製薬協

有効性に関するICHガイドライン（過去から振り返る）

第4回ICHフォーラム
森　和彦
日本製薬工業協会

はじめに

- ICHは30年を超える歴史があるのでなかなか言い出しにくい事があるのですが、いまさらですが一言
- Quality, Safety, Efficacyは医薬品評価の本質的３要素です
- ICHガイドラインは基本的にこの３つのカテゴリーに分類されています
- **ICH-Eガイドライン**はEfficacyガイドライン（有効性に関するガイドライン）と呼ばれていますが・・・・
- 本当は**臨床評価（有効性・安全性）に関するガイドライン**です
- 一方、**ICH-Sガイドライン**は**非臨床安全性ガイドライン**です

過去を振り返ると

- あくまで主観的な振り返りです。
- ICH初期（1990年代）はそれ以前（1980年代まで）の医薬品開発の様々な経験、課題を背景としてガイドラインを検討
- 2000年代に入って、ヒト全ゲノム解析等のライフサイエンスの飛躍的進歩、臨床開発の課題を踏まえてイノベーションの実現に資するガイドラインの検討も
- 2010年代からはICTやAIの進歩、データサイエンス等、ライフサイエンス以外の科学技術の進歩が医薬品開発に劇的な進化をもたらし、これに対応するガイドラインの進化が必要になった

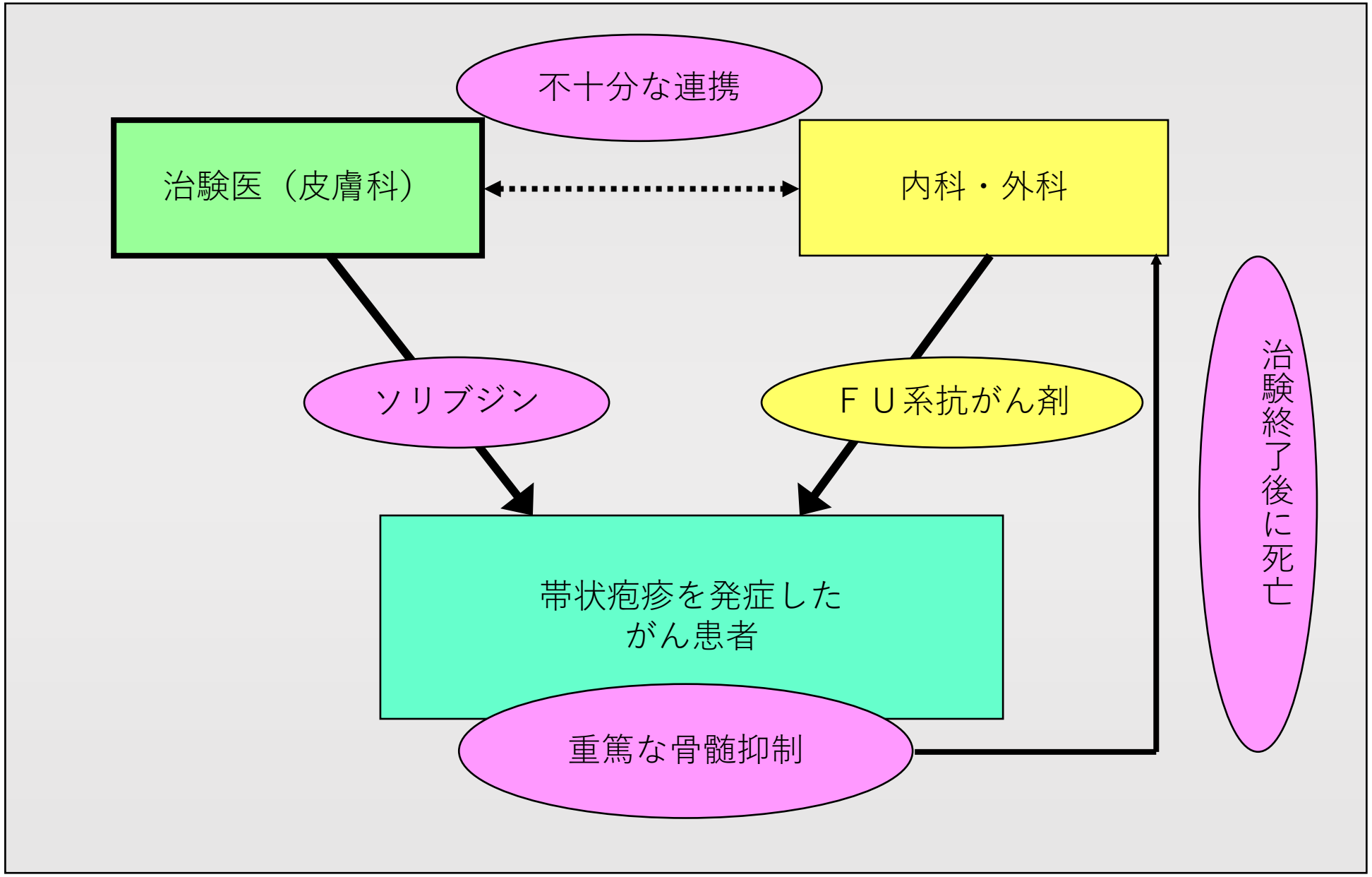
背景となる経緯

- 1980年代　様々な信頼性問題（GMP、GLP、GCPの策定）
- 1990年代　国際的な規制調和（ICHが始まった！）
- 2000年代　イノベーションへの対応（バイオ・ゲノムの時代）
  FDAのクリティカル・パス・イニシアティブ（2004年）
  治験薬TGN1412 のPhase-1 試験事故（2006年）
- 2010年代　臨床試験のイノベーションへの対応（RWDの活用）
  2017年：NEJMに掲載された“マスタープロトコール”
- 2020年代　covid-19パンデミックがもたらした劇的変化！

1980年代～1990年代

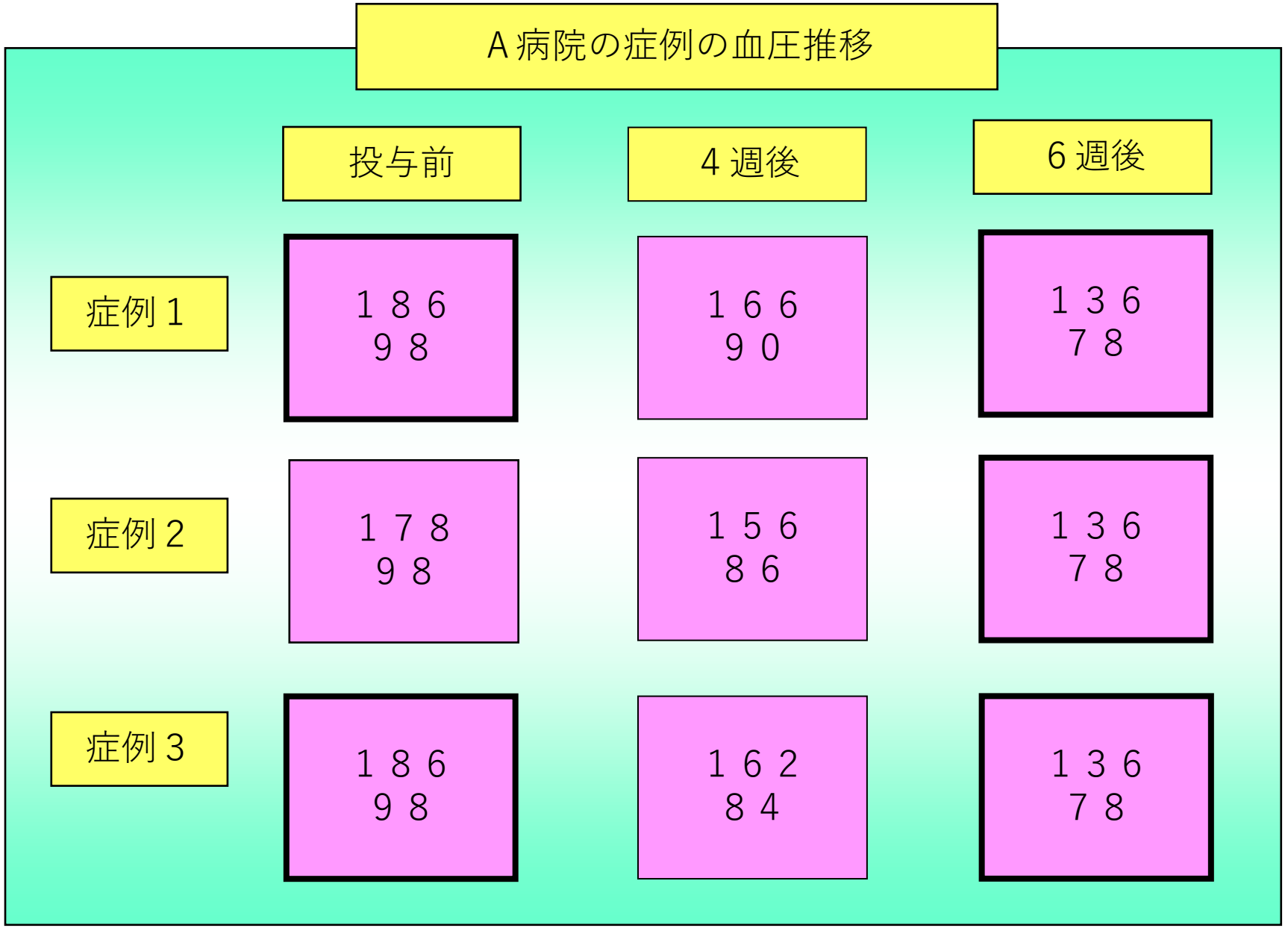
ケース1（ソリブジン問題）

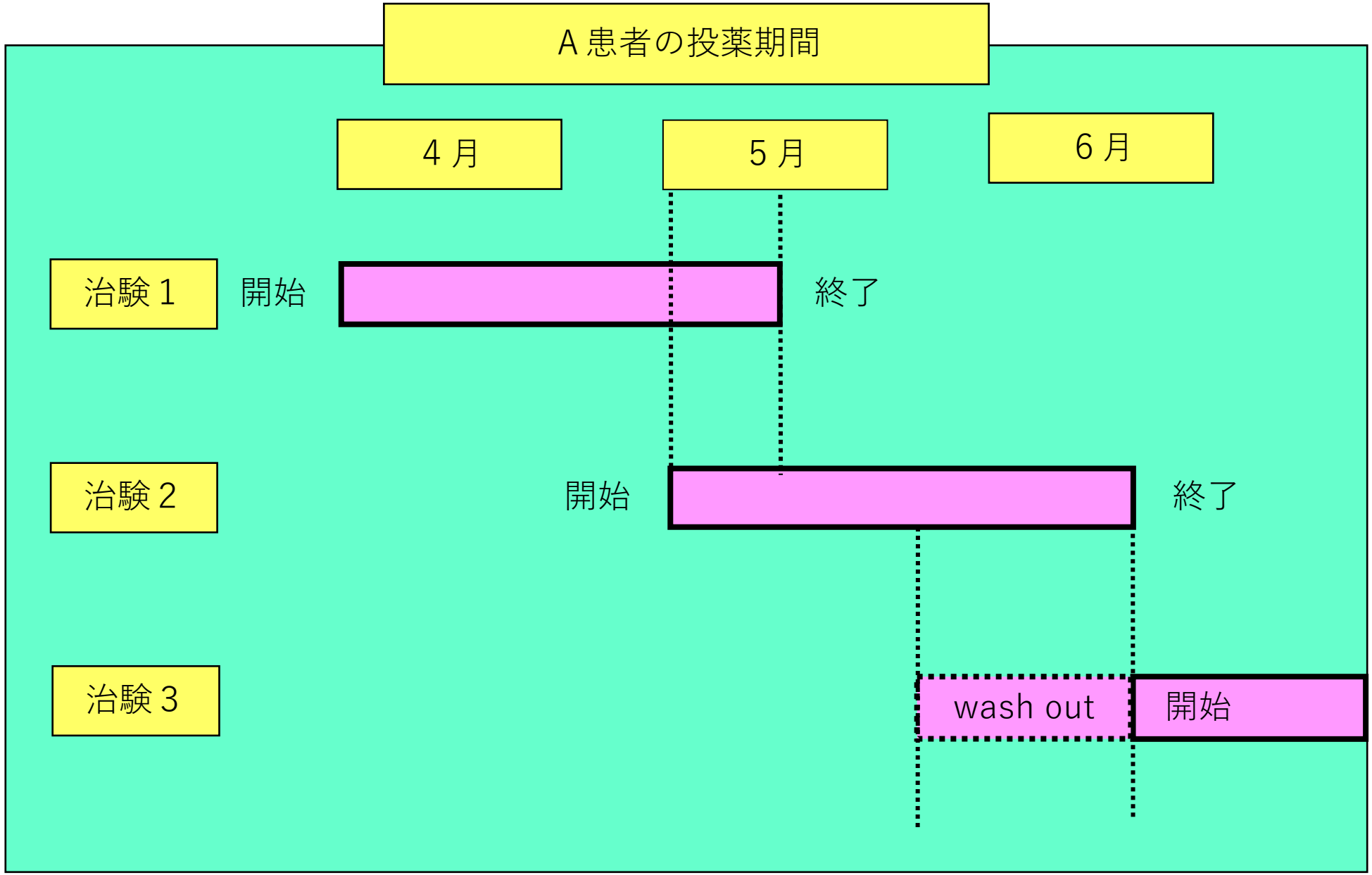
- 皮膚科領域
- 複数の大学病院
- 主な所見：
  - FU系抗がん剤との相互作用による副作用死亡例に気づかなかった（症例の類似性、動物実験との関連性、現場での併用可能性に気づかず）
  - 対象疾患（帯状疱疹）にばかり注目し、全身状態への関心低かった


不十分な連携
治験医（皮膚科）
内科・外科
ソリブジン
ＦＵ系抗がん剤
帯状疱疹を発症した
がん患者
重篤な骨髄抑制
治験終了後に死亡

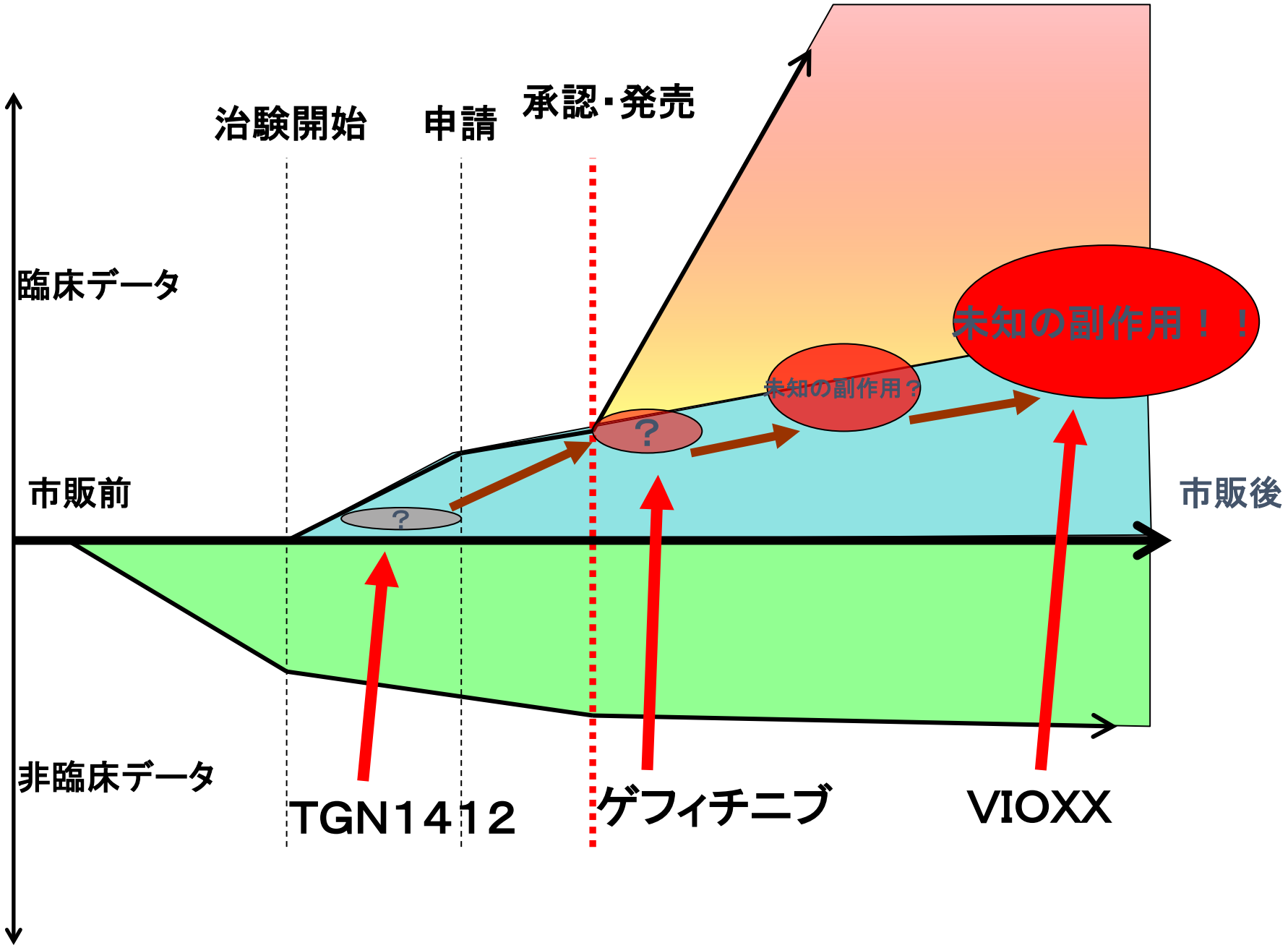
ケース2（審査中の発見）

- 循環器領域
- 私立病院
- 主な所見：
  - 不自然なデータ（同じ数値が繰り返し出現する：架空の測定値のねつ造）
  - 同一患者の多重登録（投薬期間の重複）
  - 個々の企業は気づき難い（気付いていたか？）

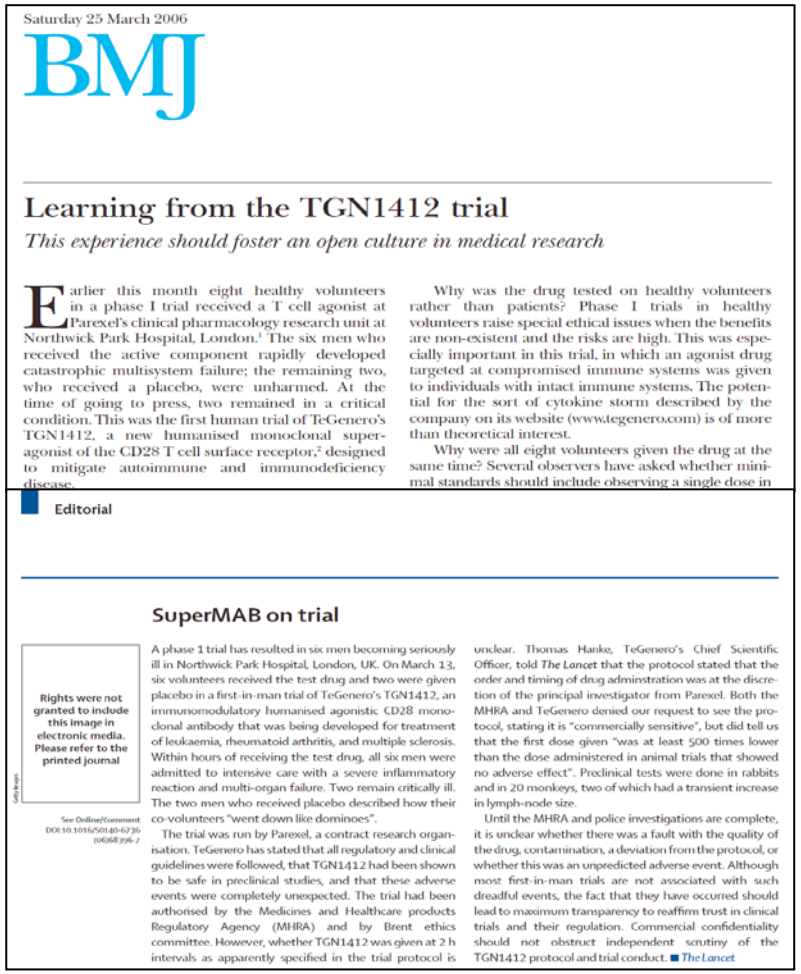

A病院の症例の血圧推移
投与前
4週後
6週後
症例1
186
98
166
90
136
78
症例2
178
98
156
86
136
78
症例3
186
98
162
84
136
78


A 患者の投薬期間
4 月
5 月
6 月
治験 1
開始
終了
治験 2
開始
終了
治験 3
wash out
開始

2000年代～2010年代


治験開始
申請
承認・発売
臨床データ
市販前
市販後
非臨床データ
?
?
未知の副作用？
未知の副作用！！
TGN1412
ゲフィチニブ
VIOXX

抗体医薬ＴＧＮ１４１２の事故（２００６．３．１３）



Saturday 25 March 2006

BMJ

Learning from the TGN1412 trial

This experience should foster an open culture in medical research

Earlier this month eight healthy volunteers in a phase I trial received a T cell agonist at Parexel's clinical pharmacology research unit at Northwick Park Hospital, London.[1] The six men who received the active component rapidly developed catastrophic multisystem failure; the remaining two, who received a placebo, were unharmed. At the time of going to press, two remained in a critical condition. This was the first human trial of TeGenero's TGN1412, a new humanised monoclonal superagonist of the CD28 T cell surface receptor,[2] designed to mitigate autoimmune and immunodeficiency disease.

Why was the drug tested on healthy volunteers rather than patients? Phase I trials in healthy volunteers raise special ethical issues when the benefits are non-existent and the risks are high. This was especially important in this trial, in which an agonist drug targeted at compromised immune systems was given to individuals with intact immune systems. The potential for the sort of cytokine storm described by the company on its website (www.tegenero.com) is of more than theoretical interest.

Why were all eight volunteers given the drug at the same time? Several observers have asked whether minimal standards should include observing a single dose in

Editorial

SuperMAB on trial

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See Online/Comment
DOI:10.1016/S0140-6736(06)68396-7

A phase 1 trial has resulted in six men becoming seriously ill in Northwick Park Hospital, London, UK. On March 13, six volunteers received the test drug and two were given placebo in a first-in-man trial of TeGenero's TGN1412, an immunomodulatory humanised agonistic CD28 monoclonal antibody that was being developed for treatment of leukaemia, rheumatoid arthritis, and multiple sclerosis. Within hours of receiving the test drug, all six men were admitted to intensive care with a severe inflammatory reaction and multi-organ failure. Two remain critically ill. The two men who received placebo described how their co-volunteers "went down like dominoes".

The trial was run by Parexel, a contract research organisation. TeGenero has stated that all regulatory and clinical guidelines were followed, that TGN1412 had been shown to be safe in preclinical studies, and that these adverse events were completely unexpected. The trial had been authorised by the Medicines and Healthcare products Regulatory Agency (MHRA) and by Brent ethics committee. However, whether TGN1412 was given at 2 h intervals as apparently specified in the trial protocol is unclear. Thomas Hanke, TeGenero's Chief Scientific Officer, told *The Lancet* that the protocol stated that the order and timing of drug adminstration was at the discretion of the principal investigator from Parexel. Both the MHRA and TeGenero denied our request to see the protocol, stating it is "commercially sensitive", but did tell us that the first dose given "was at least 500 times lower than the dose administered in animal trials that showed no adverse effect". Preclinical tests were done in rabbits and in 20 monkeys, two of which had a transient increase in lymph-node size.

Until the MHRA and police investigations are complete, it is unclear whether there was a fault with the quality of the drug, contamination, a deviation from the protocol, or whether this was an unpredicted adverse event. Although most first-in-man trials are not associated with such dreadful events, the fact that they have occurred should lead to maximum transparency to reaffirm trust in clinical trials and their regulation. Commercial confidentiality should not obstruct independent scrutiny of the TGN1412 protocol and trial conduct. ■ *The Lancet*

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

MAY 4, 2006

Injury to Research Volunteers — The Clinical-Research Nightmare

Alastair J.J. Wood, M.D., and Janet Darbyshire, M.B., Ch.B.

At 8 a.m. on Monday, March 13, 2006, eight Kingdom Medicines and Health-

Drugs tests on trial

Britain's clinical-trial regulator has no good options.

Following an alarming episode in London last month, in which six drug-trial participants needed emergency treatment, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) says it will change the way it regulates clinical trials, at least temporarily. But this may prove more easily said than done.

In the trial on 13 March, six healthy subjects suffered violent reactions within minutes of ingesting an antibody drug candidate, TGN1412, which was being developed to treat autoimmune diseases such as rheumatoid arthritis. Initial investigations suggest that the antibody itself was responsible for the side effects (see *Nature* **440**, 855–856; 2006). On 5 April, the MHRA said it will seek advice from outside experts in determining whether drug candidates with novel modes of action should be allowed to enter clinical trials.

The incident at London's Northwick Park Hospital has drawn attention to the limitations of preclinical animal trials in determining the safety of drugs in humans, especially for 'humanized' antibody drugs that are targeted at mimicking human biological processes. It has also sparked some debate about whether the participants were sufficiently aware of the dangers they faced.

For the regulator, the immediate question is whether the existing rules strike the right balance between safeguarding trial participants and promoting the study of potentially valuable cures. Previously, the MHRA allowed initial, small-scale human safety trials to go ahead on the basis of successful animal trials and a description of how the compound works.

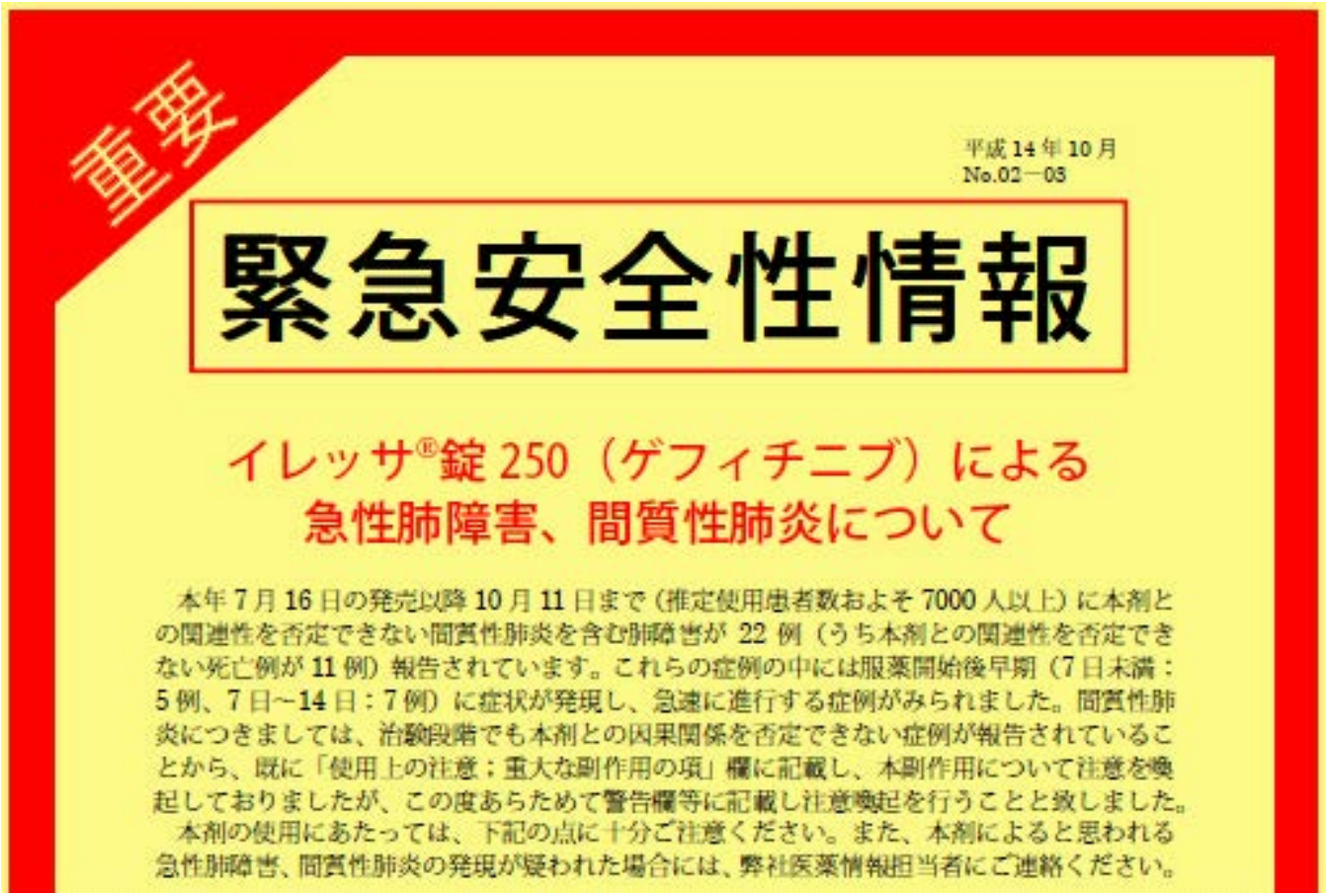
Now the agency says it will allow such trials to proceed only after review by a panel of outside experts. However, companies that have drug candidates up their sleeves don't want information on them to be shared, and any outside panel worth its salt is bound to contain people who work with rival companies. So such a provision could lead drug developers to turn their backs on Britain as a location for early-stage clinical trials.

"The incident has drawn attention to the limitations of preclinical animal trials in determining the safety of drugs in humans."

The best approach is probably that practised by the US Food and Drug Administration (FDA), the only drug regulator in the world with the in-house expertise to conduct such reviews by itself in strict confidence. The FDA, which is partly supported by fees levied on drug-makers eager to enter the lucrative US market, has 9,000 staff compared with the MHRA's 800 (although the FDA does handle food as well as drug safety).

One theoretical option would be a Europe-wide body set up to regulate and approve clinical trials, but the practical problems of constructing and operating such an agency would be daunting. In the interim, the MHRA may struggle to perform additional screening while satisfying confidentiality requirements. ■

肺がん治療薬ゲフィチニブの副作用



重要

平成14年10月
No.02－03

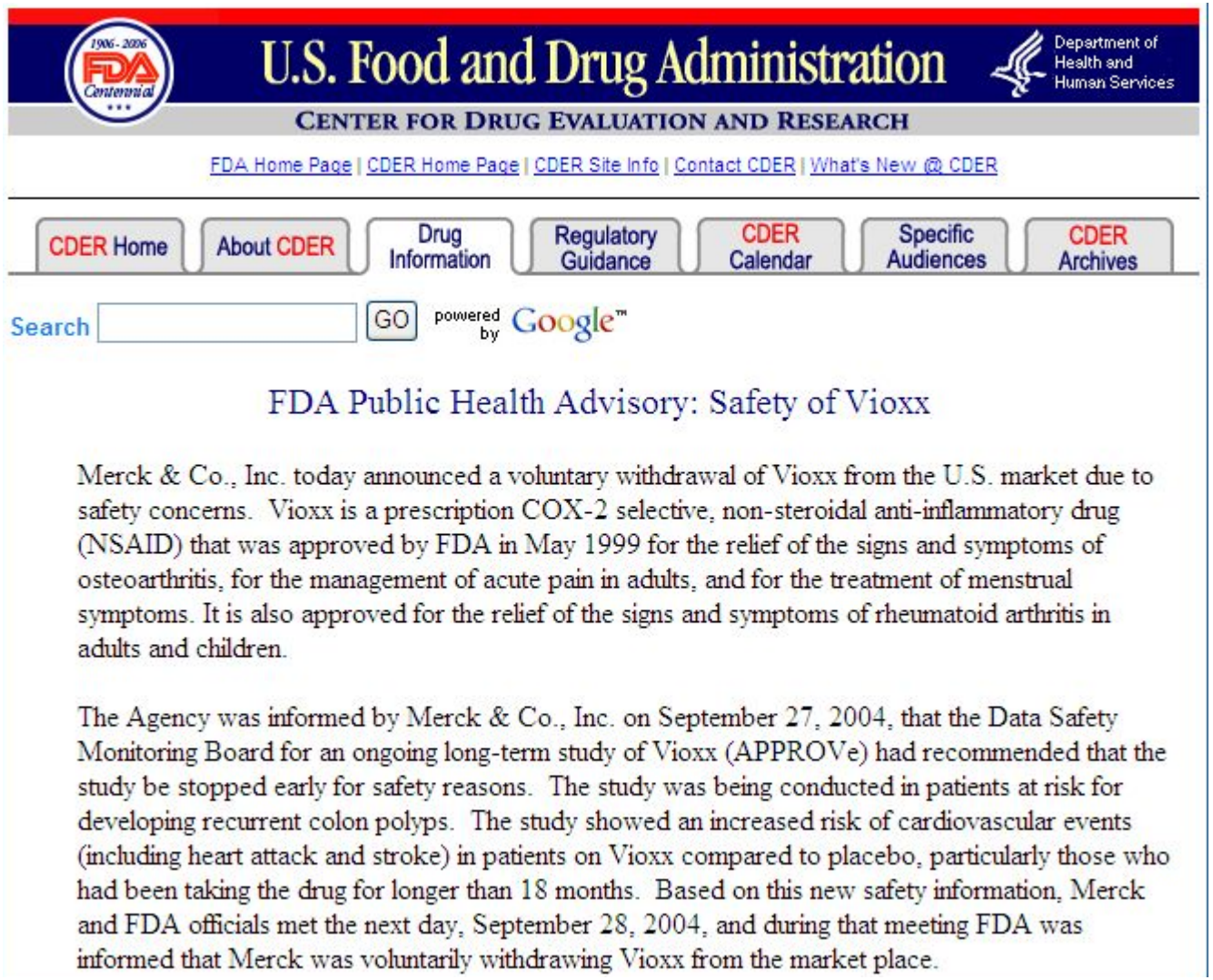
緊急安全性情報

イレッサ®錠250（ゲフィチニブ）による急性肺障害、間質性肺炎について

本年7月16日の発売以降10月11日まで（推定使用患者数およそ7000人以上）に本剤との関連性を否定できない間質性肺炎を含む肺障害が22例（うち本剤との関連性を否定できない死亡例が11例）報告されています。これらの症例の中には服薬開始後早期（7日未満：5例、7日～14日：7例）に症状が発現し、急速に進行する症例がみられました。間質性肺炎につきましては、治験段階でも本剤との因果関係を否定できない症例が報告されていることから、既に「使用上の注意：重大な副作用の項」欄に記載し、本副作用について注意を喚起しておりましたが、この度あらためて警告欄等に記載し注意喚起を行うことと致しました。

本剤の使用にあたっては、下記の点に十分ご注意ください。また、本剤によると思われる急性肺障害、間質性肺炎の発現が疑われた場合には、弊社医薬情報担当者にご連絡ください。

ＶＩＯＸＸの副作用による自主回収



U.S. Food and Drug Administration

Department of Health and Human Services

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FDA Public Health Advisory: Safety of Vioxx

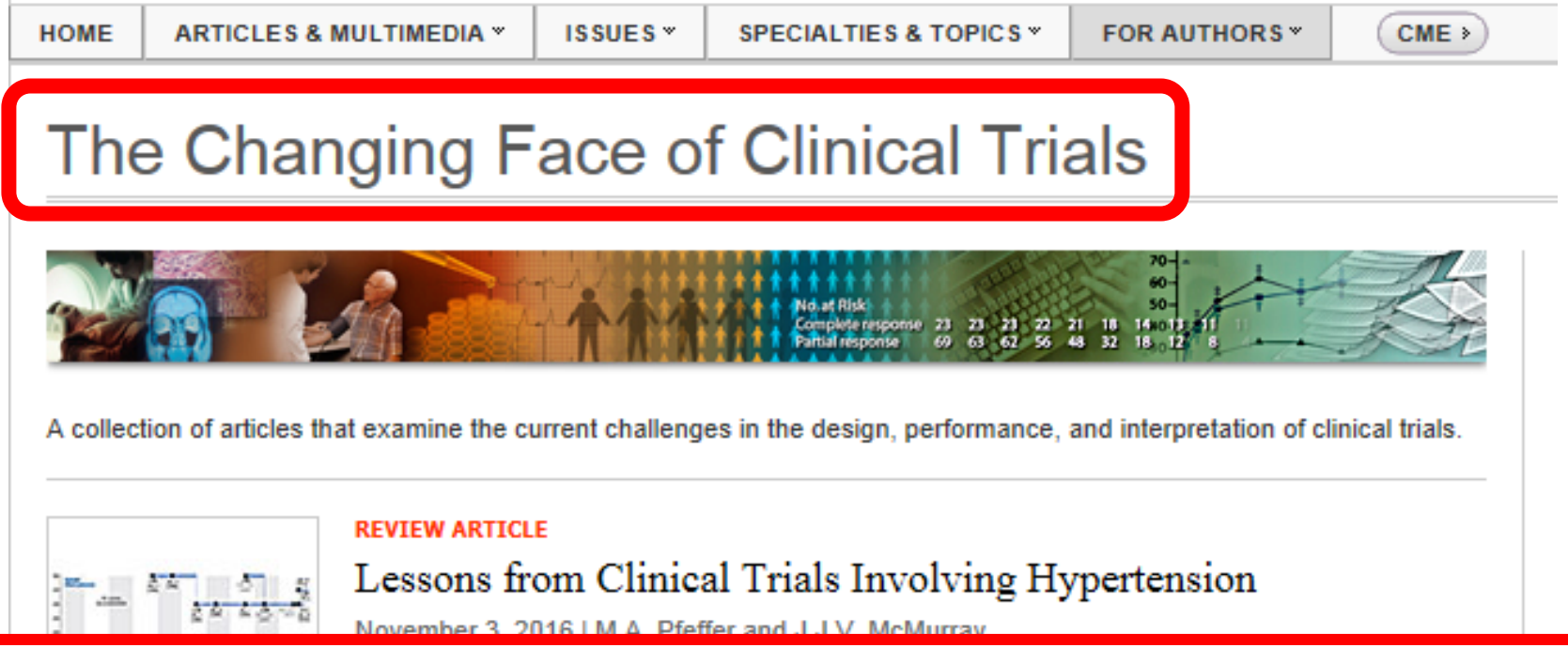
Merck & Co., Inc. today announced a voluntary withdrawal of Vioxx from the U.S. market due to safety concerns. Vioxx is a prescription COX-2 selective, non-steroidal anti-inflammatory drug (NSAID) that was approved by FDA in May 1999 for the relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of menstrual symptoms. It is also approved for the relief of the signs and symptoms of rheumatoid arthritis in adults and children.

The Agency was informed by Merck & Co., Inc. on September 27, 2004, that the Data Safety Monitoring Board for an ongoing long-term study of Vioxx (APPROVe) had recommended that the study be stopped early for safety reasons. The study was being conducted in patients at risk for developing recurrent colon polyps. The study showed an increased risk of cardiovascular events (including heart attack and stroke) in patients on Vioxx compared to placebo, particularly those who had been taking the drug for longer than 18 months. Based on this new safety information, Merck and FDA officials met the next day, September 28, 2004, and during that meeting FDA was informed that Merck was voluntarily withdrawing Vioxx from the market place.

これまでの経緯

- ◆基本方針（１９６７年)
- ◆二重盲検比較臨床試験の普及（1970年代以降）
- ◆臨床評価ガイドライン（１９９１）
- ◆新ＧＣＰ施行（１９９７）
- ◆外国臨床データ受け入れ指針（１９９８）
- ◆統計ガイドライン（１９９８）
- ◆ブリッジング試験の流行（１９９８～）
- ◆国際共同試験への移行（２００４～）
- ◆「国際共同治験の基本的考え方」（２００７）
- ◆新薬承認審査実務の留意事項（２００８）

臨床試験の変革をNEJMが特集
（2016年6月から）



In this issue, we inaugurate a series of articles called **"The Changing Face of Clinical Trials,"** in which we examine the current challenges in the design, performance, and interpretation of clinical trials.

http://www.nejm.org/page/clinical-trials-series

The NEW ENGLAND JOURNAL of MEDICINE

実践的な臨床試験
電子診療情報を利用したレジストリー試験

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

PRAGMATISM IN CLINICAL TRIALS AROSE FROM CONCERNS THAT MANY trials did not adequately inform practice because they were optimized to determine efficacy.[1] Because such trials were performed with relatively small

An attractive alternative to trials in which electronic health records are used can be found in trials of alternative interventions involving patients who are already enrolled in disease-specific or intervention-specific registries that incorporate detailed patient phenotypes and long-term follow-up data. **This framework provides an efficient and low-cost opportunity for conducting pragmatic trials** (e.g., the TASTE trial)

http://www.nejm.org/doi/full/10.1056/NEJMra1510059?query=featured_clinical-trials

FDAの審査センター長の革新的提案

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

N Engl J Med 2017;377:62-70.

ICH PRESS RELEASE
Osaka, Japan, 9-10 November 2016

Global good clinical practice (GCP) guideline amendment adopted

The 1996 ICH guideline on GCP is one of the most significant achievements of the ICH process, establishing harmonised standards for clinical trials. The ICH Assembly adopted an important amendment (ICH E6(R2)) that aims to encourage sponsors to implement improved oversight and management of clinical trials, while continuing to ensure protection of human subjects participating in trials and clinical trial data integrity. This amendment will now be implemented by ICH members through national and regional guidance.

In parallel, the Assembly agreed to look at renewing the wider package of guidelines that relate to GCP and clinical trial design. This will include updating current guidance on interventional trials and expand on novel trial methodologies for drug registration such as non-interventional trials, including use of new data sources such as real world evidence, patient registries, etc.

A reflection paper is expected to be published on the ICH website in early 2017, which will include an outline of the long-term work planning, beginning with revision of the ICH E8 guideline in 2017. ICH recognises the high level of interest in GCP guidance and is committed to working with concerned stakeholders and will be seeking views as work goes forward.

http://www.ich.org/fileadmin/Public_Web_Site/News_room/B-Press_Releases/ICH_GCG_Press_Releases/Press_Release_Osaka_10Nov2016_Final.pdf

革新的医療の最前線をNEJMが特集（2018年7月から）

The NEW ENGLAND JOURNAL of MEDICINE

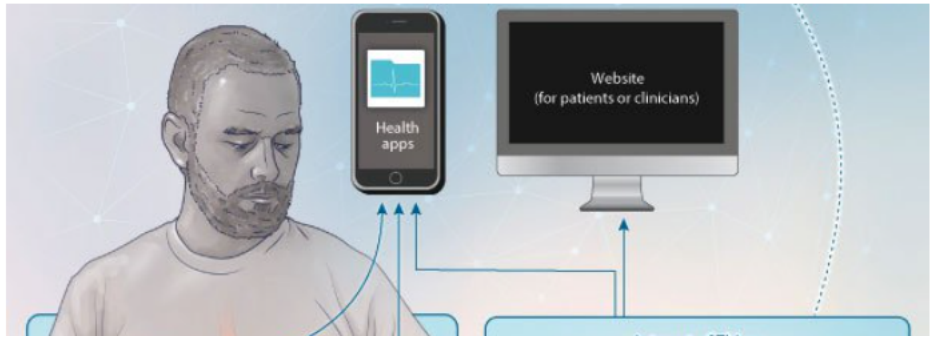
Frontiers in Medicine

A series of articles analyzing the ways in which new techn
medicine. The series explores the bridge between scientific discoveries and their development into clinically useful tools.

A Look Forward — The Frontiers in Medicine Series

Lisa Caulley, M.D., M.P.H., Ramya Ramaswami, M.B., B.S., M.P.H., Dan L. Longo, M.D., Elizabeth G. Phimister, Ph.D., Julie R. Ingelfinger, M.D., Allan H. Ropper, M.D., Kathy Stern, M.F.A., Alison E. Burke, M.A., Kimberly M. Knoper, M.A., Jeffrey J.J. Seals, B.A., Daniel C. Müller, M.A., and Jeffrey M. Drazen, M.D.

This week we introduce Frontiers in Medicine, a series of review articles that showcases the ways in which new technologies are influencing contemporary medicine and highlights the synergistic relationship between medicine and science. The series covers a number of advanced diagnostics and therapeutics that have emerged, including mentation of technological innovations, particularly as the cost of health care continues to soar, the scope and complexity of health care regulation further expands, and the social and bioethical aspects of medical technology grow more complex. For example, gene therapy represents a novel treatment strategy for patients with sickle cell disease,

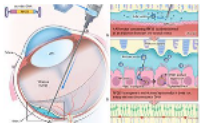


REVIEW ARTICLE

Gene Therapy Gathers Momentum

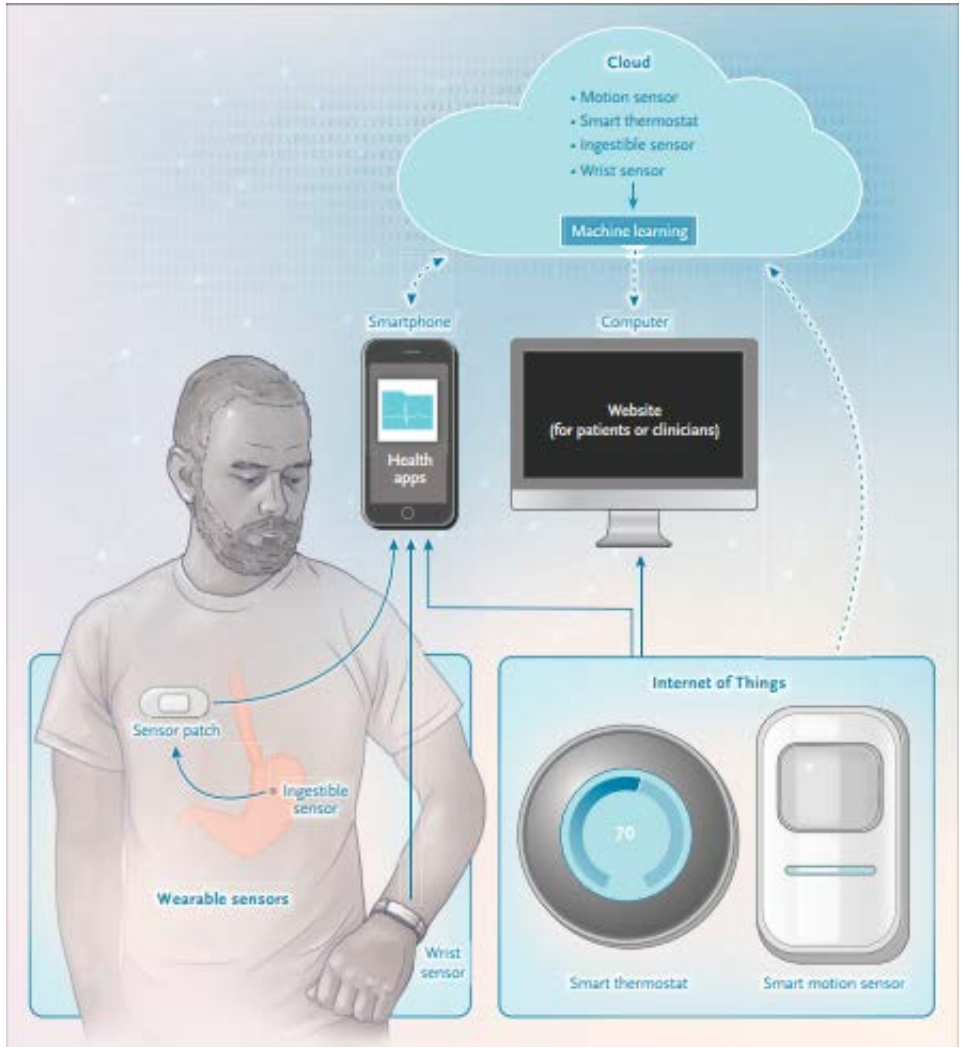
K.A. High and M.G. Roncarolo

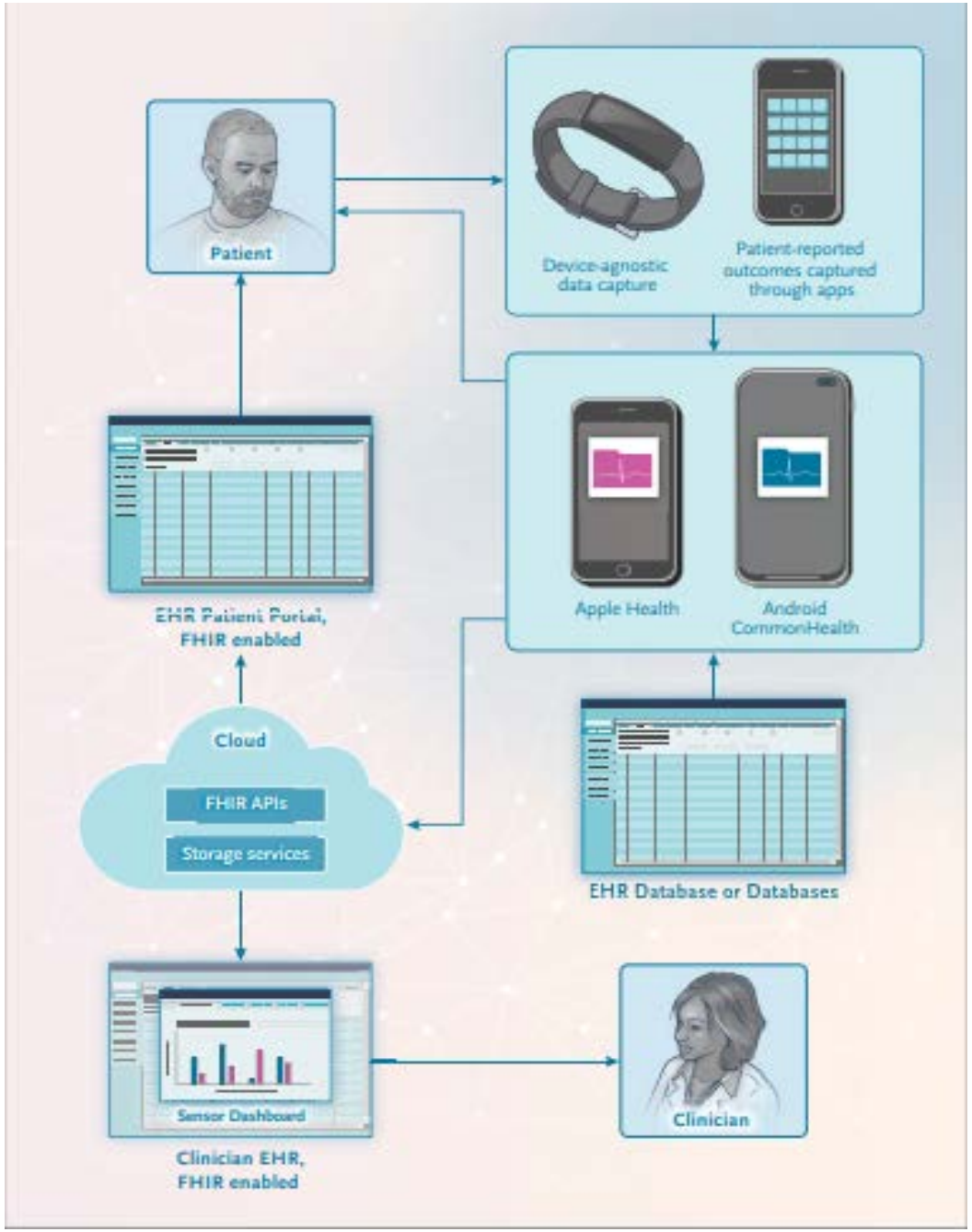
Those who have followed the gene-therapy field over the



https://www.nejm.org/frontiers-in-medicine

Mobile Devices and Health





N Engl J Med 2019; 381:956-968 September 5, 2019

ORIGINAL ARTICLE

Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation

Marco V. Perez, M.D., Kenneth W. Mahaffey, M.D., Haley Hedlin, Ph.D., John S. Rumsfeld, M.D., Ph.D., Ariadna Garcia, M.S., Todd Ferris, M.D., Vidhya Balasubramanian, M.S., Andrea M. Russo, M.D., Amol Rajmane, M.D., Lauren Cheung, M.D., Grace Hung, M.S., Justin Lee, M.P.H., Peter Kowey, M.D., Nisha Talati, M.B.A., Divya Nag, Santosh E. Gummidipundi, M.S., Alexis Beatty, M.D., M.A.S., Mellanie True Hills, B.S., Sumbul Desai, M.D., Christopher B. Granger, M.D., Manisha Desai, Ph.D., and Mintu P. Turakhia, M.D., M.A.S., for the Apple Heart Study Investigators*

ABSTRACT

BACKGROUND

Optical sensors on wearable devices can detect irregular pulses. The ability of a smartwatch application (app) to identify atrial fibrillation during typical use is unknown.

METHODS

Participants without atrial fibrillation (as reported by the participants themselves) used a smartphone (Apple iPhone) app to consent to monitoring. If a smartwatch-based irregular pulse notification algorithm identified possible atrial fibrillation, a telemedicine visit was initiated and an electrocardiography (ECG) patch was mailed to the participant, to be worn for up to 7 days. Surveys were administered 90 days after notification of the irregular pulse and at the end of the study. The main objectives were to estimate the proportion of notified participants with atrial fibrillation shown on an ECG patch and the positive predictive value of irregular pulse intervals with a targeted confidence interval width of 0.10.

RESULTS

We recruited 419,297 participants over 8 months. Over a median of 117 days of monitoring, 2161 participants (0.52%) received notifications of irregular pulse. Among the 450 participants who returned ECG patches containing data that could be analyzed — which had been applied, on average, 13 days after notification — atrial fibrillation was present in 34% (97.5% confidence interval [CI], 29 to 39) overall and in 35% (97.5% CI, 27 to 43) of participants 65 years of age or older. Among participants who

11月14日号のNEJMに
「スマートウォッチを用いて心房細動の検出を行う大規模臨床研究」の結果が発表されました

40万人の8か月にわたるモニタリングの結果
2161人（0．52%）で心拍異常を検出。
ECGパッチでフォローが出来た450人の34%で心房細動を検出。

The NEW ENGLAND JOURNAL of MEDICINE

Watched by Apple

Edward W. Campion, M.D., and John A. Jarcho, M.D.

After taking over media, social communication, and the consumer economy, the forces of digital innovation are moving into the worlds of medical practice and medical research. Both the power and the limitations of digital innovation in medicine are evident in a report by Perez and colleagues, "Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation," published in this issue of the *Journal*.[1] The study was sponsored by Apple, and in 8 months it managed to enroll some 419,000 participants through the use of a smartphone application (app). Having an iPhone and an Apple Watch were entry requirements, so the study participants were in fact customers of the sponsor. Not surprisingly, most heart monitoring. In fact, of the 219,179 participants younger than 40, over 99.8% received no notifications of an irregular pulse. It's difficult to draw any conclusions about the true frequency of atrial fibrillation, since only 21% of those with irregular pulse notifications based on monitoring by the smartwatch subsequently returned the ECG patch for analysis. In a study with easy, app-based enrollment, the percentage of people who dropped out was high and full follow-through with the research protocol was low. The study tried to exclude enrollees with a history of atrial fibrillation, but some of the detections were in patients who later admitted to a previous diagnosis of atrial fibrillation.

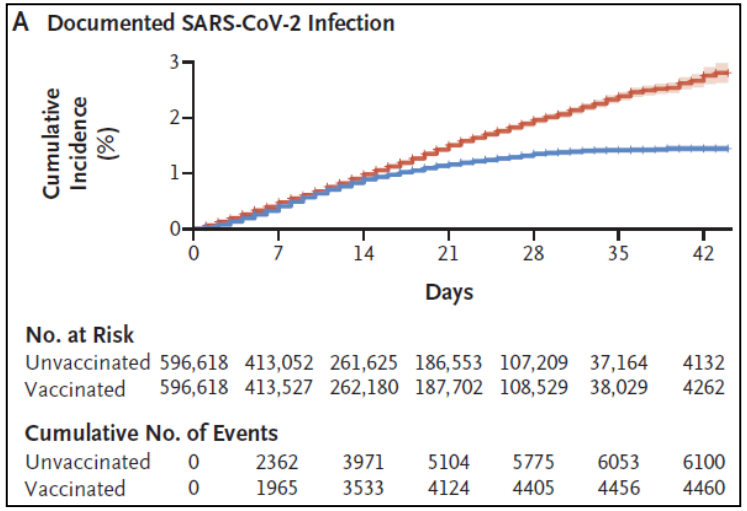
https://www.nejm.org/doi/full/10.1056/NEJMoa1901183

2020年代～

イスラエルのCOVID-19ワクチンの事例

・初回投与からわずか2か月で120万人規模のワクチンの効果を論文化
・悉皆性のある疫学データが政策や医薬品開発の重要な判断根拠となる

- イスラエルでは約20年前からデジタルヘルスインフラを整備。全人口の出生から死亡までを完全にカバーするデジタルデータに関する統合インフラがある
- イスラエルでは国民健康保険への加入が義務付けられており、4つあるヘルスプランのうちいずれかに加入する
- ヘルスプランとその関連病院は独立して運営されているがいずれも統一された統一IDを利用する電子カルテを使用している
- 最大ヘルスプラン（人口の53%をカバー）であるClalitが保有するデータを用い、COVID-19ワクチンの効果を迅速に検討し、論文化した



論文概要

- ✓ 2020年12月20日～**2021年2月1日**までにCOVID-19ワクチンを投与された選択除外基準に適合する全員における、COVID-19への感染、重症化、死亡等を検討
- ✓ **2回目投与完了7日以降の感染リスク**が92%低減したことが確認された
- ✓ この論文は**2021年2月24日**に公開された。

N Engl J Med. 2021 Feb 24 : NEJMoa2101765.

今私たちが直面する時間、空間、テクノロジー

- **時間：医薬品開発に10～15年かかる時代から1年以内も可能に**
  - Covid-19のパンデミックを契機に医薬品開発の時間スケールが劇的に変化（典型例はコロナワクチン、治療薬の開発）
  - ICHにおけるガイドライン作成の時間スケール（合意まで数年、定着には10年以上（ICH-GCPなど））
  - G7ではワクチン開発を100日で可能にする目標設定も
- **空間：日米欧の三極からグローバルなフィールドへ**
  - ICHの最初は世界の医薬品の8割を生み出している日米欧で話し合えばよかった
  - 21世紀のICHは国・地域（アジア・アフリカ・南米）を拡大し、参加する業界団体（バイオ、ジェネリック等）も拡大
- **テクノロジー：何でもありのオープンイノベーションエコシステム**

私たちのこれからの取組

- 2020年代における医薬品開発を踏まえた新しいガイドライン
- 特に臨床試験関係のガイドライン（ICH-Eガイドライン）は
- 既存のゴールデンスタンダードでの豊富な経験を踏まえ
- その限界と課題を踏まえ
- 新しいテクノロジーの導入による臨床試験の急速な変化、進化を踏まえ
- 受け身（Reactive）ではなく、
- **先見性を持って“Pro-active”に行動しましょう！**