浜松医科大学
Hamamatsu University School of Medicine

2019年7月25日

ICH E8「臨床試験の一般指針」改訂(案)説明会
ーICHの最新動向とICH E8(R1)ガイドライン(案)ー

ICH E8(R1)ガイドラインへの期待
アカデミアの立場から

浜松医科大学
渡邉裕司

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

Draft version
Endorsed on 8 May 2019
Currently under public consultation

ICH HARMONISED GUIDELINE

GENERAL CONSIDERATIONS FOR CLINICAL STUDIES

E8(R1)

ICH E8(R1)ガイドラインへの期待
アカデミアの立場から

- ✓ ICH E8(R1)ガイドラインの特徴
- ✓ アカデミアの医薬品開発とICH E8(R1)ガイドラインへの期待

ICH E8(R1)ガイドラインの特徴

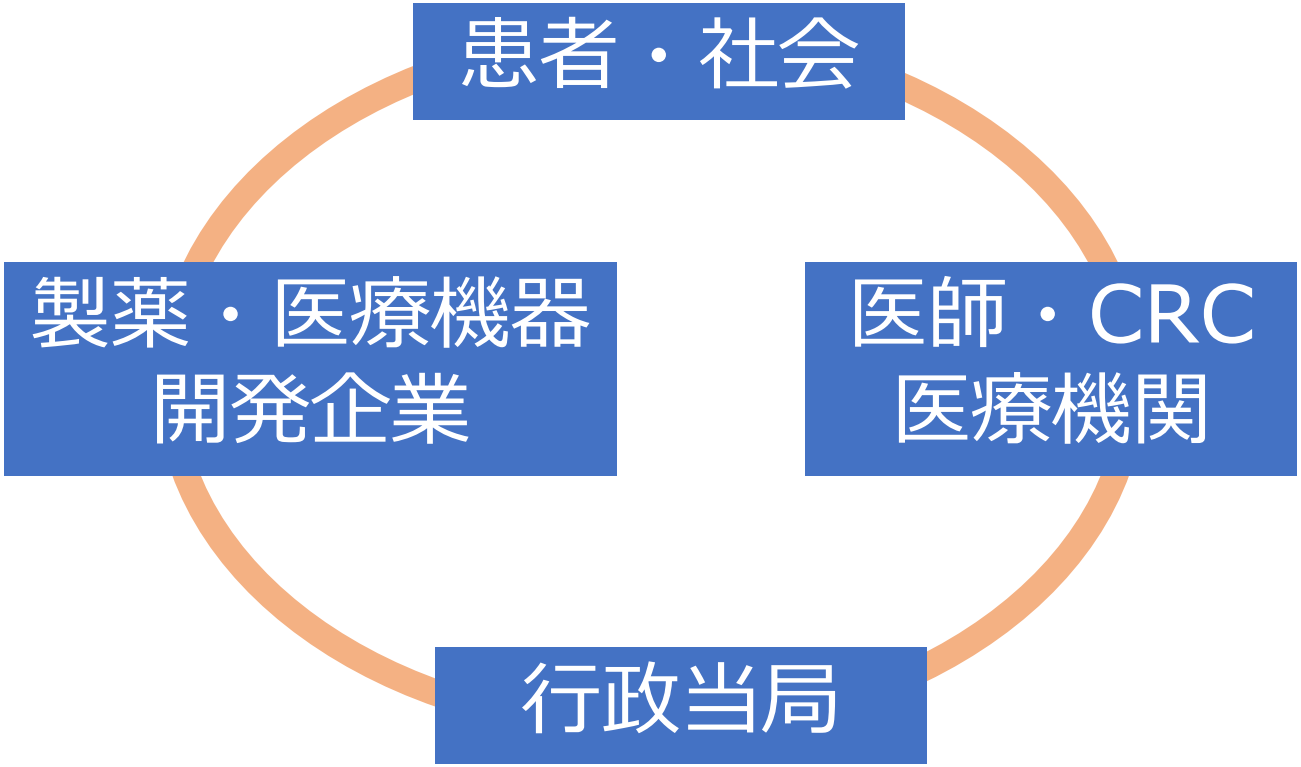
- ✓ Quality by Design of Clinical Studies
- ✓ Critical to Quality Factors
- ✓ Feasibility

Quality by Design of Clinical Studies

Quality by design in clinical research sets out to ensure that the quality of a study is driven proactively by designing quality into the study protocol and processes. This involves the use of a prospective, multidisciplinary approach to promote the quality of protocol and process design, and clear communication of how this will be achieved.

- 臨床試験の開始前、試験実施計画書や実施手順を検討する段階から、試験の質を設計することによって臨床試験の質の向上を目指す
- 明確な目的意識をもってコミュニケーションを図り前向きに、さまざまなアプローチを用いて試験プロトコールやプロセスデザインの質を向上させる

臨床試験のプレイヤー



この臨床試験のデザインは

Our study design, organisation, clinical measurements, endpoint definitions, power calculations, and recruitment rates have been published previously.[23] Briefly, between January, 2002, and December, 2004, we recruited patients to an investigator-initiated, independent, investigator-led, multicentre, controlled trial.[23] Participating centres included the four hospitals of the Jikei University in Tokyo, which has some of the largest inpatient and outpatient facilities in Japan, and 17 associated hospitals led by physicians from Jikei University.[23] We used a prospective randomised open blinded endpoint (PROBE) design.[24]

We recruited patients with hypertension, coronary heart disease, heart failure, or a combination of these cardiovascular disorders. The study population was selected and

Prospective Randomized Open Blinded Endpoint PROBE Design

Prospective Randomized Open Blinded Endpoint PROBE Design

二重盲検化されないオープン試験であるにも関わらず
ソフトエンドポイントが評価項目に組み込まれていた

- 脳卒中や一過性虚血発作による入院
- 心不全による入院
- 狭心症による入院
- 透析への移行

- オープン試験であるならばハードエンドポイントのみを評価項目とする
- ソフトエンドポイント組み入れるならば二重盲検試験とする

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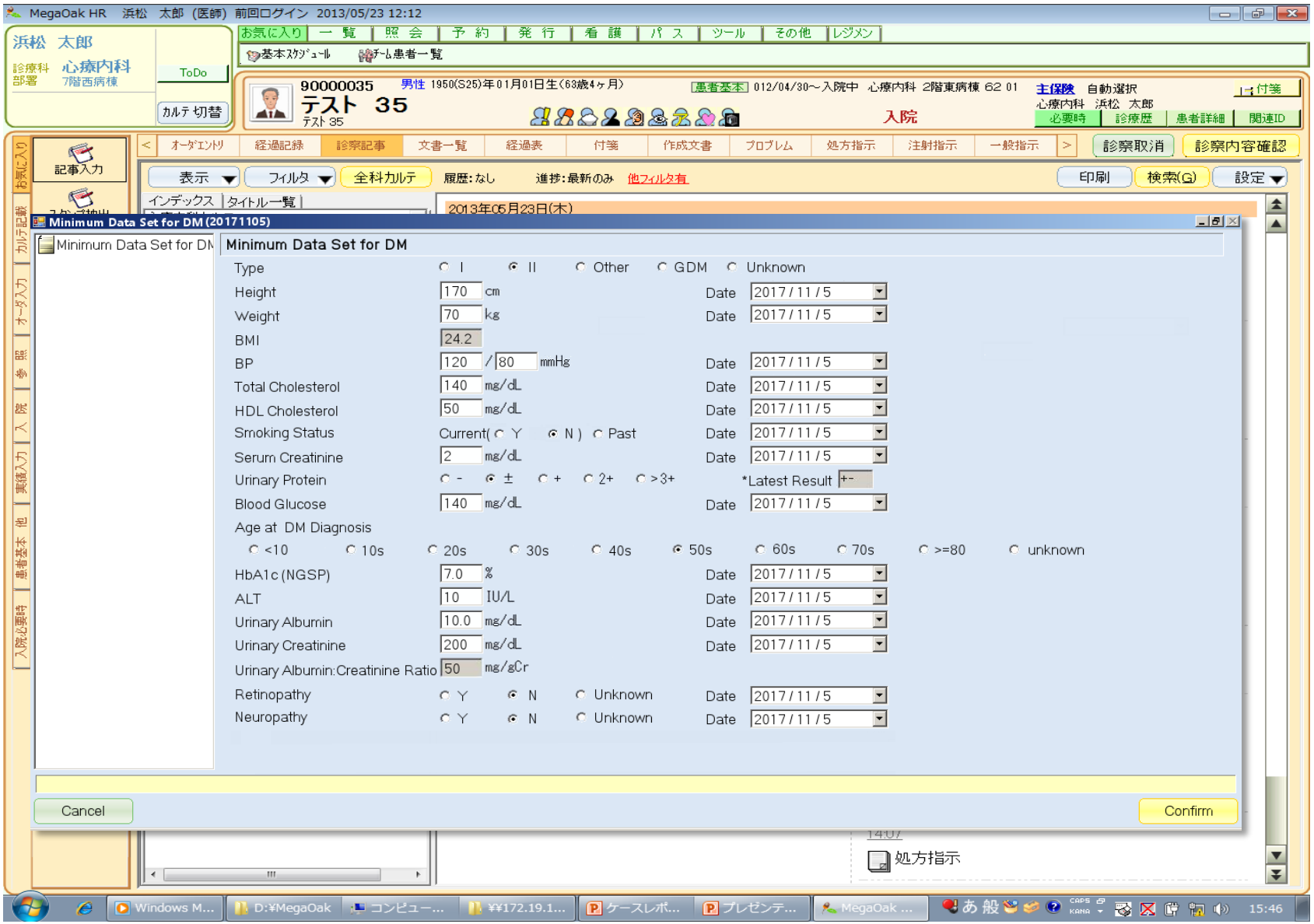
Development of a New Seamless Data Stream from EMR to EDC System Using SS-MIX2 Standards Applied for Observational Research in Diabetes Mellitus

EMR “Stamp” for “Minimum Data Set”

2019 Bridging Clinical Research & Clinical Health Care
a clinical research collaborative



EMR “Stamp” for Cardiovascular Events

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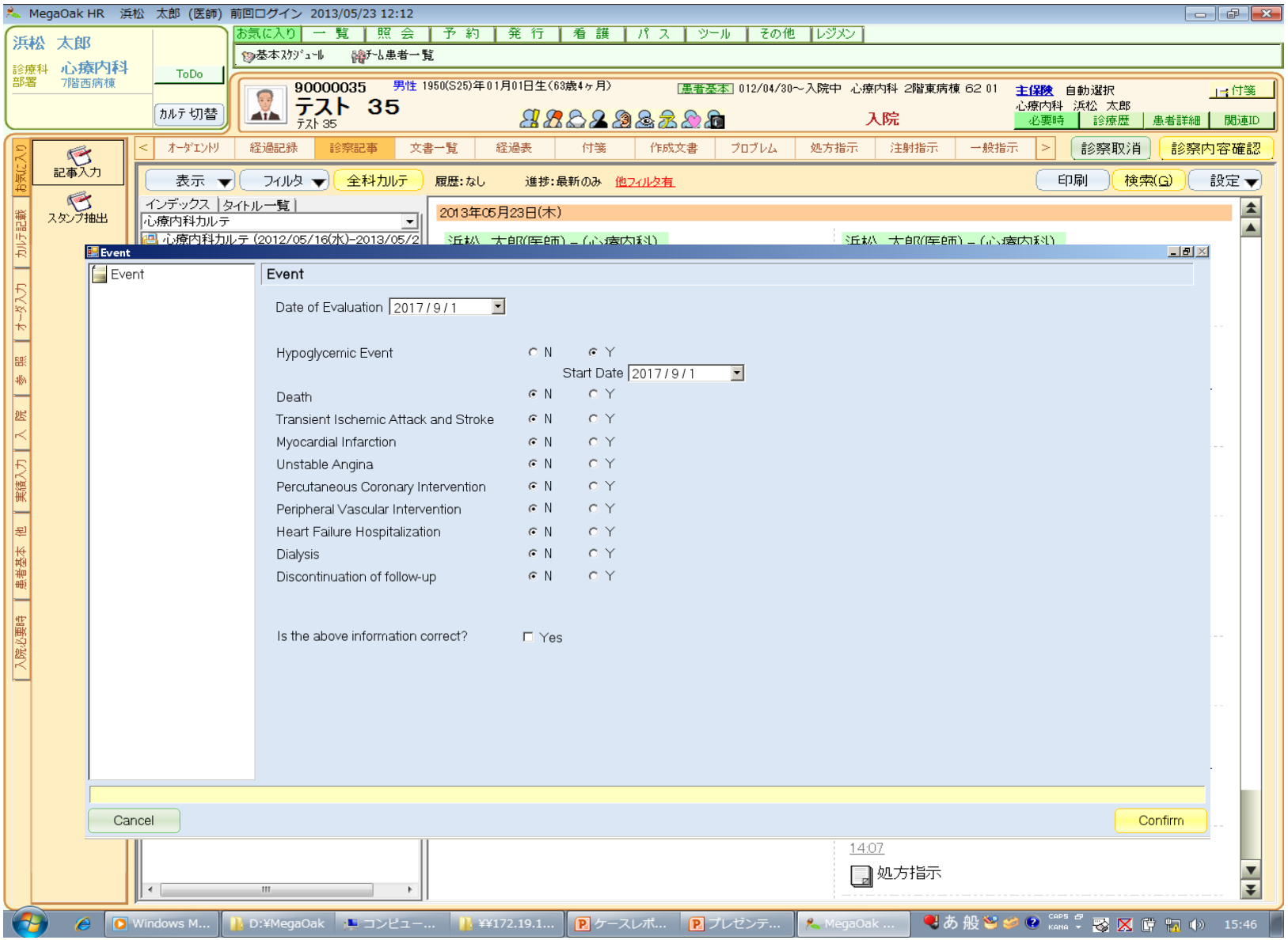


Scheme of EMR “Stamp”

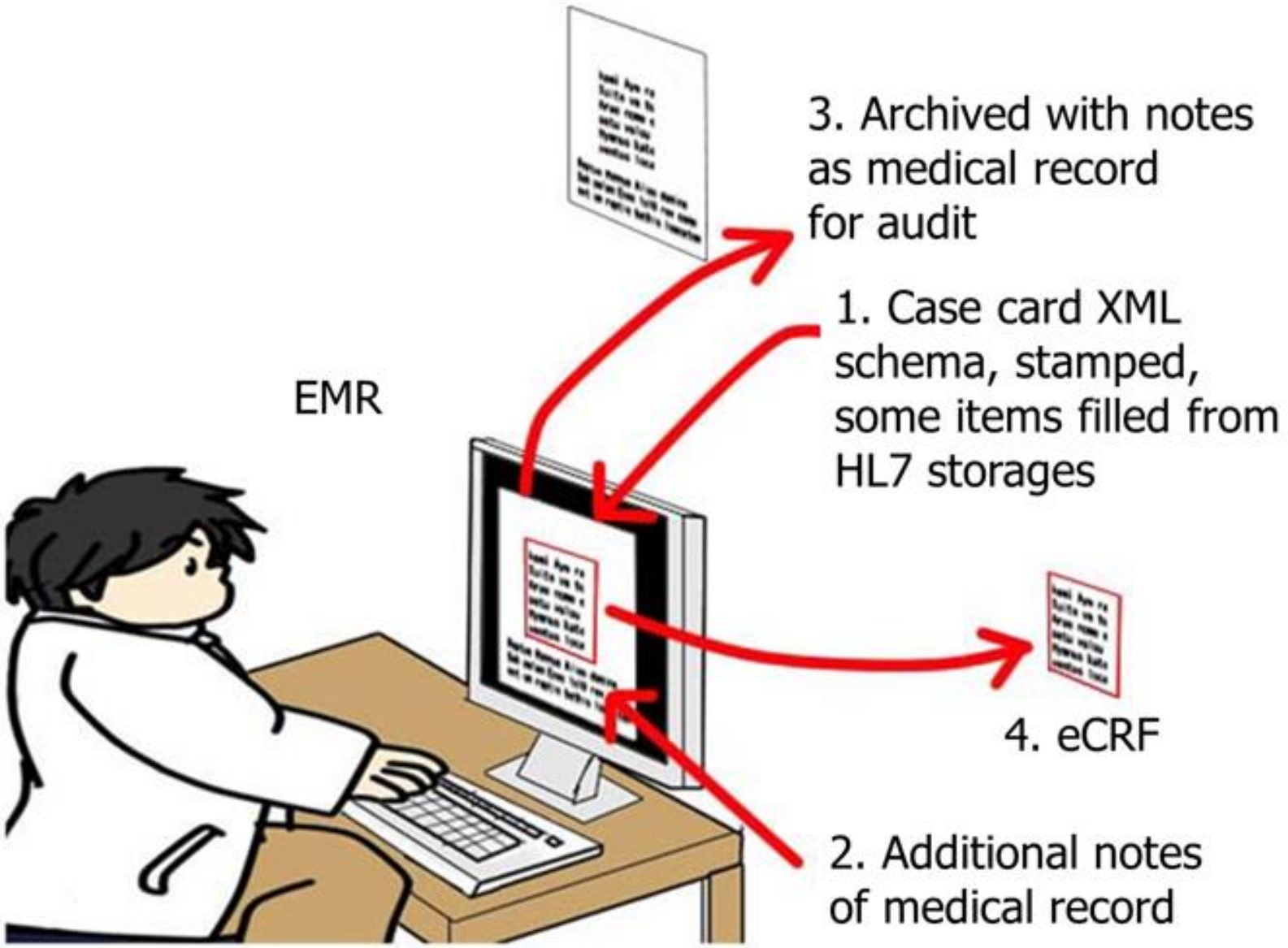
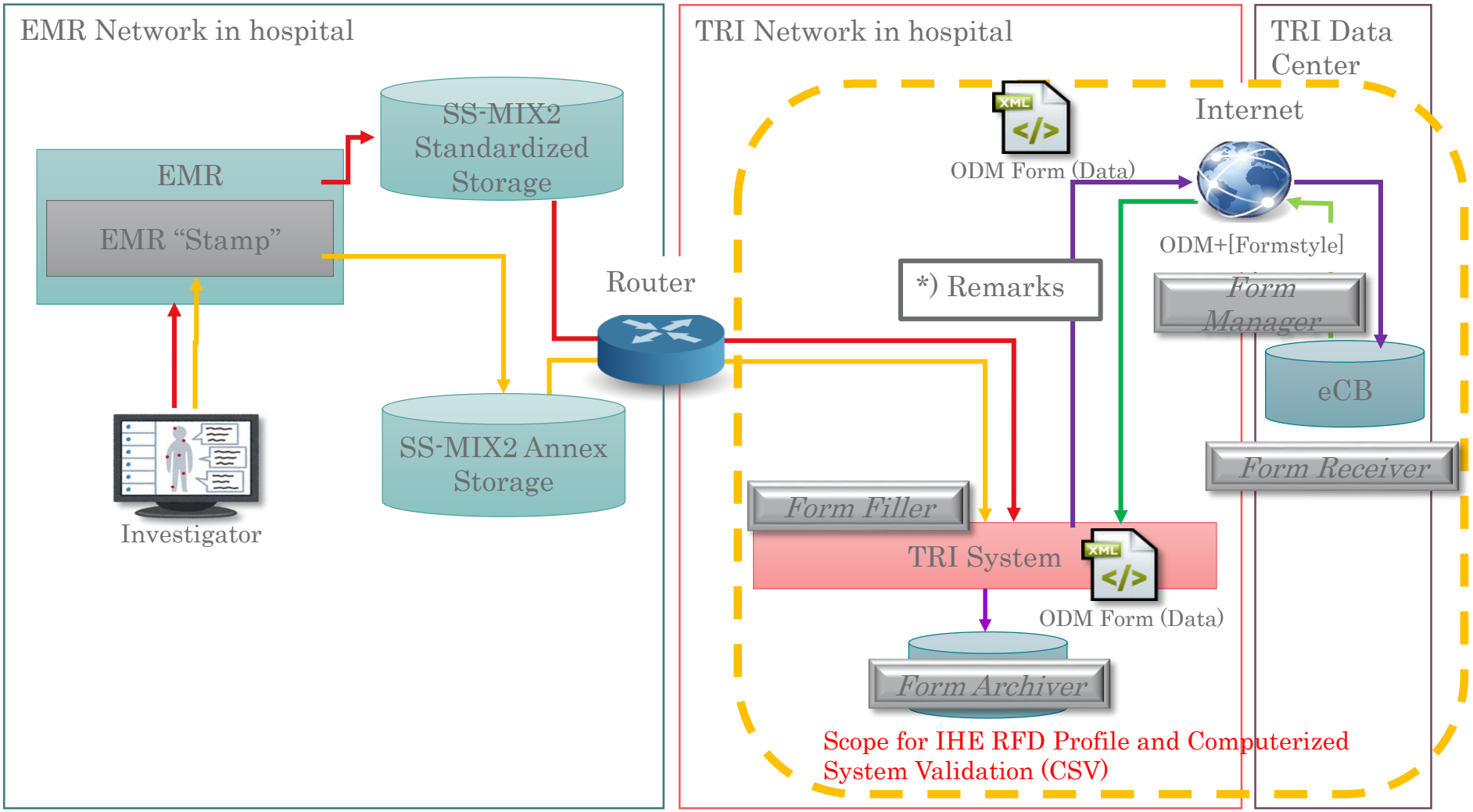


Diagram of the Total System



Real World Data (RWD) and Real World Evidence (RWE)

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- FDA uses RWD and RWE to monitor postmarket safety and adverse events and to make regulatory decisions.
- The health care community is using these data to support coverage decisions and to develop guidelines and decision support tools for use in clinical practice.
- Medical product developers are using RWD and RWE to support clinical trial designs (e.g., large simple trials, pragmatic clinical trials) and observational studies to generate innovative, new treatment approaches.

The 21st Century Cures Act, passed in 2016, places additional focus on the use of these types of data to support regulatory decision making, including approval of new indications for approved drugs. Congress defined RWE as data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials.

https://www.fda.gov/scienceresearch/specialtopics/realworldevidence/default.htm

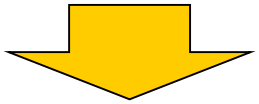
Minimize Efforts and Maximize Quality

- Eliminating the need to transcribe data
- Streamlining the clinical research process while reducing clinician burden by the system

Quality by Design of Clinical Studies

Quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, auditing or inspection. These activities are an important part of a quality assurance process but are not sufficient to ensure quality of a clinical study.

- 臨床試験における質は、適切なデザインとデザインに従った研究遂行に依存すべきであり、後から実施する文書チェック、モニタリング及び監査や査察に過度に依存するべきではない。これらの活動は臨床研究の質保証に重要であるが、臨床研究の質を確保するためには十分ではない。



モニタリングや監査にリソースが多く配分されている現状

Quality by Design of Clinical Studies

Good planning and implementation of a clinical study derive from attention to well-established principles of clinical research, which include the protection of the rights, safety and wellbeing of study subjects and scientific criteria, such as:

- the need for clear pre-defined study objectives that address the primary scientific question(s);
- selection of appropriate subjects that have the disease, condition, or molecular/genetic profile that is being studied;
- use of approaches to minimize bias, such as randomisation, blinding or masking, and/or control of confounding;
- endpoints that are well-defined and measurable, and methods of assessment of those endpoints that are accurate and able to be implemented with minimal reporting or measurement bias.

バイアスを最小化するアプローチは質を確保するために重要

ICH E8(R1)ガイドラインの特徴

- ✓ Quality by Design of Clinical Studies
- ✓ Critical to Quality Factors
- ✓ Feasibility

Critical to Quality Factors

Perfection in every aspect of an activity is rarely achievable or can only be achieved by use of resources that are out of proportion to the benefit obtained. The quality factors should be prioritized to identify those that are critical to the study, at the time of the study design, and study procedures should be proportionate to the risks inherent in the study and the importance of the information collected. The critical to quality factors should be clear and should not be cluttered with minor issues (e.g., due to extensive secondary objectives or processes/data collection not linked to the proper protection of the study subjects and/or primary study objectives).

- 研究の全ての事項に完全性を求めない
- 質を構成する要素の中から、その研究に欠かすことの出来ない要素を同定し、優先順位を付けること
- 研究のリスクや収集された情報の重要性に応じた資源配分
- 質に重要な要素は明確であるべきで、マイナーな事柄と混同すべきでない

ICH E8(R1)ガイドラインの特徴

- ✓ Quality by Design of Clinical Studies
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Feasibility

Consideration of critical to quality factors relating to study feasibility can inform study design and enhance quality implementation. Feasibility considerations include but are not limited to the availability of qualified investigators/site personnel with experience in conducting a clinical study; availability of equipment and facilities required to successfully conduct the clinical study; availability of the desired patient population; ability to enrol sufficient numbers of participants as determined by the study's power analysis; the ethical and regulatory considerations, which include informed consent, parental/caregiver consent and patient assent for paediatric studies; and regional standards of care.

- 経験を有し良質なInvestigatorの確保
- 試験を成功裡に実施しうる設備や施設
- 目標とする患者数の確保
- 統計学的評価に必要な被験者数の組み入れ能力
- 倫理および規制への考慮

Feasibility

An important aspect of study feasibility is understanding the view of potential study subjects about protocol elements that could impact their willingness to enrol or continue participation in the study (e.g., impact of study procedures, meaningfulness of the study objectives/outcomes). The retention of study subjects and the follow-up of subjects who have withdrawn from treatment are key critical to quality factors. It is important to not underestimate the value that appropriate and early consultation with patients will have on the feasibility of the study, adherence to the protocol, and, more essentially, relevance (or suitability) for patients of the drug approval based on the accumulated knowledge and experience from the clinical studies.

- 研究への参加あるいは継続の意志に影響を及ぼしうるプロトコールの要素について患者の見解を理解することは、研究の実施可能性を検討する上で重要

Patient Input into Study Design

ICH E8(R1)ガイドラインへの期待
アカデミアの立場から

- ✓ ICH E8(R1)ガイドラインの特徴
- ✓ アカデミアの医薬品開発とICH E8(R1)ガイドラインへの期待

米国の創薬の現状

1998-2007:
FDAで承認された
252新規医薬品

117　米国発

60%以上
アカデミア創薬

R. Kneller, Nature Reviews Drug Discovery 9, 867-882, 2010

新薬開発におけるパラダイムシフト

FIPC=Monopoly Model in 20th Century

Fully-integrated Pharmaceutical Company (FIPC)

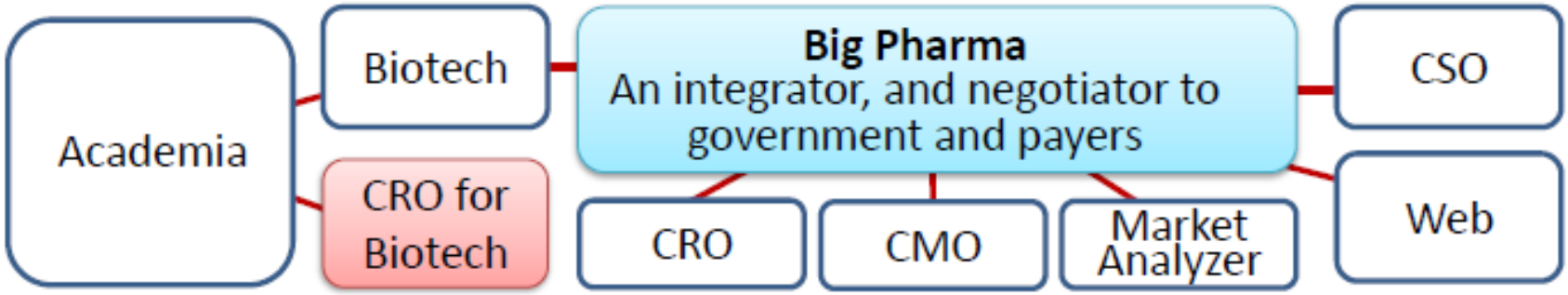
Research | Development | Manufacturing | Marketing | Sales

Biotech

CRO

Research, and Drug Research in particular, will, of course, continue. But in the twenty-first century it will no longer be a monopoly of a single industry, certainly not the monopoly of the classical pharmaceutical industry. Many partners will play a variety of roles in this new game: the biotechnology industry as the actual discoverer, the universities as important providers of ideas and preincubated projects, the classical pharmaceutical firms as developers, manufacturers, and distributors, and, increasingly, contract research organizations (CROs) as supporters of development. (In Quest of Tommorow's Medicines, Springer New York, 2000) Juergen Drews

Eco-system=Network Model in 21th Century Reality



【山梨大学/AMED PD　岩崎 甫 先生　発表スライド】

日米の創薬の比較

1998-2007:
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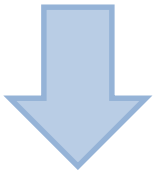
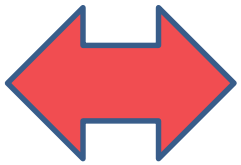


23　日本発

117　米国発

4品目 20%以下
アカデミア創薬



60%以上
アカデミア創薬

R. Kneller, Nature Reviews Drug Discovery 9, 867-882, 2010

日米の創薬の比較

アカデミア創薬の環境に工夫が必要
まだまだ成長する余地がある

23　日本発

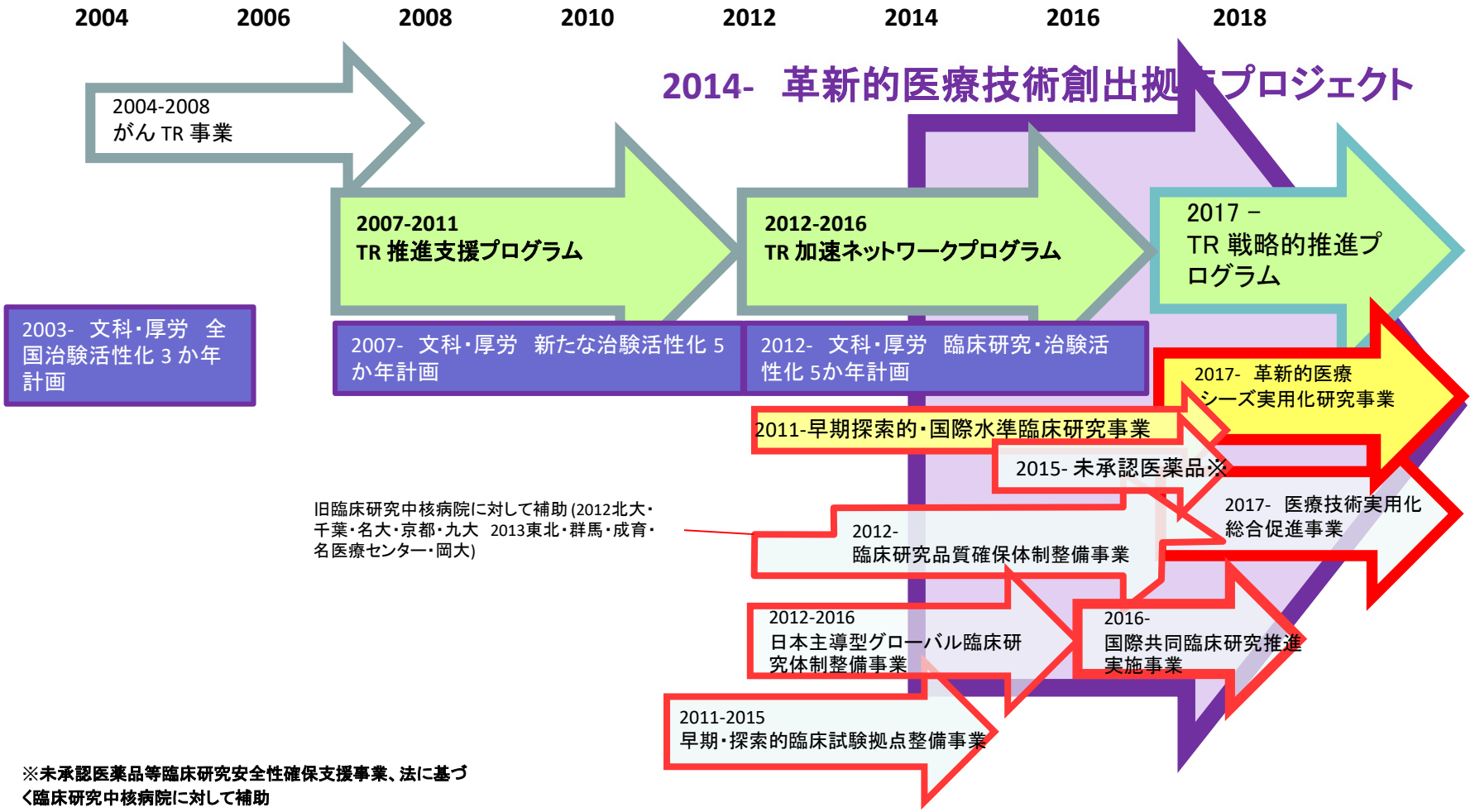
4品目 20%以下
アカデミア創薬

117　米国発

60%以上
アカデミア創薬

R. Kneller, Nature Reviews Drug Discovery 9, 867-882, 2010

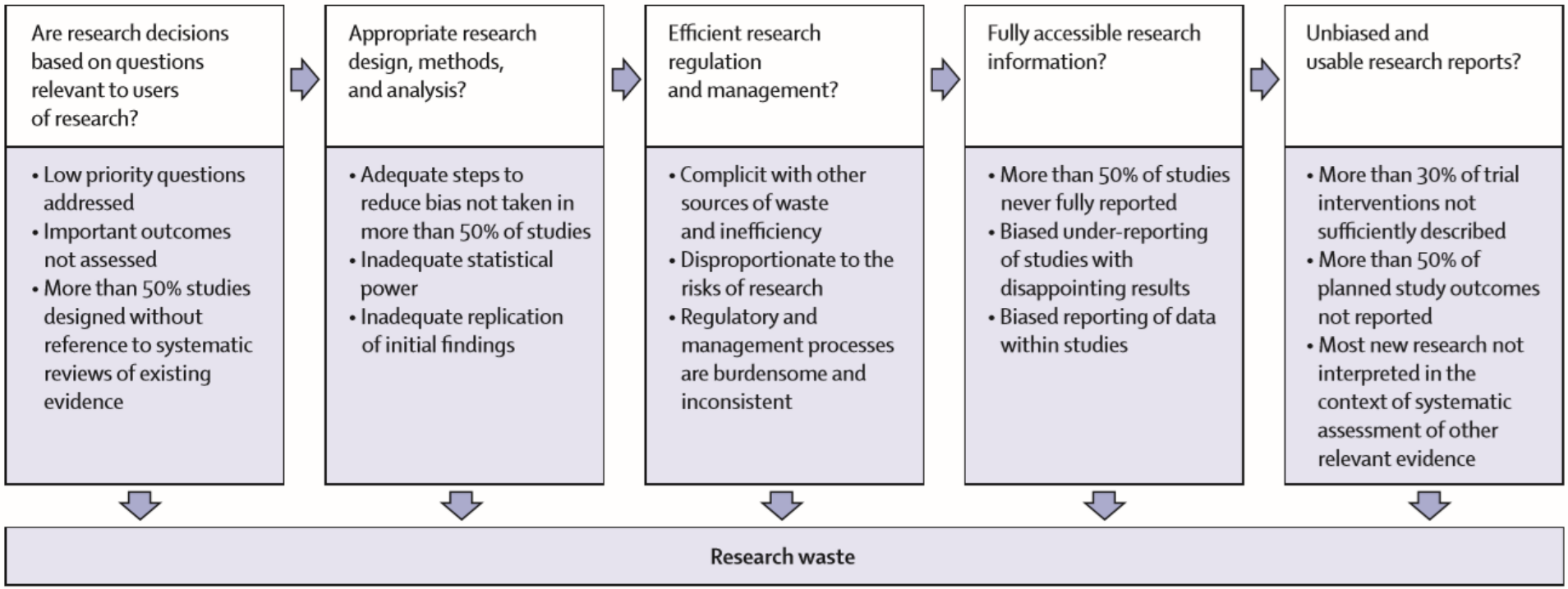
文部科学省・厚生労働省のこれまでの取組み



文部科学省提供資料

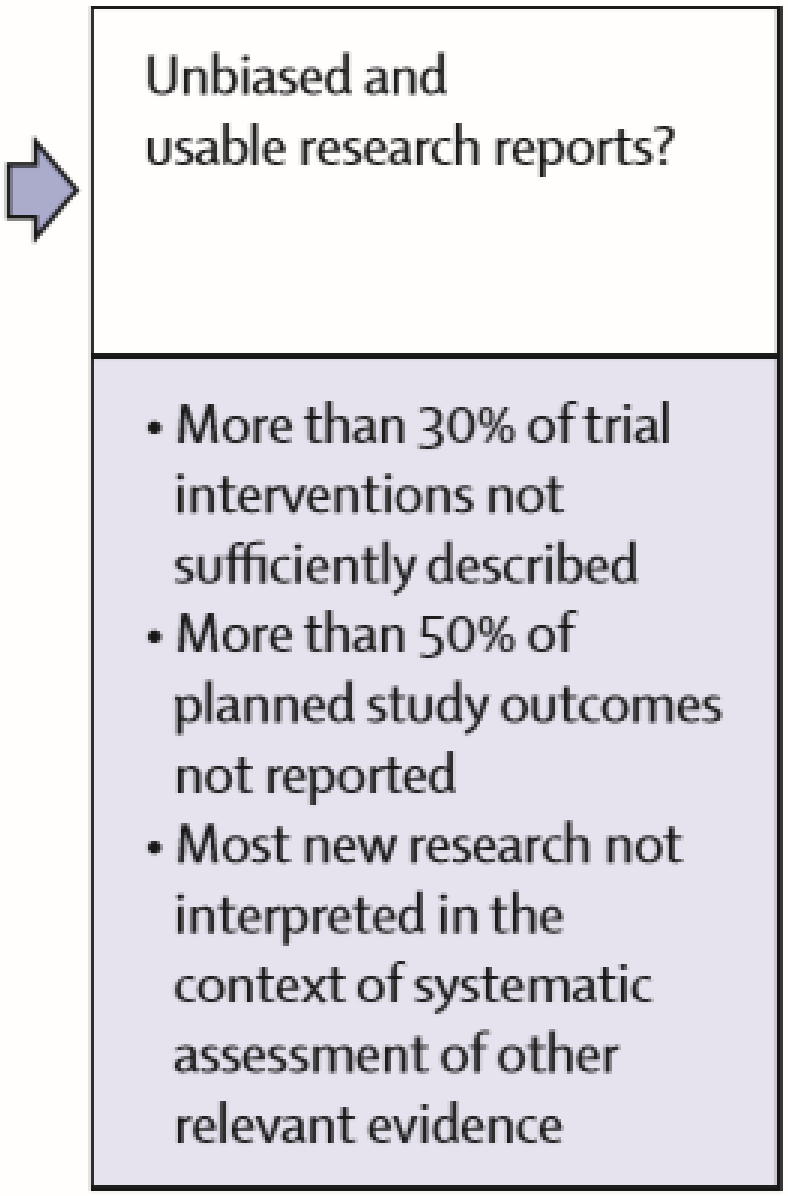
【山梨大学/AMED PD 岩崎 甫 先生 発表スライド】

Avoidable Waste or Inefficiency in Biomedical Research



Biomedical research: increasing value, reducing waste
www.thelancet.com Vol 383 January 11, 2014

Avoidable Waste or Inefficiency in Biomedical Research



Biomedical research: increasing value, reducing waste
www.thelancet.com Vol 383 January 11, 2014

ICH E8(R1)ガイドラインへの期待
アカデミアの立場から

◆不必要な臨床試験を排除し、意義のある臨床試験を実施

◆限られた人的・経済的資源の効率的活用

◆ICHは、被験者の権利、安全、福利を保護し、また、臨床試験データの信頼性を確保するしくみ

◆被験者が安心して臨床試験に参加できる環境整備につながる

臨床試験に関する日本の中の複数のRegulation

医薬品医療機器等法

臨床研究法
再生医療安全法
医学系研究倫理指針
遺伝子治療臨床研究指針

Biomedical Research: Increasing Value, Reducing Waste

Regulators of research are motivated to protect research participants, mindful of the atrocities of the past that associate biomedical researchers with war criminals (eg, in the Nuremberg trials). However, the result has been that regulatory burdens are often disproportionate to the plausible risks of the research, which jeopardizes the capacity and motivation of researchers to answer some important questions.

Across the product lifecycle, different types of studies will be conducted with different objectives and designs. Depending on the study objectives and the position of the study in the overall development plan, the data sources may vary. For purposes of this guideline, the development plan is considered to cover the entire product lifecycle and include non-clinical, clinical, and post-approval studies.

Different types of question require different types of evidence

Assessing the quality of research
BMJ 2004;328:39

臨床試験に関する国内の複数のRegulation

ICH E8(R1) ガイドライン

医薬品医療機器等法

臨床研究法
再生医療安全法
医学系研究倫理指針
遺伝子治療臨床研究指針

ICH E8(R1)ガイドラインへの期待

臨床試験の信頼性を高め
患者・社会が積極的に参加する環境へ