第1回臨床研究専門委員会	資料　5
平成19年8月17日	藤原

平成19年8月18日

第1回臨床研究倫理指針に関する専門委員会　コメント

国立がんセンター中央病院
臨床検査部長・治験管理室長
藤原康弘

総合科学技術会議　基本政策推進専門調査会
「科学技術の振興及び成果の社会への還元に向けての制度改革について」

6．治験を含む臨床研究の総合的推進

（問題点）

○制度的枠組みの不備により臨床研究が遅れている

○新薬の承認審査体制の脆弱さ

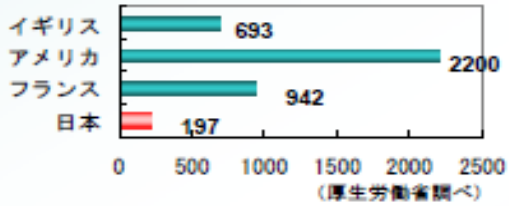
○新薬へのアクセスの遅れ（世界売上ﾄｯﾌﾟ医薬品の約3割が日本では未承認）

臨床研究での論文数の国別シェアの順位（2002）

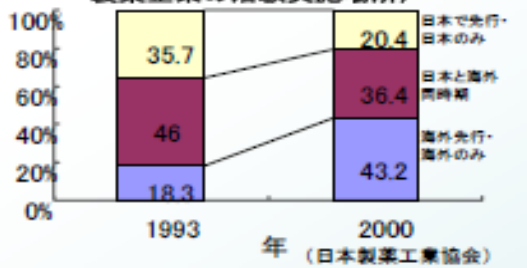
順位	臨床研究
1	アメリカ
2	イギリス
3	カナダ
14	日本

(N Engl J Med 2002;347(15):1211-12)

医薬品承認審査等の人員の国際比較（H17）



国内治験の空洞化（日本の製薬企業の治験実施場所）



（改革事項）

○「臨床研究に関する倫理指針」を改定し、臨床研究の準拠すべき実施基準を策定

○被験者の臨床研究への参加を促進するため、保険診療と研究に付随する診療が併用可能な保険制度を確立

○医薬品医療機器総合機構の審査体制の充実（機構の人員の拡大・育成等）

○国際共同治験の推進（ITを活用した施設間ネットワーク作りや治験に係る書類様式の統一化等）

等

平成18年12月18日

安心して臨床研究を実施するには

被験者保護　と

臨床研究振興　の

ふたつ（ブレーキとアクセル）の

整備が必要

米国 National Research Act ：
被験者保護を重視

PL 93-348, 1974 HR 7724
PL 93-348, JULY 12, 1974, 88 Stat 342
(Cite as: 88 Stat 342)

UNITED STATES PUBLIC LAWS
93rd Congress - Second Session
Convening January 21, 1974

DATA SUPPLIED BY THE U.S. DEPARTMENT OF JUSTICE. (SEE SCOPE)
Additions and Deletions are not identified in this document.

PL 93-348 (HR 7724)
JULY 12, 1974

1974年7月

An Act tO AMEND THE PUBLIC HEALTH SERVICE ACT TO ESTABLISH A PROGRAM OF NATIONAL RESEARCH SERVICE AWARDS TO ASSURE THE CONTINUED EXCELLENCE OF BIOMEDICAL AND BEHAVIORAL RESEARCH AND TO PROVIDE FOR THE PROTECTION OF HUMAN SUBJECTS INVOLVED IN BIOMEDICAL AND BEHAVIORAL RESEARCH AND FOR OTHER PURPOSES.

BE IT ENACTED BY THE SENATE AND HOUSE OR REPRESENTATIVES OF THE UNITED STATES OF AMERICA IN CONGRESS ASSEMBLED

この後、“コモン・ルール”と呼ばれる連邦規則ができ、詳細な臨床研究倫理規準が示されて、それにもとづいた研究がなされている

(1) THE SUCCESS AND CONTINUED VIABILITY OF THE FEDERAL BIOMEDICAL AND BEHAVIORAL RESEARCH EFFORT DEPENDS ON THE AVAILABILITY OF EXCELLENT SCIENTISTS AND A NETWORK OF INSTITUTIONS OF EXCELLENCE CAPABLE OF PRODUCING SUPERIOR RESEARCH PERSONNEL;

米国　Clinical Research Enhancement Act

公的研究費にもとづく臨床研究環境整備をうたった

Public Law 106–505
106th Congress

An Act

To amend the Public Health Service Act to provide for recon[illegible] Secretary of Health and Human Services regarding the plac[illegible] external defibrillators in Federal buildings in order to imp[illegible] of individuals who experience cardiac arrest in such buildings, and to establish protections from civil liability arising from the emergency use of the devices.

Nov. 13, 2000
[H.R. 2498]

2000年11月

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Public Health Improvement Act.
42 USC 201 note.

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Public Health Improvement Act".

(b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

NIHによる臨床研究助成の振興内容を細かく規定

http://www.fda.gov/cder/about/smallbiz/faq.htm#Types%20of%20INDs

Types of INDs

An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

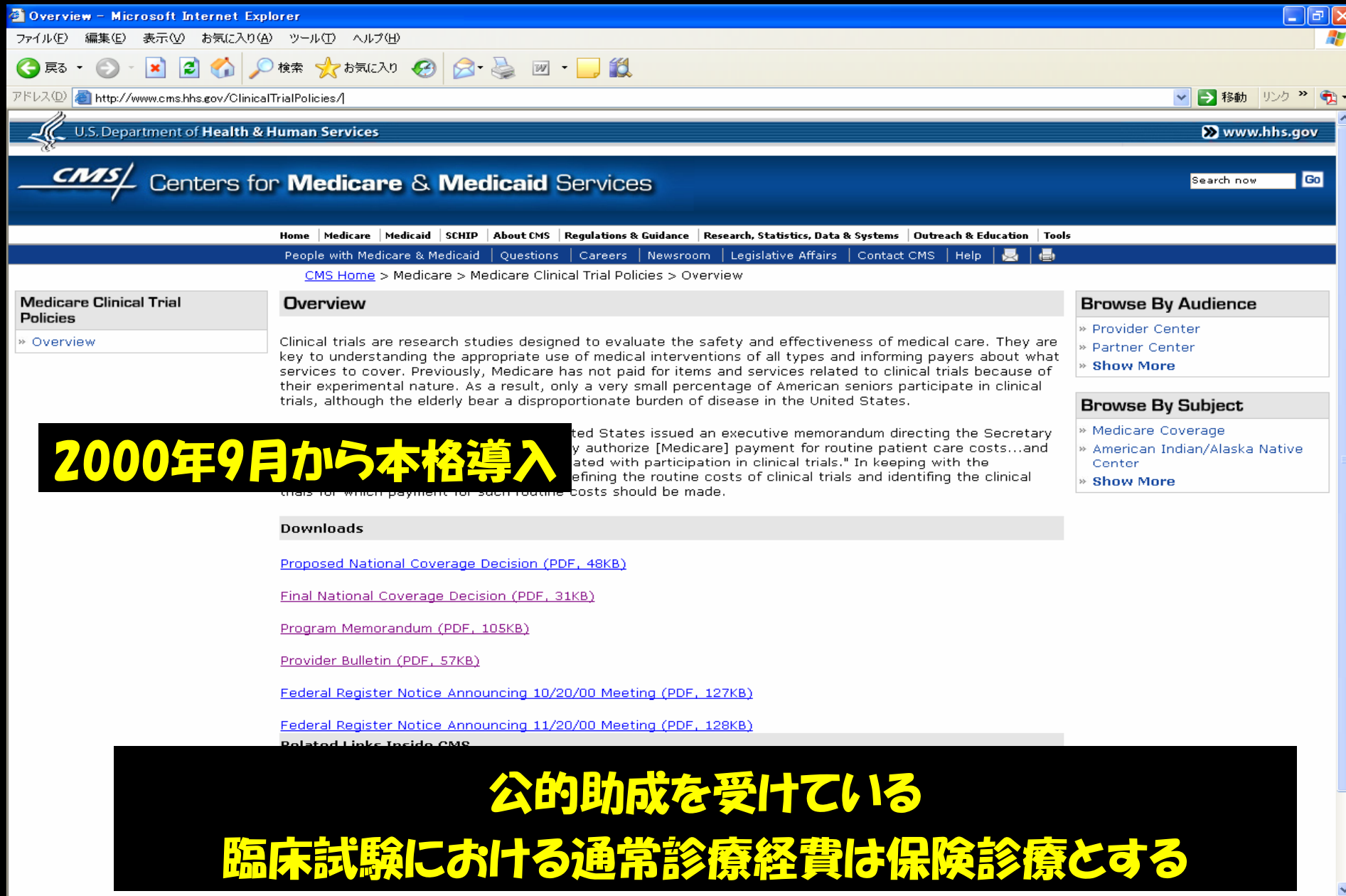
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:

- **Commercial.** These are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product.
- **Research (non-commercial)**

Emergency and **Treatment INDs** are also known as "Compassionate" INDs, but the term "Compassionate" is not in the IND regulations.

http://www.cms.hhs.gov/ClinicalTrialPolicies/



2000年9月から本格導入

公的助成を受けている
臨床試験における通常診療経費は保険診療とする

どのような臨床試験が対象となるのか

- **Deemed Trials.**

Some trials are considered automatically deemed as having desirable characteristics. They include:

Effective September 19, 2000

- **Trials funded by the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), Agency for Healthcare Research and Quality (AHRQ), CMS, Department of Defense (DOD), and Department of Veterans Affairs (VA);**

- **Trials supported by centers or cooperative groups that are funded by the NIH, CDC, AHRQ, CMS, DOD and VA;**

- **Trials conducted under an investigational new drug application (IND) reviewed by the Food and Drugs Administration (FDA);**

etc

Medicare Coverage Clinical Trial Program Memorandum

米国　臨床試験にかかるRoutine Cost とは

Routine costs DO include (and are therefore covered):

- **Items or services that are typically provided absent a clinical trial (e.g., medically necessary conventional care);**
- **Items and services required for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapeutic agent),**
- **Items and services required for the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and**
- **Items and services that are medically necessary for the diagnosis or treatment of complications arising from the provision of an investigational item or service.**

Medicare Coverage Clinical Trial　Program Memorandum

Coverage with Evidence Development (CED)

http://www.cms.hhs.gov/apps/media/press/release.asp?Counter=1897

EU 臨床試験指令　2001年4月公布

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,

Having regard to the Treaty establishing the European Community, and in pa

Having regard to the

Having regard to the
Committee (2),

Acting in accordance w
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

(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

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.

全てのヒトを対象とする「介入的試験」に対して、
①「GCPの原則を遵守、
②倫理委員会に加えて
規制当局への届出と事前審査が義務化、
③規制当局のGCP査察実施、等

規制のやり過ぎには要注意！

EDITORIAL

nature medicine

Safeguarding clinical trials

Efforts are underway to modernize clinical trial standards and normalize regulations to facilitate international collaboration. But as the European Union's Clinical Trials Directive shows, a one-size-fits-all regulatory strategy may be easier to conceive than to implement.

http://www.nature.com/naturemedicine

Nature Medicine Feb, 2007

NEWS

Tied up in red tape, European trials shut down

The chemotherapy drug doxorubicin has been used to treat soft-tissue cancers in children for more than 20 years, but doctors don't know the most effective dose, nor how it interacts with other drugs.

In 2005, European researchers set out to find these answers in a large, multi-center trial.

Two years on, fewer than half of the 600 participants needed have been recruited. Only 2 of the 16 countries originally involved—Italy and France—began on time. Denmark has yet to start, and Poland, Austria, Sweden and Germany—the last expected to provide 25% of study subjects—dropped out. Trial coordinators canceled plans to analyze data part way through the study. The trial's 2010 end date is likely to be pushed back by at least two years.

Scientists say the study is merely the latest victim of the Clinical Trials Directive, for the Research and Treatment of Cancer estimates that expenses have risen by 85% and says the number of trials it supports has dropped by 63%. The Save European Research campaign, which represents more than 3,000 scientists, says academic drug trials have dropped by 70% in Ireland and 25% in Sweden. The number of Finnish academic drug trials shrunk by 75%.

TRIAL AND ERROR

The European Clinical Trials Directive has created bureaucratic nightmares and is shutting down trials. Since the directive's launch:

Increase in the cost of academic cancer trials in the UK	200%
Drop in academic drug trials in Finland	75%
Drop in academic trial submissions in Ireland	70%
Increase in the cost of trials supported by EORTC	85%
New trials supported in 2004 by the group	19
New trials supported in 2005 by the group	7

Sources: Cancer Research UK; *Brit. Med. J.*; EORTC

Because the directive is technically not law, "They're getting overwhelmed with the

EU directiveへの対応：フランス

- 全国22ヶ所にデータセンターを整備
- 全国40ヶ所のIRBのSOPを統一化
- がん領域では国立がん研究所（仏版NCI）を設置
  - 医療機関の質のチェック
  - 臨床試験に対する助成
  - 全国22ヶ所に地域データセンターを整備
  - 全国13ヶ所のがんセンターのネットワーク化
  - 全がん患者の10%が臨床試験に参加することが目標
- 臨床研究においてroutine care costは保険で負担

EU directiveへの対応：イギリス

- National Cancer Research Network (NCRN)
  - 研究プロトコール申請をpeer review
  - 承認されたプロトコールはNCRN雇用のリサーチナースやデータマネージャー等が利用可能
- 他の6つの疾患領域でも、
  NCRNと同様な臨床研究ネットワークを組織
- Medical Research Council (MRC)：イギリス最大の臨床研究の公的研究費拠出者
  - Clinical Trial Unit (CTU)：がんとHIV研究を主に担当
  - Clnical Trial Service Unit (CTSU)：生活習慣病領域の大規模臨床研究をサポート
  - NHSと"partnership agreement"を結び、MRCの助成研究では臨床研究費用のうち医療費の一部はNHSが負担

臨床試験と保険診療の兼ね合い

- 欧米では、臨床試験にかかる診療経費の一部を医療保険でカバーしている。

- 日本では、日常診療では、適応外使用が良い例であるように、医師による査定の制度をうまく利用して灰色な研究的診療の許容がなされている。 しかし、いざ研究的診療を臨床試験として実施しようとすると、IRB等から保険診療でカバーできないとの批判を受ける。

研究的保険診療の禁止

保険医療機関及び保険医療養担当規則

（昭和32年4月30日　厚生省令第15号）

- **第18条（特殊療法の禁止）**「保険医は特殊な療法又は新しい療法等については、厚生大臣の定めるもののほか行ってはならない」

- **第19条（使用医薬品及び歯科材料）**「保険医は、厚生大臣の定める医薬品以外の薬物を患者に施用し、又は処方してはならない。ただし、薬事法（昭和35年法律第145号）第2条第7項に規定する治験に係る診療において、当該治験の対象とされる薬物を使用する場合においては、この限りでない。」

- **第20条（診療の具体的方針）**「・・・各種の検査は、研究の目的をもって行ってはならない。ただし、治験に係る検査については、この限りでない。」

適応外使用医薬品を用いる
臨床試験を
保険診療でカバーする必要性がある

未承認医薬については
医師主導治験が良いだろう

（提言）

- 適応外使用医薬品を使用する臨床試験については、ある一定の条件下（公的な研究費で実施されるもの；届出制）であれば、欧米と同様に、保険診療（保険外療養費制度の拡充）下での実施を可能とする