A New Perspective on the Ethics of Compassionate Use

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December 1st, 2023 World Medical Association's Regional Expert Meeting in Pacific on the WMA Declaration of Helsinki

“Idea of global standard”

By participation in the clinical trial

unapproved drugs will be available

However,
patients suffering from a disease
for which no satisfactory authorised alternative therapy exists
or who are not eligible for a clinical trial
can be addressed through compassionate use program.

Japan, US, Europe: to provide unapproved drugs outside of a clinical trial

- *Expanded registration-directed clinical trial (Japan)*
- *Expanded Access Program (the United States)*
- *Compassionate Use (EU)*

Compassionate Use Program “Expanded registration-directed clinical trial” ①

Revision of GCP Ordinance

● **Drugs**

- Operation since January 25, 2016

薬生審査発 0122 第 7 号
平成 28 年 1 月 22 日

各都道府県衛生主管部（局）長　殿

厚生

人道的見地から実施さ

欧米等では使用が認められているが、国
（以下「未承認薬等」という。）の解消に
検討会議」及び「医療上の必要性の高い未
承認薬等検討会議」という。）での検討に
組むとともに、独立行政法人医薬品医療機

● **Medical devices**

● **Regenerative medical products**

- Operation since July 21, 2016

薬生機審発 0721 第 1 号
平成 28 年 7 月 21 日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬・生活衛生局医療機器審査管理課長
（　　公　　印　　省　　略　　）

医療機器及び再生医療等製品における人道的見地から実施される治験の実施について

○厚生労働省令第九号

医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律（昭和三十五年法律第百四十五号）第十四条第三項（同条第九項及び同法第十九条の二第五項において準用する場合を含む。）、第十四条の四第四項及び第十四条の六第四項（これらの規定を同法第十九条の四において準用する場合を含む。）並びに第八十条の二第一項、

医療機関に選定させることができる。

第十七条に次の二項を加える。

2　治験依頼者は、前項ただし書の適切な製造管理及び品質管理の方法が記載された治験薬の容器又は被包の見やすい場所において、治験薬の容器第一項第一号及び第二号に掲げる事項を記載しなければならない。

3　第三十九条に規定する治験薬の項ただし書の場合には、当該治験薬の医薬品とを区別して適切に管理しなければならない。

第二十六条の二第一項中「次に下に「（拡大治験を実施する場合に号及び第二号に掲げる事項に限る。第二十六条の二第二項に次の一項を

ただし、拡大治験を実施する場この限りでない。

第二十六条の三に次のただし書を加える。

ただし、拡大治験を実施する場合にあっては、実施医療機関が在庫として保管する医薬品の中から、治験薬として使用する医薬品を当該実施医療機関に選定させることは自ら治験を実施する者自ら選定することができる。

療等製
療機器
の高い
での検
討に基づく開発の要請や開発企業の公募を進めるとともに、独立行政法人医薬品医療機器総合機構（以下「PMDA」という。）の審査員の増員を始めとする審査機能等

Compassionate Use Program
“Expanded registration-directed clinical trial”

https://www.pmda.go.jp/review-services/trials/0016.html

Compassionate Use Program “Expanded registration-directed clinical trial” ②

Scope

Investigational products for treating serious diseases *(Same as in Europe and the US)*

- significant impact on life
- no existing treatment methods are effective

◆ **After completion / completion of enrollment of a clinical trial**

- final stage of domestic development
- high probability that benefits will be obtained from an unapproved drug administration (“pivotal trials”).

** Pivotal trials: Registration-directed clinical trial intended to verify efficacy and safety, which are usually conducted after the indication and dosage and administration have been determined through a series of trials*

** To avoid delays in development and approval that would impede the provision of effective new drugs to large numbers of patients, the premise, as in similar systems in Europe and the US, is that the system must **in no way adversely influence the implementation of pivotal trials (and the commercialization of the drugs)***

https://www.pmda.go.jp/files/000209680.pdf

Compassionate Use Program “Expanded registration-directed clinical trial” ③

Legal Positioning

- **Implemented: within the scope of PMD Act (Registration-directed clinical trial)**

  - ensuring safety of subjects *(unapproved drugs are used to patients)*

Handling

- **Conducted : an open-label, single-arm, active drug trial**

  - focus on safety, based on the pivotal trial protocol

https://www.pmda.go.jp/files/000209680.pdf

Compassionate Use Program “Expanded registration-directed clinical trial” ④

Trial Site

The investigational sites of the pivotal trials

- ✓ Having a history of administering the relevant drug
- ✓ Sufficient knowledge and experience with adverse drug reactions of the relevant drug, etc.

Study Duration

Terminated at the following time points

- ✓ **Approval** or **Disapproval**
- ✓ **Application is withdrawn** or **Development is discontinued** (efficacy is not observed)

Expenses for Investigational Products

May be asked to the patient

- ✓ **Patient consent : obtained upon providing a thorough explanation and written information**

Compensation

Appropriate compensation measures: taken based on the GCP Ordinance

https://www.pmda.go.jp/files/000209680.pdf

EU as a whole also made a “Compassionate use program” based on the French model.

European Medicines Agency
Evaluation of Medicines for Human Use

London, 19 July 2007
Doc. Ref: EMEA/27170/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON COMPASSIONATE USE OF MEDICINAL PRODUCTS, PURSUANT TO ARTICLE 83 OF REGULATION (EC) No 726/2004

TRANSMISSION TO EUROPEAN COMMISSION	26 January 2006
TRANSMISSION TO CHMP	20 February 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 March 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	1 July 2006
ADOPTION BY CHMP AND TRANSMISSION TO THE EUROPEAN COMMISSION	19 October 2006
RELEASE FOR CONSULTATION TO THE NATIONAL COMPETENT AUTHORITIES	6 February 2007
ADOPTION BY CHMP AND IMPLEMENTATION	19 July 2007

https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-compassionate-use-medicinal-products-pursuant-article-83-regulation-ec-no-726/2004_en.pdf

U.S. Department of Health and Human Services

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Expanded Access (Compassionate Use)

Resources for Y

- FDA Form 39 Patient Expan Investigational Application(PD form functiona 3926 link and As... to save t and then oper 2.1MB)

Expanded Access (Compassionate Use)

Expanded Access to Investigational Drugs and Biologics

21 CFR part 312 subpart I provides general requirements, describes criteria that must be met to authorize expanded access, lists requirements for expanded access submissions, and describes safeguards that will protect patients and preserve the ability to develop meaningful data about the use of the investigational product.

Under FDA's current regulations for investigational drugs and biologics, there are three categories of expanded access:

- Expanded access for individual patients, including for emergency use;
- Expanded access for intermediate-size patient populations; and
- Expanded access for widespread use.

This web page primarily addresses single patient expanded access INDs.

Learn more about expanded access for intermediate-size patient populations and expanded access for widespread treatment use.

Also, see FDA's final Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use – Questions & Answers

when appropriate, through expanded access.

http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm

FDA Single Patient IND

Physician Request for a S
Compassionate or Emerge

When a physician would like to request an Inves
drug or other product for a single patient, the firs
the consent of the manufacturer, the unapprove
manufacturer agrees to provide the product, the
to the appropriate review division. The request n

1. **Request for a single patient IND** fo
of the correspondence.

Japan does not have a "Compassionate use program" which can address individual patients

Like equivalent to single patient IND in US and nominative ATU in France

Expanded Access INDs for CDER and CBER (2018-2022)

Expanded Access INDs		Individual (Single) Patient Non-Emergency IND		Individual (Single) Patient Emergency IND		Intermediate Size IND		Treatment IND	
		received	allowed to proceed	received	allowed to proceed	received	allowed to proceed	received	allowed to proceed
FY 2022	CDER	1143	1133	789	789	27	25	7	7
	CBER	181	166	283	265	5	4	1	1
FY 2021	CDER	880	876	1040	1035	6	4	2	2
	CBER	125	125	216	212	5	5	0	0

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm163982.htm

The regulatory agency is now using data for regulatory approval from compassionate use

CLINICAL CANCER RESEARCH | CCR DRUG UPDATES

FDA Approval Summary: Alpelisib for PIK3CA-Related Overgrowth Spectrum

Sonia Singh[1], Diana Bradford[1], Xiaoxue Li[1], Pallavi S. Mishra-Kalyani[1], Yuan-Li Shen[1], Lingshan Wang[1], Hong Zhao[1], Ye Xiong[1], Jiang Liu[1], Rosane Charlab[1], Jeffrey Kraft[1], Sachia Khasar[1], Claudia P. Miller[1], Donna R. Rivera[1,2], Paul G. Kluetz[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2], and Martha Donoghue[1,2]

ABSTRACT

On April 5, 2022, FDA granted accelerated approval to alpelisib for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy. Efficacy was evaluated using real-world data (RWD) from EPIK-P1 (NCT04285723), a single-arm clinical study in patients 2 years of age and older with severe or life-threatening PROS who received alpelisib as part of an expanded access program (EAP) for compassionate use. The primary endpoint was confirmed radiologic response rate at week 24 as determined by blinded independent central review (BICR), using volumetric-based criteria given the atypical growth pattern and irregular shape of PROS lesions. Radiologic response was defined as a ≥20% reduction from baseline in the sum of measurable target lesion volume in up to three lesions. Of the 37 patients in the efficacy population, 27% [95% confidence interval (CI), 14–44] had a radiologic response at week 24. Duration of response (DOR) was an additional efficacy outcome measure, and among responders, 60% had a response lasting ≥12 months. Furthermore, supportive clinical documentation suggested early signals of clinical benefit (i.e., improvement in PROS-related signs and symptoms). The most common (≥10%) adverse reactions were diarrhea, stomatitis, and hyperglycemia.

Clin Cancer Res 2023 Aug 25:CCR-23-1270. doi: 10.1158/1078-0432.CCR-23-1270. Online ahead of print.

Real World Evidence is used for regulatory approval

BRIEF REPORT

Use of Real-World Evidence in Neuroscience-Related New Drug and Biologics License Applications for Novel Therapeutics

Bartholt Bloomfield-Clagett[1,†], Motiur Rahman[1,†], Kimberly Smith[1] and John Concato[1,2,*]

The US Food and Drug Administration (FDA) is evaluating the potential use of real-world evidence (RWE) in regulatory decision making. Some groups have evaluated the use of RWE in regulatory submissions in the United States and abroad, reporting that reliance on RWE to support new product approvals is relatively common. Confusion regarding the use of RWE in drug-approval decisions may arise, however, based on different application of the terms real-world data (RWD) and RWE. We evaluated RWE in new drug applications (NDAs) and biologics license applications (BLAs) from January 2019 to June 2021 for novel drugs and biologics approved by the FDA with indications related to psychiatry, neurology, pain, or sedation (here, termed neuroscience-related). We sought to determine whether the submissions included RWE and to describe the types of data and study designs used. Thirty neuroscience-related NDAs or BLAs were identified for novel drugs and biologics approved during the time-period of interest. Among these approvals, three applications (10%) were adjudicated as containing RWE, one of which included RWE as primary evidence of effectiveness. Our findings highlight how different operational definitions of the terms RWD and RWE can result in demonstrably different reporting of the use of RWE in regulatory decision making for neuroscience-related novel drugs and biologics. A better understanding of this topic, along with awareness of regulatory definitions of RWE, are important factors to promote accurate tracking and reporting of regulatory submissions involving RWE. These factors can also improve awareness among the stakeholder community regarding the role of RWD and RWE in regulatory decision making.

Clin Pharmacol Ther. 2023 Nov;114(5):1002-1005. doi: 10.1002/cpt.3018.

- **Since the last revision of the DoH in 2013, the concept of "clinical research" seems to have been changing.**

  - Real-world evidence (RWE) and real-world data (RWD), including data from the CU program obtained in medical care settings, have been increasingly used for regulatory approval and safety monitoring, as research data.

  - However, the blurring of the boundary between medical research and clinical practice has not been reflected in the DoH.

  - It is mentioned only in Article 37 vaguely.

However, in the current Declaration of Helsinki

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

- **Given this era of digital health, in the next revision of the DoH and in preparation for the next pandemic or disaster,**

  - **We think that the DoH must address a new type of clinical research, CU and RWD/RWE, to facilitate development of drugs, devices, and diagnostics which will promote global human health.**

- Article 37 should be amended to state that unproven interventions, including CU, should be restricted for the duration.

  Otherwise, such interventions may cause not only individual harm but distrust of public health care.

- It should also be noted that conducting clinical trials after CU for the same condition is very difficult.

  The phrase "intervention should subsequently be made the object of research" now seems to be an empty slogan.

Disruption over the "Fabricated" big data of Surgisphere

Lancet May 1 2020 epub

Retraction notice June 4, 2020 epub

Articles

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

RETRACTED

Open letter of inquiry May 28, 2020

Open letter to MR Mehra, SS D

"Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis". Lancet. 2020 May 22:S0140-6736(20)31180-6. doi: 10.1016/S0140-6736(20)31180-6. PMID: 32450107

and to Richard Horton (editor of The Lancet).

Concerns regarding the statistical analysis and data integrity

The retrospective, observational study of 96,032 hospitalized COVID-19 patients from six continents reported substantially increased mortality (~30% excess deaths) and occurrence of cardiac arrhy
chlor

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The New York Times | https://nyti.ms/2Au654f

F.D.A. Revokes Emergency Approval of Malaria Drugs Promoted by Trump

The agency said that a review of some studies showed that the drugs' potential benefits in treating Covid-19 did not outweigh the risks.

By Katie Thomas

June 15, 2020 Updated 6:18 p.m. ET

The Food and Drug Administration said on Monday that it was revoking emergency authorization of two malaria drugs to treat Covid-19 in hospitalized patients, saying that they are "unlikely to be effective" and could carry potential risks.

The drugs, hydroxychloroquine and chloroquine, were heavily promoted by President Trump after a handful of small, poorly controlled studies suggested that they could work against the disease caused by the coronavirus. Mr. Trump said he took hydroxychloroquine after he had been exposed to two people who tested positive for the coronavirus.

This article has been retracted: N Engl J Med. DOI: 10.1056/NEJMc2021225.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

S. Desai, M.D., Ph.D., ry, M.D., and Amit N. Patel, M.D.

RACT

nay disproportionately affect people with en aroused regarding a potential harmful e (ACE) inhibitors and angiotensin-recep- text.

169 hospitals in Asia, Europe, and North of cardiovascular disease and drug therapy ed patients with Covid-19 who were admit- March 15, 2020, and were recorded in the ry as having either died in the hospital or 020.

whom discharge status was available at the l in the hospital (5.8%) and 8395 survived be independently associated with an in- an age greater than 65 years (mortality of s of age; odds ratio, 1.93; 95% confidence ery disease (10.2%, vs. 5.2% among those CI, 2.08 to 3.51), heart failure (15.3%, vs. e; odds ratio, 2.48; 95% CI, 1.62 to 3.79), ong those without arrhythmia; odds ratio, bstructive pulmonary disease (14.2%, vs. ds ratio, 2.96; 95% CI, 2.00 to 4.40), and ng former smokers or nonsmokers; odds creased risk of in-hospital death was found nhibitors (2.1% vs. 6.1%; odds ratio, 0.33; s (6.8% vs. 5.7%; odds ratio, 1.23; 95% CI,

observations sug
an increased risk
r results did not c
n of ACE inhibito
by the William Harvey Distinguished Chair in Ad-
ne at Brigham and Women's Hospital.)

From Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston (M.R.M.); Surgisphere, Chicago (S.S.D.); Baylor College of Medicine and Department of Veterans Affairs, Houston (S.K.); Christ Hospital, Cincinnati (T.D.H.); the Department of Biomedical Engineering, University of Utah, Salt Lake City (A.N.P.); and HCA Research Institute, Nashville (A.N.P.). Address reprint requests to Dr. Mehra at Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at mmehra@bwh.harvard.edu.

This article was published on May 1, 2020, and updated on May 8, 2020, at NEJM.org.

N Engl J Med 2020;382:e102.
DOI: 10.1056/NEJMoa2007621

NEJM May 1 2020 epub

Retraction notice June 4, 2020 epub

Following this Surgisphere matter, Lancet's editors changed its peer review process.

Learning from a retraction

Published Online
September 17, 2020
https://doi.org/10.1016/
S0140-6736(20)31958-9

See Editorial *Lancet* 2020;
396: 799

The publication and subsequent retraction[1,2] in June, 2020, of the Article Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis, based on an alleged dataset associated with Surgisphere, prompted us to examine *The Lancet*'s peer-review processes to identify ways of further reducing risks of research and publication misconduct. As a result of this review, with immediate effect, we have made changes to the declarations we seek from authors, the data sharing statements we require for published research papers, and the peer-review process for similar papers based on large datasets or real-world data.

Changes to the signed declarations by authors in the author statements form will require that more than one author has directly accessed and verified the data reported in the manuscript. We will require that the authors who (eg, the study protocol), when data will become available, and by what access criteria data will be shared. Investigators should be aware that editors will take data-sharing statements into account when making editorial decisions.

All *Lancet* journals will now introduce additional peer-review requirements for papers based on large, real-world datasets. Editors will ensure that at least one peer reviewer is knowledgable about the details of the dataset being reported and can understand and comment on its strengths and limitations in relation to the research question being addressed. For studies that use very large datasets, editors will ensure that in addition to statistical peer review, a review from an expert in data science is obtained. Finally, we will explicitly ask reviewers if they have concerns about research integrity or publication ethics regarding the manuscript they are reviewing.

Lancet 396: 1056, 2020 (Oct 10)

Regulatory authorities should try

- to gather individual patient data,

- to summarize results for transparency, and

- to validate data obtained

from CU and RWD/RWE.

Thank you for your attention