
# ICH M11 Guideline: A Breakthrough for Future Clinical Trials in the Data Society

データ社会での臨床試験に向けたブレークスルー

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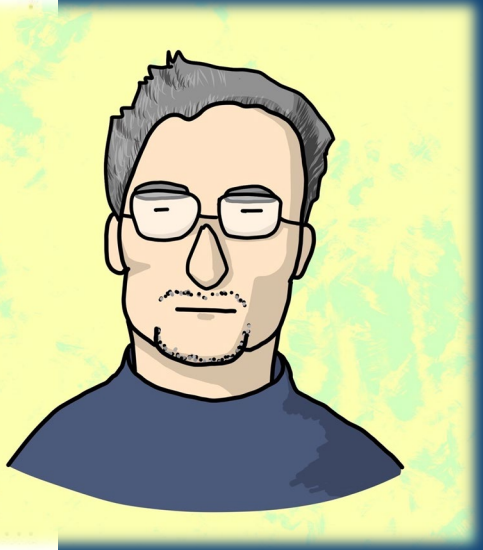
VP, Head of Global Data Design Office, Sumitomo Pharma, Co., Ltd.
Vice Chair, Data Science Expert Committee, Drug Evaluation Committee, JPMA

# Meet the Speaker



## Satoru Tsuchiya 土屋悟

**Title: ICH M11 Guideline: Expectations for Clinical Trials in the Data Society**

**Organization: Sumitomo Pharma, Co., Ltd.**

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Currently working as the Head of Data & Analytics function

Over 25 years of experience at Sumitomo Pharma, primarily as a biostatistician for clinical development

Professional community:

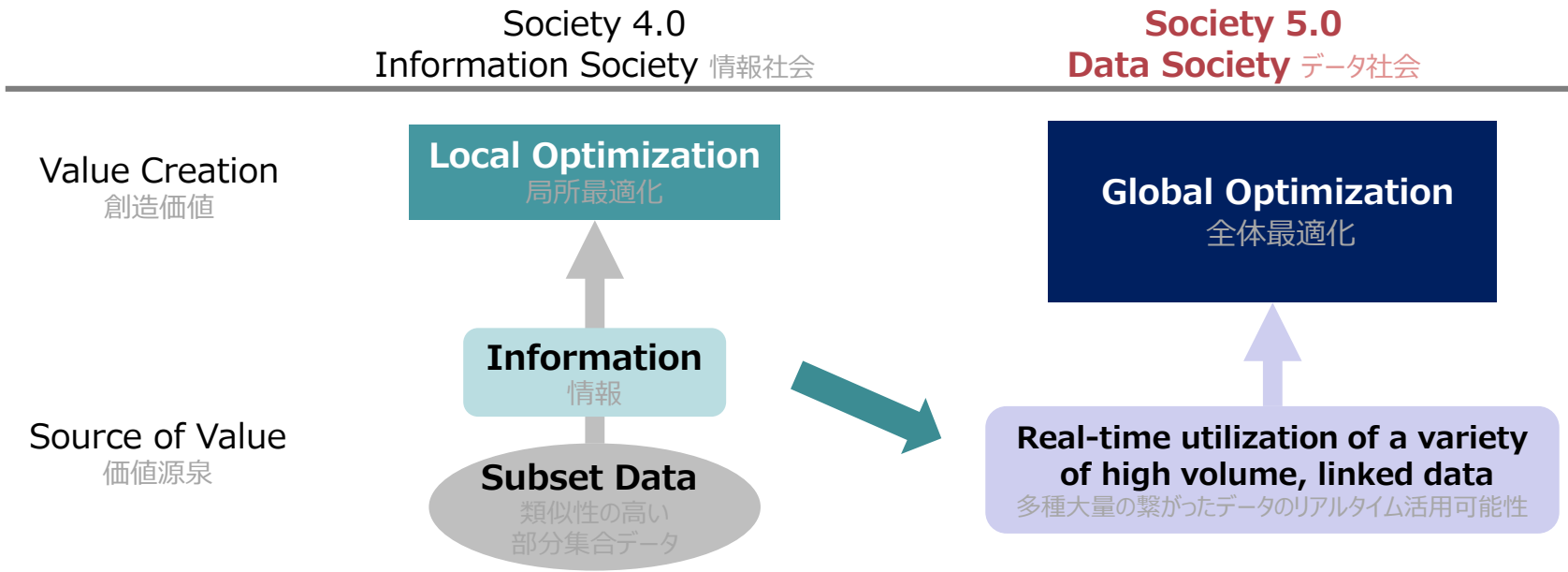
- ✓ Vice-chair of Data Science Expert committee of Drug Evaluation Committee, JPMA. (2016 -)
- ✓ Member of the Japan CDISC Coordinating Committee (J3C) (2014 - 2019)
- ✓ Topic Leader from JPMA of ICH-E9R1 EWG (2014 - 2022), ICH-M11 EWG (2021 -)
- ✓ Member of the Biometric Society of Japan

# Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of CDISC or the organizations to which the author belongs.*

- *The author has no real or apparent conflicts of interest to report.*

# Aiming to solve increasingly complex social issues
## 複雑化する社会課題の解決を目指す




NEC会長 遠藤信博氏　一部改変　https://xtech.nikkei.com/atcl/nxt/special/18/00001/111200039/?P=2

# JPMA DS expert committee's Themes of Activity

JPMA DS部会の活動テーマ

**1** **Creating an infrastructure that enables the use of a wide variety of data**

多種多様なデータの活用を可能にする基盤づくり

**2** **Business transformation through end-to-end data utilization**

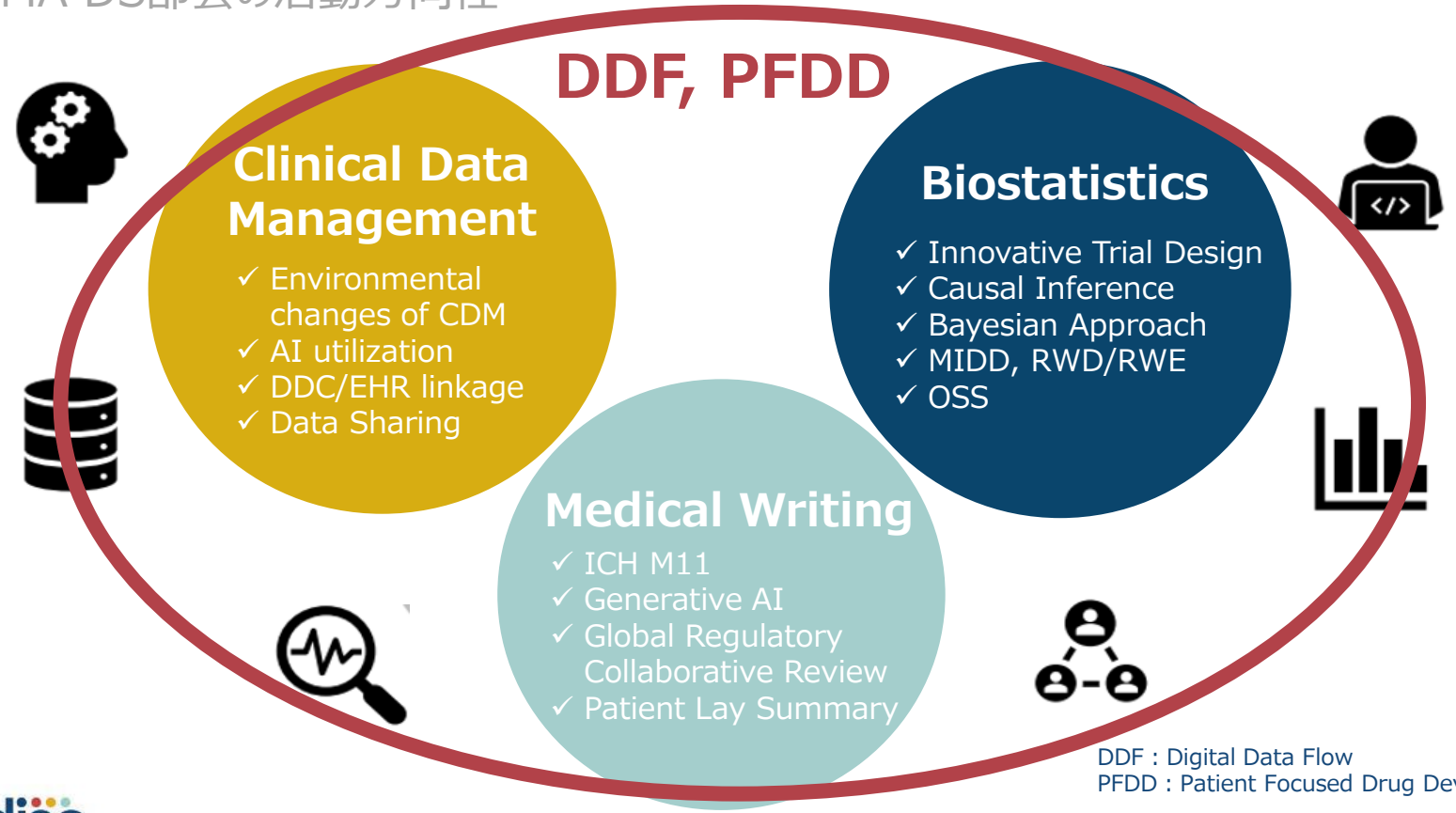
End-to-endのデータ活用による業務変革

**3** **Evidence generation throughout the drug lifecycle**

医薬品ライフサイクルを通したエビデンス構築

# New Direction of JPMA DS expert committee

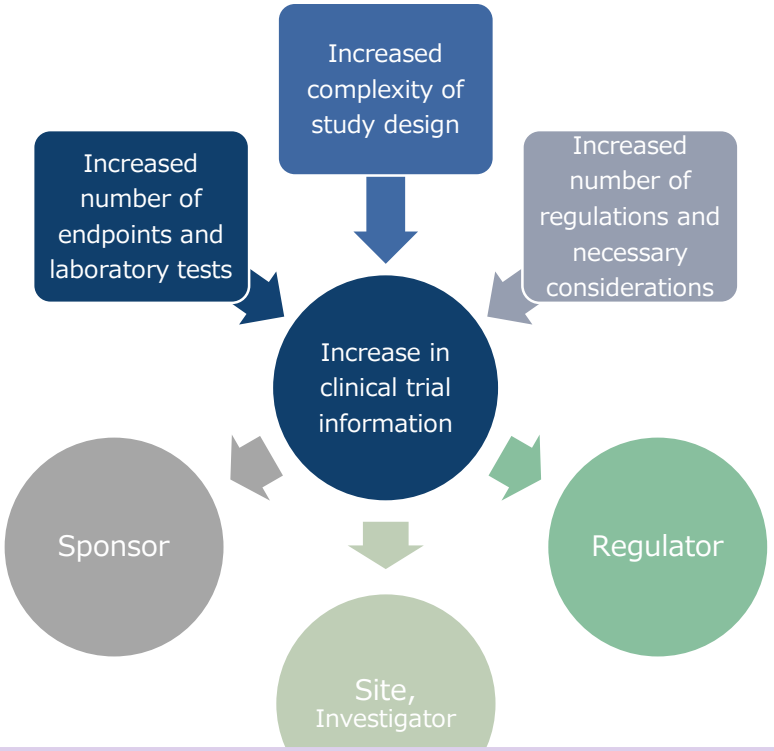
JPMA DS部会の活動方向性




DDF : Digital Data Flow
PFDD : Patient Focused Drug Development

# Increased clinical trial information and barriers to digital technology activities

臨床試験情報の増加とデジタル技術の活動の障壁




**Increased resources/costs**

臨床試験や医薬品開発にかかるリソースの増大

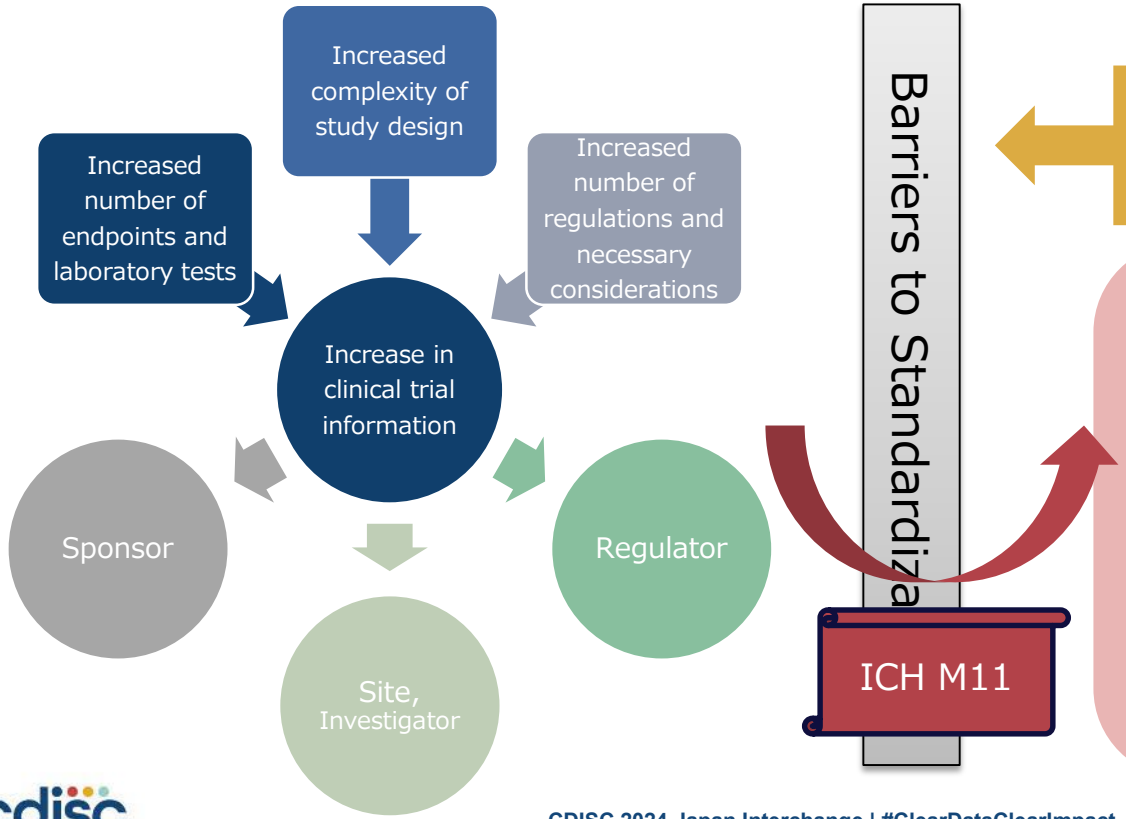
Barriers to Standardization

IT vendor

Support through continuously innovating digital technology

# Increased clinical trial information and barriers to digital technology activities

臨床試験情報の増加とデジタル技術の活動の障壁




Barriers to Standardiza

ICH M11

IT vendor

Support through continuously innovating digital technology

**M11 only covers protocol, but this is an great opportunity to promote standardization, accelerate the use of digital technology, and contribute to the clinical trial ecosystem**

M11はプロトコルのみを対象とするが、これを契機に標準化を進め、デジタル技術の活用を促進し、治験エコシステムに貢献できる

# Agenda

1. ICH M11: Current state and work plan
   現状と今後の予定
2. Expectations for ICH M11 implementation
   M11実装へ向けた期待
3. Agile Mindset for Digital Transformation
   DXのためのアジャイルマインド

# 1. ICH M11: Current state and work plan

現状と今後の予定

# ICH M11: Three deliverables…

## 1. Guideline is a high-level document that: ガイドライン本文

- Provides the background on why a harmonized clinical protocol template is needed, and
- Describes how the template and technical specification were developed.

## 2. Template テンプレート

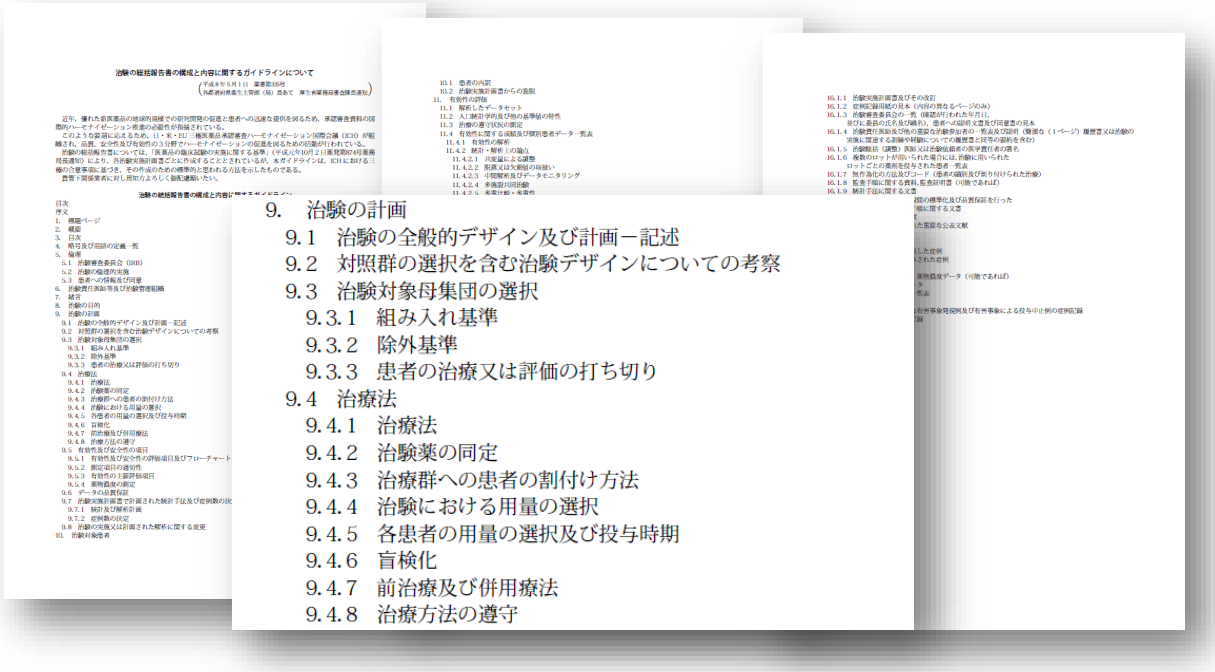
- Includes identification of headers, common text, instructions, data fields and terminologies.

## 3. Technical Specification 技術仕様

- Serves as a technical representation of the ICH M11 protocol template.
- Aligns with the latest version of the ICH M11 guideline and template standard to enable electronic exchange of the clinical protocol information.

# Example of structured document: CSR

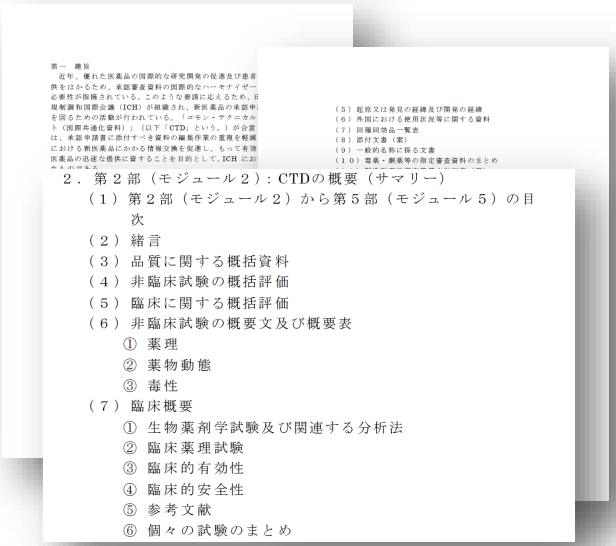
## **ICH E3:** Structure and Content of Clinical Study Reports



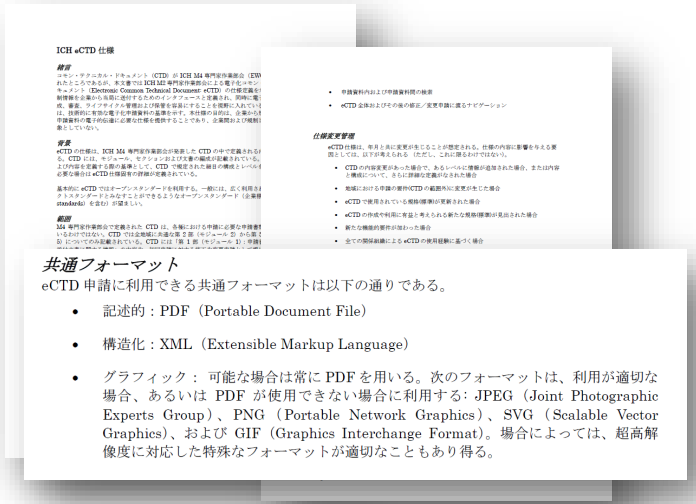
# Example of structured and electronic document: CTD/eCTD

**ICH M4:** Organisation of the Common Technical Document for the registration of pharmaceuticals for human use

**ICH M8:** electronic Common Technical Document (eCTD)



２．第２部（モジュール２）：CTDの概要（サマリー）
（１）第２部（モジュール２）から第５部（モジュール５）の目次
（２）緒言
（３）品質に関する概括資料
（４）非臨床試験の概括評価
（５）臨床に関する概括評価
（６）非臨床試験の概要文及び概要表
① 薬理
② 薬物動態
③ 毒性
（７）臨床概要
① 生物薬剤学試験及び関連する分析法
② 臨床薬理試験
③ 臨床的有効性
④ 臨床的安全性
⑤ 参考文献
⑥ 個々の試験のまとめ



ICH eCTD 仕様

*共通フォーマット*

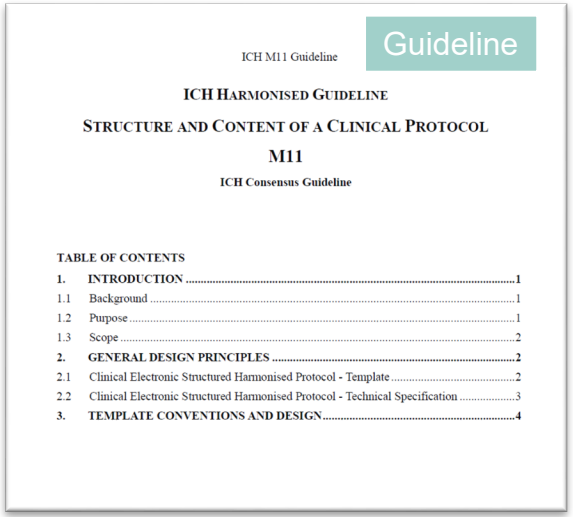
eCTD 申請に利用できる共通フォーマットは以下の通りである。

- 記述的：PDF（Portable Document File）
- 構造化：XML（Extensible Markup Language）
- グラフィック： 可能な場合は常に PDF を用いる。次のフォーマットは、利用が適切な場合、あるいは PDF が使用できない場合に利用する: JPEG（Joint Photographic Experts Group）、PNG（Portable Network Graphics）、SVG（Scalable Vector Graphics）、および GIF（Graphics Interchange Format）。場合によっては、超高解像度に対応した特殊なフォーマットが適切なこともあり得る。

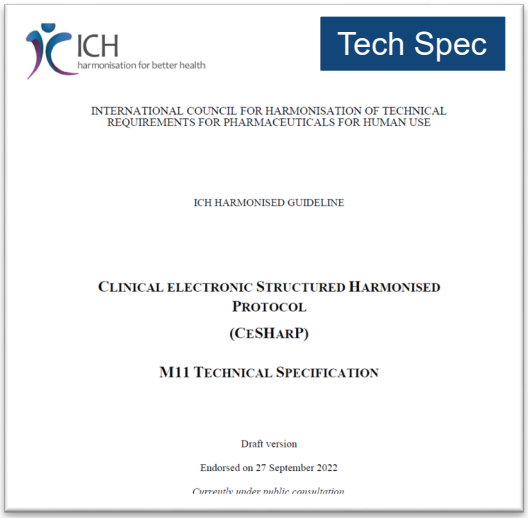
# Clinical Trial Protocol

## ICH M11 aims to make clinical trial protocol both structured and electronic in a single guideline

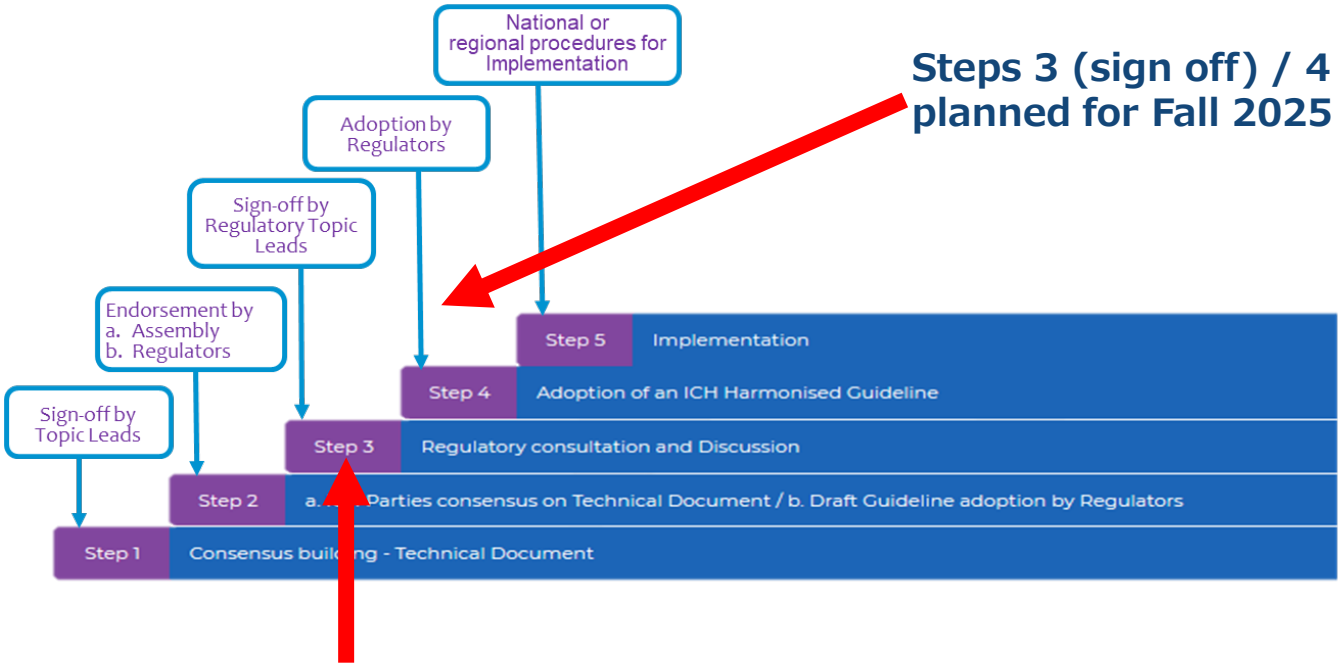
ICH-M11は、単一のトピックで、治験実施計画書について構造化及び電子化の両方を目指す







# ICH step process



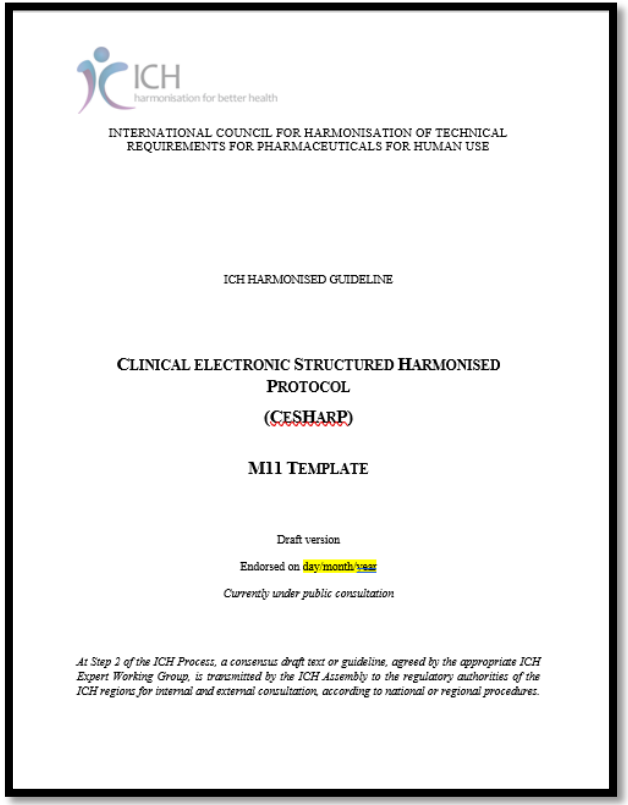

**Steps 3 (sign off) / 4 are planned for Fall 2025**

**M11 is at Step 3 - Adjudication of Public Comments and Re-write of Guideline, Template and Technical Specification**

# ICH M11 Terminology

- **M11 / M2 collaborating with CDISC to create draft semantics for the *Protocol Template / Tech Specification***
  - ✓ Data Elements
  - ✓ Valid Value Sets / Terms

- **Regulatory public consultation of *Tech Specification* will be conducted in early 2025.**



ICH
harmonisation for better health

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

ICH HARMONISED GUIDELINE

CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

(CESHARP)

M11 TEMPLATE

Draft version

Endorsed on day/month/year

*Currently under public consultation*

*At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.*

# 2. Expectations for ICH M11 implementation

M11実装へ向けた期待

# Value of ICH M11
M11の価値

## ICH Protocol Template

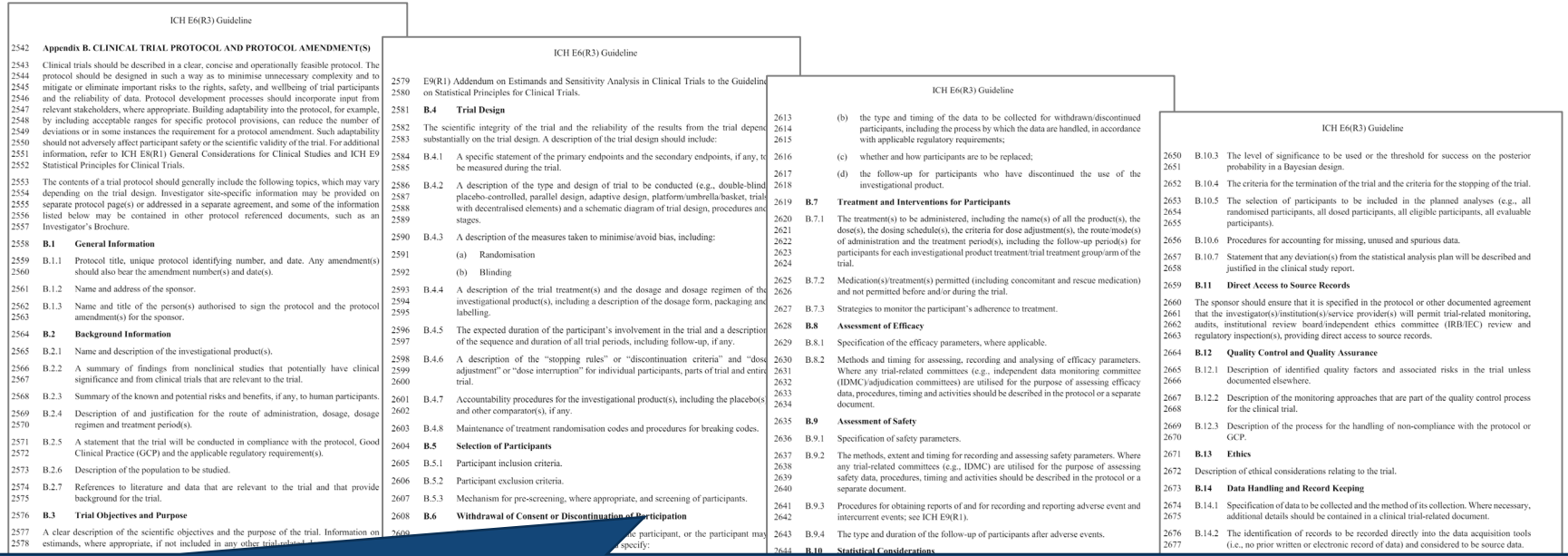
- **Predictable**
  - ✓ Structure
  - ✓ Content
  - ✓ Level of detail
  - ✓ Presentation (of some content)
- **Provides flexibility where needed**
- **Common instructions**
- **Consistent with all other relevant ICH Guidelines**
- **Acceptable in all ICH countries**

## Electronic, structured; Digital protocol

- **Foundational step toward a "digitized protocol"**
- Granular content can be exchanged, extracted, translated, reassembled, or processed as individual pieces or as a whole set
- Additional standards can be developed in the future by ICH or other SDOs to govern contents within the protocol
- Creates foundational requirements to enable informatics and software development

# ICH E6 (R3) step2 (2023)

## Appendix B. Clinical Trial Protocol and Protocol Amendment



ICH E6(R3) Guideline

**Appendix B. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)**

Clinical trials should be described in a clear, concise and operationally feasible protocol. The protocol should be designed in such a way as to minimise unnecessary complexity and to mitigate or eliminate important risks to the rights, safety, and wellbeing of trial participants and the reliability of data. Protocol development processes should incorporate input from relevant stakeholders, where appropriate. Building adaptability into the protocol, for example, by including acceptable ranges for specific protocol provisions, can reduce the number of deviations or in some instances the requirement for a protocol amendment. Such adaptability should not adversely affect participant safety or the scientific validity of the trial. For additional information, refer to ICH E8(R1) General Considerations for Clinical Studies and ICH E9 Statistical Principles for Clinical Trials.

The contents of a trial protocol should generally include the following topics, which may vary depending on the trial design. Investigator site-specific information may be provided on separate protocol page(s) or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

**B.1 General Information**

B.1.1 Protocol title, unique protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

B.1.2 Name and address of the sponsor.

B.1.3 Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the sponsor.

**B.2 Background Information**

B.2.1 Name and description of the investigational product(s).

B.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

B.2.3 Summary of the known and potential risks and benefits, if any, to human participants.

B.2.4 Description of and justification for the route of administration, dosage, dosage regimen and treatment period(s).

B.2.5 A statement that the trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

B.2.6 Description of the population to be studied.

B.2.7 References to literature and data that are relevant to the trial and that provide background for the trial.

**B.3 Trial Objectives and Purpose**

A clear description of the scientific objectives and the purpose of the trial. Information on estimands, where appropriate, if not included in any other trial-related

ICH E6(R3) Guideline

E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials.

**B.4 Trial Design**

The scientific integrity of the trial and the reliability of the results from the trial depend substantially on the trial design. A description of the trial design should include:

B.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

B.4.2 A description of the type and design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design, adaptive design, platform/umbrella/basket, trials with decentralised elements) and a schematic diagram of trial design, procedures and stages.

B.4.3 A description of the measures taken to minimise/avoid bias, including:

(a) Randomisation

(b) Blinding

B.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s), including a description of the dosage form, packaging and labelling.

B.4.5 The expected duration of the participant's involvement in the trial and a description of the sequence and duration of all trial periods, including follow-up, if any.

B.4.6 A description of the "stopping rules" or "discontinuation criteria" and "dose adjustment" or "dose interruption" for individual participants, parts of trial and entire trial.

B.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and other comparator(s), if any.

B.4.8 Maintenance of treatment randomisation codes and procedures for breaking codes.

**B.5 Selection of Participants**

B.5.1 Participant inclusion criteria.

B.5.2 Participant exclusion criteria.

B.5.3 Mechanism for pre-screening, where appropriate, and screening of participants.

**B.6 Withdrawal of Consent or Discontinuation of Participation**

participant, or the participant may specify:

ICH E6(R3) Guideline

(b) the type and timing of the data to be collected for withdrawn/discontinued participants, including the process by which the data are handled, in accordance with applicable regulatory requirements;

(c) whether and how participants are to be replaced;

(d) the follow-up for participants who have discontinued the use of the investigational product.

**B.7 Treatment and Interventions for Participants**

B.7.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the criteria for dose adjustment(s), the route/mode(s) of administration and the treatment period(s), including the follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial.

B.7.2 Medication(s)/treatment(s) permitted (including concomitant and rescue medication) and not permitted before and/or during the trial.

B.7.3 Strategies to monitor the participant's adherence to treatment.

**B.8 Assessment of Efficacy**

B.8.1 Specification of the efficacy parameters, where applicable.

B.8.2 Methods and timing for assessing, recording and analysing of efficacy parameters. Where any trial-related committees (e.g., independent data monitoring committee (IDMC)/adjudication committees) are utilised for the purpose of assessing efficacy data, procedures, timing and activities should be described in the protocol or a separate document.

**B.9 Assessment of Safety**

B.9.1 Specification of safety parameters.

B.9.2 The methods, extent and timing for recording and assessing safety parameters. Where any trial-related committees (e.g., IDMC) are utilised for the purpose of assessing safety data, procedures, timing and activities should be described in the protocol or a separate document.

B.9.3 Procedures for obtaining reports of and for recording and reporting adverse event and intercurrent events; see ICH E9(R1).

B.9.4 The type and duration of the follow-up of participants after adverse events.

**B.10 Statistical Considerations**

ICH E6(R3) Guideline

B.10.3 The level of significance to be used or the threshold for success on the posterior probability in a Bayesian design.

B.10.4 The criteria for the termination of the trial and the criteria for the stopping of the trial.

B.10.5 The selection of participants to be included in the planned analyses (e.g., all randomised participants, all dosed participants, all eligible participants, all evaluable participants).

B.10.6 Procedures for accounting for missing, unused and spurious data.

B.10.7 Statement that any deviation(s) from the statistical analysis plan will be described and justified in the clinical study report.

**B.11 Direct Access to Source Records**

The sponsor should ensure that it is specified in the protocol or other documented agreement that the investigator(s)/institution(s)/service provider(s) will permit trial-related monitoring, audits, institutional review board/independent ethics committee (IRB/IEC) review and regulatory inspection(s), providing direct access to source records.

**B.12 Quality Control and Quality Assurance**

B.12.1 Description of identified quality factors and associated risks in the trial unless documented elsewhere.

B.12.2 Description of the monitoring approaches that are part of the quality control process for the clinical trial.

B.12.3 Description of the process for the handling of non-compliance with the protocol or GCP.

**B.13 Ethics**

Description of ethical considerations relating to the trial.

**B.14 Data Handling and Record Keeping**

B.14.1 Specification of data to be collected and the method of its collection. Where necessary, additional details should be contained in a clinical trial-related document.

B.14.2 The identification of records to be recorded directly into the data acquisition tools (i.e., no prior written or electronic record of data) and considered to be source data.

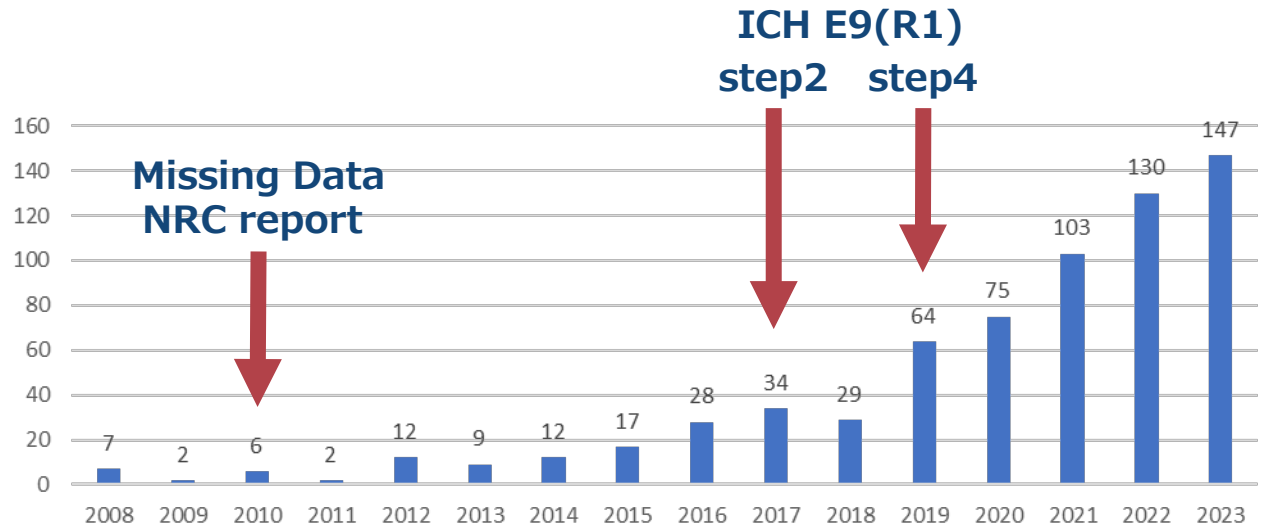
✓ **E6 (R3) specifies what to include in the protocol, including estimands.**

Estimand含め、E6 (R3)では、プロトコルに含める内容を規定

# Estimand

✓**A precise description of the treatment effect reflecting the clinical question posed by the trial**

試験の目的によって提起される臨床的疑問を反映する治療効果の詳細な説明




**Number of articles: PubMed: search =“estimand”**

# Estimand in published protocols of RCTs: Urgent improvement needed (Kahan 2021)

**This article reviewed the 50 most recently published protocols in *Trials* and *BMJ Open* on the date of our search (October 20, 2020)**, in order to evaluate the description of estimands in trial protocols nearly 1 year after the final version and 3 years after the draft version of the ICH E9(R1) Addendum was published. We chose *Trials* and *BMJ Open* as they publish the majority of RCT protocols.

2020年10月に、TrialとBMJ Openで公開された直近50試験のプロトコルをレビュー

**Description of Overall Estimand from 50 published protocols in 2020**

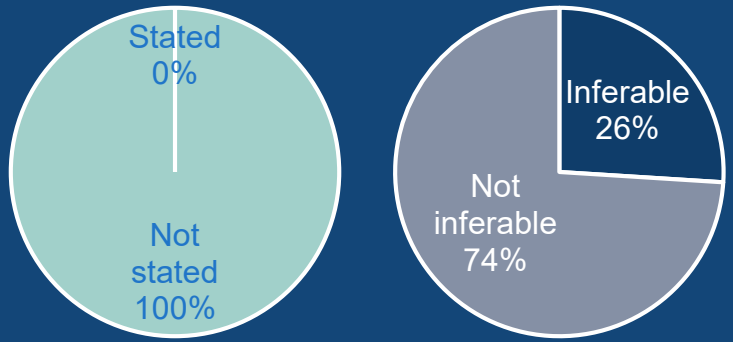



**Table 3** Description of the primary estimand

| Question | Trials ($n$ = 50)—no. (%) |
|---|---|
| Used term "estimand" | 0 (0%) |
| Cited ICH E9(R1) Addendum | 0 (0%) |
| **Estimand attributes** | |
| Population | |
| Stated | 0 (0%) |
| Inferable | 32 (64%) |
| Not inferable | 18 (36%) |
| Treatment condition(s) | |
| Stated | 0 (0%) |
| Inferable | 40 (80%) |
| Not inferable | 10 (20%) |
| Outcome | |
| Stated | 50 (100%) |
| Inferable | 0 (0%) |
| Not inferable | 0 (0%) |
| Population-level summary measure | |
| Stated | 0 (0%) |
| Inferable | 33 (66%) |
| Not inferable | 17 (34%) |
| Handling of intercurrent event(s) | |
| Stated | 0 (0%) |
| Inferable | 20 (40%) |
| Not inferable | 30 (60%) |
| **Overall estimand** | |
| Stated | 0 (0%) |
| Inferable | 13 (26%) |
| Not inferable | 37 (74%) |
| **Number of attributes not inferable** | |
| 0 | 13 (26%) |
| 1 | 14 (28%) |
| 2 | 9 (18%) |
| 3 | 13 (26%) |
| 4 | 1 (2%) |
| 5 | 0 (0%) |



https://link.springer.com/article/10.1186/s13063-021-05644-4

# Current developments of the estimand concept (Fierenz 2024)

| authors | year | title | content |
|---|---|---|---|
| | | | |
| | | **Strategies for handling intercurrent events** | |
| Darken et al. | 2020 | The attributable estimand: A new approach to account for intercurrent events | Attributable Estimand: chose the strategy based on the relation of the ICE to the outcome |
| Michiels et al. | 2021 | A novel estimand to adjust for rescue treatment in randomized clinical trials | Balanced strategy for ICE; ICE occurrence independent of treatment arm |
| Qu, Lipkovich | 2021 | Implementation of ICH E9 (R1): A Few Points Learned During the COVID-19 Pandemic | Analyses of the different strategies, and considerations on two ICEs at the same time |
| | | | |
| | | **Methods for different strategies** | |
| Ratitch et al. | 2018 | Points to consider for analyzing efficacy outcomes in long-term extension clinical trials | |
| Wang et al. | 2018 | An evaluation of the trimmed mean approach in clinical trials with dropout | |
| Keene | 2019 | Strategies for composite estimands in confirmatory clinical trials: Examples from trials in nasal polyps and steroid reduction | |
| Magnusson et al. | 2019 | Bayesian inference for a principal stratum estimand to assess the treatment effect in a subgroup characterized by postrandomization event occurr | |
| Roger et al. | 2019 | Treatment policy estimands for recurrent event data using data collected after cessation of randomised treatment | |
| Wie et al. | 2021 | Properties of Two While-Alive Estimands for Recurrent Events and Their Potential Estimators | |
| Lipkovich et al. | 2022 | Using principal stratification in analysis of clinical trials | |
| Mao | 2022 | Nonparametric inference of general while-alive estimands for recurrent events | |
| Han, Zhou | 2023 | Defining estimands in clinical trials: A unified procedure | |
| Wang et al. (b) | 2023 | Statistical methods for handling missing data to align with treatment policy strategy | |
| | | | |
| | | **Application of estimands in different trial designs** | |
| Okwuokwnye, Peace | 2019 | Adaptive Design and the Estimand Framework | |
| Rufibach | 2019 | Treatment effect quantification for time-to-event endpoints–Estimands, analysis strategies, and beyond | |
| Kilpatrick et al. | 2020 | Estimands and inference in cluster-randomized vaccine trials | |
| Ring et al. | 2020 | The potential of the estimands framework for clinical pharmacology trials: Some discussion points | |
| Collignon et al. | 2022 | Estimands and Complex Innovative Designs | |
| Kahan et al. | 2022 | Estimands for factorial trials | |
| Li et al. | 2022 | Estimands in observational studies: Some considerations beyond ICH E9 (R1) | |
| Fu et al. | 2023 | Application of estimand framework in ICH E9 (R1) to vaccine trials | |
| Kahan et al. | 2023 | Estimands in cluster-randomized trials: choosing analyses that answer the right question | |
| Ren et al. | 2023 | Estimand in benefit-risk assessment | |
| Wang et al. (a) | 2023 | Application of estimand framework in ICH E9 (R1) to safety evaluation | |
| | | | |
| | | **Further estimand related topics** | |
| Fang et al. | 2021 | Sample Size Calculation When Planning Clinical Trials with Intercurrent Events | |
| Kahan et al. | 2021 | Estimands in published protocols of randomised trials: urgent improvement needed | |
| Cro et al. | 2022 | Evaluating how clear the questions being investigated in randomised trials are: systematic review of estimands | |
| Kang et al. | 2022 | Incorporating estimands into clinical trial statistical analysis plans | |
| Lynggaard et al. | 2022 | Principles and recommendations for incorporating estimands into clinical study protocol templates | |

**Table S1** Overview of the literature research

- ✓ **Different modified strategies for intercurrent events are presented, as well as examples of methods to implement the estimand in clinical studies.**
  中間事象に対する異なる戦略や、estimandを実装するための方法の例示が報告されている
- ✓ **The article reflects that the estimand is an ongoing research field with further exploration.**
  Estimandは、現在進行中の研究分野であり、さらなる検討が必要

# Impact on Quality

- **57% of Phase II – III protocols[1] are amended at least once**
  - Substantial global protocol amendments
  - 57% of protocols had at least one substantial amendment
  - 45% of these amendments were deemed “avoidable”
- **In U.S., cost to implement a substantial amendment was $141,000 for Phase II protocol and $535,000 for a Phase III protocol**
- Protocol amendment review is a tedious manual process during clinical trial application review (IND/CTA) or at the time of NDA/MAA: Efficiency gain here would be helpful

[1] The Impact of Protocol Amendments on Clinical Trial Performance and Cost
Kenneth A. Getz, et al, https://doi.org/10.1177/2168479016632271

# Expectations for ICH M11 implementation
M11実装への期待

## ICH Protocol Template

- Predictable
  - ✓ Structure
  - ✓ Content
  - ✓ Level of detail
  - ✓ Presentation (of some content)
- Provides flexibility where needed
- Common instructions
- Consistent with all other relevant ICH Guidelines
- Acceptable in all ICH countries

## Electronic, structured; Digital protocol

- **Foundational step toward a "digitized protocol"**
- Granular content can be exchanged, extracted, translated, reassembled, or processed as individual pieces or as a whole set
- Additional standards can be developed in the future by ICH or other SDOs to govern contents within the protocol
- Creates foundational requirements to enable informatics and software development

# Why Global Data Standard? (Komiyama 2020)

世界標準のデータ標準の意義

RSMP vol.10 no.3, 169–174, Sep 2020

特集（臨床試験の電子データ標準化と活用）

**製薬企業における臨床試験データの CDISC 標準化**

**Standardization of Clinical Trial Data in Japanese Pharmaceutical Companies**

小宮山　靖[1,4,*]，淡路　直人[1,5]，土屋　悟[1,6]，
橋尾　美穂[1,7]，鈴木　正人[2,8]，月田あづさ[3,9]

Osamu KOMIYAMA, Naoto AWAJI, Satoru TSUCHIYA,
Miho HASHIO, Masato SUZUKI and Azusa TSUKIDA

**Abstract**

Regulatory authorities in Japan and US, i. e., PMDA and FDA, have mandated the submission of electronic data according to CDISC standards at the time of new drug application. That has had a major impact on the Japanese pharmaceutical industry. The world-wide data standards for clinical trial data, i. e., CDISC, should bring significant benefits for us, i. e., 1) reusability, 2) interoperability, and 3) an ability to integrate data from different sources and obtain a knowledge beyond a single clinical trial. However, the industry has not fully reaped such benefits. This is mainly because currently we are spending a lot of resources on converting data from completed clinical trials, which did not comply with CDISC standards, into CDISC-compliant data. We should move away from the data conversion just before the new drug application and hasten the end-to-end implementation of the CDISC standard. What we, the pharmaceutical companies, expect from PMDA is that PMDA will conduct many regulatory science studies, which is possible only with accumulated data, and that PMDA will continue to provide feedback to companies and researchers who are developing drugs, and that PMDA will continue to disseminate useful information to the world.

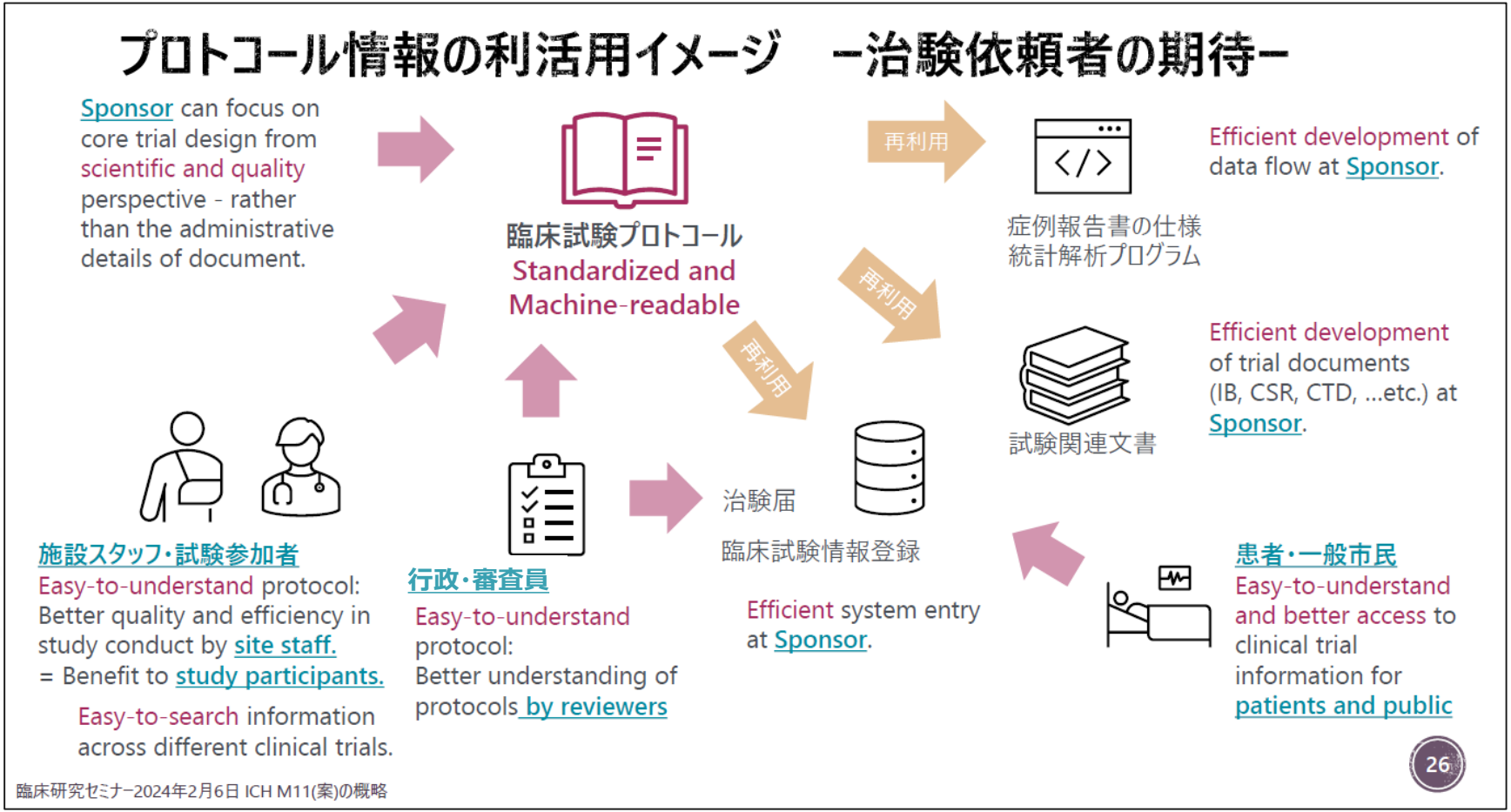
https://www.jstage.jst.go.jp/article/rsmp/10/3/10_169/_article/-char/ja/

1. **Reusability** 再利用を可能にする力
2. **Interoperability** 相互利用を可能にする力
3. **Ability to integrate and utilize data from different studies**
   異なる試験のデータを併合し活用していく力

# Sponsor perspective: Use case of using Protocol Information (Ito 2024)

治験依頼者によるプロトコル情報の活用イメージ

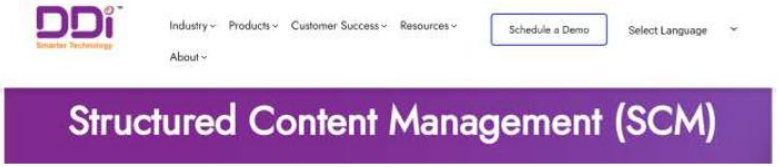
MSD株式会社　伊藤友香



# Structured Content Management/Authoring (SCM/A)

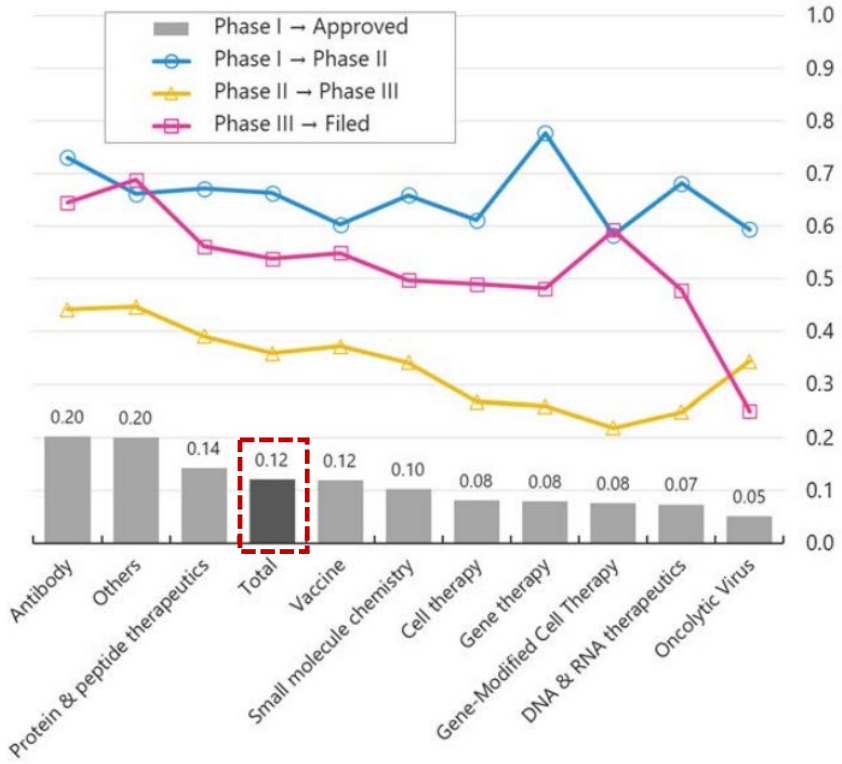




# Probability of Success: by Modality
## (Office of Pharmaceutical Industry Research, JPMA 2024)

図 1-26　モダリティ別の成功確率




**Target trials**
P1: Initiate after 2010
P2: Initiate after 2005
P3: Initiate after 2000
File: Submit after 2000

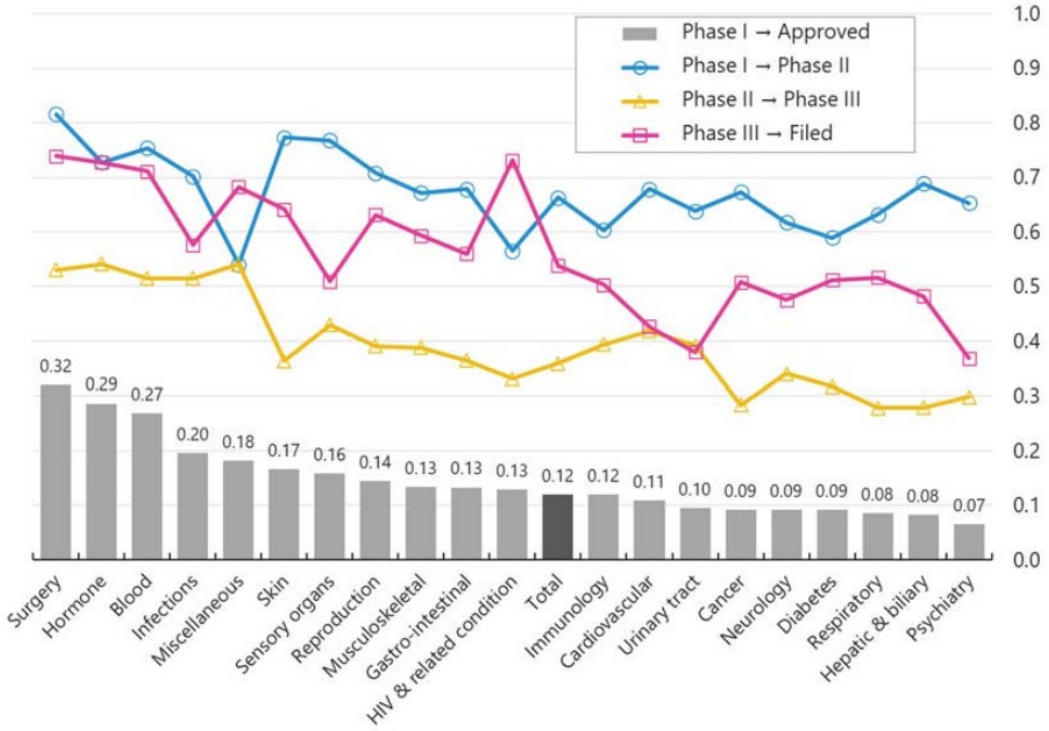
https://www.jpma.or.jp/opir/research/rs_082/article_082.html

**Overall: 12%**
**From P1 to Approval**

出所：Evaluate Pharma®（2024 年 1 月時点）をもとに医薬産業政策研究所にて作成

# Probability of Success by Disease Area
## (Office of Pharmaceutical Industry Research, JPMA 2024)

図 1-28　疾患領域別の成功確率




**Target trials**
P1: Initiate after 2010
P2: Initiate after 2005
P3: Initiate after 2000
File: Submit after 2000

https://www.jpma.or.jp/opir/research/rs_082/article_082.html

出所：Evaluate Pharma®（2024 年 1 月時点）をもとに医薬産業政策研究所にて作成

# Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review (Fogel 2018)

失敗した臨床試験に関連する要因と成功可能性を高める機会：レビュー

**Table 1**
A list of factors associated with problems or challenges when preparing for or executing a clinical trial, along with the opportunities for artificial intelligence to help alleviate these issues. Abbreviation: NLP = natural language processing.

| Factor | Opportunity | Role for Artificial Intelligence |
|---|---|---|
| Poor study design | More complete literature review | NLP of available literature, finding similar trials, trials addressing similar issues, or trials addressing different issues utilizing similar techniques, summarized for the study designer |
| Ineffective site s | | assess trade-offs site history, staff |
| Poor recruitment | Improved use of funds | Optimizing communication/advertising to maximize cost effectiveness. Targeting communication to meet patient profile, including sentiment analysis. |
| Patient burden/safety | Minimize travel and wait times | Adaptive patient scheduling, also potentially turn-by-turn driving instructions, using evolutionary algorithms. Incorporate patient profiles to tailor site assignment/schedules to patient constraints |
| Poor trial execution | Automating reporting of events | Automated prompting of events for patients and staff, reporting requirements, notes missed events, |
| Overall | Factor analysis to improve trade-offs based on budget and other constraints | Multicriteria decision making based on Pareto analysis or single aggregated evaluation function (Valuated State Space) to quantify and illuminate trade-offs. |

Poor Study Design

Ineffective sites selection

Poor recruitment

Patient burden/safety

Poor trial execution

- ✓ Literature from the past 30 years was reviewed.
- ✓ Specific instances where artificial intelligence can help improve clinical trials are identified.

過去30年間の文献を検討
AIが臨床試験の改善に役立つ具体的な事例を示す

**Table 1**
A list of factors associated with problems or challenges when preparing for or executing a clinical trial, along with the opportunities for artificial intelligence to help alleviate these issues. Abbreviation: NLP = natural language processing.

| Factor | Opportunity | Role for Artificial Intelligence |
|---|---|---|
| Poor study design | More complete literature review | NLP of available literature, finding similar trials, trials addressing similar issues, or trials addressing different issues utilizing similar techniques, summarized for the study designer |
| | Appropriate endpoints | NLP of available literature, showing endpoints/measures used in other similar studies |
| | Inappropriate eligibility criteria | NLP assessment of similar published trials to determine suitability of eligibility criteria and any potentially important omissions. |
| | Appropriate statistical analysis | NLP of available literature, summarizing statistical methods and associating these methods with successful or failed outcomes. |
| | Determination of appropriate sample size | Nonlinear modeling, such as with neural networks, to predict patient drop-out rates and better estimate sample size to avoid becoming underpowered. Agent-based modeling to simulate trial before execution. Use of NLP to mine previously published trials to determine sample sizes used in successful trials |
| | Reducing likelihood of amendments | NLP and knowledge-based processing to present designer with pertinent information to consider. |
| | Inconsistencies in protocol | NLP (including table-based format) to check time and events schedule against text, as well as summary of changes for any amendments. |

Poor Study Design

**Accumulated database of protocols and related information enables NLP to conduct exhaustive / efficient reviews and propose appropriate study design**

蓄積されたプロトコルおよび関連情報のデータベースがあれば、NLPによる網羅的・効率的なレビューや、適切な試験デザイン案の提案が可能

cdisc

**Table 1**

A list of factors associated with problems or challenges when preparing for or executing a clinical trial, along with the opportunities for artificial intelligence to help alleviate these issues. Abbreviation: NLP = natural language processing.

| Factor | Opportunity | Role for Artificial Intelligence |
|---|---|---|
| Poor trial execution | Automating reporting of events | Automated prompting of events for patients and staff, reporting requirements, notes missed events, prompts for required reporting, including protocol deviations and adverse events. |
| | Preparing data and reporting for write-up | Automatic brand/generic conversion, skeletal form generation for narratives, table creation based on specified cut-offs. |
| | Lack of general awareness | Situation awareness provided to investigator/study coordinator monitoring study progress, patient progress, indicating interventions if needed. |

Poor trial execution

**Improving the quality of studies through the automation of clinical trial-related tasks**

治験関連業務の自動化などを通して、試験の品質向上

# Pilot projects using LLM



## Writing the Clinical Study Protocol

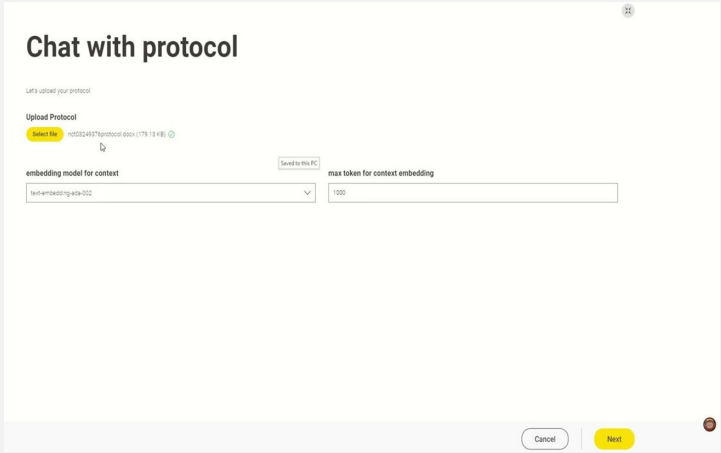
**KarXT Emergent-1**

https://www.clinicaltrials.gov/ct2/show/NCT03697252

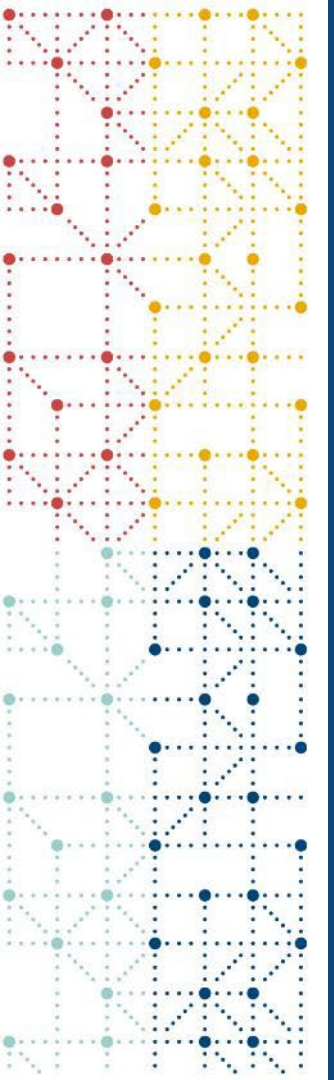
| PROCEDURE | SCREENING PHASE | TREATMENT PHASE | TREATMENT PHASE | TREATMENT PHASE | TREATMENT PHASE | TREATMENT PHASE | TREATMENT PHASE | TREATMENT PHASE | TREATMENT PHASE | |
|---|---|---|---|---|---|---|---|---|---|---|
| VISIT | 1 (Day -7 TO -1)(a) 2 (Day 1) | 3 (Day 3 ± 1 day) | 4 (Day 7 ± 2 days) | 5 (Day 8 ± 2 days) | 6 (Day 14 ± 2 days) | 7 (Day 21 ± 2 days) | 8 (Day 28 ± 2 days) | 9/ET (Day 35 ± 2 days) | Unscheduled Visits(b) | |
| WEEKS PAST RANDOMIZATION | NA | 0 | | 1 | | 2 | 3 | 4 | 5 | |
| Written informed consent | X | | | | | | | | | |
| Collect demographic information (date of birth, gender, race) | X | | | | | | | | | |
| Pregnancy test (females of childbearing potential only) (c) | X(c) | X(c) | | | | | | | X(c) | |
| Urine drugs of abuse test and alcohol testing(d) | X | | | | | | | | | |
| Review of inclusion/exclusion criteria | X | X | | | | | | | | |
| Subject eligibility verification process | X | | | | | | | | | |
| Medical, psychiatric, and medication history | X | | | | | | | | | |
| Complete physical examinationе | Xe | | | | | | | | X(e) | |
| Spontaneous AEs and medical status(f) | | X | X | X | X | X | X | X | X | X |
| Review of concomitant medications | X | X | X | X | X | X | X | X | X | X |

**PROMPT: Write the Study Procedures section of the study protocol based on the table of assessment**

## Chatbot for Protocol




**Site monitor and/or site personnel can ask questions about the study at anytime**

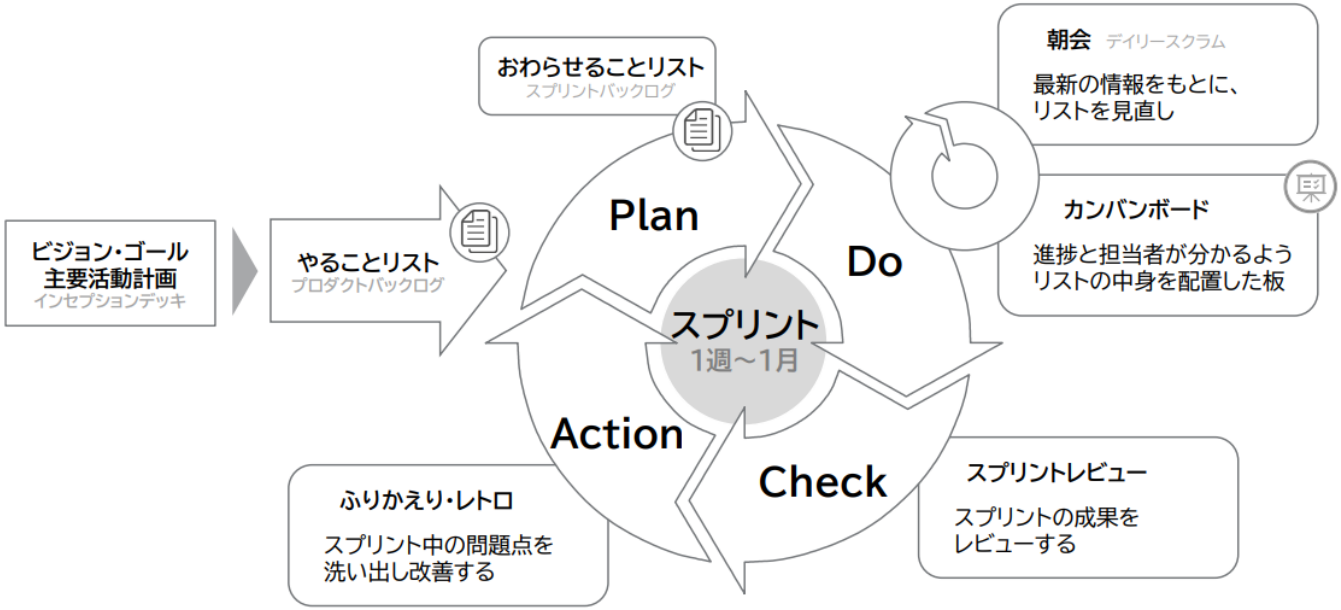


# 3. Agile Mindset for Digital Transformation

DXのためのアジャイルマインド

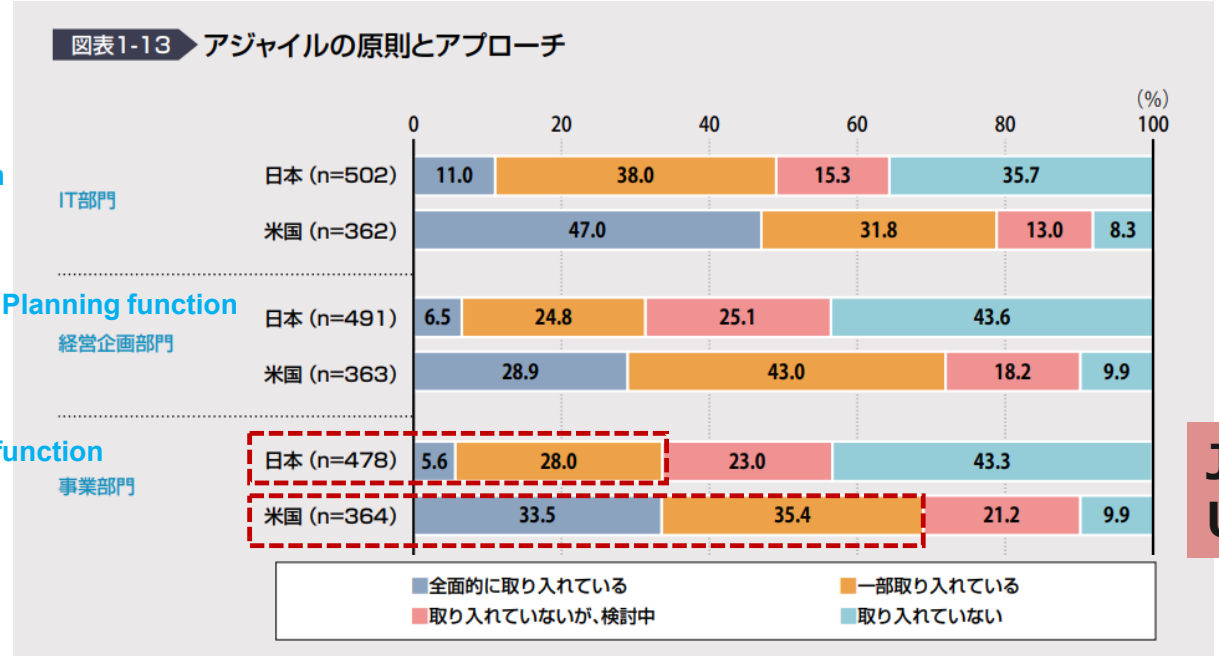
# Agile: Methodology for high-speed PDCA cycles

PDCAを高速に回すための手法であるアジャイル



# Agile: More adopted in office work in the U.S.

米国ではオフィスワークでもアジャイルアプローチが取り入れられている




**Japan: 34%**
**US: 69%**

DX白書2023

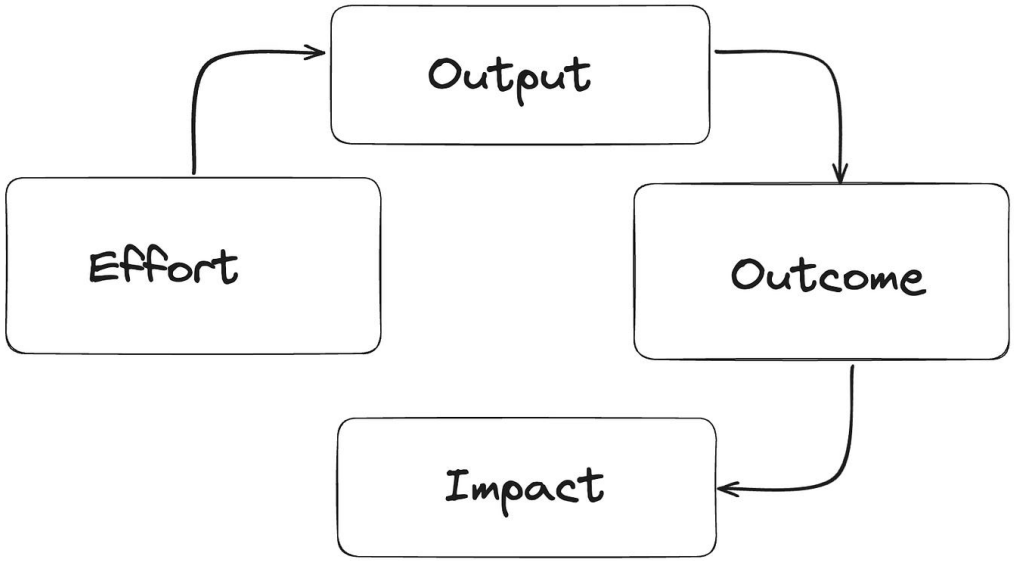


https://www.ipa.go.jp/publish/wp-dx/dx-2023.html

# Key to promote DX
## DX推進のコツ

アウトカムを重視する

OUTCOME



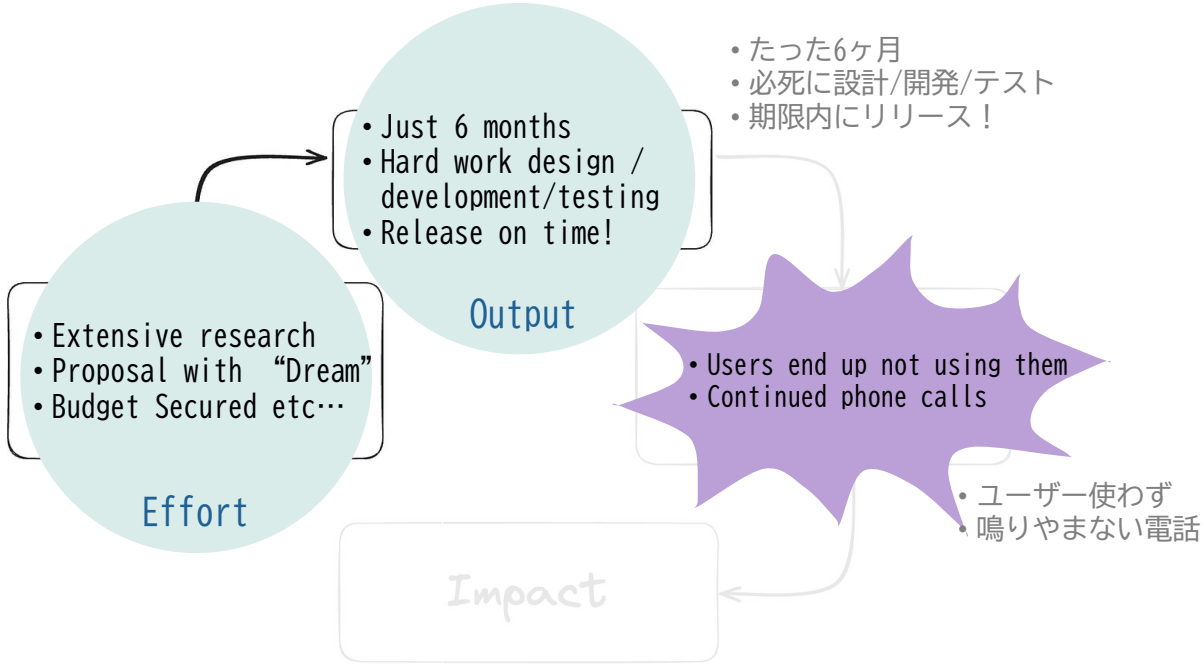

Kent Beck / Software Design: Tidy First? and pragmaticengineer.com

参考 | https://newsletter.pragmaticengineer.com/p/measuring-developer-productivity
The Pragmatic Engineer, The effort/output/outcome/impact mental model, 2024/02/09

# Key to promote DX
## DX推進のコツ

### アウトカムを重視する
OUTCOME

Failure example: Stop at Output
失敗例：Outputで止まってしまう

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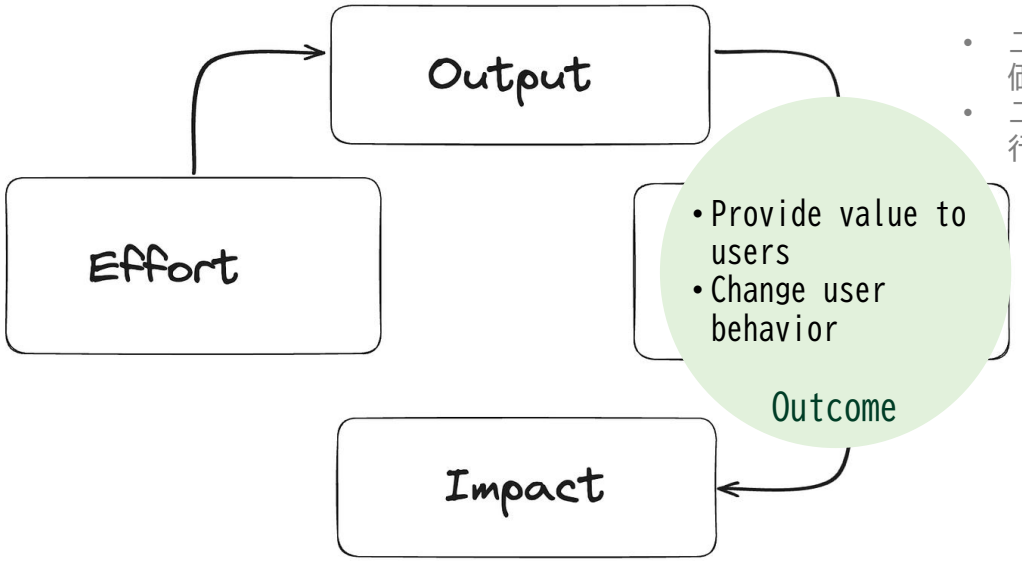
# Key to promote DX
## DX推進のコツ

Recommendation: Place the Goal in Outcome
推奨：ゴールはOutcomeに置く

アウトカムを重視する

OUTCOME




- ユーザに価値を与える
- ユーザーの行動を変える

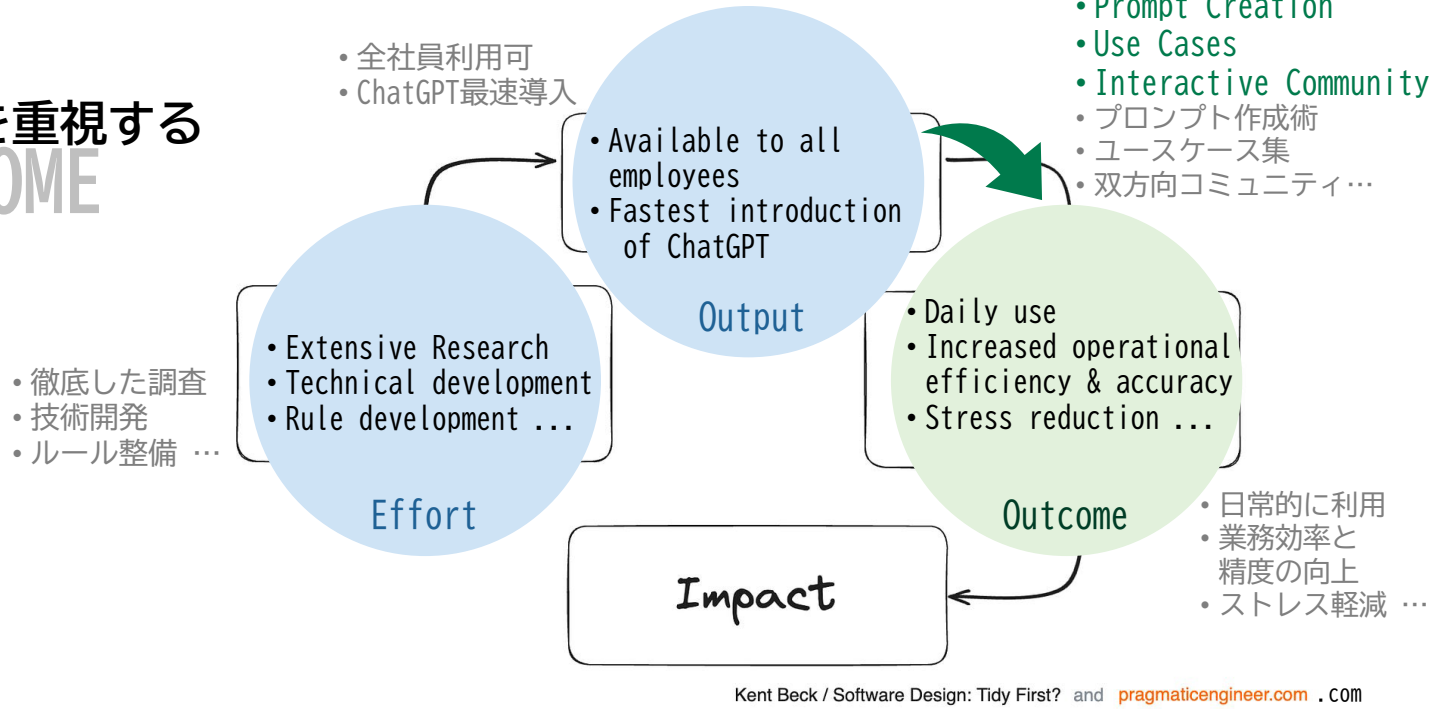
Kent Beck / Software Design: Tidy First? and pragmaticengineer.com .com

参考 | https://newsletter.pragmaticengineer.com/p/measuring-developer-productivity
The Pragmatic Engineer, The effort/output/outcome/impact mental model, 2024/02/09

# Key to promote DX
## DX推進のコツ

Recommendation: Place the Goal in Outcome
推奨：ゴールはOutcomeに置く

アウトカムを重視する
OUTCOME

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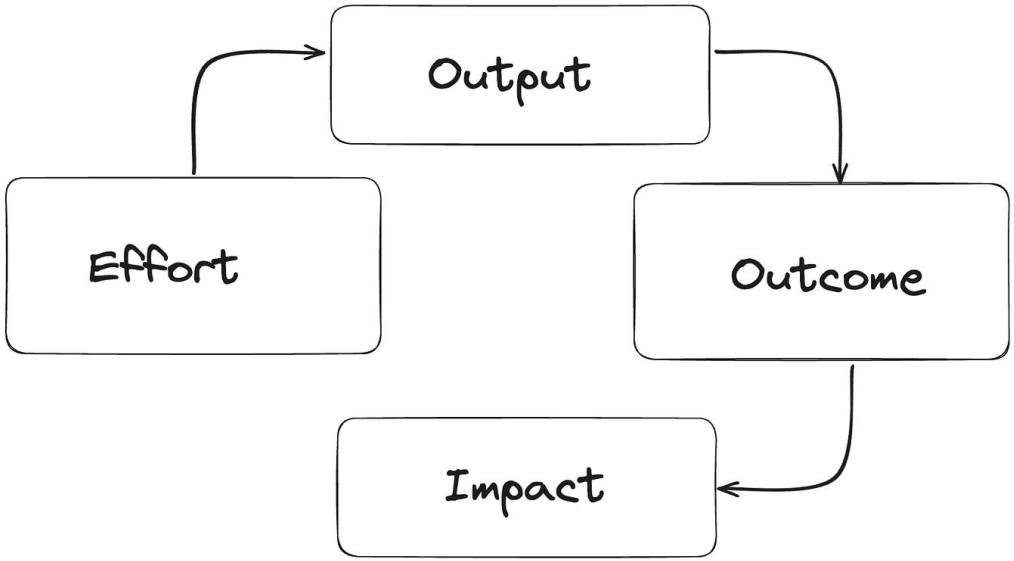
The Pragmatic Engineer, The effort/output/outcome/impact mental model, 2024/02/09

# Key to promote DX
## DX推進のコツ

アウトカムを重視する

OUTCOME

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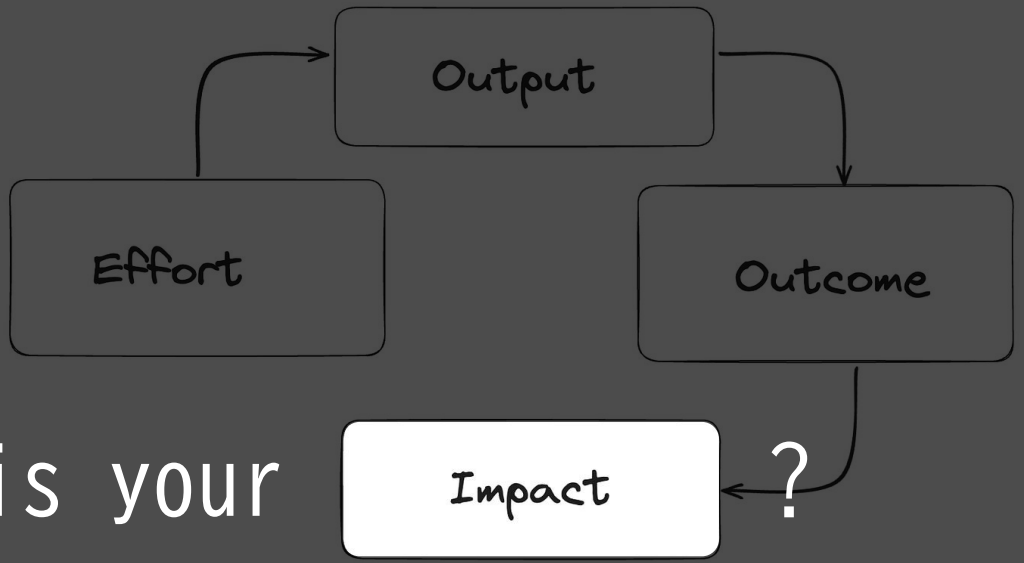
The Pragmatic Engineer, The effort/output/outcome/impact mental model, 2024/02/09

# Question to you

アウトカムを重視する

OUTCOME

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参考 | https://newsletter.pragmaticengineer.com/p/measuring-developer-productivity
The Pragmatic Engineer, The effort/output/outcome/impact mental model, 2024/02/09

# Acknowledgments


- ICH M11: EWG members
  - ✓ Rapporteur: Ron Fitzmartin, Regulatory Chair: Noemie Manent
  - ✓ PMDA: Hiroshi Sakaguchi, Toshinori Takagi
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- JPMA: Drug Evaluation Committee, Data Science expert committee
  - ✓ Chair: Hideharu Yamamoto
  - ✓ ICH M11 & Medical Writing TF members
- MSD
  - ✓ Yuka Ito
- Sumitomo Pharma
  - ✓ Agile Scrum Master: Hidekazu Sugawara

# Thank You!