

Part I

Process, Approach, and Standards

Learning from the TGN London

Phase I Study

Phase I Clinical Trials

Las Vegas, Nevada, USA

12-13 October 2006



Francis P. Crawley



Good Clinical Practice Alliance - Europe

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What should we expect from the new
European & Global GCP frameworks
for phase I clinical trials?

within the Member States?
across Europe?
globally?

What does GCP mean for early stage trials
to sponsors, researchers, & patients?

Research



Confirming Fears



'Human guinea pig
Raste Khan'

The Sun 15-03-2006

TGN 1412 Placebo Group, TeGenero & Paraxel CRO

TGN 1412 Background

- **TeGenero AG**: a privately held biopharmaceutical company engaged in developing therapeutic drugs for severe immunological disorders.
Science Park Würzburg, Germany (since 2000)
- **Paraxel CRO** (US firm)
- **Northwick Park Hospital**, northwest London
- (first submitted for trial in **Germany**, but approval delayed pending a request for **further information**)

TGN 1412 Trial Design

- an immunomodulatory humanized agonistic anti-CD28 monoclonal antibody targeted at diseases such as multiple sclerosis, rheumatoid arthritis, and certain cancers
- ‘first in man’ study
- 8 volunteers (males - paid £2,000 each):
6 received the test drug, 2 on placebo
- Medicines and Healthcare Products Regulatory Agency (MHRA) approval
- local research ethics committee (REC) approval

TGN 1412 Result

- Adverse events: swelled heads and failed organs in 6 volunteers – 2 in critical conditions ('catastrophic **multisystem failure**' - BMJ)
- MHRA, UK, **investigation**
- Paul Ehrlich Institute, Germany, **investigation**
- Scotland Yard homicide division **investigation**
- Global **press** coverage (Sunday Times: '**Focus: poison chalice**')
- BMJ Editorial: '*This experience should foster an **open culture** in medical research*'

TGN 1412 Outcomes

MHRA Report recommended:

- trials of immune drugs only on ill patients;
- centres be set up for riskier studies; and
- the first dose be given to one person at a time

Company Failure

‘TeGenero regretfully announces that, as of **July 4, 2006**, the management of the company has filed for the commencement of **insolvency proceedings** at the competent local court / insolvency court Würzburg. . . . The unforeseeable adverse reactions caused by TGN1412 in the TGN1412-HV phase 1 trial have made it **impossible to attract the investment** necessary for the company to continue operations.’

Part II

Overseas Phase I Trials

Examining the Status and Future of Partnerships Abroad

Phase I Clinical Trials

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EU Directive 2001/20/EC

‘OF THE EUROPEAN
PARLIAMENT AND OF THE
COUNCIL of 4 April 2001
on the approximation of the laws,
regulations and administrative
provisions of the Member States
relating to the implementation of
good clinical practice in the conduct
of clinical trials on medicinal
products for human use’

L 121/34	EN	Official Journal of the European Communities	1.5.2001
DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001			
on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use			
THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,		(3) Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect. Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent. Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks. However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down.	
Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,		(4) In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.	
Having regard to the proposal from the Commission (1),		(5) The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for by national law.	
Having regard to the opinion of the Economic and Social Committee (2),		(6) In order to achieve optimum protection of health, obsolete or repetitive tests will not be carried out, whether within the Community or in third countries. The harmonisation of technical requirements for the development	
Acting in accordance with the procedure laid down in Article 251 of the Treaty (3),			
Whereas:			
(1) Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (4) requires that applications for authorisation to place a medicinal product on the market should be accompanied by a dossier containing particulars and documents relating to the results of tests and clinical trials carried out on the product, Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products (5) lays down uniform rules on the compilation of dossiers including their presentation.			
(2) The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data.			
<p>(1) OJ C 306, 8.10.1997, p. 9 and OJ C 161, 8.6.1999, p. 5. (2) OJ C 95, 30.3.1998, p. 1. (3) Opinion of the European Parliament of 17 November 1998 (OJ C 379, 7. 12. 1998, p. 27), Council Common Position of 20 July 2000 (OJ C 300, 20.10.2000, p. 32) and Decision of the European Parliament of 12 December 2000, Council Decision of 26 February 2001. (4) OJ L 22, 9.2.1965, p. 1 (65 Directive as last amended by Council Directive 93/9/EEC (OJ L 214, 24.8.1993, p. 22). (5) OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).</p>			

The Path of the Directive

(now one year after)

- **1 May 2003** Implementation into Member States legislation
- **1 May 2004** Entered into force in all (25) Member States?
- **1 May 2004** EU became 25 Member States
- **June 2004** European Parliament Elections (and the proposal for EU Constitution in October 2004)



Ethics Committee

Article 2, Definitions

(k) ‘ethics committee’: an independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent;



Investigator

Article 2, Definitions

(f) ‘investigator’: a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is **responsible for the conduct of a clinical trial at a trial site**. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator;



Sponsor

Article 2, Definitions

(e) ‘sponsor’: an individual, company, institution or organisation which takes **responsibility** for the initiation, management and/or financing of a clinical trial;



Competent Authority

EU GCP Inspections

‘The **verification of compliance** with the standards of good clinical practice and the need to subject data, information and documents to inspection in order **to confirm** that they have been properly generated, recorded and reported are essential in order to justify the involvement of human subjects in clinical trials.’

EU Directive (15)



The Cornerstone of Health Research Ethics

It is the duty of the physician **to promote and safeguard** the health of the people.

His or her **knowledge and conscience** are dedicated to the fulfilment of this duty.

(DoH, Intro, Paragraph 2)

Initiated: 1964

17.C
Original: English

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

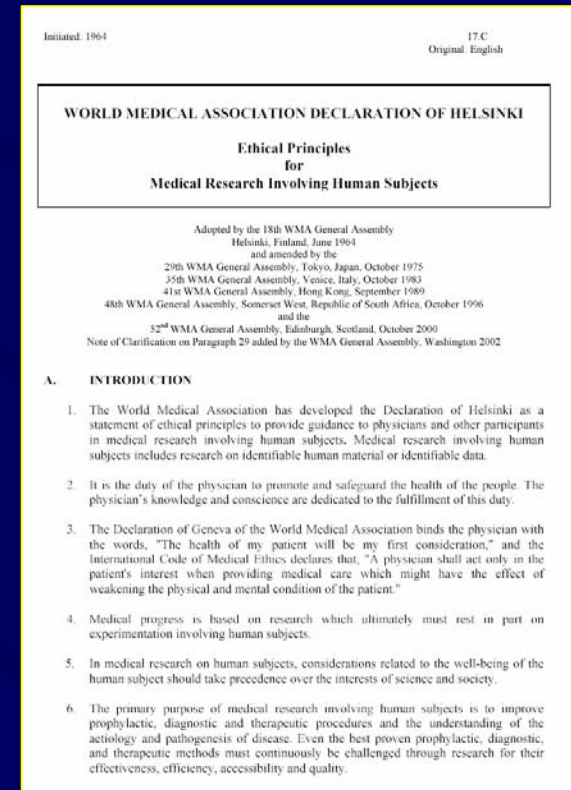
Helsinki on Ethical Review 1964

Helsinki on Ethical Review 1975

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted **for consideration, comment and guidance** to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed. (I.2)

Helsinki on Ethical Review 2000

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted **for consideration, comment, guidance, and where appropriate, approval** to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.



Ethical Review

A Government Responsibility

‘For the purposes of implementation of the clinical trials, **Member States** shall take the measures necessary for establishment and operation of Ethics Committees.’



Timeline for Ethical Review

The Ethics Committee shall have a maximum of **60 days** from the date of receipt of a valid application to give its reasoned opinion to the applicant and the competent authority in the Member State concerned.

Article 6.5

Ethics Committees

For multi-centre clinical trials limited to the territory of a single Member State, Member States shall establish **a procedure** providing, notwithstanding the number of Ethics Committees, for the adoption of **a single opinion** for that Member State.

In the case of multi-centre clinical trials carried out in more than one Member State simultaneously, a single opinion shall be given for each Member State concerned by the clinical trial.

Article 7

Detailed Guidance

(Article 8)

The Commission, in consultation with Member States and interested parties, shall draw up and publish detailed guidance on **the application format and documentation to be submitted in an application** for an ethics committee opinion, in particular regarding the **information that is given to subjects**, and on the appropriate safeguards for the protection of personal data.



The Guidance Documents

- Detailed Guidelines on the principles of good clinical practice in the conduct in the EU of clinical trials on medicinal products for human use
- Detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion on a clinical trial on a medicinal product for human use
- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities in the European Union, notification of substantial amendments and declaration of the end of a clinical trial
- Detailed guidelines on the trial master file and archiving to implement the directive on Clinical Trials on medicinal products for human use
- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use
- Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance -Clinical Trial Module)
- Detailed guidance on the European clinical trials database (EUDRACT Database)

The Guidance Documents (cont.)

- Detailed guidelines on inspection procedures for the verification of GCP compliance to implement the directive on Clinical Trials on medicinal products for human use
- Detailed guidelines on the qualifications of inspectors who should verify compliance in clinical trials with the provisions of Good Clinical Practice for an investigational medicinal product to implement the directive on Clinical Trials on medicinal products for human use
- Manufacturing and/or Import Authorisation of Investigational Products for Human Use-Contents of the Application
- Authorization Referred to in Article 13, Paragraph 1 of Directive 2001/20/EC: Requirements to Obtain Authorization and Requirements to Be Met by the Holder of This Authorization
- Draft Proposal for a Commission Directive.../.../EC Amending 91/356/EEC, Laying Down the Principles and Guidelines of Good Manufacturing Practice for Medicinal Products for Human Use
- Modifications of Commission Directive 91/356/EEC of 13 June 1991 Laying Down the Principles and Guidelines of Good Manufacturing Practice for Medicinal Products for Human Use (*two column informal working document*)
- Volume 4: Good Manufacturing Practices; Annex 13: Manufacture of Investigational Medicinal Products; November 2001

Information for the Ethics Committees

INFORMATION FOR ETHICS COMMITTEES

INFORMATION REQUIRED FOR ETHICS COMMITTEES	AU S.	BE L.	DE N.	FI N.	FR A.	GE R.	GR E.	IT A.	IR E.	LU X.	NE T.	PO R.	SPA .	SW E.	UK
MS SPECIFIC INFORMATION															
Receipt of confirmation of the EUDRACT number		Yes			Yes	Yes		Yes			Yes	Yes		Yes	Yes
Covering letter	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Application form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Clinical trial protocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Investigator's brochure	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
List of Competent Authorities to which the application has been submitted and details of decisions	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Subject related															
Informed consent form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes A	Yes	Yes	Yes	Yes
Subject information leaflet	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes A	Yes	Yes	Yes	Yes
Arrangements for recruitment of subjects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Protocol related															
Summary of the protocol in the national language	No	Yes		Yes	Yes	Yes		Yes	Yes		Yes	Yes	Yes	Yes	Yes
Outline of all active trials with the same IMP	No	A	No	No	No	No	Yes	Yes	No		Yes	No	No	No	No
Peer review of trial when available	Yes	No	No	No	Yes	No	Yes	Yes	No		Yes	Yes	No	No	Yes
Ethical assessment made by the principal/coordinating investigator	No	No	Yes	Yes	Yes	No		No	No		Yes	No	Yes	Yes	Yes
IMP related															
Investigational Medicinal Product Dossier (IMPD)	A	No	No	No	No	No	Yes ^A	Yes	No		Yes	No	No	No	No
Simplified IMPD for known products. See table 1 in application to competent authorities	A	No	No	No	No	No	Yes ^B	Yes	No		Yes	No	No	No	No
Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)		No		No	No	Yes		Yes	Yes		Yes	No	Yes	Yes	No
If IMP manufactured in E.U.:															
– copy of the manufacturer authorization referred to in Art. 13.1. of the Directive stating the scope of this authorization		No		No	No	No		Yes	No		Yes	No	No	No	No

^A and ^B : only information according to application to competent authorities, attachment 2, point 2.1.S Drug Substance, points 2.1.S.1 to 2.1.S.1.3 and 2.1.P Medicinal Product, under point 2.1.P.2.1 Components of the Medicinal Product, point 2.1.P.2.2.1 Drug Substance

Information to be Submitted to the Competent Authorities

INFORMATION REQUIRED	AUS.	BEL.	DEN.	FIN.	FRA.	GER.	GRE.	ITA.	IRE.	LUX.	NET.	POR.	SPA.	SWE.	UK
CORE INFORMATION															
Receipt of confirmation of EUDRACT number	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Covering letter	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Application form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Protocol with all current amendments	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Investigator's brochure	Yes	Yes A	Yes A	Yes	Yes	Yes	Yes A	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Investigational Medicinal Product Dossier (IMPD)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Simplified IMPD for known products. See table 1	Yes	Yes	Yes B	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes A	Yes	Yes
Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)	Yes	Yes	Yes C	Yes	Yes	Yes		Yes	Yes		Yes	Yes	Yes	Yes	Yes
List of Competent Authorities to which the application has been submitted and details of decisions	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Copy of ethics committee opinion when available	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
MS SPECIFIC INFORMATION															
Subject related															
Informed consent form	Yes	No	Yes D	Yes	Yes	Yes	Yes	Yes	Yes		No	Yes	No	Yes	No
Subject information leaflet	Yes	No	Yes D	Yes	Yes	Yes	Yes	Yes	Yes		No	No	Yes	Yes	No
Arrangements for recruitment of subjects	Yes	No	No	Yes	No	No	No	No	No		No	No	No	No	No
Protocol related															
Summary of the protocol in the national language	No	B	No	No	Yes	No		Yes	Yes A		No	No	Yes	Yes	Yes
Outline of all active trials with the same IMP	No	No	No	Yes	Yes	Yes	Yes	Yes	No		Yes	No	Yes	Yes	Yes
Peer review of trial when available	Yes	No	No	No	Yes	Yes	Yes	Yes	No		No	No	No	No	No
Ethical assessment made by the principal/coordinating investigator	No	No	Yes E	No	No	No			No		No	No	No	No	No

The UK Situation

The Medicines for Human Use (Clinical Trials) Regulation 2004 (SI 2004/1031)

DRAFT	
STATUTORY INSTRUMENTS	
2003 No.	
MEDICINES	
The Medicines for Human Use (Clinical Trials) Regulations 2003	
Made - - - -	2003
Laid before Parliament	2003
Coming into force - -	2003
ARRANGEMENT OF REGULATIONS	
PART 1	
INTRODUCTORY PROVISIONS	
1.	Citation and commencement
2.	Interpretation
3.	Responsibility for functions under the Directive
PART 2	
ETHICS COMMITTEES	
4.	United Kingdom Ethics Committees Authority
5.	Establishment of ethics committees
6.	Recognition of ethics committees
7.	Revocation of recognition
8.	Constitution and operation of ethics committees
9.	Other functions of the Authority
PART 3	
AUTHORISATION FOR CLINICAL TRIALS AND ETHICS COMMITTEE OPINION	
10.	Interpretation of Part 3
11.	Requirement for authorisation and ethics committee opinion
12.	Supply of investigational medicinal products for the purpose of clinical trials
13.	Application for ethics committee opinion
14.	Ethics committee opinion
15.	Second ethics committee opinion
16.	Request for authorisation to conduct a clinical trial
17.	Authorisation procedure for clinical trials involving general medicinal products
18.	Authorisation procedure for clinical trials involving medicinal products for gene therapy etc.
19.	Authorisation procedure for clinical trials involving medicinal products with special characteristics
20.	Clinical trials conducted in third countries

The UK ‘Sponsor’

- “sponsor” means, in relation to a clinical trial, **the person** who takes on ultimate responsibility for the initiation and management (or arranging the initiation and management) of, and the financing (or arranging the financing) for, that trial

DRAFT

STATUTORY INSTRUMENTS

2003 No.

MEDICINES

The Medicines for Human Use (Clinical Trials) Regulations
2003

<i>Made</i>	- - - -	2003
<i>Laid before Parliament</i>		2003
<i>Coming into force</i>	- -	2003

ARRANGEMENT OF REGULATIONS

PART 1
INTRODUCTORY PROVISIONS

1. Citation and commencement
2. Interpretation
3. Responsibility for functions under the Directive

PART 2
ETHICS COMMITTEES

4. United Kingdom Ethics Committees Authority
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PART 3
AUTHORISATION FOR CLINICAL TRIALS AND ETHICS COMMITTEE OPINION

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14. Ethics committee opinion
15. Second ethics committee opinion
16. Request for authorisation to conduct a clinical trial
17. Authorisation procedure for clinical trials involving general medicinal products
18. Authorisation procedure for clinical trials involving medicinal products for gene therapy etc.
19. Authorisation procedure for clinical trials involving medicinal products with special characteristics
20. Clinical trials conducted in third countries

Sponsor Responsibilities

Sponsor's main responsibilities under the UK Regulations

Part 3: authorisation and ethics committee opinion

- Request clinical trial authorisation (CTA), amend the request,
- Produce undertaking to allow inspection of premises in third countries if required
- Give notice of amendments to CTA, make representations about amendments
- Give notice of amendments to the protocol
- Give notice a trial has ended

Part 4: Good Clinical Practice and conduct



- Put and keep in place arrangements to adhere to GCP (if no other person is specified)
- Ensure Investigational Medicinal Products available to subjects free of charge
- Take appropriate urgent safety measures (with investigator)

Part 5: pharmacovigilance

- Keep records of all adverse events reported by investigators
- Ensure recording and prompt reporting of suspected unexpected serious adverse reactions (SUSARs)
- Ensure investigators are informed of SUSARs
- Ensure all SUSARs including those in third countries entered into European database
- Provide annual list of suspected serious adverse reactions and a safety report

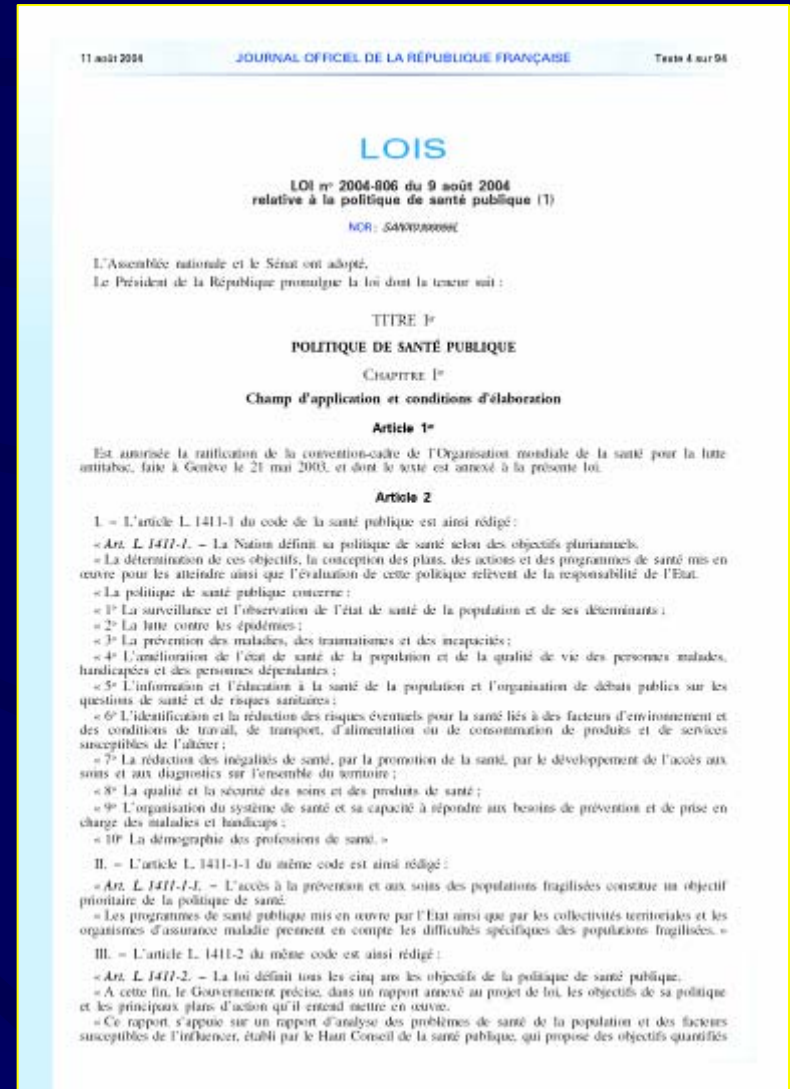
The Belgian Law on Human Research

Wet inzake
experimenten op de
menselijke persoon
Loi relative aux
expérimentations sur
la personne humaine
dated 7 May 2004
published 18 May 2004
effective 1 May 2004

BELGISCH STAATSBLAD	MONITEUR BELGE
Publicatie overeenkomstig artikelen 472 tot 478 van de programmawet van 24 december 2002 gepubliceerd in het <i>Belgisch Staatsblad</i> van 31 december 2002. Dit <i>Belgisch Staatsblad</i> kan geconsulteerd worden op: www.staatsblad.be Bestuur van het Belgisch Staatsblad, Leuvenseweg 40-42, 1000 Brussel, tel. 02 552 22 11 - Adviseur: A. Van Damme	Publication conforme aux articles 472 à 478 de la loi- programmée du 24 décembre 2002 publiée au <i>Moniteur belge</i> du 31 décembre 2002. Le <i>Moniteur belge</i> peut être consulté à l'adresse : www.moniteur.be Direction du Moniteur belge, rue de Louvain 40-42, 1000 Bruxelles, tél. 02 552 22 11 - Conseiller: A. Van Damme
	
174e JAARGANG	N. 175
DINSDAG 18 MEI 2004 TWEDE EDITIE	MARDI 18 MAI 2004 DEUXIEME EDITION
INHOUD	SOMMAIRE
Wetten, decreten, ordonnanties en verordeningen <i>Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedsel- keten en Leefmilieu</i> 7 MEI 2004. — Wet inzake experimenten op de menselijke persoon, bl. 39516.	Lois, décrets, ordonnances et règlements <i>Service public fédéral Santé publique, Sécurité de la Chaîne alimentaire et Environnement</i> 7 MAI 2004. — Loi relative aux expérimentations sur la personne humaine, p. 39516.
<i>Federale Overheidsdienst Mobiliteit en Vervoer</i> 11 MEI 2004. — Koninklijk besluit houdende goedkeuring van de eerste aanvulling van het Beheersprotocol tussen de Staat, de HST-Fin, de Nationale Maatschappij der Belgische Spoorwegen en de Federale Participatiemaatschappij, bl. 39534. 12 MEI 2004. — Koninklijk besluit tot uitvoering van de artikelen 3, § 4, en 6, § 1, tweede lid van de wet van 17 maart 1997 betreffende de financiering van het HST-project, bl. 39537.	<i>Service public fédéral Mobilité et Transports</i> 11 MAI 2004. — Arrêté royal portant approbation du premier avenant au Protocole de gestion conclu entre l'Etat, la Financière TGV, la Société nationale des Chemins de Fer belges et la Société fédérale de Participations, p. 39534. 12 MAI 2004. — Arrêté royal portant exécution des articles 3, § 4, et 6, § 1 ^{er} , alinéa 2 de la loi du 17 mars 1997 relative au financement du projet TGV, p. 39537.
<i>Federale Overheidsdienst Economie, K.M.O., Middenstand en Energie</i> 14 MEI 2004. — Ministerieel besluit tot wijziging van het ministerieel besluit van 21 februari 2000 tot verlagings van de prijzen van sommige terugbetaalbare geneesmiddelen, bl. 39539.	<i>Service public fédéral Economie, P.M.E., Classes moyennes et Energie</i> 14 MAI 2004. — Arrêté ministériel modifiant l'arrêté ministériel du 21 février 2000 diminuant les prix de certains médicaments remboursables, bl. 39539.
Officiële berichten <i>Arbitragehof</i> Bericht voorgeschreven bij artikel 74 van de bijzondere wet van 6 januari 1989 op het Arbitragehof, bl. 39540.	Avis officiels <i>Cour d'arbitrage</i> Avis prescrit par l'article 74 de la loi spéciale du 6 janvier 1989 sur la Cour d'arbitrage, p. 39541.
Schiedshof	
Bekanntmachung vorgeschrieben durch Artikel 74 des Sondergesetzes vom 6. Januar 1989 über den Schiedshof, S. 39540.	
28 bladzijden/pages	

The French Law

LOI no 2004-806 du 9 août 2004 relative à la politique de santé publique



The Path of Research

- Methodology
- Community
- Institutions

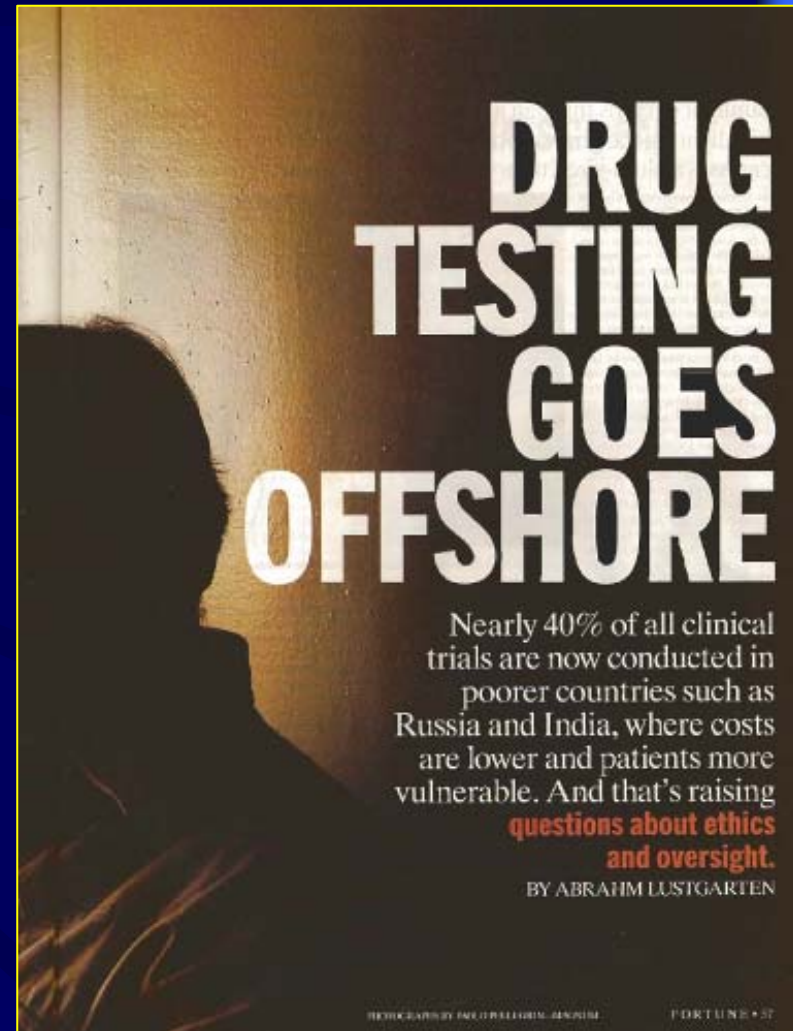


Fortune Magazine

8 August 2005

‘Nearly 40% of all clinical trials are now conducted in poorer countries such as **Russia and India**, where costs are lower and patients more vulnerable. And that’s raising **questions about ethics and oversight.**’

Exploitation of patients & GCP by the CRO industry.



The Globalisation of Clinical Trials and of GCP & Ethics

News Feature

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Chinese clinical trials: Consenting adults? Not necessarily...

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1. David Cyranoski is Nature's Asian-Pacific correspondent.

Abstract

Companies and scientists in the West are keen to test their drugs in China, which is an important future market. But those running clinical trials need to be on their guard, says David Cyranoski.

‘The episode is a sign that China’s clinical research is jumping ahead of its system for ethical oversight.’ *Nature*

Dimensions of GCP

General Frameworks

- WHO GCP
- ICH GCP

Regional/Applied Frameworks

- EU GCP
- US CFR

National/Applied GCP Guidelines

- India, China, Russia, Singapore, Malaysia, Indonesia, South America, South Africa, Turkey



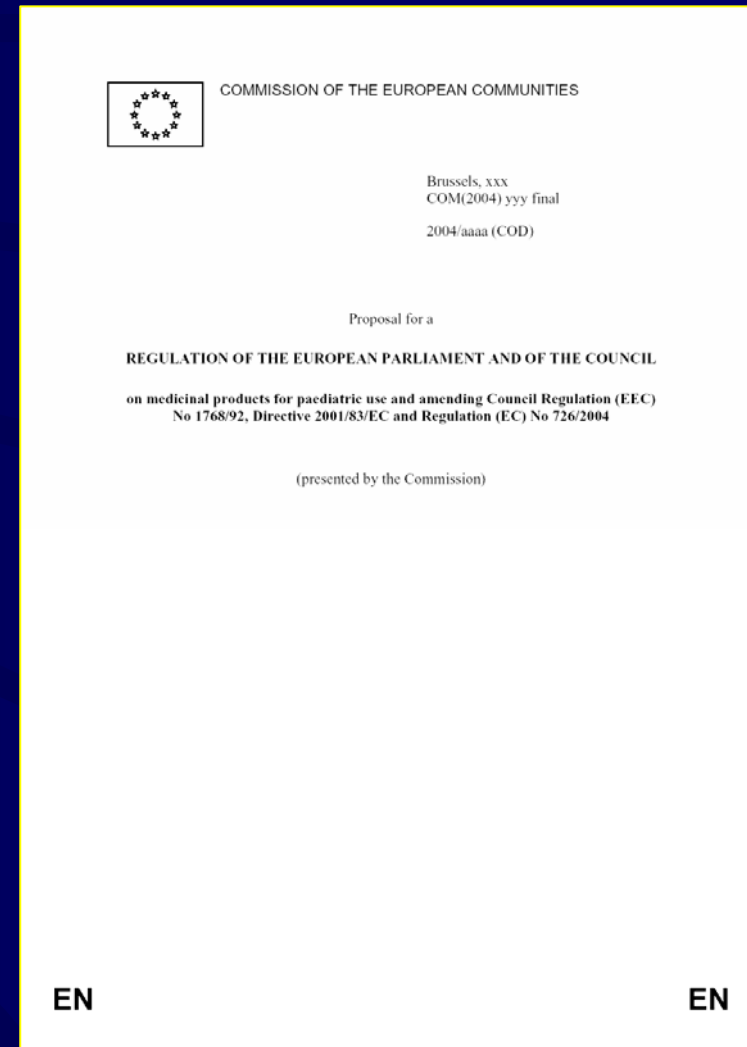
Phase I Clinical Trials in European & Global Paediatric Medicines Research



Medicines for Children

European Actions

- European Council and Parliament **Regulation on Medicinal Products for Paediatric Use** 2006
- A European Initiative on Developing **a European Network of Researchers** for the Evaluation of Medicinal Products in Children European Commission, 19 April 2005
- A GCPAlliance Roundtable Discussion on the Establishment of an **International Platform** for the Development of Paediatric Medicines Washington, DC, 30 June – 1 July 2005 European Commission, 19 October 2005



Expectations Regarding EU Legislation on Medicines for Paediatric Use

- Paediatric Board (EMA)
- New medicines **required** to have data on use in children (all medicines, possibly used in children, required to have a **Paediatric Investigation Plan [PIP]** – includes all MAA's & new indications, etc.; waiver or deferral possible)
- New medicines **gain 12 (6) month extension to supplementary protection certificate (SPC)** if data in children
- Established medicines can apply for **ad-hoc paediatric marketing authorisation** (10 years data exclusivity; marketed within 12 months)
- Studies in established medicines will have access to the **Paediatric Study Programme (EMA)**

EU Ethics Guidance for Paediatric Research

Commission Guideline Guideline on the Ethics of Clinical Trials in Children

in the Framework of Directive
2001/20/EC

draft, 6 October 2006

06 October 2006

ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS PERFORMED IN CHILDREN

Recommendations of the Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use

DRAFT AGREED BY AD HOC WORKING GROU	12 September 2006
RELEASE FOR CONSULTATION	4 October 2006
END OF CONSULTATION (DEADLINE FOR COMMEN	31 January 2007
AGREED BY WORKING GROUP	

Comments should be provided and sent to entri-pharmaceuticals@ec.europa.eu , or Fax +32-2-29 98046

KEYWORDS	Ethics, Clinical trials, Child, Neonate, Minor, Directive, Consent, Ethics Committee, Assent
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Children in Phase I Studies

15. Healthy children/ 'volunteers' studies

In principle, healthy children should not be enrolled as healthy volunteers, because they cannot consent and are vulnerable. Studies should not be performed in children when they can be performed in adults. In some situations however, studies have to be performed in healthy children. Prevention trials or paediatric vaccine trials, including immunogenicity studies, may fall into this category as an example of such trials.

Whenever possible the older age groups should be considered for inclusion before the younger ones. Proof of concept should be obtained in relevant animal models and/or in adults whenever possible. Studies such as pharmacokinetic studies, which cannot be performed in adults, should be done in the intended population as far as possible, i.e., the one affected by the disease, although it is recognised that data obtained in affected children may have increased variability. Vaccines trials are performed in healthy children, but who represent the intended population.

What impact will the
evolving European and Global
Good Clinical Practice environments
have on *your* early phase clinical
trials?

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