduct Policy, Federal Register, December 6, 2000

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The case of Sudbo

Lancet. 2005 Oct 15-21;366(9494):1359-66.

Related Ar

ELSEVIER FULL-TEXT ARTICLE

Retraction in:

- Horton R. Lancet. 2006 Feb 4;367(9508):382.

Comment in:

- Lancet. 2006 Jan 21;367(9506):196.

Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study.

Sudbo J, Lee JJ, Lippman SM, Mork J, Sagen S, Flatner N, Ristimaki A, Sudbo A, Mao L, Zhou X, Kildal W, Evensen JF, Reith A, Dannenberg AJ.

Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway. jon.sudbo@rh.uio.no

The case of Woo Suk Hwang

Editorial

Nature
Published online: 11 January 2006; |
doi:10.1038/439117a

Ethics and fraud

The trajectory of the Hwang scandal highlights the shortness of the path between unethical behaviour and outright misconduct.

Publicly adressed examples of fraud in clinical trials

person	area
R. Fiddes (1997)	testing medicines for high blood pressure, migraine, asthma, diabetes, etc.
M. McGee (2000)	melanoma vaccine trial
R. Borison (1990)	testing new psychopharmaceuticals
W. Bezwoda (2000)	high dose chemotherapy for high risk primary breast cancer
R. Poisson (1990)	lumpectomy with or without radiation to mastectomy for early stage breast cancer

On-site audit of the South-African trial of high-dose chemotherapy for metastatistic breast cancer *

- protocol was apparently written within 9 years after study start
- no patient signed a consent form
- only 61 of 90 patients could be found
- of these, only 27 had sufficient records to verify eligibility
- of these, 18 did not meet one ore more eligibility criteria
- only 25 of 61 patients did actually receive the treatment recorded on the enrollment log

**Weiss et al., J Clin Oncol 2001; 19: 2771-2777*

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Prevalence of fraud*

- difficult to determine but still considered rare
- reported to significantly impact 1-5% of pharmaceutical clinical trials – Frank Wells, Medico Legal Investigations (Reuters Health, Jan. 2002)
- only ~3% of FDA inspections uncover serious GCP violations

**Below: Fraud and misconduct at investigator sites – a CRAs perspective*
Southeast Louisiana Chapter ACRP March 15, 2005
http://www.pbelow-consulting.com/fraud.html

Prevalence of fraud

audits	prevalence (%)
ad hoc estimates in Europe[1]	0.4 - 7
FDA- audits (1997–1990)[2]	1.7
on- site audits in Europe / South- Africa (1990-1994)[3]	0.4

[1] *O'Donnell, Appl Clin Trials 1993;2:36-40*
[2] *Lock et al., in: Fraud and misconduct in medical research, BMJ Publishing Group, London, 1993*
[3] *Schmidt et al., 1995;4:40-49*

The case of Dr. Fiddes*

- removed exclusionary data from medical history in patient clarks
- made up fictious study subjects
- fabricated lab results by substituting clinical specimens and manipulating lab instrumentation

**Below: Fraud as misconduct at investigator sites – a CRA perspective*
Southeast Louisiana Chapter ACRP March 15, 2005
http://www.pbelow-consulting.com/fraud.html

The case of Dr. Fiddes*

„Monitors from the government and the industry never noticed any problems with Fiddes`bogus paperwork, which they reviewed during routine audits.“

**Eichenwald et al., New York Times May 17, 1999*

Impact of fraud / misconduct*

While scientific misconduct is rare, when it does occur, it affects public confidence in the clinical trial process and raises questions about the effectiveness of trial monitoring and its follow-up by sponsors.

**Wollen: Patient misuse and investigator fraud in clinical trials: what can be done? Part I*
Division of Scientific Investigations, Center for Drug Evaluation and Research, FDA
DIA Meeting, June 2000

Fraud
- summary -

- very rarely observed/detected
- difficult to detect even with monitoring or audit
- major threat to confidence in clinical trials if detected

Overview on data quality in clinical trials

- summary of the presentation -

- data quality and protocol compliance usually high in study goups with established quality management (*even without on- site monitoring*)
- little information about data quality/protocol compliance outside established study groups
- many specific deficiencies but relatively few serious deficiencies in FDA- audits and rarely actions taken
- fraud rarely detected with monitoring/ audits but a major threat to confidence in clinical trials
- audit itself improves quality
- gradual improvement of quality of clinical trials by time

Overview on data quality in clinical trials

- conclusion for trials on adaptive monitoring strategies -

- baseline quality management in a clinical trial has to be taken into consideration as a major influence factor
- selection of outcome criteria critical for planning of the trial *(low incidence of severe deficiencies expected even with adapted monitoring)*
- audit of monitoring strategies itself may be a confounding factor