

# La ricerca «accademica» in Italia: una svolta?!



FONDAZIONE IRCCS  
ISTITUTO NAZIONALE  
DEI TUMORI



UNIVERSITÀ  
DEGLI STUDI  
DI MILANO

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# DISCLOSURES

## Personal

none

## Institutional

financial support to clinical studies from Pharma to my Unit at Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy:

*Advenchen Laboratories, Amgen Dompé, AROG Pharmaceuticals, Bayer, Blueprint Medicines, Daiichi Sankyo, Deciphera, Eisai, Eli Lilly, Epizyme Inc, Glaxo, Karyopharm Pharmaceuticals, Novartis, Pfizer, PharmaMar*



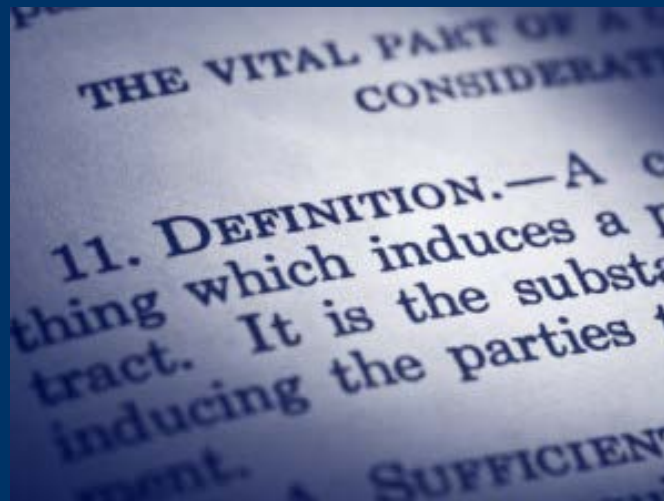
These photos show the difference in paperwork needed before and after the implementation of the Clinical Trials Directive

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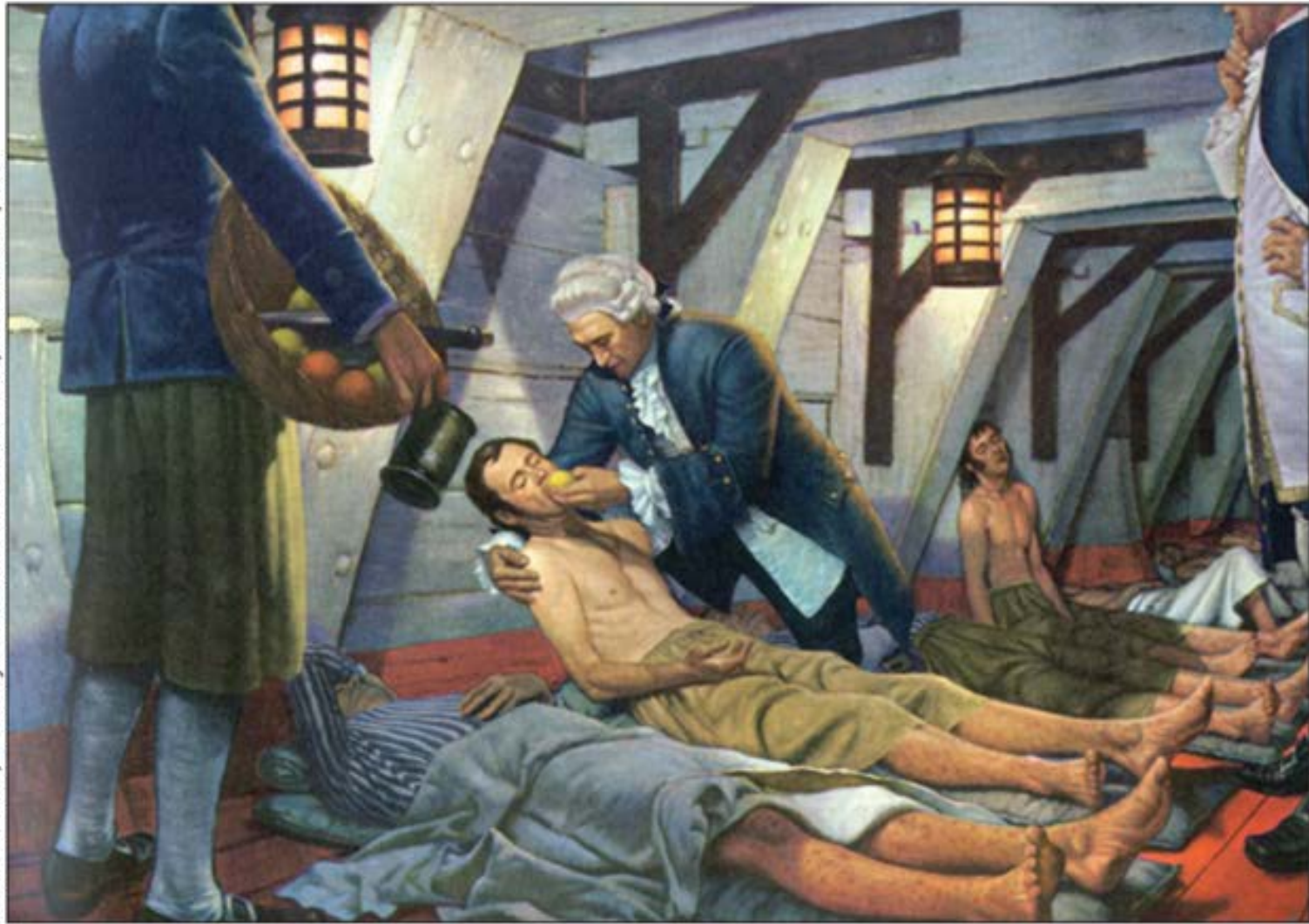


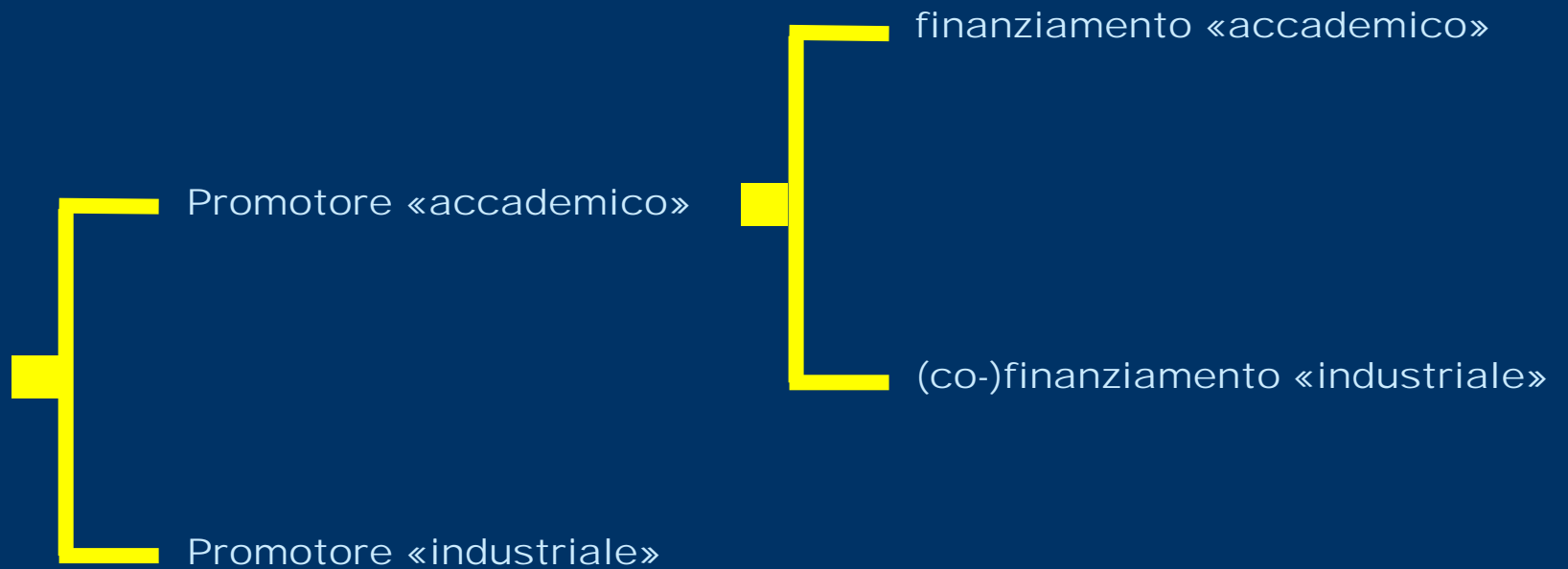
*Supporting Research, Protecting Patients  
Cancer Research UK, Feb 2012*

# La ricerca clinica «accademica»



Robert A. Thon, A History of Medicine in Pictures. Parke, Davis and Co., 1957







...la ricerca che l'industria non farebbe!

“I farmaci orfani”...





## Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated With Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas

Paolo G. Casali, Axel Le Cesne, Andres Poveda Velasco, Dusan Kotasek, Piotr Rutkowski, Peter Hohenberger, Elena Fumagalli, Ian R. Judson, Antoine Italiano, Hans Gelderblom, Antoine Adenis, Jörg T. Hartmann, Florence Duffaud, David Goldstein, Javier M. Broto, Alessandro Gronchi, Angelo P. Dei Tos, Sandrine Maréchal, Winette T.A. van der Graaf, John R. Zalcberg, Saskia Litère, and Jean-Yves Blay

Author affiliations appear at the end of this article.

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### ABSTRACT

#### Purpose

In 2004, we started an intergroup randomized trial of adjuvant imatinib versus no further therapy after R0-R1 surgery patients with localized, high- or intermediate-risk GI stromal tumor (GIST).

#### Patients and Methods

Patients were randomly assigned to 2 years of imatinib 400 mg daily or no further therapy after surgery. The primary end point was overall survival; relapse-free survival (RFS), relapse-free interval, and toxicity were secondary end points. In 2009, given the concurrent improvement in prognosis of patients with advanced GIST, we changed the primary end point to imatinib failure-free survival (IFFS), with agreement of the independent data monitoring committee. We report on a planned interim analysis.

#### Results

A total of 908 patients were randomly assigned between December 2004 and October 2008: 454 to imatinib and 454 to observation. Of these, 835 patients were eligible. With a median follow-up of 4.7 years, 5-year IFFS was 87% in the imatinib arm versus 84% in the control arm (hazard ratio, 0.79; 95% CI, 0.50 to 1.25;  $P = .21$ ); RFS was 84% versus 66% at 3 years and 69% versus 63% at 5 years (log-rank  $P < .001$ ); and 5-year overall survival was 100% versus 99%, respectively. Among 528 patients with high-risk GIST by local pathologist, 5-year IFFS was 79% versus 73%; among 336 centrally reviewed high-risk patients, it was 77% versus 73%, respectively.

#### Conclusion

This study confirms that adjuvant imatinib has an overt impact on RFS. No significant difference in IFFS was observed, although in the high-risk subgroup there was a trend in favor of the adjuvant arm. IFFS was conceived as a potential end point in the adjuvant setting because it is sensitive to secondary resistance, which is the main adverse prognostic factor in patients with advanced GIST.

J Clin Oncol 33:4276-4283. © 2015 by American Society of Clinical Oncology

## Phase II Study of Imatinib in Advanced Chordoma

Silvia Stacchiotti, Elena Tamborini, Virginia Ferraresi, Giovanni Grignani, Alessandro Comandone, Roger Stupp, Alexia Bertuzzi, Elena Tamborini, Silvana Pilotti, Antonella Messina, Carlo Spreafico, Alessandro Gronchi, Paola Amore, Vincenza Vinaccia, and Paolo Giovanni Casali

See accompanying editorial on page 896

### ABSTRACT

#### Purpose

To explore the antitumor activity of imatinib in patients with advanced platelet-derived growth factor  $\beta$  (PDGFB)/PDGF receptor  $\beta$  (PDGFRB)-positive chordomas.

#### Patients and Methods

In a collaborative Italian-Swiss, prospective, phase II clinical study conducted from November 2004 through April 2006, 56 patients with advanced PDGFB and/or PDGFRB chordoma received 800 mg/d of imatinib until progression. The primary end point was the overall tumor response rate (ORR), defined by RECIST. Secondary, exploratory end points included tissue response (ie, changes in tumor density or signal intensity/contrast enhancement, and/or [18F]-fluorodeoxyglucose positron emission tomography [PET] uptake), overall survival, progression-free survival (PFS), and pain score.

#### Results

Among 50 patients evaluable by RECIST, the best response was one partial response (PR) obtained at 6 months (ORR, 2%). There were 35 patients with stable disease (SD, 70%) and a 64% clinical benefit rate (ie, RECIST complete response + PR + SD  $\geq 6$  months). A minor dimensional response (< 20%) was detected in nine patients. A maximum standard uptake value decrease  $\geq 25\%$  was observed in 10 (39%) of 26 patients evaluable for PET response at 3 months. Changes in the Brief Pain Inventory score were consistent with the response assessment. Median PFS (intention-to-treat population, 56 patients) was 9 months. No unexpected toxicities were observed.

#### Conclusion

This is the largest phase II study in chordoma to date. It confirms anecdotal evidence that imatinib has antitumor activity in this orphan disease, and therefore, it is worth further investigation.

J Clin Oncol 30:914-920. © 2012 by American Society of Clinical Oncology

Silvia Stacchiotti, Elena Tamborini, Silvana Pilotti, Antonella Messina, Carlo Spreafico, Alessandro Gronchi, and Paolo Giovanni Casali, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale Tumori, Milan; Alessandra Longhi, Istituto Oncopedico Rizzoli, Bologna; Virginia Ferraresi, Istituto Fisioterapico Ospitalieri-Polo Oncologico Regina Elena, Rome; Giovanni Grignani, Istituto per la Ricerca e la Cura del Cancro, Candiolo; Alessandro Comandone, Presidio Sanitario Gradengo, Turin; Alexia Bertuzzi, Istituto di Ricovero e Cura a Carattere Scientifico Istituto Clinico Humanitas, Rozzano; Paola Amore, Vincenza Vinaccia, Novartis Farma, Origlio, Italy; and Roger Stupp, University of Lausanne Hospitals, Lausanne, Switzerland.

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Supported by Novartis Farma, Origlio, Italy.

Presented at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2007, Chicago, IL (abstract 10003).



# Current models, challenges and best practices for work conducted between European academic cooperative groups and industry

Rolf A Stahel,<sup>1</sup> Denis Lacombe,<sup>2</sup> Fatima Cardoso,<sup>3</sup> Paolo G Casali,<sup>4</sup> Anastassia Negrouk,<sup>2</sup> Richard Marais,<sup>5</sup> Anita Hiltbrunner,<sup>6</sup> Malvika Vyas,<sup>7</sup> on behalf of the Clinical Academic Cancer Research Forum (CAREFOR)

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**Table 2** Industry sponsored clinical trials versus investigator initiated trials

Industry-sponsored clinical trials	Investigator initiated trials
Designed to evaluate the efficacy and safety and often effectiveness of new drugs.	Often dedicated to questions on how to best use treatments.
Gain marketing authorisation and patient access for a new product, extend labelling for an approved product.	Can focus on patient-centric endpoints, for example, response rate.
Provide data for submission to health technology assessment (HTA) bodies.	Establish proof of concept for combination trials or exploratory studies.
Designed with the requirements of regulatory agencies in mind.	May seek to answer questions from the scientific community, regulators and/or payers for data that was not generated as part of the regulatory data provided under industry sponsored clinical trials.
Industry's research portfolios are generally segmented to include research and early development trials (Phase I First in Human and Phase II), product development trials (Phase Ib-III) and medical affairs studies (both post first-indication as well as pre-first indication supportive of filing studies, proof of concept studies and evidence generation for access/reimbursement purposes), all of which may include academic cooperative group studies.	Academia's research portfolios seek to increase knowledge and is centred on advancing patient care. Here, one can generally describe academic trials that are designed to learn followed by subsequent academic clinical trials designed to conclude.
See a marked need for Phase Ib trials (traditional Phase 1 trial is seen as a serial approach that adds time and cost to the development process).	Pragmatic clinical trials that test effectiveness of different therapy types in clinical practice. <sup>12</sup>
Need to meet regulatory requirements for regulators globally in order to achieve drug approval and generate data to facilitate HTA review and patient access. The European Medicines Agency and many HTAs, for instance, accept well-established efficacy endpoints, and consequently, many industry-sponsored clinical trials use progression-free survival as the primary endpoint. <sup>13</sup>	Can incorporate new endpoints (which are also a focus area of industry) to take advantage of advancing understanding of tumour biology, and these may include endpoints based on imaging, tumour kinetics, biological markers, quality of life and patient reported outcomes.
Concerned with the concept of sustainability, the ability to invest in research that will build new businesses that provide future revenue to sustain continued investment in research. Scientific advancement and satisfaction of unmet medical needs are required, but are not, on their own, sufficient to generate a sustainable research-driven business enterprise. An additional consideration for industry is the need to meet regulatory requirements for regulators globally in order to achieve drug approval and generate data to facilitate HTA review and patient access.	Decisions are made by volunteer members, are driven by the science, but also by the needs of the patients they see in daily practice. Investigators must be concerned with conducting research that is financially sustainable for themselves and the institutions they support, although they do not work primarily for profit.

I

*(Legislative acts)*

REGULATIONS

**REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL**  
**of 16 April 2014**  
**on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC**  
*(Text with EEA relevance)*

# «One-time consent»...

## CHAPTER V

### PROTECTION OF SUBJECTS AND INFORMED CONSENT

#### *Article 28*

#### **General rules**

2. Without prejudice to Directive 95/46/EC, the sponsor may ask the subject or, where the subject is not able to give informed consent, his or her legally designated representative at the time when the subject or the legally designated representative gives his or her informed consent to participate in the clinical trial to consent to the use of his or her data outside the protocol of the clinical trial exclusively for scientific purposes. That consent may be withdrawn at any time by the subject or his or her legally designated representative.

# «Low-intervention» trials...

## *Article 2*

### **Definitions**

- (3) 'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions:
  - (a) the investigational medicinal products, excluding placebos, are authorised;
  - (b) according to the protocol of the clinical trial,
    - (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or
    - (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
  - (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;

# «Co-sponsorship»...

## *Article 72*

### **Co-sponsorship**

1. Without prejudice to Article 74, where a clinical trial has more than one sponsor, all sponsors shall have the responsibilities of a sponsor set out in this Regulation, unless the sponsors decide otherwise in a written contract setting out their respective responsibilities. Where the contract does not specify to which sponsor a given responsibility is attributed, that responsibility shall lie with all sponsors.
2. By way of derogation from paragraph 1, the sponsors shall be jointly responsible for establishing:
  - (a) a sponsor responsible for compliance with the obligations of a sponsor in the authorisation procedures set out in Chapters II and III;
  - (b) a sponsor responsible for being a contact point for receiving all questions from subjects, investigators or any Member State concerned regarding the clinical trial and providing answers to them;
  - (c) a sponsor responsible for implementing the measures taken in accordance with Article 77.





# Cessione dei dati...

*SERIE GENERALE*

*Spediz. abb. post. - art. 1, comma 1  
Legge 27-02-2004, n. 46 - l'Espresso di Roma*

Anno 163° - Numero 42

**GAZZETTA UFFICIALE**  
**DELLA REPUBBLICA ITALIANA**

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**MINISTERO DELLA SALUTE**

DECRETO 30 novembre 2021.

**Misure volte a facilitare e sostenere la realizzazione degli studi clinici di medicinali senza scopo di lucro e degli studi osservazionali e a disciplinare la cessione di dati e risultati di sperimentazioni senza scopo di lucro a fini registrativi, ai sensi dell'art. 1, comma 1, lettera c), del decreto legislativo 14 maggio 2019, n. 52.**





These photos show the difference in paperwork needed before and after the implementation of the Clinical Trials Directive

CANCER RESEARCH UK



*Supporting Research, Protecting Patients  
Cancer Research UK, Feb 2012*



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

1 December 2016  
EMA/CHMP/ICH/135/1995  
Committee for Human Medicinal Products

## Guideline for good clinical practice E6(R2)



EUROPEAN MEDICINES AGENCY  
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**U.S. FOOD & DRUG**  
ADMINISTRATION

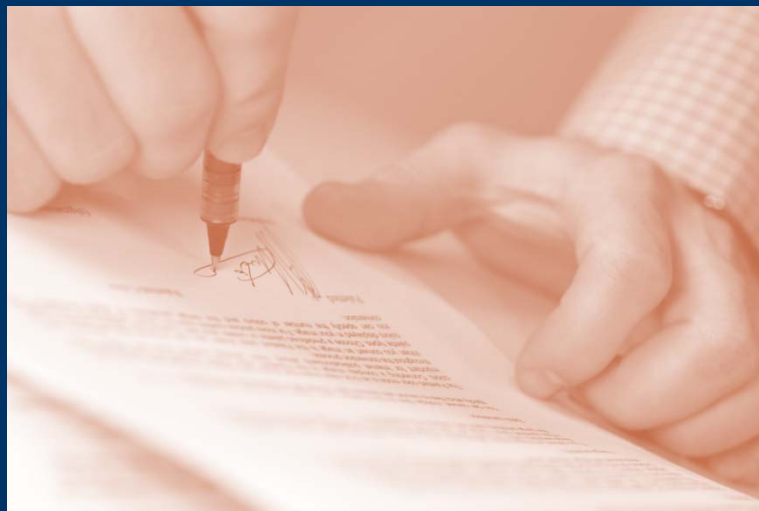
## Guideline for good clinical practice E6(R2)

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

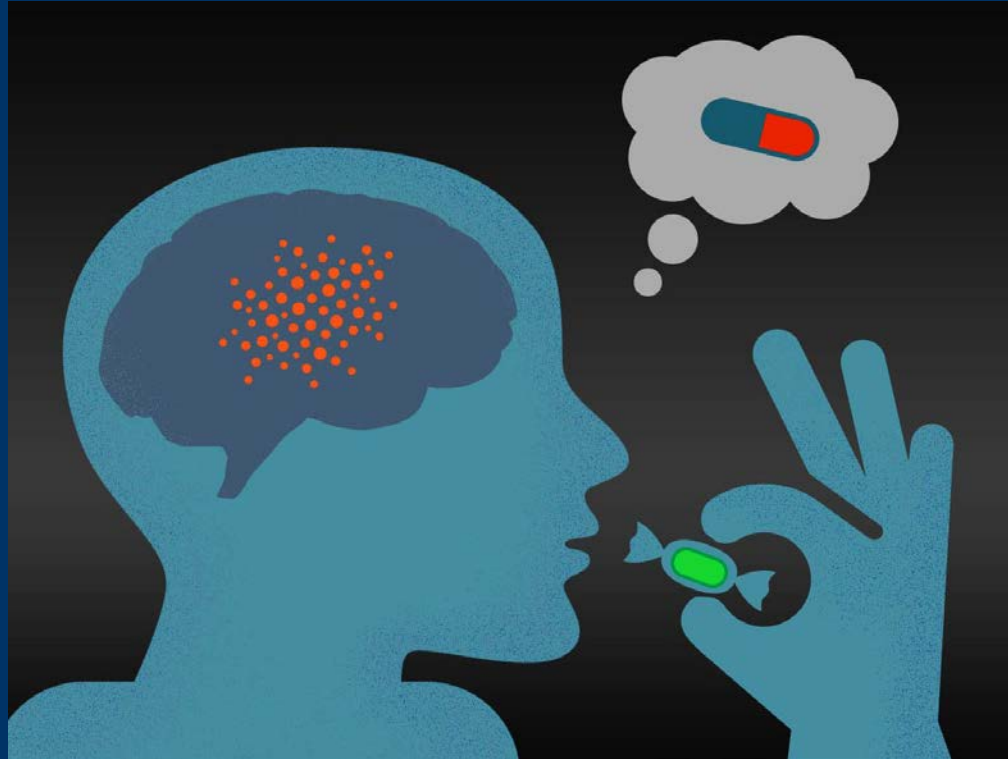


*Doctors' trial*  
Nuremberg, 1946-7

# Il consenso informato...



# Il controllo con placebo...



# L'etica della ricerca...

paziente  
attuale



paziente  
futuro



# L'etica della ricerca...

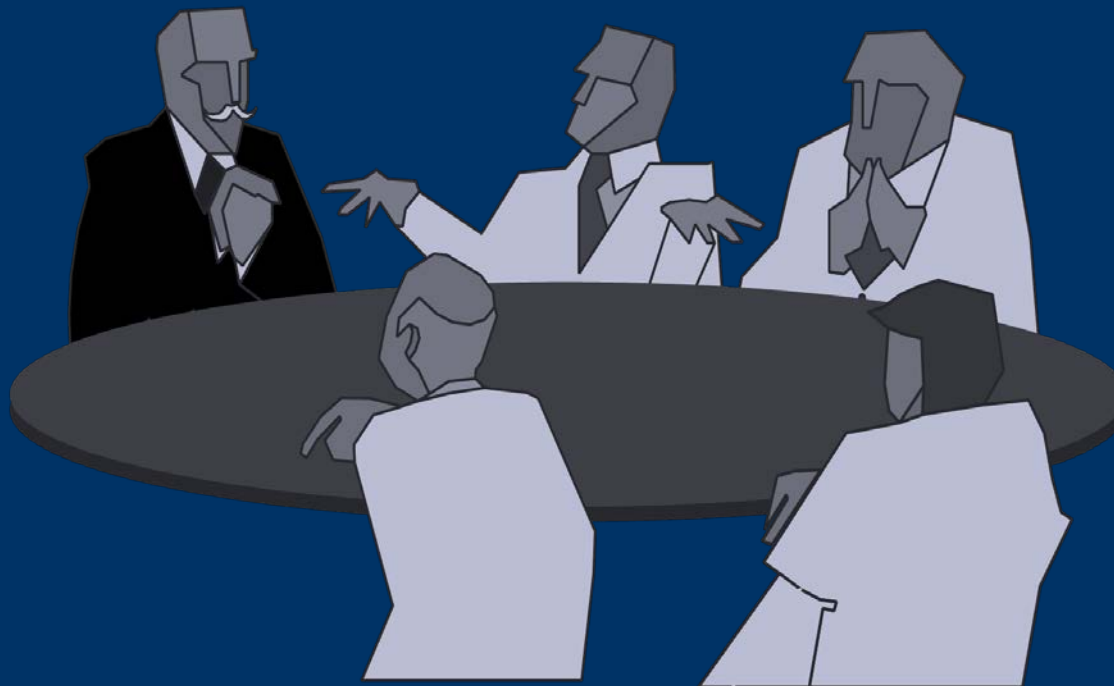
il medico come...

clinico



ricercatore

# I Comitati etici...



COMITATO ETICO INDIPENDENTE (CEI) DELL'ISTITUTO

[REDACTED]

[REDACTED]

Notifica del cambiamento dell'inchiostro utilizzato per apporre il marchio sulle compresse di [REDACTED] (farmaco sperimentale) [REDACTED]

Spettabile Comitato Etico,

per quanto riguarda lo studio in oggetto, a causa di un recente cambiamento da parte della Società produttrice del farmaco sperimentale, ci è stato richiesto di notificare a Codesto Comitato Etico che l'inchiostro utilizzato per apporre il marchio sul nuovo lotto di compresse di [REDACTED] verrà cambiato. Invece del tipo di colore rosso opacode S-1-15038, verrà utilizzato il rosso opacode S-1-15095. Il nuovo inchiostro per apporre il marchio è una sostanza approvata. Il Sommario delle Caratteristiche del Prodotto aggiornato relativo al farmaco sperimentale, verrà inviato non appena disponibile.

Si invia tale informazione come notifica, e non come emendamento sostanziale, sulla base di considerazioni di carattere etico, dal momento che la fornitura delle compresse sopra menzionate, prodotte utilizzando la precedente composizione di inchiostro, è quasi esaurita. Dal momento che non si desidera il verificarsi di una interruzione della fornitura di medicinale ai pazienti mentre si attende l'approvazione, i pazienti verranno provvisti del farmaco sperimentale sopra citato, fabbricato con la nuova composizione di inchiostro. Si prega di farci pervenire eventuali obiezioni a questa notifica.

Si allega alla presente una copia della dichiarazione, da parte dello Sponsor, che si ritiene che questo cambiamento, nell'inchiostro utilizzato per apporre il marchio, non metterà a repentaglio la sicurezza dei pazienti coinvolti nello studio [REDACTED]



ISTITUTO NAZIONALE  
PER LO STUDIO  
E LA CURA DEI TUMORI

Partecipanti: G. Bonadonna, S. Monfardini,  
M. De Lena, F. Fossati-Bel-  
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ta.

20131 - Milano - via Venezian, 1 - p.le Gori, 22 - tel. 29.21.76 - 29.21.77 - 29.21.20 - 21.63.940

Somministrazione di adriamicina in tumori solidi mediante  
un nuovo schema terapeutico.

- A) SCOPO: determinare (con il D.W.C.C.S.G.) la tossicità e l'efficacia dell'adriamicina in vari tumori solidi dell'adulto e dell'infanzia mediante un nuovo schema terapeutico intermittente.
- B) SCELTA DEI PAZIENTI: sono candidati tutti i pazienti con linfoma o neoplasia solida in fase avanzata. Sono esclusi i casi trattati con chemioterapici nelle tre settimane precedenti la somministrazione dell'adriamicina, i casi con riserva midollare compromessa, con iperazotemia e con anamnesi di malattie coronariche o aritmia cardiaca.
- C) ESAMI DI LABORATORIO: emometria completa, creatininemia, uricemia, SGOT, SGPT, fosfatasi alcalina, BSF, elettroforesi, HCG, CPK; ove possibile, mielogramma. L'emometria va ripetuta 2-3 volte la settimana (con particolare attenzione attorno al 14° giorno), mentre gli altri esami verranno ripetuti prima di ogni ciclo terapeutico.
- D) DOSE PIENA: 25 mg/m<sup>2</sup>/die x 3 i.v. (G.B. 5000; PP 150.000)  
DOSE RIDOTTA: 20 mg/m<sup>2</sup>/die x 3 i.v. (G.B. 3-5000; PP 100-150.000)

Il dosaggio può essere modificato nel tempo usando le seguenti dosi in base ai valori minimi dell'emometria ottenuti nelle tre settimane di intervallo:

dose iniziale piena	15 - <sup>20-</sup> 25 - 30 - 35 (mg/m <sup>2</sup> /die x 3)		
	G.B.	PP	Dose seguente
	5000 e	150000	aumentare di un livello
	3-5000 o	100-150000	invariata
	2-3000 o	50-100000	diminuire di un livello
	2000 o	50000	diminuire di due livelli
dose iniziale ridotta			
	G.B.	PP	Dose seguente
	3-5000 e	100-150000	aumentare di un livello
	2-3000 o	50-100000	invariata
	2000 o	50000	diminuire di un livello

E) DURATA DEL TRATTAMENTO: se vi è risposta obiettiva, proseguire ogni tre settimane fino alla ripresa della neoplasia. Se vi è arresto della crescita della neoplasia, la terapia può essere proseguita a discrezione del ricercatore. Se vi è progressione della malattia, il trattamento viene proseguito fino a produrre mielodepressione. Se il tumore a questo punto continua a proliferare il trattamento viene interrotto.

Il trattamento viene considerato adeguato se l'adriamicina viene somministrata per un minimo di due cicli. Per ogni tipo istologico è necessario trattare 15 pazienti in modo adeguato per poter determinare una risposta terapeutica del 20% o più.

# The New England Journal of Medicine

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## MAJOR ADVANCE IN BREAST-CANCER THERAPY

Elsewhere in this issue of the *Journal* Bonadonna et al. report a work of monumental importance. The foundations for this advance are fourfold, the first being an understanding that breast cancer is fundamentally not a local disease. The rapture of "five-year cures" has given way to a recognition that the risk of death from disseminated breast-cancer metastases continues for more than 10 years, with a death rate approximating 8 per cent per year (the rate is even higher in the first three years.<sup>2</sup>) At 10 years, 24 per cent of women in whom metastases were not found in axillary nodes at the time of operation have already relapsed; those with one to three, or four or more nodes have recurrent cancer in 65 per cent and in 86 per cent respectively.<sup>3</sup> Death is not long delayed.

In general application, the horizons of surgery should expand because of medical input for the nonresectable and, in the individual patient, nondefinable micrometastatic tumor. The lessons of strategy, timing, multidisciplinary participation, experimental design, combination chemotherapy and a responsibility to view accepted surgical and medical procedures without complacency will not be lost on American observers, who now can admire more in Milan than La Scala.

Our own (American) National Cancer Institute merits recognition for effective use of research-contract funding and for its appreciation of the continuing critical importance of internationalism in cancer research.

Mount Sinai School of Medicine  
New York, NY 10029

JAMES F. HOLLAND, M.D.







James Lind  
1753

The following are the experiments.

On the 20th of *May* 1747, I took twelve patients in the feurvy, on board the *Salisbury* at sea. Their cases were as similar as I could have them. They all in general had putrid gums; the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all, *viz.* water-gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times puddings, boiled biscuit with sugar, &c.; and for supper, barley and raisins, rice and currants, sago and wine, or the like. Two of these were ordered each a quart of cyder a-day. Two others took twenty-five gutts of *elixir vitriol* three times a-day, upon an empty stomach; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a-day, upon an empty stomach; having their gruels and their other food well acidulated with it, as also the gargle for their mouth. Two of the worst patients, with the tendons in the ham rigid, (a symptom none of the rest had), were put under a course of sea-water. Of this they drank half a pint every day, and sometimes more or less as it operated, by way of gentle phyfic. Two others had each two oranges and one lemon given them every day. These they eat with green-

dinefs, at different times, upon an empty stomach. They continued but six days under this course, having consumed the quantity that could be spared. The two remaining patients, took the bigness of a nutmeg three times a-day, of an electuary recommended by an hospital-furgeon, made of garlic, mustard-seed, *rad. raphan.* balsam of *Pern.* and gum myrrh; using for common drink, barley-water well acidulated with tamarinds; by a decoction of which, with the addition of *cremer tartar*, they were gently purged three or four times during the course.

The consequence was, that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of six days fit for duty. The spots were not indeed at that time quite off his body, nor his gums sound; but without any other medicine, than a gargilism of *elixir vitriol*, he became quite healthy before we came into *Plymouth*, which was on the 16th of *June*. The other was the best recovered of any in his condition; and being now deemed pretty well, was appointed nurse to the rest of the sick.



These photos show the difference in paperwork needed before and after the implementation of the Clinical Trials Directive

CANCER RESEARCH UK



*Supporting Research, Protecting Patients  
Cancer Research UK, Feb 2012*



# Cosa servirebbe in Italia...



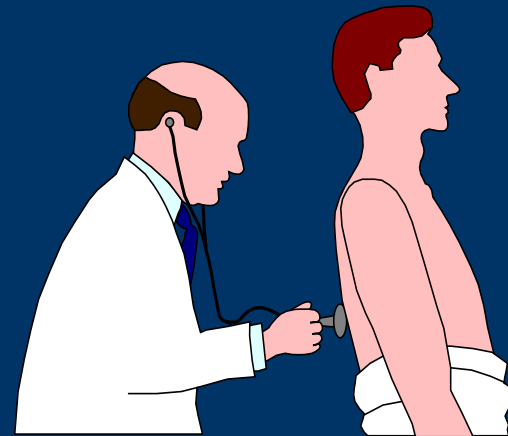
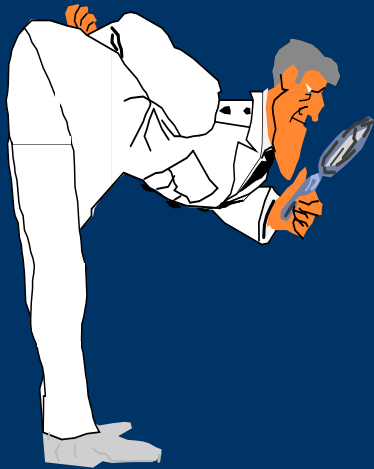
# Cosa servirebbe in Italia...



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