



***8. Lilly Jahressymposium
zur Versorgung der Krebspatienten
„Prinzipien gerechter Verteilung –
Onkologie, quo vadis?“
Berlin, 19./20. Februar 2010***

***„Versorgungsforschung mit Routinedaten?“
Impulsreferat***

Wolf-Dieter Ludwig

Robert-Rössle-Klinik im HELIOS Klinikum Berlin-Buch
Klinik für Hämatologie, Onkologie und Tumorimmunologie

Resümee/Impulse

- Anstieg der Kosten für neue Arzneimittel in der Onkologie rascher als wissenschaftlich nachgewiesene Wirksamkeit bzw. Nutzen
- derzeit zahlreiche Defizite bei Zulassungsstudien (z.B. Design, Endpunkte, vorzeitiger Abbruch, Beobachtungsdauer, Risiken, „publication/sponsorship bias“)
- signifikant # klinisch relevant, neuer Wirkstoff # Innovation
- nach Zulassung Evidenzlücken rasch schließen
- **verstärkt benötigt:** unabhängige (wissenschaftsinitiierte) versorgungsrelevante Studien nach Zulassung
- *conditional approval, - reimbursement, coverage with evidence development, RCT vs. Nicht-Interventionelle Studien (NIS), cost sharing, payment for results, § 73d SGB V*



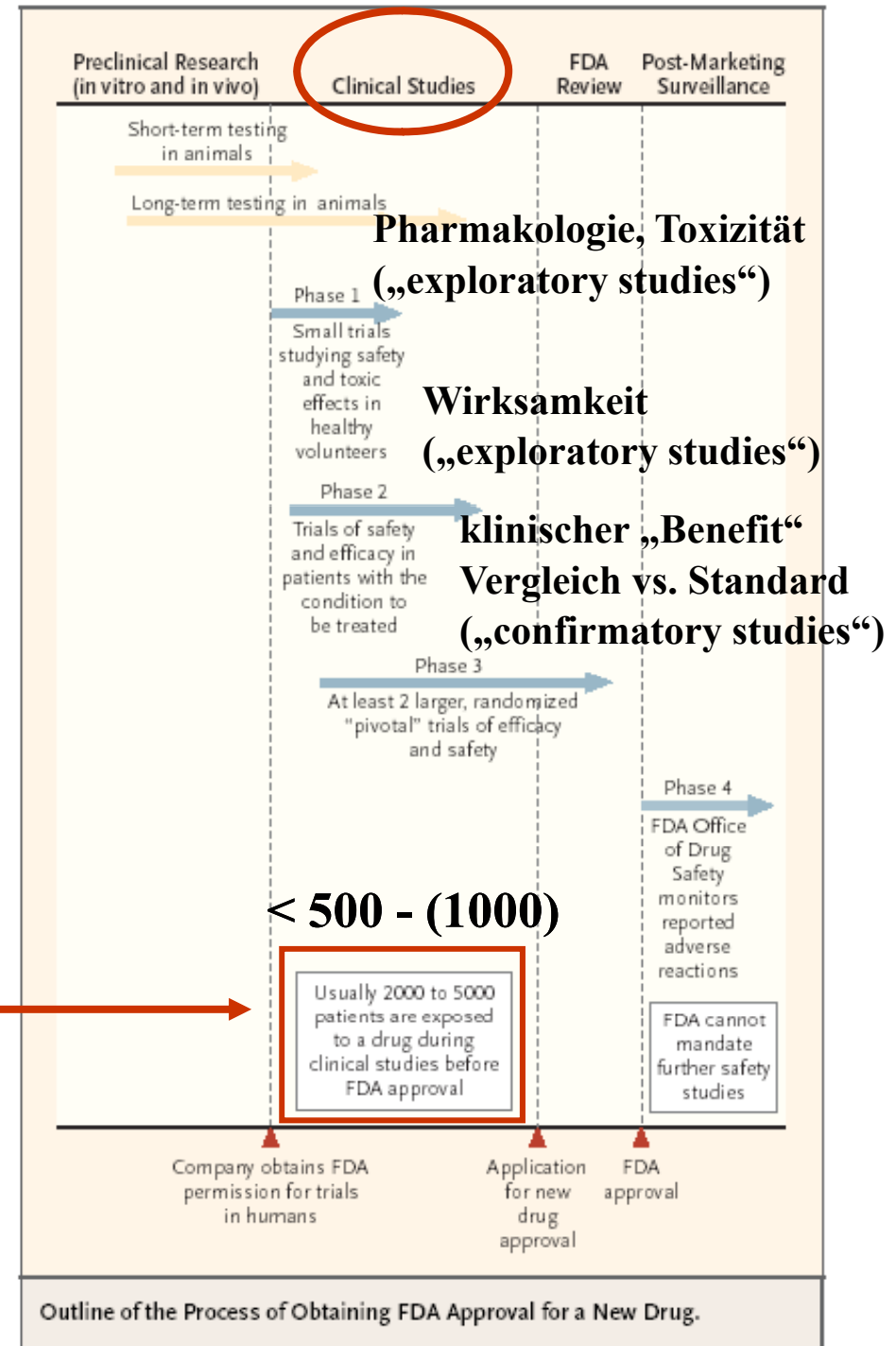
Zulassung von Arzneimitteln

Balance zwischen Patientennutzen,
regulatorischen Anforderungen,
ökonomischem Interesse

► **Wirksamkeit, Sicherheit**
*aber auch: Biomarker,
Pharmakoökonomie*

Onkologie

*Okie S: Safety in numbers –
Monitoring risk in approved drugs
NEJM 2005; 352:1173*



Neue Wirkstoffe in der Onkologie*: *Übergang Phase-I bis -III (FDA)*

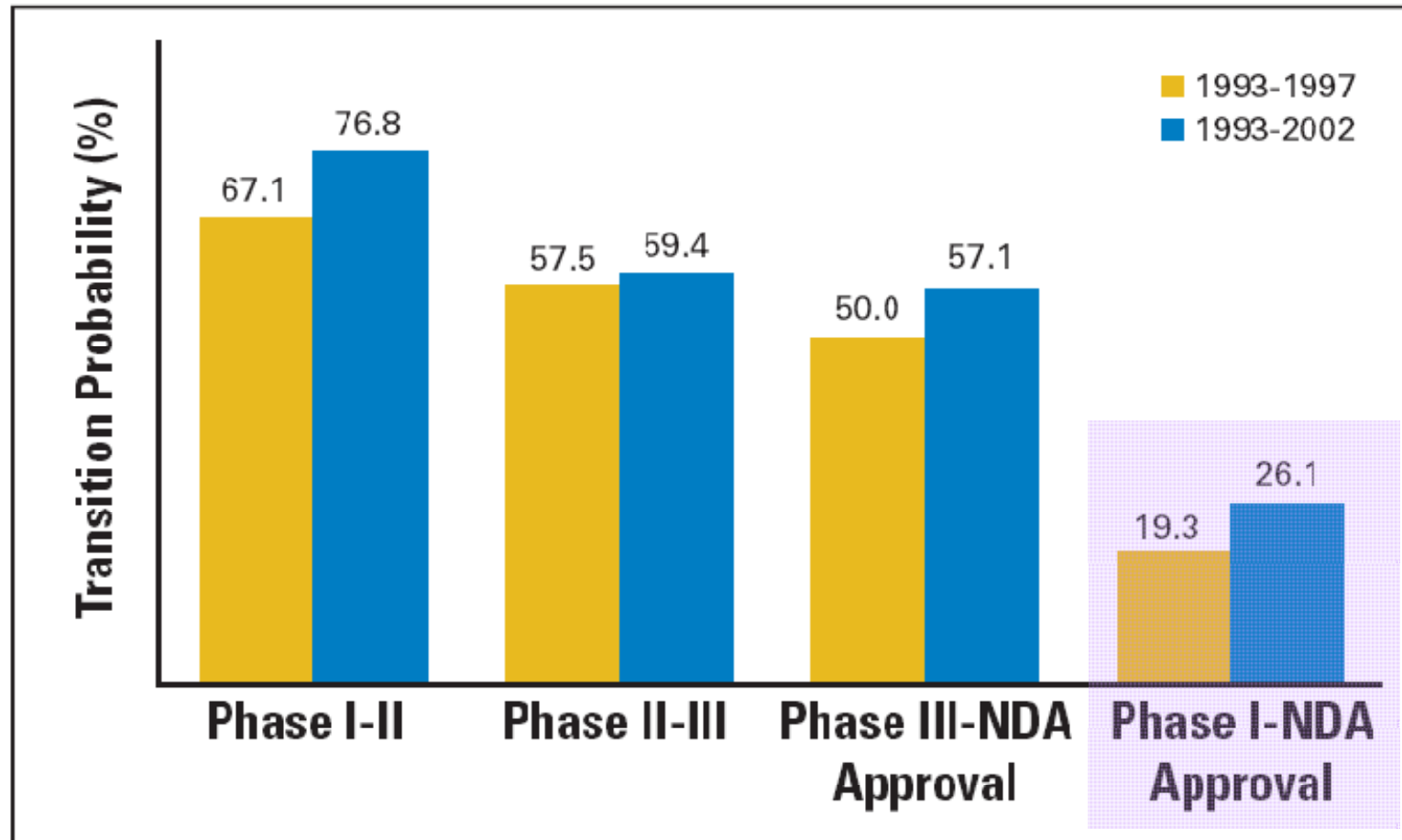


Fig 2. Clinical phase transition probabilities for investigational oncology compounds for the 20 largest firms by pharmaceutical sales (2005) by period during which compound first entered clinical testing. NDA, new drug application.



Neue Wirkstoffe in der Onkologie*: *Zulassung in den USA vs. andere Wirkstoffe*

Table 2. Regulatory Characteristics of New Therapeutic Oncology and Other Drugs Approved in the United States, 1990-2005

| Characteristic | % | |
|-------------------------|----------------|-------------|
| | Oncology Drugs | Other Drugs |
| FDA priority rating* | 70.9 | 40.2 |
| Orphan drug designation | 48.5 | 18.5 |
| Expedited access† | 47.1 | 13.4 |

*Therapeutic new molecular entities approved by FDA's Center for Drug Evaluation and Research (CDER).

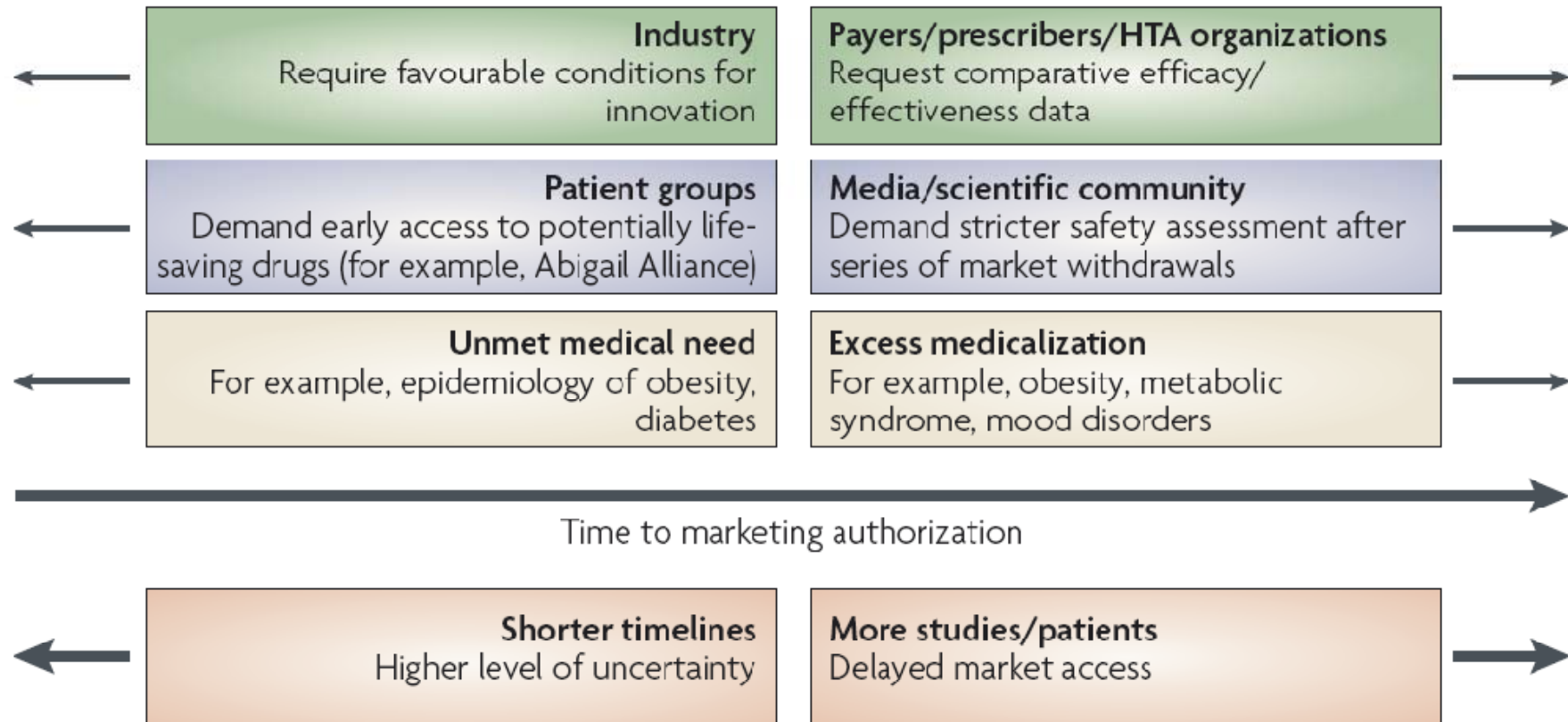
†Drugs that were developed under at least one of the following three FDA regulatory mechanisms: subpart E, accelerated approval, fast track.

* *DiMasi JA & Grabowski HG: JCO 2007; 25:209-216*



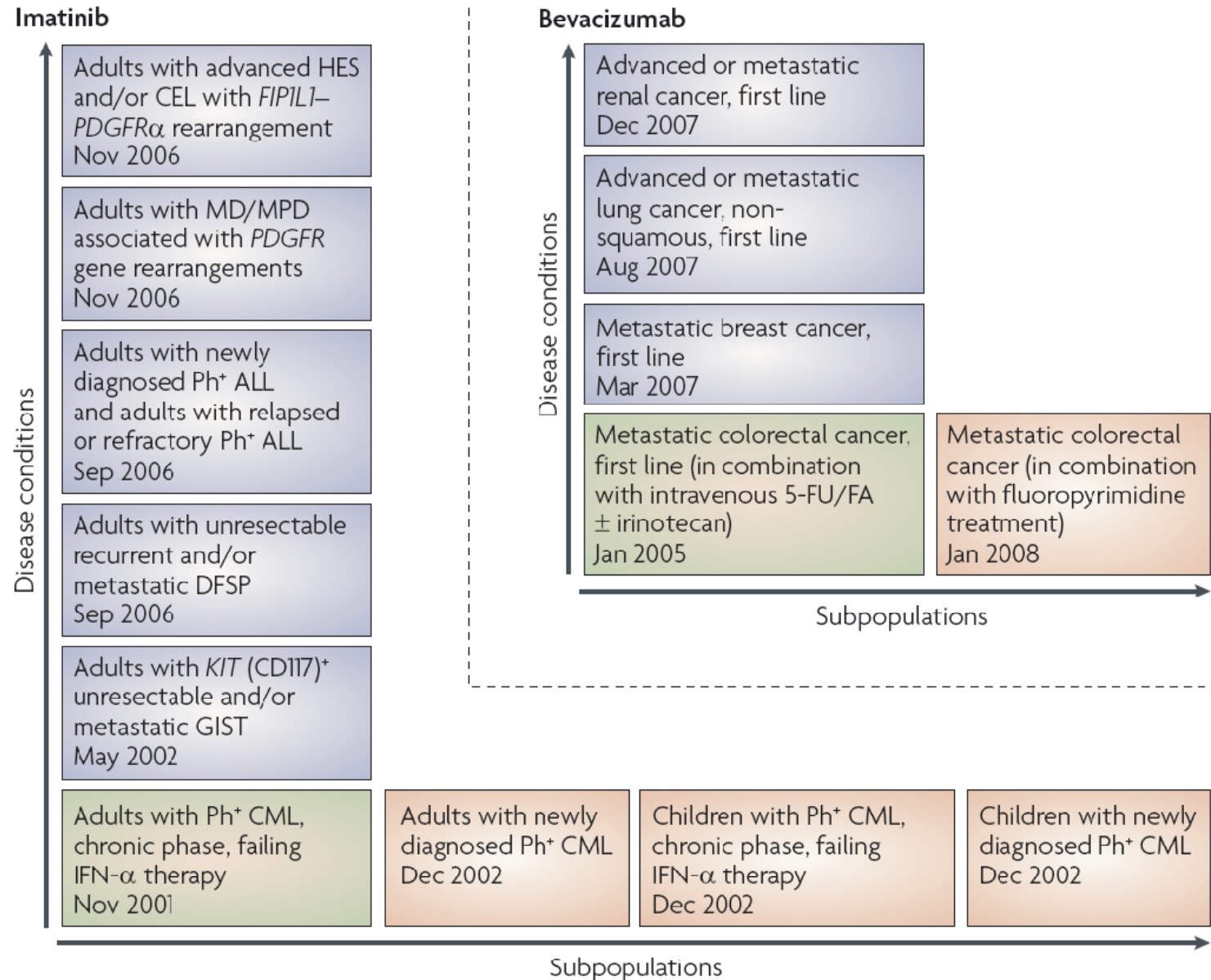
The regulator's dilemma

Eichler H-G et al.





Staggered approval — the regulatory life cycle.





**APPENDIX 2 TO THE GUIDELINE ON THE EVALUATION OF ANTICANCER
MEDICINAL PRODUCTS IN MAN (CPMP/EWP/205/95 REV. 3) ON HAEMATOLOGICAL
MALIGNANCIES**

The general principles as laid down in the main document apply. Thus confirmatory trials should be designed with the aim to establish the benefit - risk profile of the experimental medicinal product, including supportive measures, in a well-characterised target population of relevance for clinical practice. These studies are randomised, reference-controlled in nature and the target population, as well as the reference regimen (may be BSC), are normally defined by disease, stage and prior lines of therapy.

**GUIDELINE ON THE EVALUATION OF ANTICANCER MEDICINAL PRODUCTS IN
MAN**

III.1. Design

June 2006

III.1.1 Eligibility criteria

Prior experience with the experimental compound in terms of anti-tumour activity and safety in relation to dose and schedule should be sufficient to initiate phase III studies in the defined target population. As the aim of these studies should be to provide a basis for evidence-based clinical practice, any exclusion criteria, e.g. related to age, performance status, impaired organ function, or tumour localisation has to be well justified from the perspective of patients in the study and patients to be treated in clinical practice. Therefore investigators should be encouraged to include patients representative of those likely to be treated with the experimental compound in clinical practice. Restrictions as regards, e.g. performance status should be reflected in the SPC.



Outlook

Translated from *Rev Prescrire* March 2009; 29 (305): 218-221

Effects of cancer drugs on survival: often poorly evaluated



- Overall survival is the gold-standard endpoint when evaluating the efficacy of cancer drugs.
- Progression-free survival is an endpoint that combines two very different components: death or objective worsening of the tumour. It is a heterogeneous endpoint and measurement of the second component is imprecise. There are few examples where a correlation has been established between progression-free survival and overall survival.
- Time to progression is an endpoint of limited interest: it only takes into account the second component of the progression-free survival composite endpoint.
- Disease-free survival is a variant of progression-free survival and is most frequently used for adjuvant treatments.



Marketing authorisations granted on a shaky basis: in Europe too

● **Only 7% of marketing authorisations for cancer drugs are based on trials where the primary objective was to evaluate survival.**

A team from the Mario Negri Institute for Pharmacological Research in Italy have investigated the basis on which the European Medicines Agency (EMA) approves marketing authorisations (MAs) for new cancer drugs or new therapeutic indications for cancer drugs that are already licensed (1).

Their evaluation dealt only with solid tumours and not haematological malignancies. It was based on data available on the EMA website from January 1995 to December 2004.

MA usually granted without survival data. Marketing authorisations were granted for 14 cancer drugs in 27 different indications during this period. These MAs were granted on the basis of a total of 48 clinical trials. 12 indications (44%) were granted solely on the basis of non-comparative trials (a). 7% of MAs were granted on the basis of trials in which the primary endpoint was overall survival. 41% of MAs were granted on the basis of trials in which the primary endpoint was time to progression. 48% of MAs were granted on the basis of trials in which the primary endpoint was tumour response rate.

Overall survival was a primary or secondary endpoint in 13 of the trials. The difference in survival between groups ranged from 0 to 3.7 months (median value).

More than one comparative trial was

available for only 4 indications, and overall survival was the primary endpoint for only one indication (*docetaxel* as second-line therapy for advanced non-small cell lung cancer).

Stopping trials early due to “benefit” = lost information. The same team analysed comparative trials published over the last 11 years that were stopped early because a protocol-planned interim analysis showed a benefit for patients (2).

Out of a total of 25 trials, only 8 had overall survival as an endpoint in both the protocol and the interim analysis. In the other cases, stopping the trial early meant that much information was lost.

In summary. Just as in the United States, European marketing authorisations are rarely granted for cancer drugs on the basis of trials that evaluate survival, yet in many cases this is the benefit that patients expect.

©Prescrire

.....
a- One indication was granted on the basis of a literature review (*mitotane* in adrenocortical carcinoma, a rare disease) (ref. 3).

.....
1- Apolone G et al. “Ten years of marketing approvals of anticancer drugs in Europe: regulatory policy and guidance documents need to find a balance between different pressures” *Br J Cancer* 2005; 93: 504-509.

2- Trotta F et al. “Stopping a trial early in oncology: for patients or for industry?” *Ann Oncol* 2008; 19 (7): 1347-1353.

3- Prescrire Rédaction “Mitotane: forme pharmaceutique différente et nouveau nom” *Rev Prescrire* 2005; 25 (265): 661.



Zulassungsstudien Onkologie: *einige Merkmale*

Erkenntnisdefizite, Evidenzlücken

- verantwortlich: meistens pharmazeutische Hersteller
- restriktive Einschluss- und Ausschlusskriterien
- Design (Standardarm tatsächlich Standard?, häufig Vergleich neuer Wirkstoff mit alleiniger Chemotherapie, Dosierung?)
- „non-inferiority“ > „equivalence“ oder „superiority“
- Zwischenanalysen, vorzeitiger Abbruch (sinnvoll?)
- Endpunkte (statistisch signifikant = klinisch relevant?)
Überlebenszeit, krankheitsbezogene Lebensqualität, Toxizität
- Folgebehandlung, Nachbeobachtung, Cross-Over
- Transparenz, Publikation von Ergebnissen?



Defizite bei Arzneimittelzulassung und Marktüberwachung (**Sicherheit**)

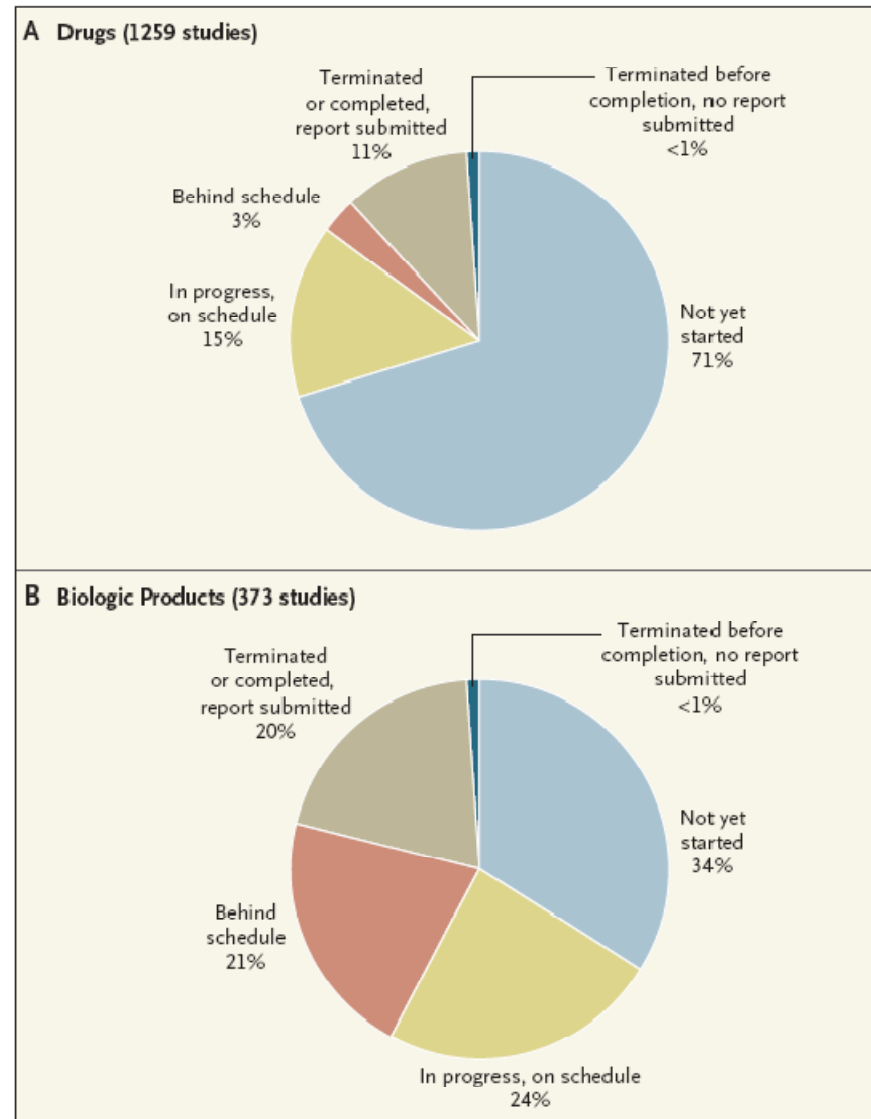
- RCTs nicht repräsentativ für Verordnung von Arzneimitteln nach Zulassung („real-life“ Patienten)
- Positive und **negative Effekte** (Nutzen) **von Arzneimitteln bzw. Therapiestrategien** im Rahmen von Zulassungsstudien **nicht ausreichend beurteilbar**
- **nach Zulassung von Arzneimitteln:**
 - > 50% Änderung von Fachinformation/Packungsbeilage
 - ca. 20% neue Warnhinweise („black box warnings“)
 - 3% - 4% Marktrücknahmen
 - nur in ca. 10% (114/1191) Auflagen der Zulassungsbehörden (FDA) erfüllt
- Konsequenzen?, u.a.
 - Post-Marketing Surveillance verbessern
 - Risikomanagementsystem für spezielle Arzneimittel
 - Spontanerfassung verbessern



Paying for Drug Approvals — Who's Using Whom?

Jerry Avorn, M.D.

Perspective
APRIL 26, 2007



*Postmarketing
studies:*

terminated

or completed

11% - 20%



„Provide a balanced discussion of benefits and harms“

CONSORT - Ioannidis JPA et al.: Ann Intern Med 2004

„The widespread marketing of a new drug is in fact a large experiment on a population. This is especially the case when it concerns a novel molecular entity with potentially a new set of clinical experiences. As the marketing of new drugs includes the discovery of adverse effects, the public's health would be best protected by a complementary set of techniques for the detection, verification and quantification of safety issues.“*

****Stricker BH & Psaty BM: BMJ 2004; 329:44-7***



JAMA[®]

Online article and related content
current as of September 23, 2009.

Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union

Thijs J. Giezen; Aukje K. Mantel-Teeuwisse; Sabine M. J. M. Straus; et al

JAMA. 2008;300(16):1887-1896 (doi:10.1001/jama.300.16.1887)


Biopharmazeutika: Sicherheit betreffende regulatorische Maßnahme bei 29% innerhalb von 10 Jahren

| Class of Biological | Active Substance | Drug Name | Drug Approval Date | Warning | Time to DHPC, y |
|---------------------|---------------------------------------|------------|--------------------|--|-----------------|
| Antibodies | Alemtuzumab | MabCampath | July 6, 2001 | Cases of death related to infections | 6.6 |
| | Bevacuzimab | Avastin | January 12, 2005 | Tracheoesophageal fistula | 2.3 |
| | Infliximab | Remicade | August 13, 1999 | Tuberculosis | 1.4 |
| | | | | Worsening heart failure | 2.2 |
| | | | | Infections including tuberculosis; contraindication: heart failure | 2.5 |
| | | | | Hepatosplenic T-cell lymphoma | 6.8 |
| | Rituximab | Mabthera | June 2, 1998 | Cytokine release syndrome | 0.5 |
| | | | | Progressive multifocal leukoencephalopathy | 8.8 |
| | Trastuzumab | Herceptin | August 28, 2000 | Cardiotoxicity in combination with anthracyclines and need for cardiac monitoring | 1.7 |
| Cytokines | Anakinra | Kineret | March 8, 2002 | Serious infections and neutropenia in combination with etanercept | 0.9 |
| Enzymes | Lepirudin | Refludan | March 13, 1997 | Fatal anaphylactic reactions | 5.6 |
| Growth Factors | Dibotermine alfa | Inductos | November 9, 2002 | Postoperative edema at application site | 1.9 |
| | | | | Implant site fluid collections | 4.5 |
| Hormones | Insulin human inhalation powder | Exubera | June 18, 2008 | Primary lung carcinoma | 2.4 |
| Others/Various | Botulinum toxin | Neurobloc | March 14, 2001 | Muscle weakness, dysphagia, aspiration | 6.3 |
| Receptors | Etanercept | Enbrel | February 3, 2000 | Blood dyscrasia (pancytopenia, aplastic anemia) | 0.7 |
| | | | | Serious infections and neutropenia in combination with kineret | 3.0 |

Wirksamkeit vs. Nutzen: externe Validität?*

Table 1. The gap between licensing (efficacy) and appraisal (effectiveness)

Zulassung



| Assessment of efficacy | Assessment of effectiveness |
|--|--|
| Explanatory trials | Comparator: 'current practice' |
| Selected populations | Outcomes: final outcomes; life expectancy; patient-focused outcomes, downstream resource utilisation |
| Comparator: placebo | The real-life effect |
| Outcomes: surrogate end points, morbidity, adverse effects | |
| What the package insert says | |

* McCabe C et al.: *Ann Oncol* 2009; 20:403-12



„Mehr Forschung in der Versorgung“*

„Die Gesundheitsforschung trägt dazu bei, mit Innovationen die Lebensqualität von Menschen aller Lebenslagen zu erhöhen und gleichzeitig die Finanzierbarkeit des Gesundheitssystems zu sichern.

Erkenntnisse über das Versorgungsgeschehen unter Alltagsbedingungen sind dabei besonders wichtig, damit die Qualität und Effizienz der Gesundheitsversorgung bei begrenzten Ressourcen weiter steigt. Daher werden wir die Versorgungsforschung systematisch ausbauen.“*

Koalitionsvertrag 2009, S. 92



Versorgungsforschung: Definition*

„letzte Meile“ des Gesundheitswesens

- Outcomes research – the study of the end results of health services that takes patients' experiences, preferences and values into account (*Clancy et al. 1998*)
- „Grundlagen- und problemorientierte fachübergreifende Forschung, welche die Kranken- und Gesundheitsversorgung in ihren Rahmenbedingungen beschreibt, kausal erklärt und aufbauend darauf Versorgungskonzepte entwickelt, deren Umsetzung begleitend erforscht und/oder unter Alltagsbedingungen evaluiert“
- „konkrete Kranken- und Gesundheitsversorgung in den Krankenhäusern, Arztpraxen und sonstigen Gesundheitseinrichtungen“

* *Pfaff H. Versorgungsforschung – Begriffsbestimmung, Gegenstand und Aufgaben. 2005*

Studien zur Versorgungsforschung. Eine Hilfe zur kritischen Rezeption

Norbert Donner-Banzhoff^{1,2,*}, Matthias Schrappe³, Monika Lelgemann⁴

¹Abteilung für Allgemeinmedizin, Präventive und Rehabilitative Medizin, Philipps-Universität Marburg

²Studienprogramm „Klinische Evaluation“, Koordinierungszentrum für Klinische Studien, Philipps-Universität Marburg

³Klinikum der Universität Frankfurt

⁴HTA-Zentrum in der Universität Bremen

„Studien der VF sind von klinischen Studien abzugrenzen.

Letztere untersuchen die Wirksamkeit therapeutischer, diagnostischer und präventiver Maßnahmen. Die VF fragt dagegen, ob und mit welcher Qualität diese Maßnahmen im Alltag des Gesundheitswesens erbracht werden kann bzw. wie diese Qualität erhöht werden kann. Zur VF rechnen wir eine Studie dann, wenn die Forschungsfrage auf die Erbringungsqualität (Versorgungsalltag) fokussiert und die klinische Wirksamkeit zur Bedingung wird“.

- **multidisziplinärer Ansatz, Design: von Fall-Berichten bis zu RCTs**
Erkennen von Ü-, U- und F-Versorgung, Qualitätssicherung,
hierfür benötigt evidenzbasierte Therapieempfehlungen
- **Innovationstransfer aus klinischen Studien in klinische Praxis**



Observational Research, Randomised Trials, and Two Views of Medical Science

Jan P. Vandenbroucke

Box 1. Hierarchy of Study Designs for Intended Effects of Therapy

1. Randomised controlled trials
2. Prospective follow-up studies
3. Retrospective follow-up studies
4. Case-control studies
5. Anecdotal: case report and series

Box 2. Hierarchy of Study Designs for Discovery and Explanation

1. Anecdotal: case reports and series, findings in data, literature
2. Case-control studies
3. Retrospective follow-up studies
4. Prospective follow-up studies
5. Randomised controlled trials

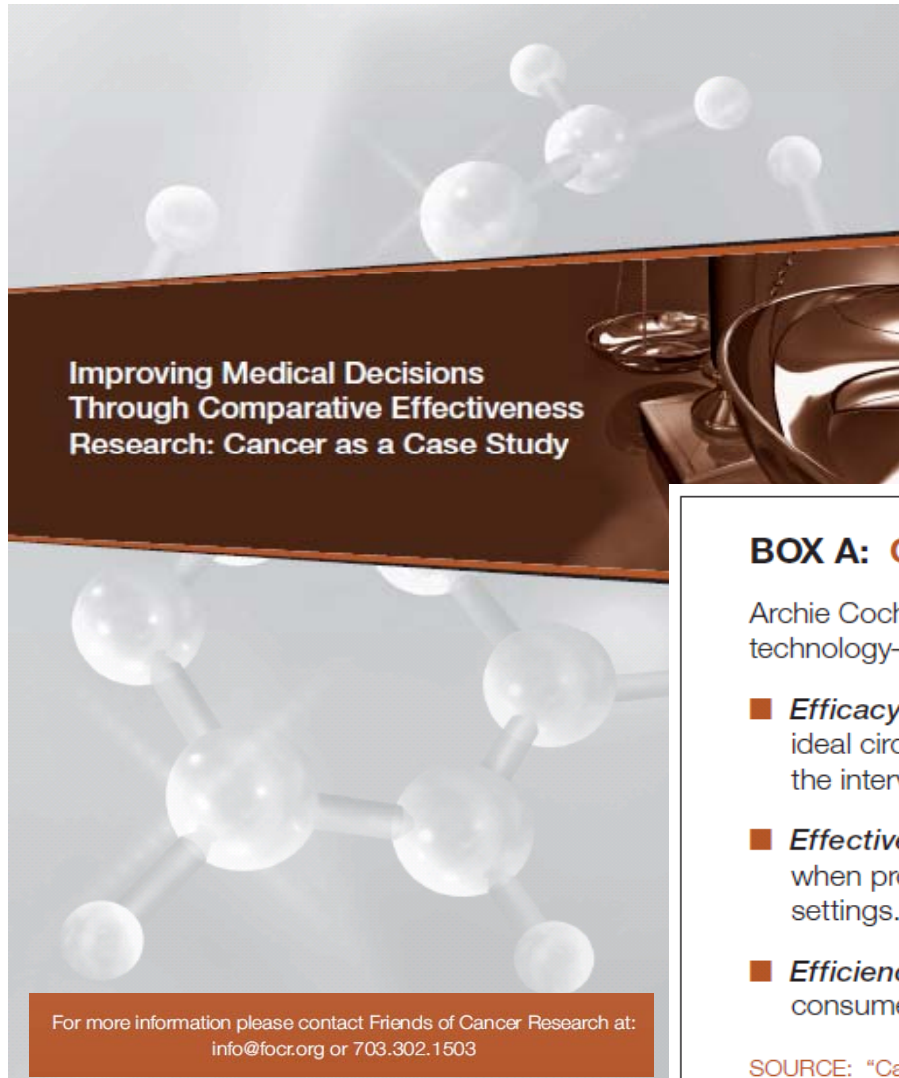


Comparative-Effectiveness Research

4 Recommendations



„... performance of CER must be structured to ensure continuous learning and the rapid translation of the best available evidence into clinical practice“.

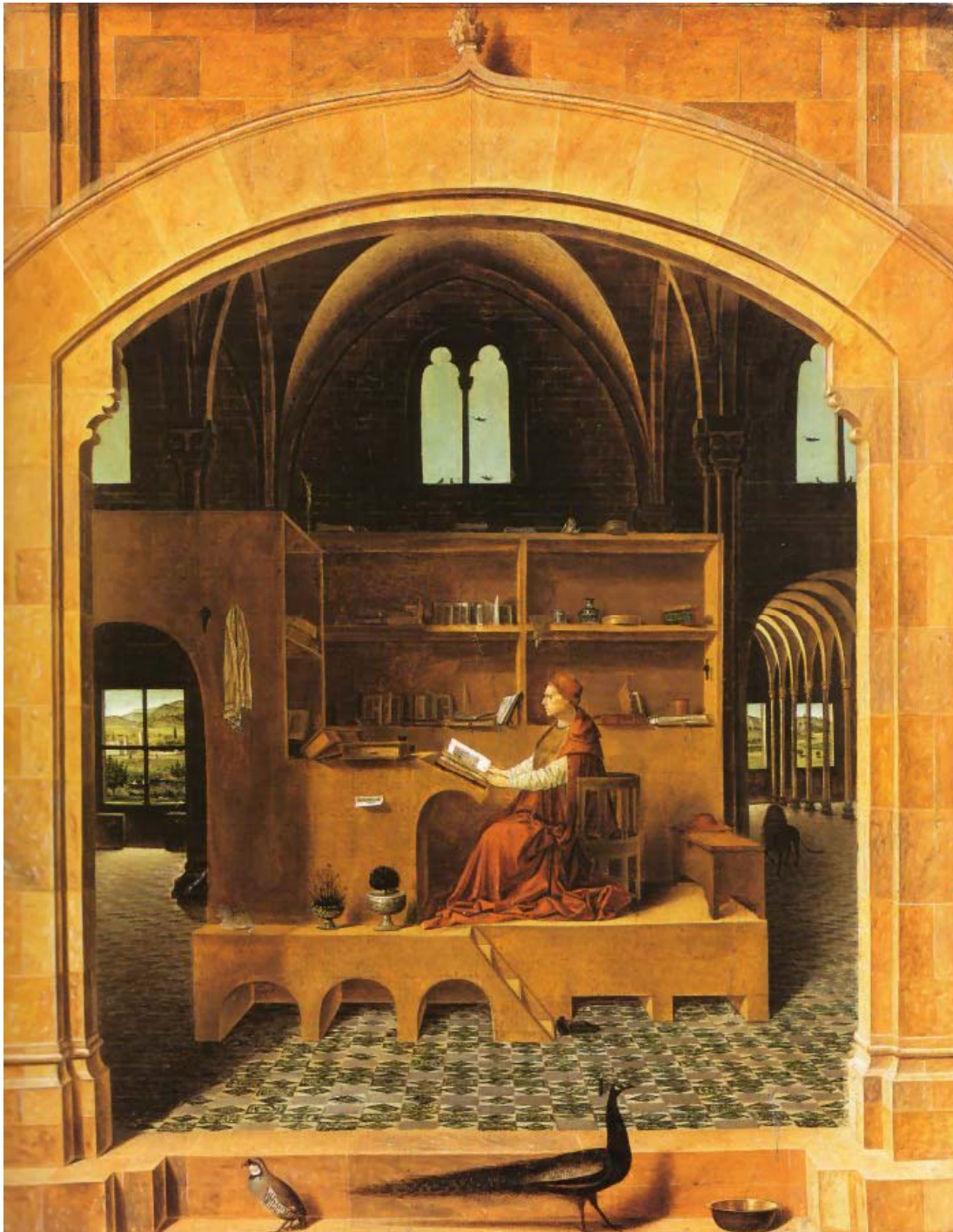


BOX A: Can It Work? Does It Work? Is it Worth It?

Archie Cochrane identified three concepts related to the evaluation of a medical technology—efficacy, effectiveness, and efficiency:

- **Efficacy** is the extent to which an intervention does more good than harm under ideal circumstances (i.e., in circumstances designed to maximize the effect of the intervention and eliminate confounding factors). (“Can it work?”)
- **Effectiveness** is the extent to which an intervention does more good than harm when provided to real-world patients by physicians practicing in ordinary clinical settings. (“Does it work in practice?”)
- **Efficiency** measures the effect of an intervention in relation to the resources it consumes. (“Is it worth it?”)

SOURCE: “Can It Work? Does It Work? Is It Worth It?” (editorial) *British Medical Journal* 319:652-653, September 11, 1999.



Resümee Perspektiven

*Antonello
da Messina
(ca. 1430-1479)
Saint Jerome in
His Study*



aus:
 Löffler M &
 Brosteanu O:
 Onkologie
 2008; 14:1252-9

| Merkmale | Zulassungsstudien | versorgungsnahe Studien |
|---|-------------------------------------|--|
| verantwortlich | pharmazeutische Hersteller | Studiengruppen, klinische Institutionen |
| Ziel | Zulassung | Kenntnislücken schließen, Therapieoptimierung |
| Arzneimittel | nicht zugelassen | zugelassen |
| Einschlusskriterien | stark selektiert | wenig selektiert |
| studienbezogenes Qualitätsmanagement | ressourcenaufwendig | ressourcenschonend und problemorientiert |
| Fallpauschalen | sehr hoch | niedrig |
| Finanzierung | Industrie | öffentliche Förderer, (GKV) |
| Resümee | Zulassung ja/nein Nutzen-Risiko? | Verbesserung der Qualität der Behandlung |



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JOURNAL OF CLINICAL ONCOLOGY

CELEBRATING 25 YEARS OF JCO

Reflections on Medical Oncology: 25 Years of Clinical Trials—Where Have We Come and Where Are We Going?

Christopher M. Booth, *National Cancer Institute of Canada Clinical Trials Group, Queen's University, Kingston, Ontario, Canada*
Ian Tannock, *Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada*

RCTs 1975-1984, 1985-1994, 1995-2004

Mamma-, kolorektale, nicht-kleinzellige Bronchialkarzinome

RCTs N=321, 171.161 Pat.



Emerging themes in design
of oncology RCTs

CONSORT-Statements

A. Appropriate design of
clinical trials.

***„...the conduct of countless small single-arm trials
is not an efficient use of patient or financial resources.“***

I. Tannock, 1983

B. Clinically relevant
endpoints.

C. Reporting of trials and
avoidance of bias.

Appeal for better clinical trials and
improved reporting (2008)

1. Investigators (and editors) should
adhere to guidelines for the design and
reporting of clinical trials.

2. Oncologists should reduce their
participation in phase II trials; they
should be given more academic and
other credit for supporting phase III
trials with potential to change practice.

3. Surrogate endpoints for survival,
including biomarkers in trials of
targeted therapy, should only be used if
they have been demonstrated to
correlate with overall survival.

4. RCTs should include appropriate
and validated measures of quality of
life and/or symptom control.

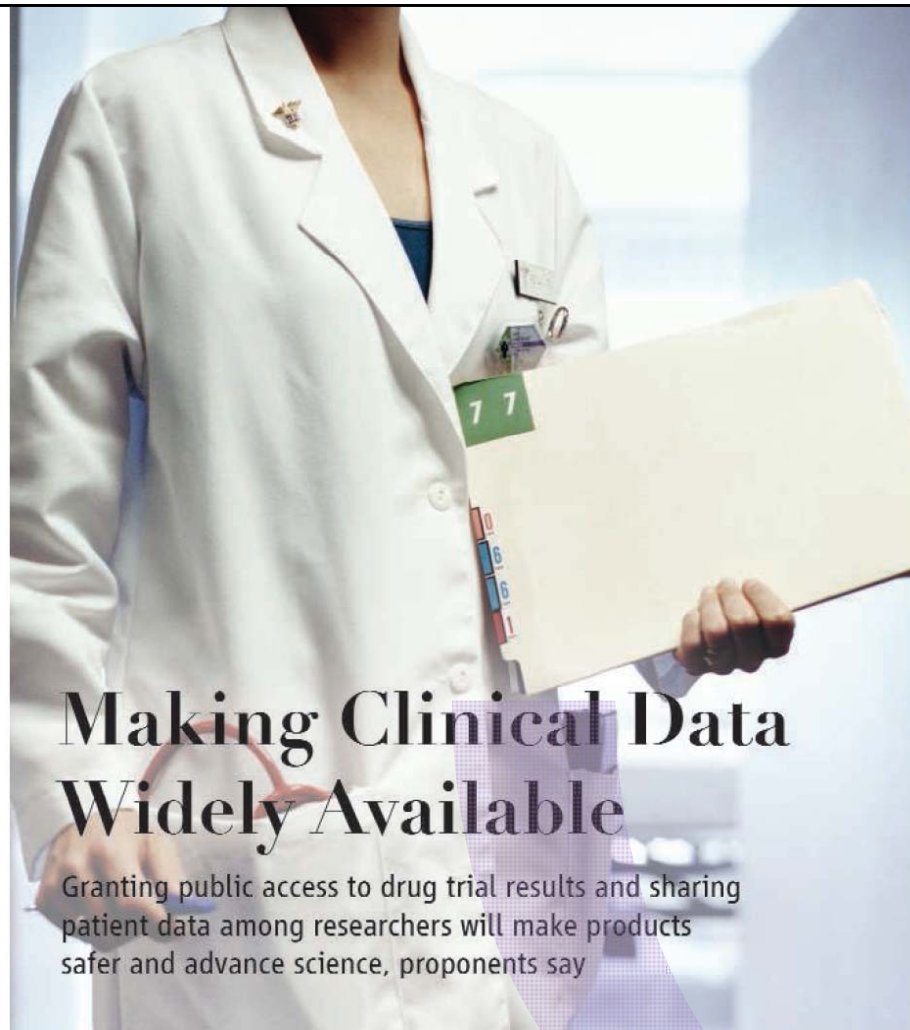
5. RCTs should include a
pharmacoeconomic analysis to
evaluate the cost-benefit of new
treatments.

6. Efforts should continue to reduce
publication and sponsorship biases.

aus:

***Booth CM et al.
JCO 2008; 26:6-8***

(neue) Transparenz



CONFIDENTIAL DATA REMOVED

Policies on sharing human subjects data

| Organization | Applies to ... | Effective | Policy |
|------------------------------------|---------------------------------|----------------|--|
| NIH | Grants over \$500,000 | 2003 | Provide data sharing plan or explain why not |
| NIH | Genome-wide association studies | January 2008 | Pls "encouraged" to submit cleaned data to dbGaP |
| FDA | Approved drugs | September 2008 | Post summary results in ClinicalTrials.gov 12 months after trial |
| <i>Annals of Internal Medicine</i> | Original research papers | April 2007 | State whether protocol and data set are available |

Science 2008; 322:217-8