Adaptive Design

FDA and ICH guideline discussions

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disclaimer

- The content of this presentation is my opinion. It does not represent the views of any organization.

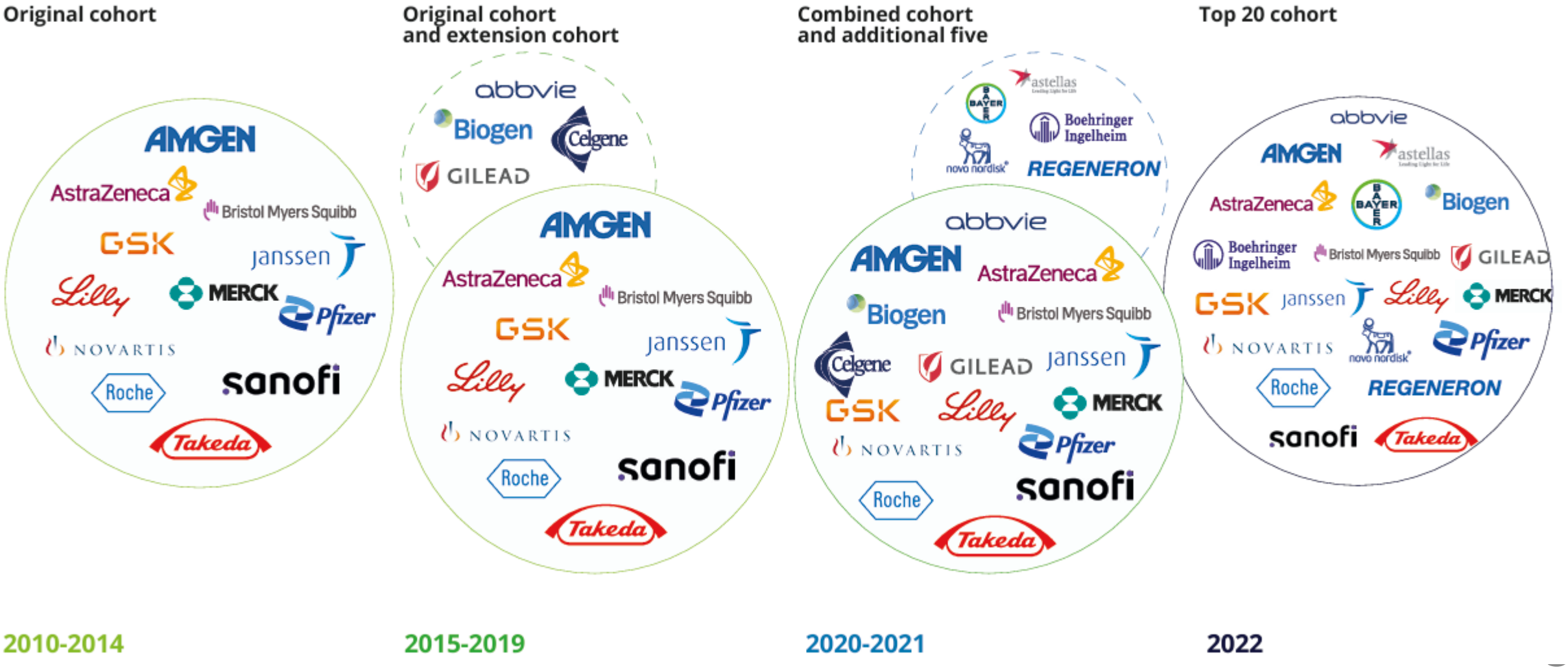
Agenda

- Motivations for adaptive design studies
  - Investment efficiency in the pharmaceutical industry
  - How to improve efficiency of development
- ICH activities and FDA activities
- My experiences working in ICH expert working groups
- Adaptive design discussions in regulatory guidelines
  - Point estimate
  - Bioequivalence study

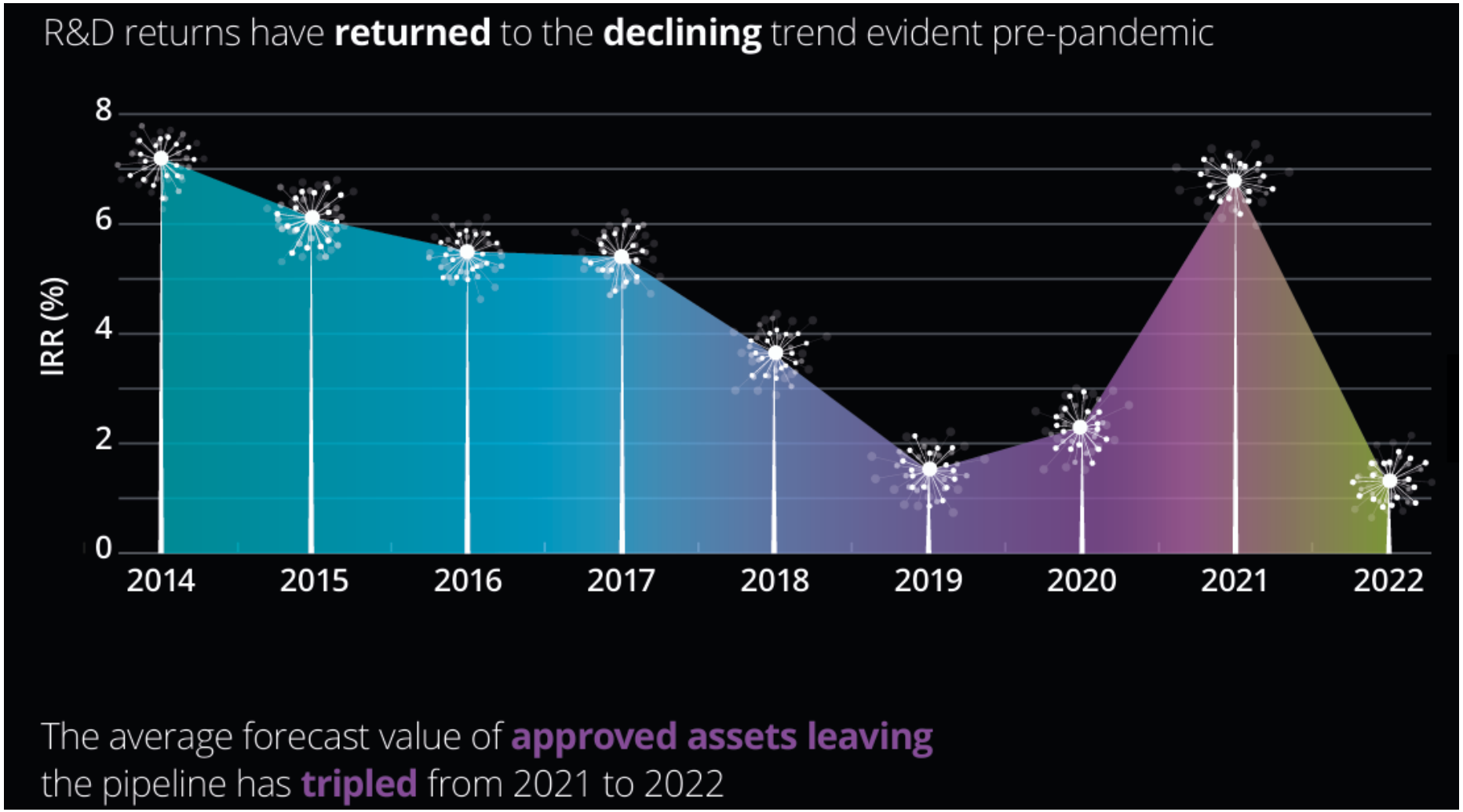
Deloitte report

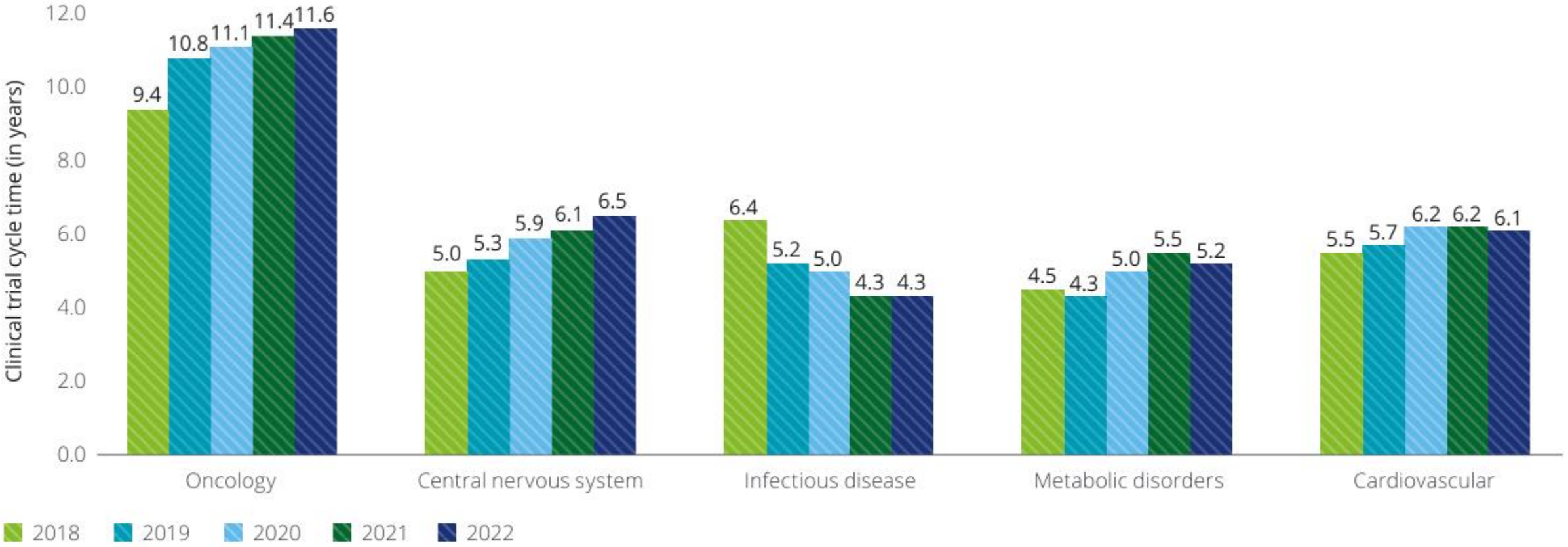
Deloitte, Seize the digital momentum Measuring the return from pharmaceutical innovation 2022, Seize the digital momentum Measuring the return from pharmaceutical innovation 2022, January 2023

Figure 1. The composition of our cohorts over time, 2010-2022



Internal Rate of Return





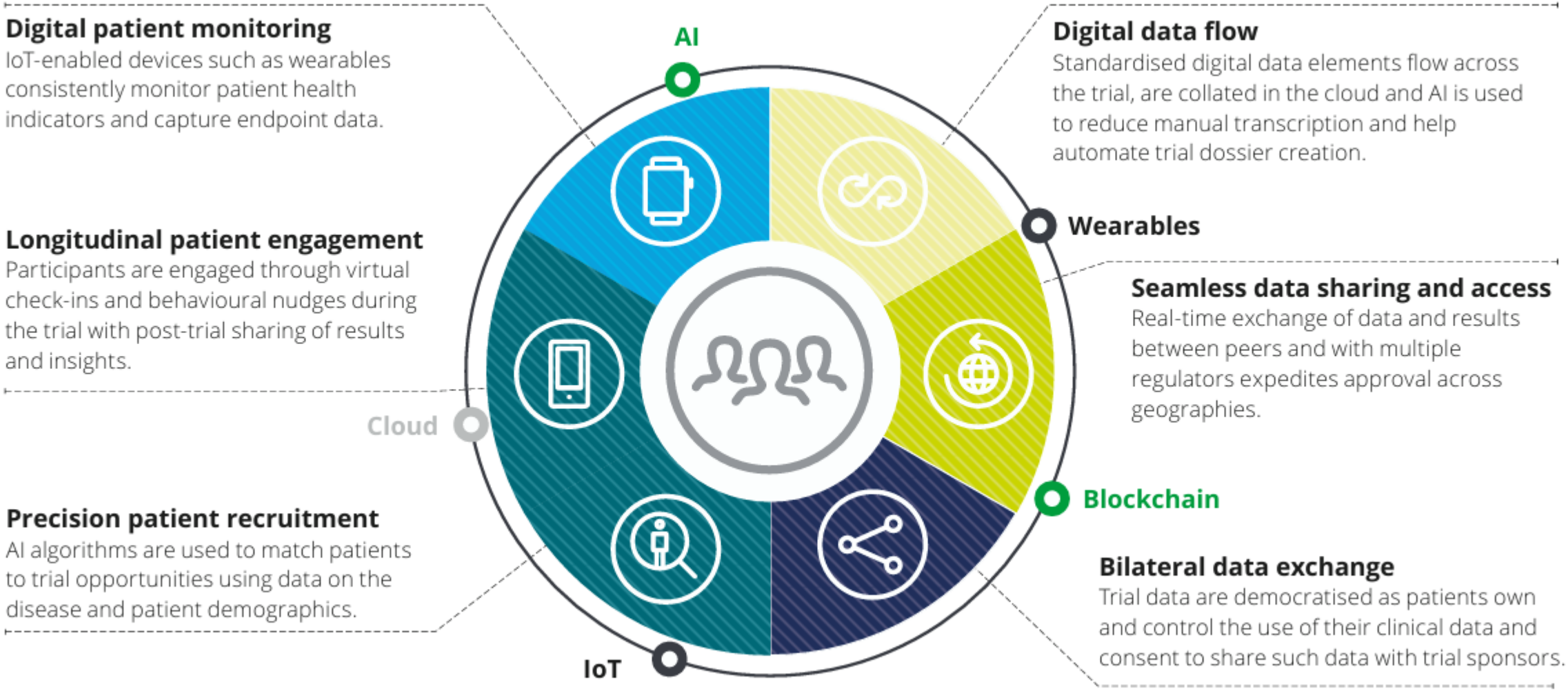
Source: Deloitte analysis, 2022

Deloitte, Seize the digital momentum Measuring the return from pharmaceutical innovation 2022, Seize the digital momentum Measuring the return from pharmaceutical innovation 2022, January 2023

What next?

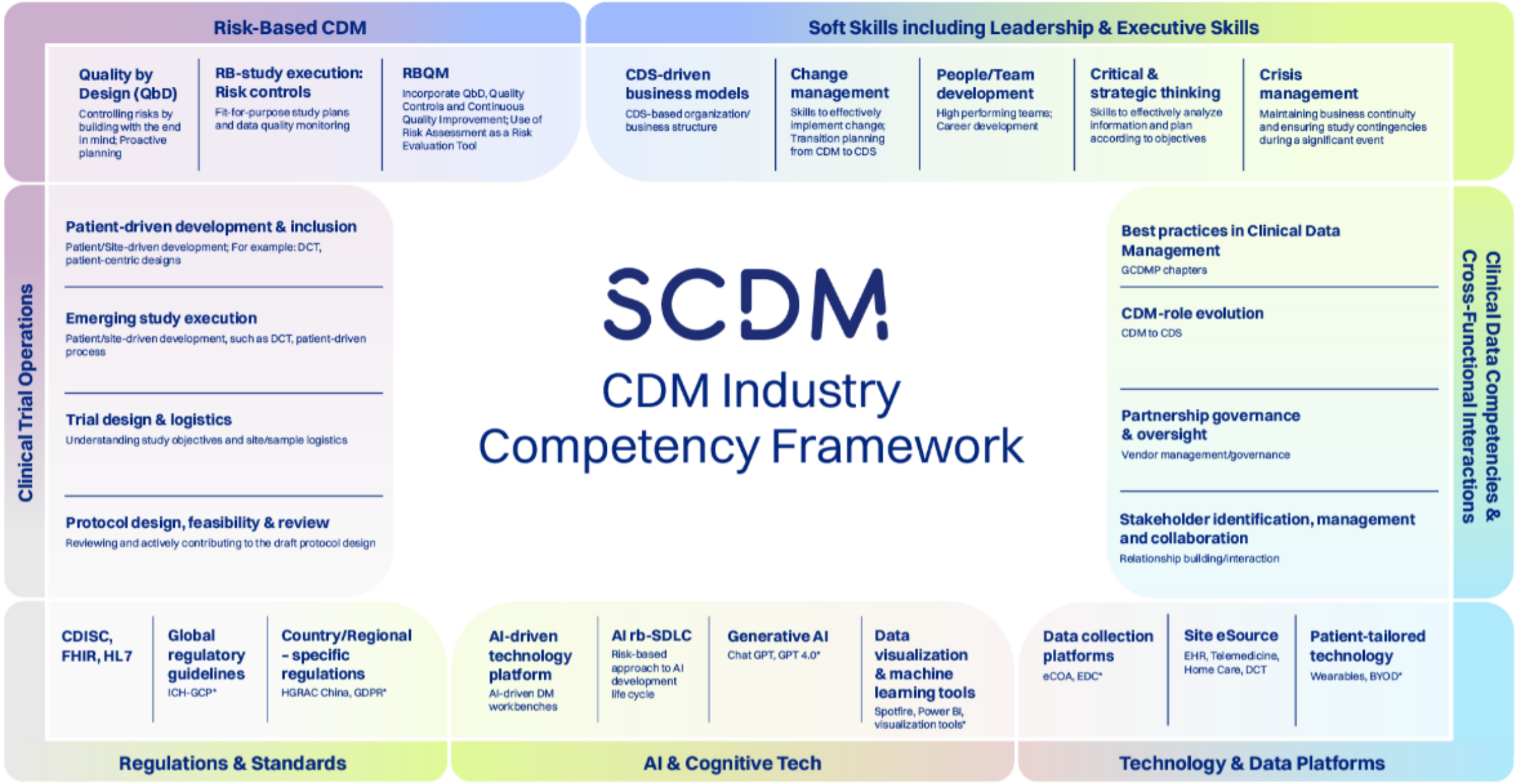
- The time required for clinical development is probably one of the factors contributing to the lower yields, IRR, in the pharmaceutical industry.
- So how should we deal with this problem?
- In this context, the pharmaceutical industry is striving both in industry and in regulatory affairs.

Figure 15: Sample digital innovations for seamless clinical trials of tomorrow



Source: Deloitte analysis, 2022.

Deloitte, Seize the digital momentum Measuring the return from pharmaceutical innovation 2022, Seize the digital momentum Measuring the return from pharmaceutical innovation 2022, January 2023



*This is not an exhaustive list.

https://scdm.org/cdm-competency-framework/

FDA's activities

- Breakthrough Therapy Designation
- Accelerated Approval Program
  - Intercept Pharmaceuticals
- Real world data
  - Update: Use of Real-World Evidence in FDA Approvals and Product Promotion | Advisories | Arnold & Porter (arnoldporter.com)

2006

FDA, Critical Opportunities List, U.S. Department of Health and Human Services Food and Drug Administration, March 2006

Critical Path Opportunities list

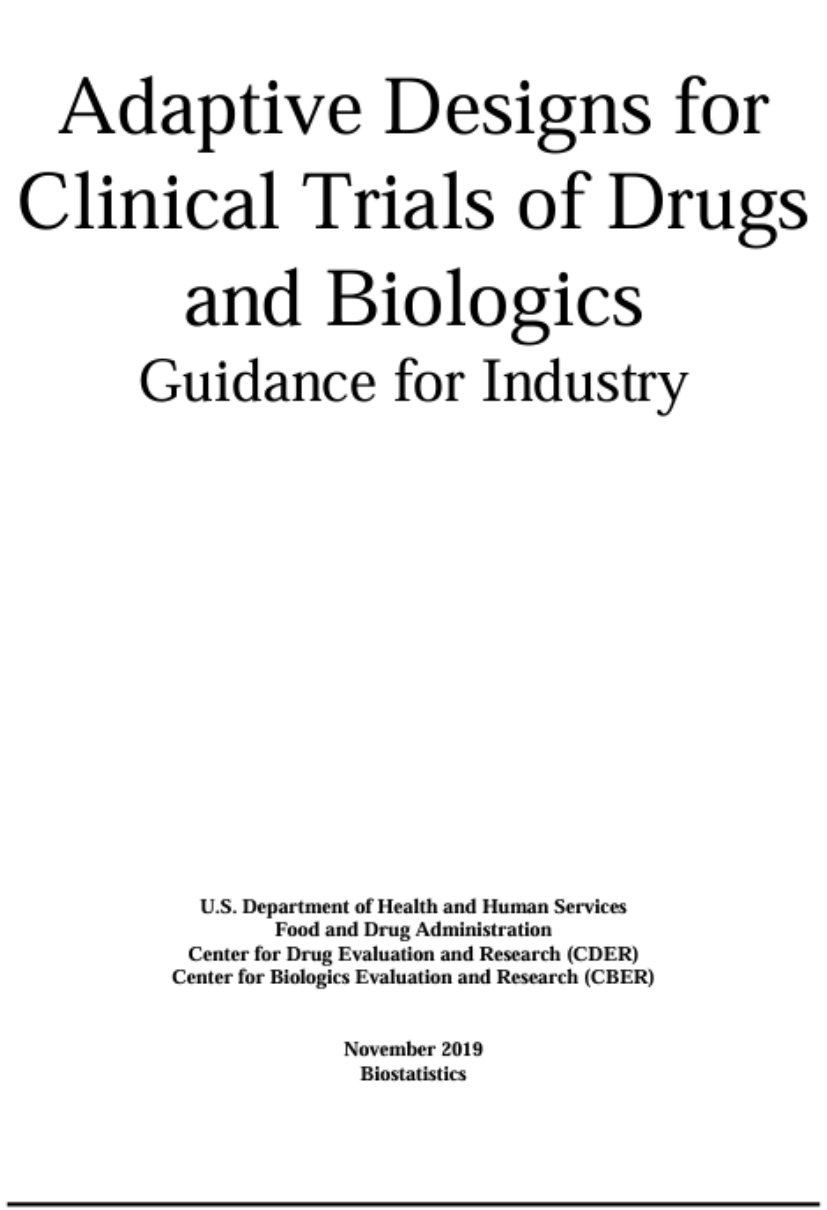
- "36. Use of Prior Experience or Accumulated Information in Trial Design. Adaptive Trial Design Stakeholders are looking for clear rules on when it is valid to make changes to a clinical trial protocol, based on early or interim study results, when unblinded treatment results may be known. "
- "Consensus and clarification is needed on questions such as:
  - When can extra trial arms be dropped?
  - When can an early marker be used to choose which treatment to carry forward or to choose a subset for analysis?
  - When is it valid to modify randomization based on results, for example, in a combined phase 2/3 cancer trial?
  - When is it valid and under what situations can one stage or phase of a study be combined with the second stage or phase? "

FDA, Critical Opportunities List, U.S. Department of Health and Human Services Food and Drug Administration, March 2006

FDA(2019)

FDA, Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) November **2019**

FDA, Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics DRAFT GUIDANCE, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER), February **2010**


Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2019
Biostatistics

Critical Path Opportunities list

- "Non-Frequentist Methods Statistical techniques that allow for increased reliance on historical data, under assumptions and models that can be justified, might be used to develop predictive inferences. "
- "The use of these techniques in product development holds promise, but work remains to adapt and qualify such methods for use to answer specific product development questions for both clinical and preclinical applications. "
- "For example, we urgently need to improve use of animal data to predict human experience (see Opportunity 30). Many believe that Bayesian and similar non frequentist statistical methods that use empirically derived prior information and models to develop predictive probabilities could provide a basis for supplementing the traditional methods for human equivalent dose calculations and for maximizing the usefulness of data derived from animal safety and efficacy studies."

FDA, Critical Opportunities List, U.S. Department of Health and Human Services Food and Drug Administration, March 2006

General guidance has not been yet.

FDA(2020)

Bayesian framework,
Adaptive design,
Master protocol,
SMARTS

Sequential Multiple Assignment Randomized Trials

FDA, Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Center for Drug Evaluation and Research, December 2020

Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

ICH activity

ICH official video

Harmonisation for Better Health

- “The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. “
- “Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner. “
- “Harmonisation is achieved through the development of ICH Guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side. Key to the success of this process is the commitment of the ICH regulators to implement the final Guidelines.”

https://www.ich.org
https://www.ich.org/page/mission

ICH Members
(as of June 2024)

ICH harmonisation for better health

23 Members:

- Founding Regulatory:
  - EC, Europe; MHLW/PMDA, Japan; FDA, United States
- Founding Industry:
  - EFPIA; JPMA; PhRMA
- Standing Regulatory:
  - Swissmedic, Switzerland; Health Canada, Canada
- Regulatory:
  - ANMAT, Argentina; ANVISA, Brazil; COFEPRIS, Mexico; EDA, Egypt; HSA, Singapore; JFDA, Jordan; MFDS, Republic of Korea; MHRA, UK; NMPA, China; SFDA, Saudi Arabia; TFDA, Chinese Taipei; TITCK, Turkey
- Industry:
  - BIO; Global Self-Care Federation; IGBA

See https://www.ich.org/page/members-observers for details

Legislative or Administrative Authorities

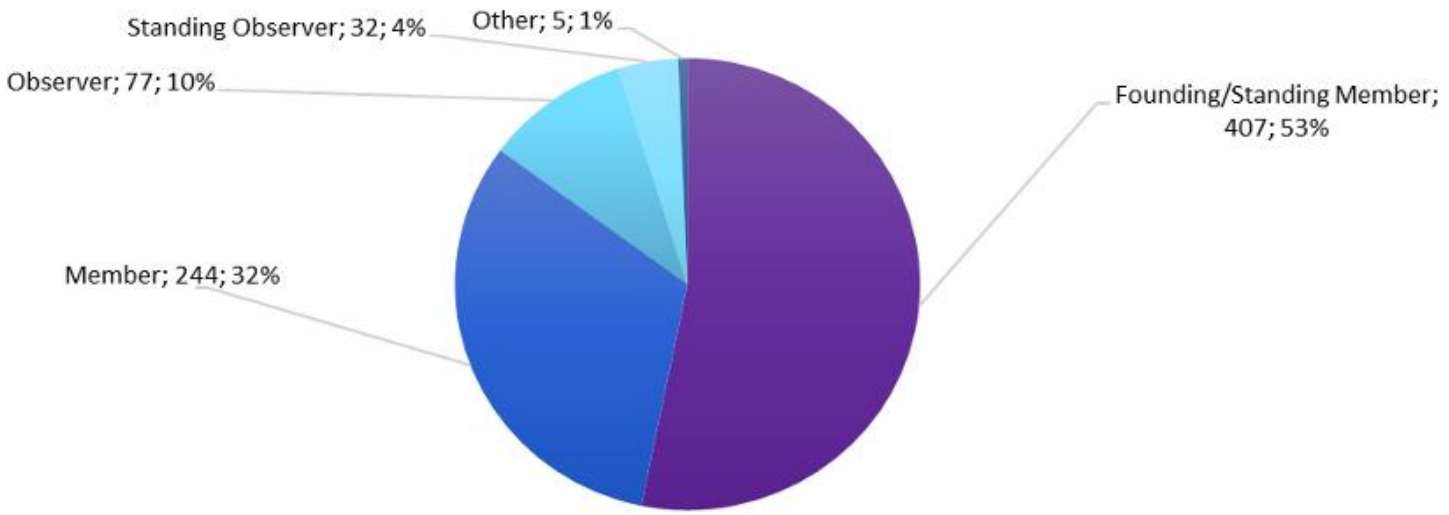
- AEC, Azerbaijan
- ANPP, Algeria
- CDSCO, India
- CECMED, Cuba
- CPED, Israel
- DPM, Tunisia
- Indonesian FDA, Indonesia
- INVIMA, Colombia
- MMDA, Moldova
- MOPH, Lebanon
- NAFDAC, Nigeria
- National Center, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- PPBHK, Hong Kong, China
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- SECMOH, Ukraine
- TGA, Australia

ICH harmonisation for better health

Composition of ICH WGs

With over 765 technical experts in over 33 WGs – as of June 2024

Number of experts in ICH WGs



ICH Products (as of June 2024)

75 Guidelines on technical requirements on:

- Safety – 16 Guidelines
- Quality - 26 Guidelines
- Efficacy – 22 Guidelines
- Multidisciplinary - 11 Guidelines

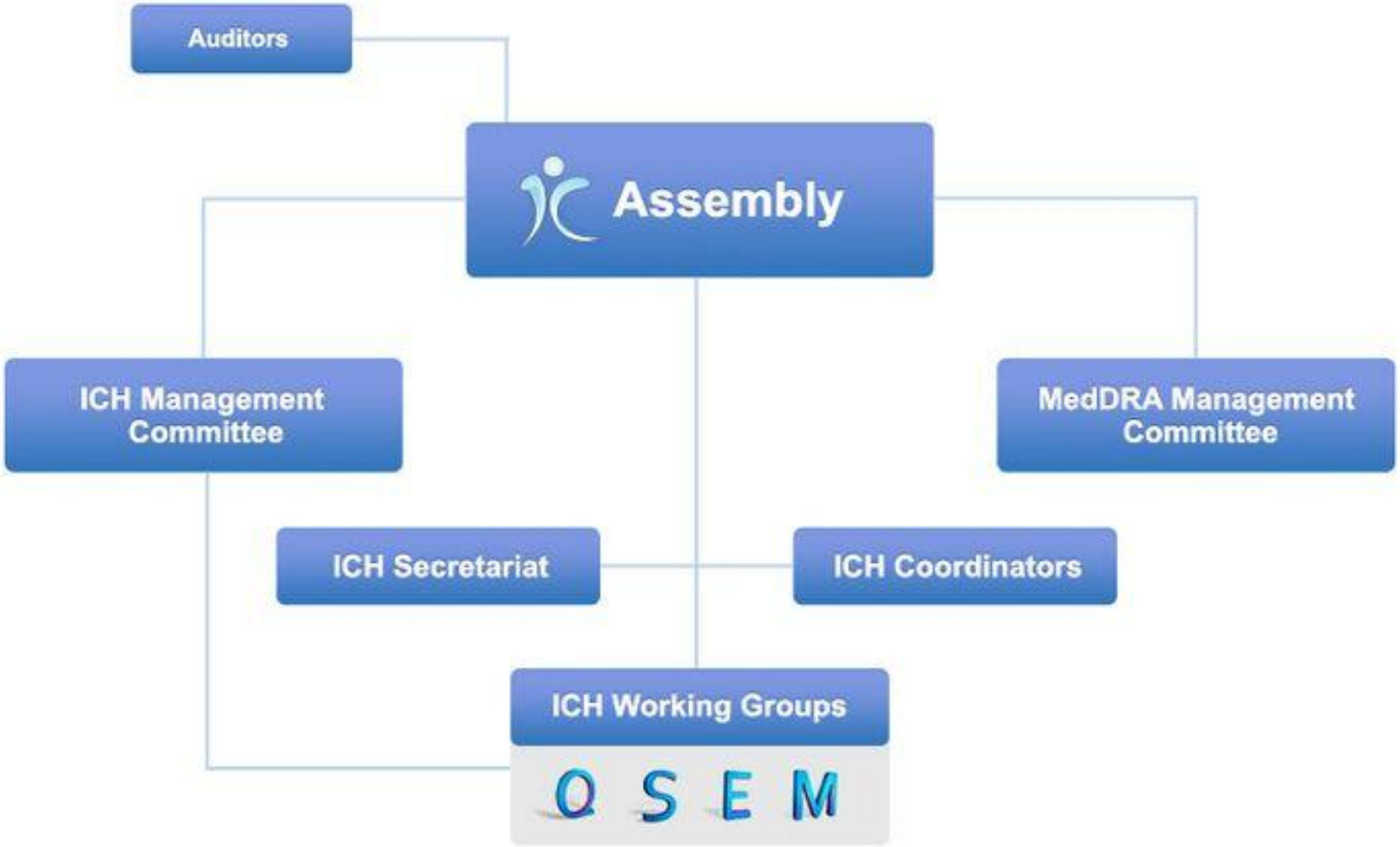
Electronic Standards for the Transfer of Regulatory Information (ESTRI)

CTD/eCTD

MedDRA (standardised medical terminology)

See https://www.ich.org/page/ich-guidelines for details

organization



The International Council for Harmonisation of
Technical Requirements for Pharmaceuticals
for Human Use

Standard Operating Procedure of the ICH Working Groups

Version 13.0
Approval by the ICH Management Committee on 12 May 2023

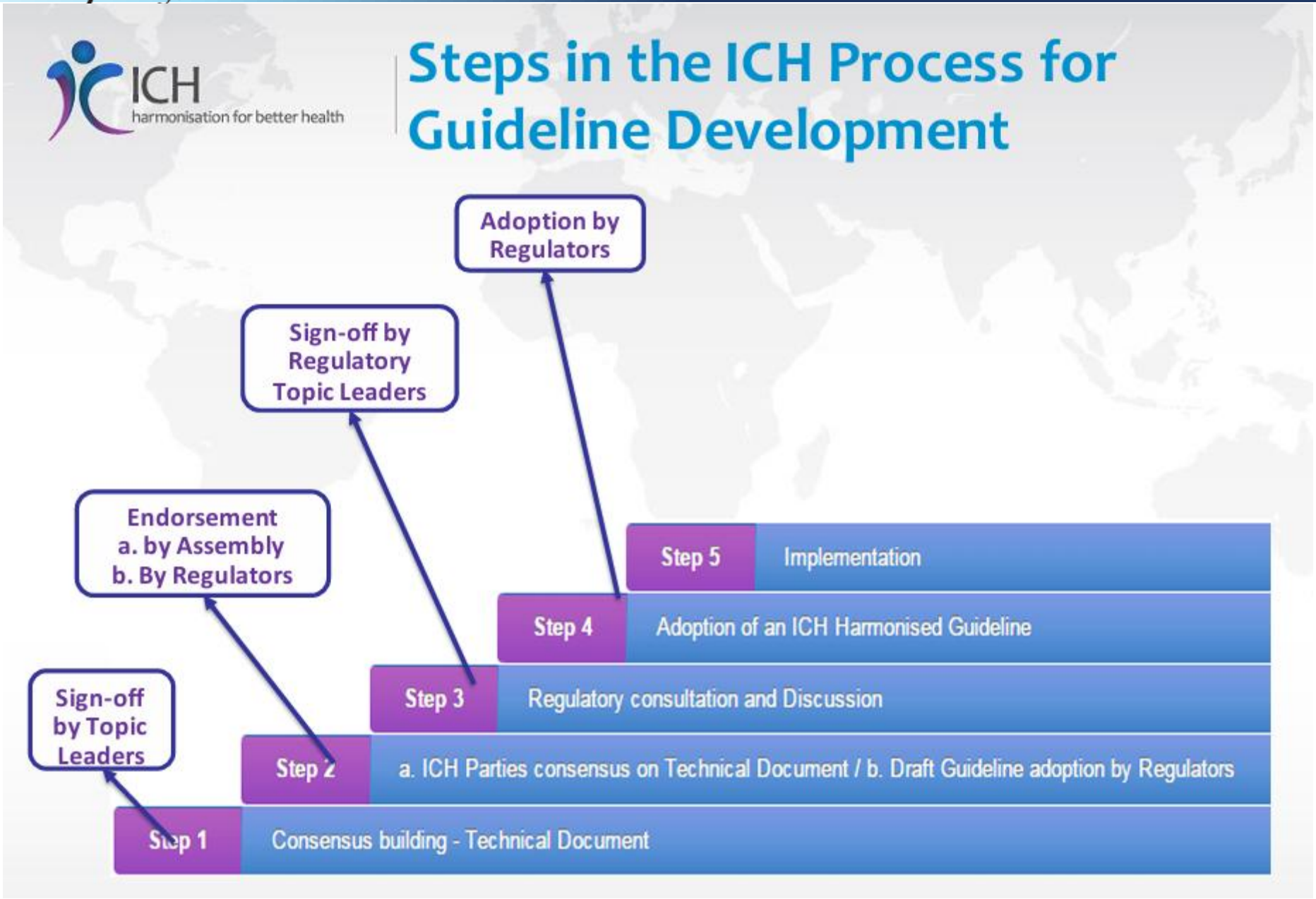
ICH, Standard Operating Procedure of the ICH Working Groups, Version 13.0 Approval by the ICH Management Committee on 12 May 2023

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Route de Pré-Bois 20, 1215 Geneva, Switzerland
Telephone: +41 (22) 710 74 80 - admin@ich.org, http://www.ich.org

Schedule

- A one-week face-to-face meeting is held every six months.

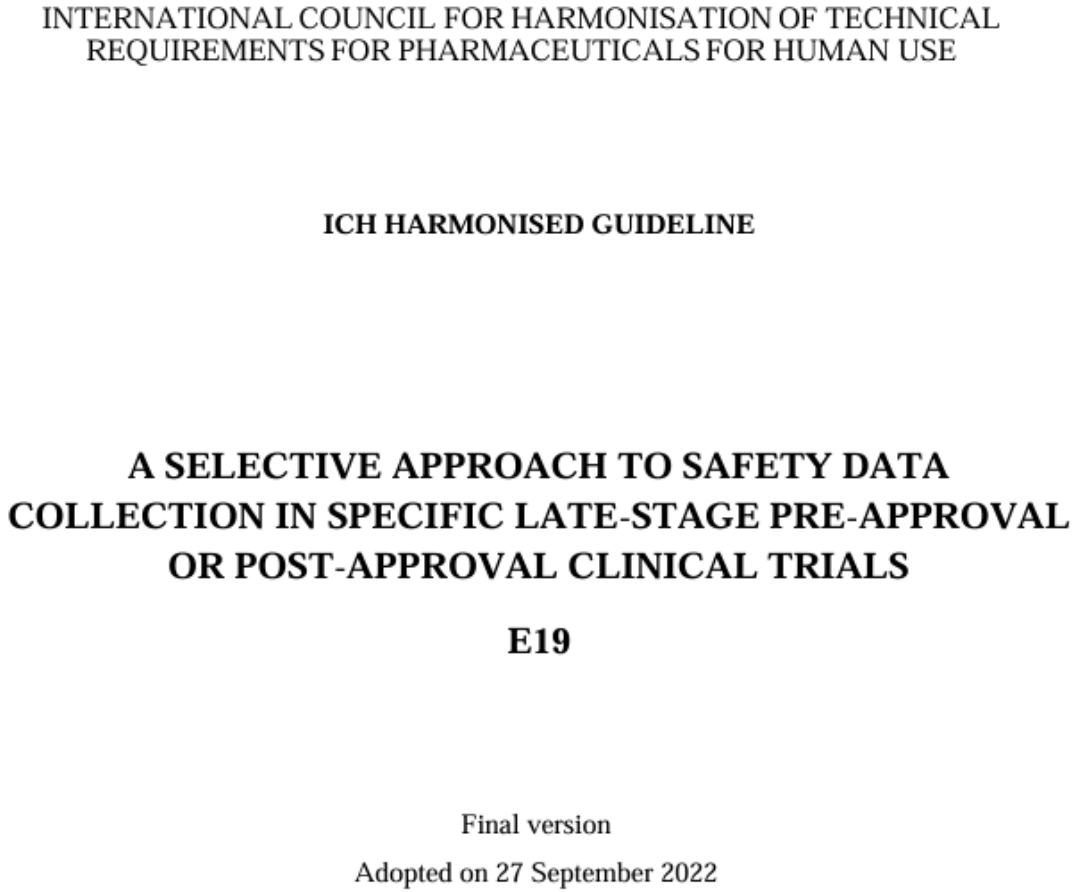
- 2 – 5 June 2024 in Fukuoka, Japan
- 5 – 6 November 2024 in Montréal, Canada
- 13 - 14 May 2025 in Madrid, Spain


ICH
harmonisation for better health
Steps in the ICH Process for Guideline Development
Adoption by Regulators
Sign-off by Regulatory Topic Leaders
Endorsement a. by Assembly b. By Regulators
Sign-off by Topic Leaders
Step 5 Implementation
Step 4 Adoption of an ICH Harmonised Guideline
Step 3 Regulatory consultation and Discussion
Step 2 a. ICH Parties consensus on Technical Document / b. Draft Guideline adoption by Regulators
Step 1 Consensus building - Technical Document

Definition of each step

- Step 1
  - The Working Groups (WG) works to prepare a consensus draft of the technical document.
- Step 2
  - ✓ Step 2a: The Members of the ICH Assembly are invited to endorse the technical document.
  - ✓ Step 2b: The Regulatory Members of the ICH Assembly are invited to endorse the draft Guideline
- Step 3
  - Public consultation by the ICH Regulatory Members and ICH Secretariat. All comments are considered by the WG.
  - Step 3 is finalised once consensus is reached by the regulatory experts of the WG.
- Step 4
  - The Regulatory Members of the ICH Assembly adopt the final ICH harmonised Guideline

One of the activities of ICH is the E19 guideline. It has usually been thought that it takes more time and more participants to obtain safety data than to obtain efficacy data. However, large trials may be needed to perform clinical trial that are close to true endpoints, like survival. In such cases, it was clearly stated that it is not always necessary to collect safety data in detail in every participants. This is expected to reduce the effort and cost of conducting clinical trials.



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

ICH HARMONISED GUIDELINE

A SELECTIVE APPROACH TO SAFETY DATA COLLECTION IN SPECIFIC LATE-STAGE PRE-APPROVAL OR POST-APPROVAL CLINICAL TRIALS

E19

Final version

Adopted on 27 September 2022

ICH
harmonisation for better health

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

ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3)

Draft version

Endorsed on 19 May 2023

Currently under public consultation

GCP: ICH E6

Clinical trials vary widely in scale, complexity and cost. Careful evaluation of the priorities involved in each trial and the risks associated with the priorities will help ensure efficiency by focusing on activities critical to achieving the trial objectives.

Clinical trials should be designed to protect the rights, safety and well-being of participants and assure the reliability of results. Quality by design should be implemented to identify the factors (i.e., data and processes) that are critical to ensuring trial quality and the risks that threaten the integrity of those factors and ultimately the reliability of the trial results. Clinical trial processes and risk mitigation strategies implemented to support the conduct of the trial should be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability. Trial designs should be operationally feasible and avoid unnecessary complexities.

ICH E6 (R3) Guideline on good clinical practice (GCP), Step 2b, May 2023

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.

ICH E6 (R3) Guideline on good clinical practice (GCP), Step 2b, May 2023

B.10. Statistical Considerations

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

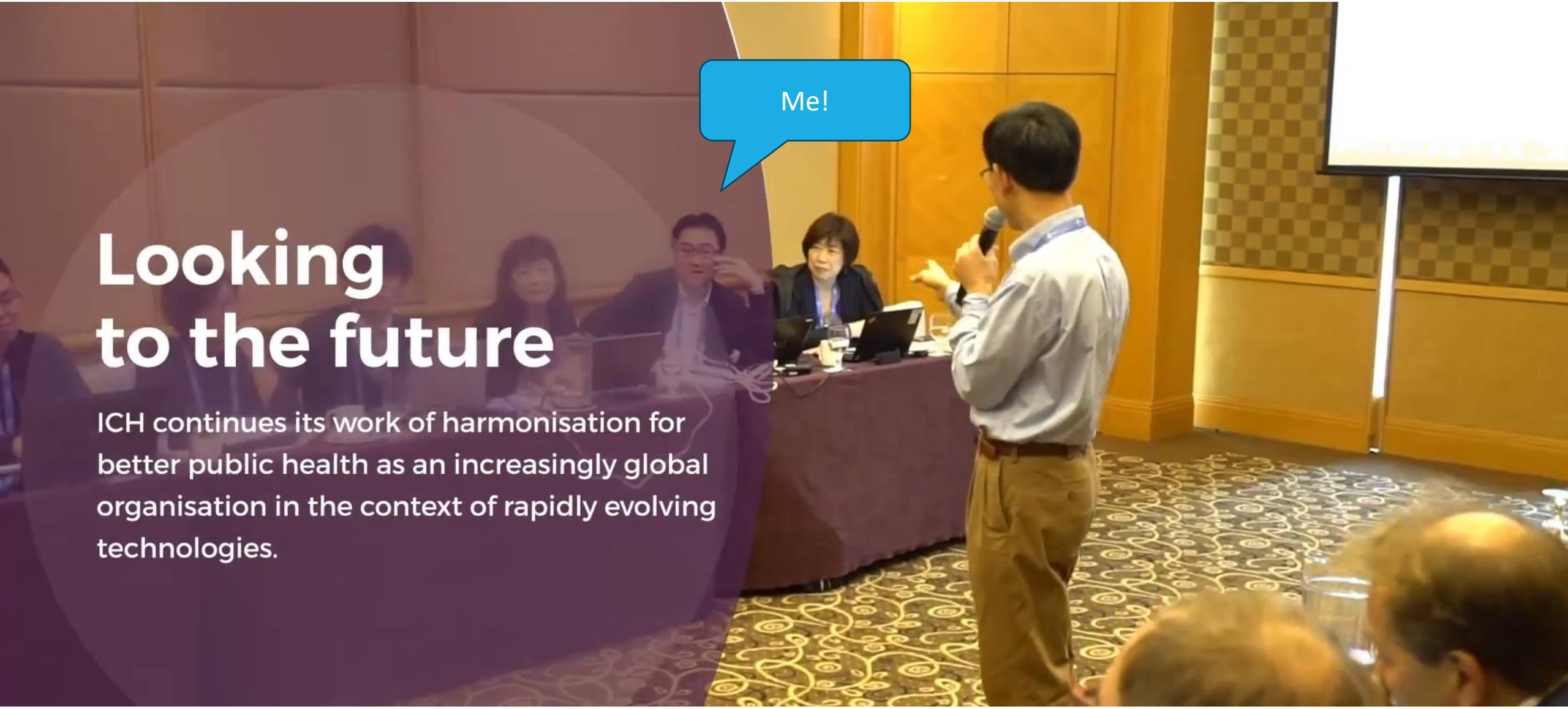
B.10.4 The criteria for the termination of the trial and the criteria for the stopping of the trial.

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.

ICH E6 (R3) Guideline on good clinical practice (GCP), Step 2b, May 2023


Me!
Looking to the future
ICH continues its work of harmonisation for better public health as an increasingly global organisation in the context of rapidly evolving technologies.

ICH E-20

E20 Adaptive Clinical Trials

E20 EWG Adaptive Clinical Trials

This topic was endorsed by the ICH Assembly in June 2018.

The E20 EWG is working on the development of a new E20 Guideline on "Adaptive Clinical Trials" on the design, conduct, analysis, and interpretation of adaptive clinical trials that provides a transparent and harmonized set of principles for the regulatory review of these studies in a global drug development program. These principles should also provide the flexibility to evaluate / discuss innovative approaches to clinical trial design throughout the development process.

Rapporteur: Dr. John Zhong (PhRMA)

Regulatory Chair: Dr. Gregory Levin (FDA, United States)

Status: *Step 1*

Endorsed Documents

- E20 Concept Paper
- E20 Business Plan
- E20 Work Plan

WG list

Final Concept Paper
E20: Adaptive Clinical Trials
Dated 7 November 2019
Endorsed by the Management Committee on 18 November 2019

Type of Harmonisation Action Proposed

A new guideline on the design, conduct, analysis, and interpretation of adaptive clinical trials that provides a transparent and harmonized set of principles for the regulatory review of these studies in a global drug development program. These principles should also provide the flexibility to evaluate / discuss innovative approaches to clinical trial design throughout the development process. For the purposes of this document, adaptive clinical trials are defined as trials planned with an adaptive design.

Statement of the Perceived Problem

1.b. Future anticipated key milestones

Expected future completion date	Milestone
Jun. 2024	*Face-to-face meeting in Fukuoka, Japan*
Sep. 2024	*Final draft of E20 Technical Document with E20 EWG consensus*
Oct. 2024	*Step 1 PWP consultation of E20 draft Technical Document*
Nov. 2024	• *Steps 1 and 2a/b Sign-off of E20 draft Technical Document by E20 EWG Topic Leaders and ICH Assembly Regulatory Members* • *Finalize Step 2 Informational Presentation*
Dec. 2024 – Mar. 2025	• *Step 3: Public Regulatory Consultation* • *Progress on development of Step 4 introductory presentation*
Apr. 2025 – Feb 2026	• *Incorporate comments and revise document* • *Develop training materials*
Feb. 2026	*Step 3 PWP consultation of draft E20 draft Guideline*
Apr. 2026	• *Steps 3 and 4 Sign-off of E20 draft Guideline by E20 EWG Topic Leaders and ICH Assembly Regulatory Members* • *Finalize Step 4 Introductory Presentation*

https://database.ich.org/sites/default/files/ICH_E20_EWG_WorkPlan_2024_0308.pdf

My feeling: not ICH EWG comments

- Point estimation
- Type 1 error rate evaluation
- Bayesian framework

FDA: adaptive design

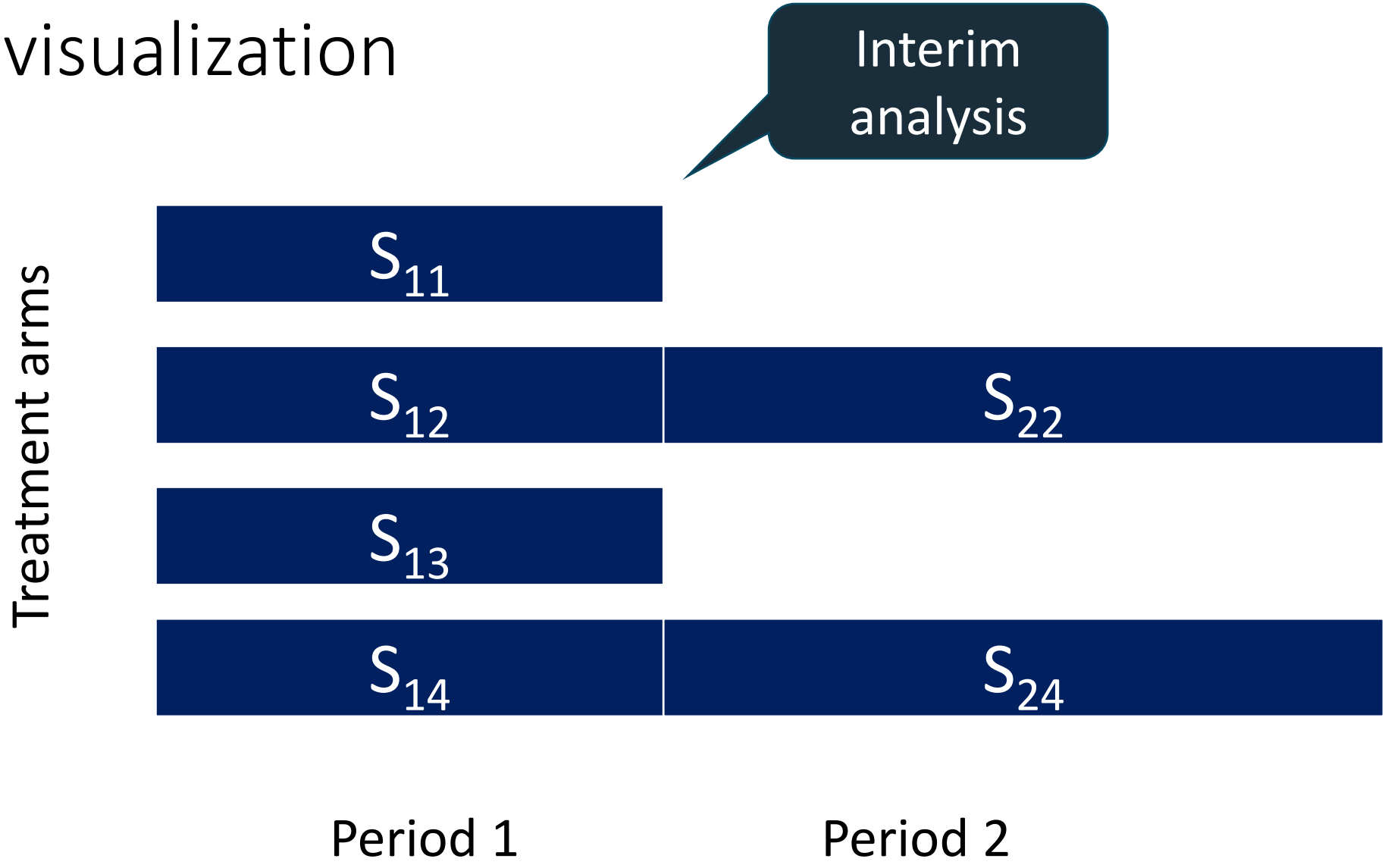
- “an adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial. ”

FDA, Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) November 2019

examples

- Group Sequential Designs
- Adaptations to the Sample Size
- Adaptations to the Patient Population
- Adaptations to Treatment Arm Selection
- Adaptations to Patient Allocation
- Adaptations to Endpoint Selection
- Adaptations to Multiple Design Features

visualization



Sample size re-estimation

- Eliprodil
- severe head injury (Bolland et al. 1998).
- three-category outcome defining the functional status of the patient after six months of treatment.
- Placebo response
- non-comparative data -> sample size re-estimation
- led to a sample size increase from 400 to 450 patients.

Bolland K, Sooriyarachchi MR, Whitehead J. Sample size review in a head injury trial with ordered categorical responses. Stat Med. 1998 Dec 30;17(24):2835-47

Arm selection: Sydes et al. 2012

- prostate cancer
- standard androgen deprivation therapy (ADT) with several different treatment regimens that combined ADT with one or more approved therapies
- Interim analysis -> drop treatment arms
- The use of a common control group is more efficiently than multiple individual trials.

Sydes MR, Parmar MK, Mason MD, Clarke NW, Amos C, Anderson J, de Bono J, Dearnaley DP, Dwyer J, Green C, Jovic G, Ritchie AW, Russell JM, Sanders K, Thalmann G, James ND. Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial. Trials. 2012 Sep 15;13:168

Motivation: statistical efficiency

- "an adaptive design can provide a greater statistical power
  - group sequential designs and designs with adaptive modifications to the sample size. "
- "an adaptive design may provide the same statistical power with a smaller expected sample size or shorter expected duration"

FDA, Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry, November 2019

Motivations: Ethical considerations

- "an adaptive design can provide ethical advantages"
- "stop a trial early if it becomes clear can reduce the number of patients
  - Prevent being exposed to the unnecessary risk of an ineffective treatment
  - to explore more promising therapeutic alternatives. "

FDA, Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry, November 2019

Adaptive design FDA guidance (2019)　Bias !!

- “Bias is a systematic tendency for the estimate of treatment effect to deviate from its true value. “
- “Biased estimation in adaptive design is currently a less well-studied phenomenon than Type I error probability inflation, however, and methods may not be available for other designs.”

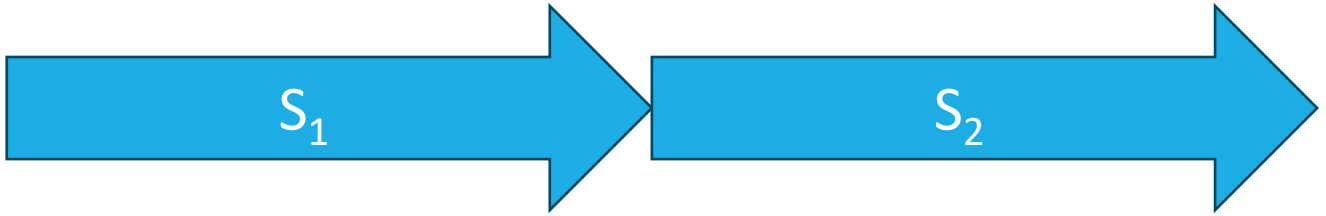
FDA, Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry, November 2019

Bias as a theoretical definition

$$\operatorname{Bias}(\hat{\theta}, \theta) = \operatorname{Bias}_{\theta}[\hat{\theta}] = \mathrm{E}_{x|\theta}[\hat{\theta}] - \theta = \mathrm{E}_{x|\theta}[\hat{\theta} - \theta],$$

Over the distribution P(X|θ)

Source of bias



S_1 if $S_1 > C_1$

$f(S_1, S_2)$ if $S_1 < C_1$

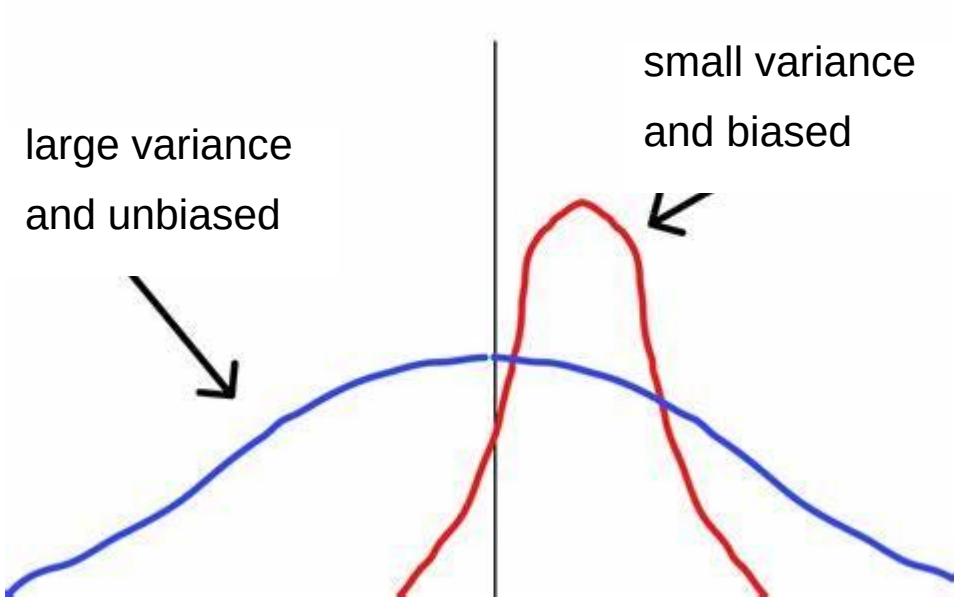
$$bias(\hat{\theta}) = E_\theta[\hat{\theta}] - \theta = \sum_{k=1}^{2} E_\theta[\hat{\theta}|T = k] \Pr_\theta[T = k] - \theta.$$

$$bias_\theta(\hat{\theta}) = \frac{I_2 - I_1}{I_2\sqrt{I_1}}\phi\left(e - \theta\sqrt{I_1}\right),$$

Robertson DS, Choodari-Oskooei B, Dimairo M, Flight L, Pallmann P, Jaki T. Point estimation for adaptive trial designs II: Practical considerations and guidance. Stat Med. 2023 Jun 30;42(14):2496-2520

What is the best estimator

- precise estimators can potentially be biased while unbiased estimators tend to be less precise, which reflects the classical bias-variance trade-off.



$$\mathrm{MSE}(\hat{\theta}) = \mathrm{Var}(\hat{\theta}) + (\mathrm{Bias}(\hat{\theta}))^2$$

MUSEC (multiple sclerosis and extract of cannabis) trial

TABLE 3 Observed data from the MUSEC trial at the interim and final analyses, with standardized test statistics and O'Brien-Fleming (OBF) group sequential boundary (one-sided, with early stopping only for superiority).

	Interim data		Final data	
	Placebo	**CE arm**	**Placebo**	**CE arm**
Number of subjects with relief from muscle stiffness	12	27	21	42
Total number of subjects	97	101	134	143
Standardized test statistic	2.540		2.718	
OBF boundary	2.797		1.977	

Robertson DS, Choodari-Oskooei B, Dimairo M, Flight L, Pallmann P, Jaki T. Point estimation for adaptive trial designs II: Practical considerations and guidance. Stat Med. 2023 Jun 30;42(14):2496-2520

Estimators 1

- uniformly minimum variance unbiased estimator (UMVUE)

$$UMVUE = \hat{\theta}_{obs} - \frac{\sqrt{I_2 - I_1}}{\sqrt{I_1 I_1}} \frac{\phi\left(\frac{e - Z_2\sqrt{I_1/I_2}}{\sqrt{(I_2 - I_1)/I_2}}\right)}{\Phi\left(\frac{e - Z_2\sqrt{I_1/I_2}}{\sqrt{(I_2 - I_1)/I_2}}\right)},$$

- median unbiased estimator (MUE)

$$P(\theta) = \int_{-\infty}^{e}\int_{z_2}^{\infty} f_2\left((x_1 x_2), \left(\theta\sqrt{I_1}\theta\sqrt{I_2}\right), \begin{pmatrix} 1 & \sqrt{I_1/I_2} \\ \sqrt{I_1/I_2} & 1 \end{pmatrix}\right) dx_2 dx_1,$$

Robertson DS, Choodari-Oskooei B, Dimairo M, Flight L, Pallmann P, Jaki T. Point estimation for adaptive trial designs II: Practical considerations and guidance. Stat Med. 2023 Jun 30;42(14):2496-2520

Estimators 2

- uniformly minimum variance conditionally unbiased estimator (UMVCUE)

$$UMVCUE = \hat{\theta}_{obs} - w_1 \frac{\phi\left(w_2\left(\hat{\theta}_{obs} - e/\sqrt{I_1}\right)\right)}{\Phi\left(w_2\left(\hat{\theta}_{obs} - e/\sqrt{I_1}\right)\right)}, \quad \text{where } w_1 = \frac{1}{(I_2 - I_1)\sqrt{I_1^{-1} + (I_2 - I_1)^{-1}}}, w_2 = I_1\sqrt{I_1^{-1} + (I_2 - I_1)^{-1}}.$$

- conditional MUE (CMUE)

$$0.5 = \int_{-\infty}^{\hat{\theta}_{obs}} f(\hat{\theta}|T = 2)d\hat{\theta},$$

Robertson DS, Choodari-Oskooei B, Dimairo M, Flight L, Pallmann P, Jaki T. Point estimation for adaptive trial designs II: Practical considerations and guidance. Stat Med. 2023 Jun 30;42(14):2496-2520

TABLE 4 Naive, unconditionally and conditionally unbiased/bias-adjusted estimates calculated using the observed data and O'Brien-Fleming efficacy stopping boundaries from the MUSEC trial.

Type of estimator	Estimator	Difference in proportions (SE)	Relative difference to overall MLE
MLE/naive	MLE (overall)	0.1370 (0.054)	–
Unconditionally unbiased/bias-adjusted	MLE (stage 1)	0.1436 (0.057)	+5%
	Median unbiased estimator (MUE)	0.1341 (0.054)	−2%
	UMVUE	0.1278 (0.054)	−7%
	Bias-corrected MLE (UBC-MLE)	0.1328 (0.055)	-3%
Conditionally unbiased/bias-adjusted	MLE (stage 2)	0.1139 (0.111)	−17%
	Conditional MUE (CMUE)	0.1851 (0.080)	+35%
	UMVCUE	0.1724 (0.071)	+26%
	Bias-corrected MLE (CBC-MLE)	0.1909 (0.073)	+39%

Note: Standard errors (SEs) are calculated using a parametric bootstrap approach with 10^5 replicates, assuming that the true difference in proportions is equal to 0.14.

Robertson DS, Choodari-Oskooei B, Dimairo M, Flight L, Pallmann P, Jaki T. Point estimation for adaptive trial designs II: Practical considerations and guidance. Stat Med. 2023 Jun 30;42(14):2496-2520

TABLE 5 Simulation results showing the mean values of the point estimators and the corresponding standard errors (SE) under different assumed values of θ. There were 10^5 trial replicates for each value of θ.

		Difference in proportions (SE)		
Type of estimator	**Estimator**	**θ = 0.10**	**θ = 0.14**	**θ = 0.18**
MLE/naive	MLE (overall)	0.103 (0.054)	0.144 (0.054)	0.184 (0.053)
Unconditionally unbiased/bias-adjusted	MLE (stage 1)	0.100 (0.057)	0.140 (0.057)	0.180 (0.057)
	Median unbiased estimator (MUE)	0.101 (0.053)	0.142 (0.054)	0.182 (0.054)
	UMVUE	0.100 (0.052)	0.140 (0.054)	0.180 (0.055)
	Bias-corrected MLE (UBC-MLE)	0.101 (0.054)	0.142 (0.055)	0.183 (0.054)
Conditionally unbiased/bias-adjusted	MLE (stage 2)	0.100 (0.111)	0.140 (0.111)	0.180 (0.111)
	Conditional MUE (CMUE)	0.115 (0.083)	0.152 (0.080)	0.190 (0.081)
	UMVCUE	0.100 (0.062)	0.140 (0.071)	0.179 (0.080)
	Bias-corrected MLE (CBC-MLE)	0.111 (0.067)	0.154 (0.073)	0.194 (0.078)

Note: The probability of stopping at stage 1 was 0.15, 0.37 and 0.65 for θ = 0.10, 0.14 and 0.18, respectively.

Robertson DS, Choodari-Oskooei B, Dimairo M, Flight L, Pallmann P, Jaki T. Point estimation for adaptive trial designs II: Practical considerations and guidance. Stat Med. 2023 Jun 30;42(14):2496-2520

TABLE 6 Simulation results showing the mean values of the unconditional point estimators and the corresponding standard errors (SE) under different assumed values of θ, separated by trial replicates that stop at the interim analysis and those that continue to stage 2. There were 10^5 trial replicates in total for each value of θ.

		Difference in proportions (SE)		
	Estimator	**θ = 0.10**	**θ = 0.14**	**θ = 0.18**
Trial stops early at the interim analysis	MLE (stage 1)	0.188 (0.025)	0.197 (0.031)	0.212 (0.038)
Trial continues to stage 2	MLE (overall)	0.087 (0.043)	0.113 (0.038)	0.132 (0.033)
	MLE (stage 1)	0.084 (0.045)	0.106 (0.038)	0.120 (0.030)
	Median unbiased estimator (MUE)	0.086 (0.041)	0.109 (0.034)	0.126 (0.027)
	UMVUE	0.084 (0.039)	0.106 (0.030)	0.120 (0.023)
	Bias-corrected MLE (UBC-MLE)	0.085 (0.041)	0.110 (0.036)	0.128 (0.032)

Note: The probability of stopping at stage 1 was 0.15, 0.37, and 0.65 for θ = 0.10, 0.14, and 0.18, respectively.

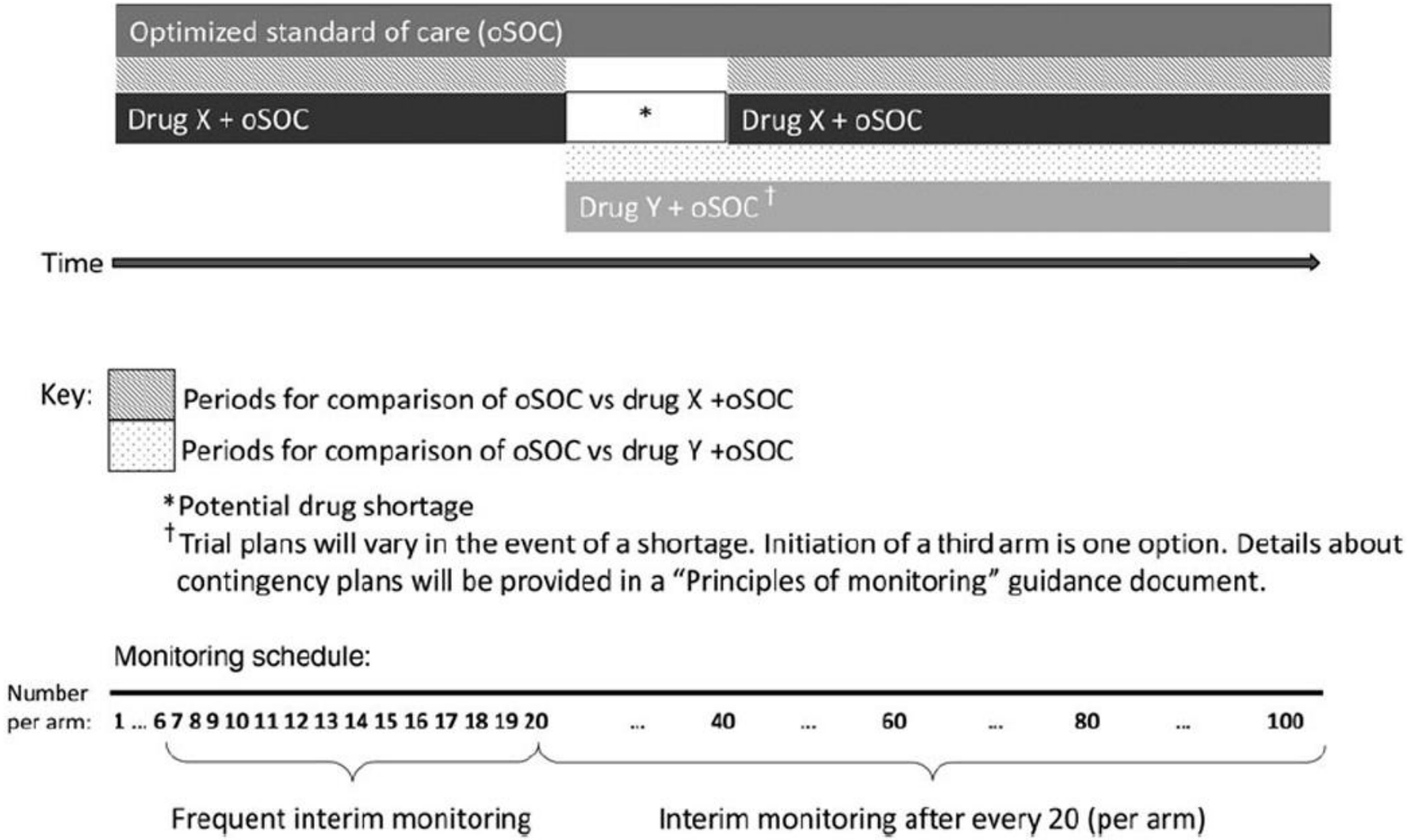
Robertson DS, Choodari-Oskooei B, Dimairo M, Flight L, Pallmann P, Jaki T. Point estimation for adaptive trial designs II: Practical considerations and guidance. Stat Med. 2023 Jun 30;42(14):2496-2520

Operational characteristics of the trial

- Bias depends on study design
- Bias correction may be possible in simple cases
- Inherently dependent on true values, so correction is not possible
- Important to examine the degree of bias by considering some study design options, such as the timing of interim analyses, how likely the study may be stopped, and assuming various true values for power calculation and type 1 error evaluation

Bias evaluation by simulation

Complex i



ClinicalTrials.gov Identifier: NCT02363322

Table 1. Simulation development process.

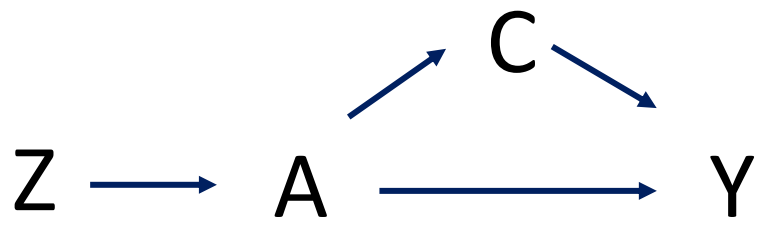
Simulation elements	Description of the simulation steps
1. Study objectives	Discuss background of the trial: phase(s) of development, the primary and secondary objectives, primary and key secondary endpoints, treatment arms, dosages, controls, study population, recruitment, etc. Understand the purpose of the study in the context of the development program.
2. Key design characteristics	Determine basic characteristics for different design options to match the study objectives (e.g., fixed design, dose finding design, or seamless design, etc.) and their rationale (e.g., based on clinical, commercial, and/or regulatory considerations). Outline the decision rules and adaptations embedded in the designs including number of required interim analyses and their timing.
3. Assumptions, clinical scenarios, and metrics	Discuss assumptions for each design parameter, the scenarios to be simulated, the metrics for comparing the competing designs (e.g., statistical, operational or financial quantities).
4. Operational details	Discuss the logistics related to the execution of the chosen design: timing of interim analyses, sites and speed of recruitment, expedite data cleaning for decision making and implementation of adaptations.
5. Sensitivity scenarios	Discuss the sensitivity scenarios applied to establish robustness of the design features under more extreme situations.
6. Simulation runs	Determine the adequate number of simulation runs to allow sufficient precision. Specify the software/code to be used and the random seed. Perform the simulations for each scenario and candidate design.
7. Results	Summarize and compare the operating characteristics in tables and graphs; present and discuss the selected design options and relevant results to choose the "best" design.
8. Simulation report	Focus on a limited number of designs; when the design elements are finalized compare their operating characteristics to draw conclusions and select the "best" design.

Mayer et., al. (2019) Simulation Practices for Adaptive Trial Designs in Drug and Device Development
TATISTICSINBIOPHARMACEUTICALRESEARCH 2019,VOL.11,NO.4,325–335

Estimate what?

Estimation is more difficult than testing

- The statistical test is easier than estimation because it can be performed under the null hypothesis.
- Estimation cannot be done under any conditions.
  - Location and/or dispersions
- If there are deviations, those should be handled under some assumption in real world setting.
- What is the treatment effect based on ITT?



Estimation

- Hernan and Robins (2017) Per-Protocol Analyses of Pragmatic Trials.
  - Pragmatic trial: Trials conducted to estimate treatment effects in situations that closely resemble actual clinical practice
- Hideki (2018)
  - There are intercurrent events that only arise in double-blind new drug trials.

Hernán MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. N Engl J Med. 2017 Oct 5;377(14):1391-1398

E9(R1)

- “It remains undisputed that randomisation is a cornerstone of controlled clinical trials and that analysis should aim at exploiting the advantages of randomisation to the greatest extent possible. However, the question remains whether estimating an effect in accordance with the ITT principle always represents the treatment effect of greatest relevance to regulatory and clinical decision making. “

E9(R1) Supplementary Analysis

- “Interpretation of trial results should focus on the main estimator for each agreed estimand providing that the corresponding estimate is verified to be robust through the sensitivity analysis. Supplementary analyses for an estimand can be conducted in addition to the main and sensitivity analysis to provide additional insights into the understanding of the treatment effect. They generally play a lesser role for interpretation of trial results. **The need for, and utility of, supplementary analyses should be considered for each trial. “**

What is ITT effect

- Clinical trials are conducted in an ideal space, so ITT does not reflect actual clinical practice.
  - Five too's (too small, too homogeneous, etc.)
  - RWD / RWE
- Since the treatment effect cannot be estimated without setting strong assumptions in RWD / RWE, ITT effect is accepted a biased estimator as the lower bound of a reliable treatment effect in clinical trial.

My thought

- In clinical trials, there are usually ways to make the estimation more conservative. Also, assumptions can be made to understand the phenomenon. However, these cannot be done in adaptive designs.
- Adaptive design may make this approach impossible.
- Operating characteristics of the trial should be investigated in advance

My thought

- Point estimate is not necessarily essential or important in clinical trials.
  - Strong bias should be avoided.
    - In other words, small bias can be exchangeable for high efficiency.
  - Randomization and blinding are necessary
  - In preplanned adaptive trials, evaluation of operation characteristics by simulation may be sufficient.
- Adaptive design has many operational problems.
  - Operations staffs need to remain blinded.
  - If a situation arises that looks strange, it is difficult to prove that it is not operations-dependent
  - Should be aware of the potential for damaging integrity of the trial.

Test only situation

BE trial

EMA: GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

- "Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy. "

EMA, COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE, Aug 2010

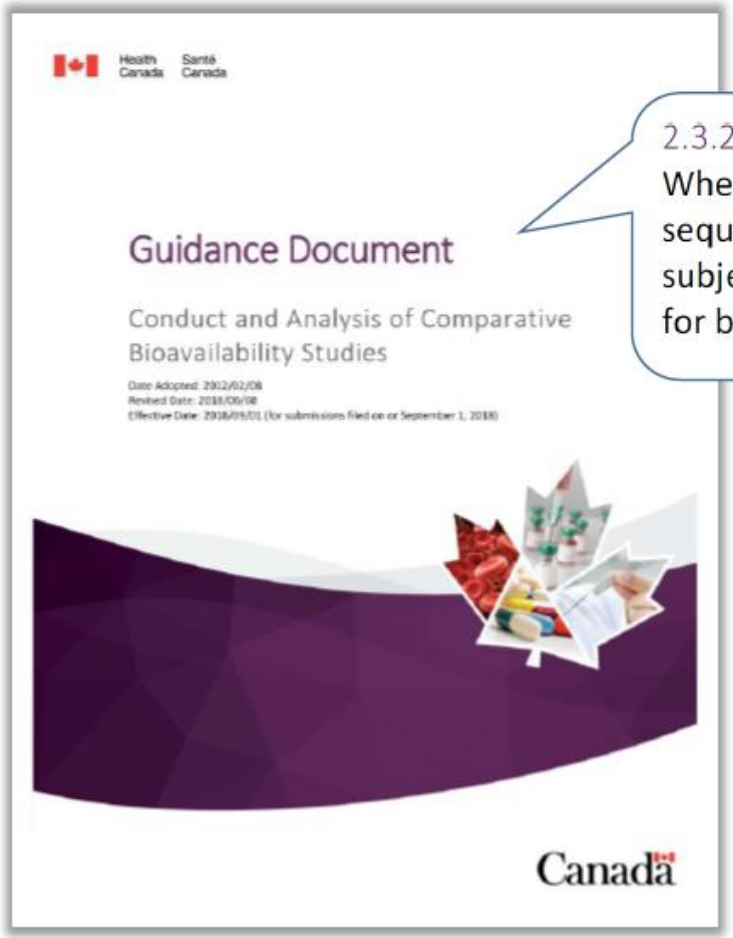
EMA BE: Parameters to be analysed and **acceptance limits**

- "In studies to determine bioequivalence after a single dose, the parameters to be analysed are AUC(0-t), or, when relevant, AUC(0-72h), and Cmax. For these parameters the 90% confidence interval for the ratio of the test and reference products should be contained within the acceptance interval of 80.00 125.00%."

EMA, Committee For Medicinal Products For Human Use (CHMP) Guideline On The Investigation Of Bioequivalence, Aug 2010

Judging by whether it is within the criteria and not how far from the center it is.

Health Canada BE Guidance



2.3.2.2 Adaptive designs

When there is very little information on the intra-subject variance, another approach similar to the sequential design is the adaptive design where the second stage sample size is based on the estimated intra-subject variance from the first stage. Method C in Potvin et al. (D. Potvin et al. Sequential design approaches for bioequivalence studies with crossover designs Pharmaceut. Statist. 2008; 7: 245-262) is recommended.

Health Canada, Guidance Document Conduct and Analysis of Comparative Bioavailability Studies Date Adopted: 2012/02/08 Revised Date: 2023/01/30 Effective Date: 2018/09/01 (for submissions filed on or September 1, 2018)

Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuirmann DJ, Smith RA. Sequential design approaches for bioequivalence studies with crossover designs. Pharm Stat. 2008 Oct-Dec;7(4):245-62

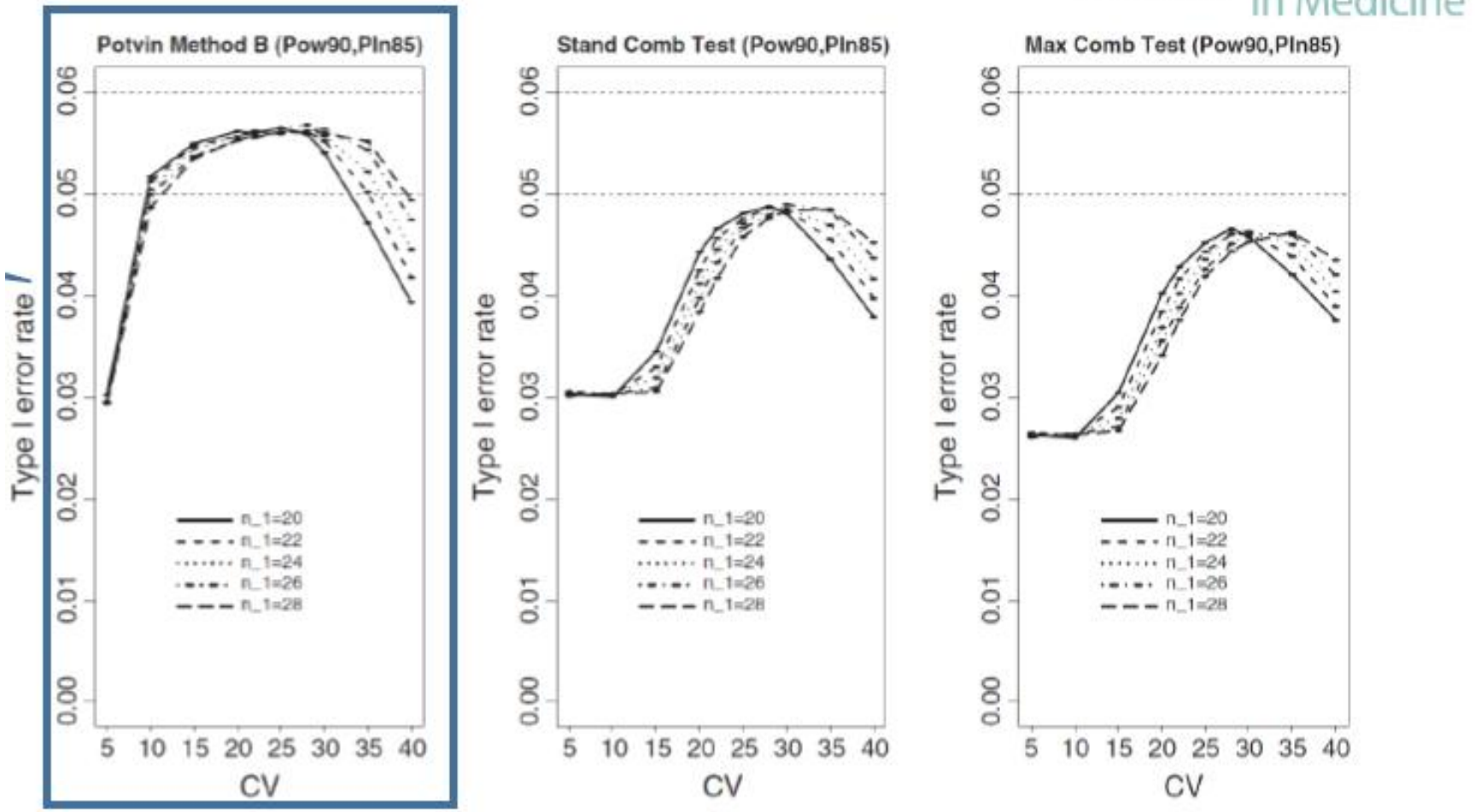
Table I. Estimated type I error rates and powers.

Sample size Stage 1 (N_1)	Intrasubject CV (%)	Estimated type I error rate			Estimated power		
		Method B	Method C	Method D	Method B	Method C	Method D
12	10	0.0336	0.0499	0.0498	0.8858	0.9050	0.9048
24	10	0.0295	0.0501	0.0501	0.9789	0.9898	0.9897
36	10	0.0295	0.0499	*0.0504*	0.9986	0.9994	0.9995
48	10	0.0295	0.0502	0.0503	0.9999	1.0000	1.0000
60	10	0.0294	0.0503	0.0498	1.0000	1.0000	1.0000
12	20	***0.0538***	***0.0547***	*0.0518*	0.8107	0.8114	0.8097
24	20	0.0471	0.0497	0.0475	0.8326	0.8346	0.8330
36	20	0.0386	0.0480	0.0477	0.8379	0.8494	0.8503
48	20	0.0313	0.0499	0.0499	0.8585	0.8942	0.8945
60	20	0.0294	0.0504	0.0498	0.9074	0.9425	0.9429
12	30	0.0437	0.0437	0.0414	0.7777	0.7773	0.7753
24	30	***0.0529***	***0.0531***	0.0506	0.8128	0.8127	0.8108
36	30	0.0512	0.0513	0.0489	0.8221	0.8225	0.8216
48	30	0.0483	0.0485	0.0470	0.8260	0.8265	0.8259
60	30	0.0449	0.0466	0.0449	0.8284	0.8289	0.8291

Maurer W, Jones B, Chen Y. Controlling the type I error rate in two-stage sequential adaptive designs when testing for average bioequivalence. Stat Med. 2018 May 10;37(10):1587-1607

Statistician should be included in all area whenever data are used.

WILEY-Statistics in Medicine



Maurer W, Jones B, Chen Y. Controlling the type I error rate in two-stage sequential adaptive designs when testing for average bioequivalence. Stat Med. 2018 May 10;37(10):1587-1607

TABLE 1 General concepts of the FDA and the EMA BE guidelines when interpreted using the estimands framework of the guideline ICH E9 (R1)

General concept	FDA BE guideline	EMA BE guideline
Trial objective	Demonstrate that rate and extent of absorption of the drug is equivalent between two formulations/drug products	Demonstrate that rate and extend of absorption of the drug is equivalent between two formulations/drug products
Estimand	Difference in rate and extent of absorption between test and reference formulation based on the missing at random (MAR) premise	Difference in rate and extent of absorption between test and reference formulation based on the missing completely at random (MCAR) premise
Main analysis strategy	Hypothetical strategy	Principal stratum strategy
Population of interest	Population for which the reference formulation/drug product is approved	Population for which the reference formulation/drug product is approved
Analysis variables	C_{max}, AUC_{inf} and AUC_t derived using NCA, as surrogates for rate and extend of absorption, based on reliable concentration profiles	C_{max} and AUC_t derived using NCA, as surrogates for rate and extend of absorption, based on reliable concentration profiles
Population-level summary	Ratio of variable means between formulations, estimated using a *mixed* effect analysis with log-transformed variables	Ratio of variable means between formulations, estimated using a *fixed* effect analysis with log-transformed variables
Estimator	The REML[a] estimator for the difference in means and corresponding two-sided 90% CI limits in log-transformed variables assuming normally distributed errors	The OLS[b] estimator for the difference in means and corresponding two-sided 90% CI limits in log-transformed variables assuming normally distributed errors
Estimate	Antilog of the point estimate and two-sided 90% confidence interval limits calculated from data based on the estimator	

Abbreviation: C_{max}, maximum concentration following study drug administration; CI, confidence interval; AUC_t, area under the concentration time curve from 0 to the last quantifiable concentration; AUC_{inf}, total area under the concentration versus time curve extrapolated to infinity; NCA, noncompartmental approach; OSL, ordinary least squares; REML, restricted maximum likelihood.

Ring A, Wolfsegger MJ. The potential of the estimands framework for clinical pharmacology trials: Some discussion points. Br J Clin Pharmacol. 2020 Jul;86(7):1240-1247

Key messages

- Investment efficiency in the pharmaceutical industry is declining.
- Clinical trials are taking longer, and the probability of success is not high.
- Attempts are being made to increase the efficiency of development
  - Bayesian framework, use of external data, adaptive design
- Unbiased point estimates are difficult to obtain
  - What about the idea of not giving special importance to point estimates?
  - Can we choose estimators with small Mean Square Errors?
- BE studies are an area where only binary decisions are made
  - BE Guidance may not be well described as explained in the previous slide
- Let's think for ourselves
- Be aware that the estimand may be different from authorities.

References

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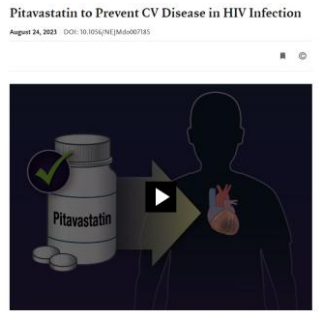
To obtain unbiased estimator

- Even if the interim analysis shows a significant benefit, the estimation can be made with high precision and accuracy if the trial is not stopped.
- In recent years, case of the REPRIVE trial, trial had been continued after obtaining good efficacy for them.
- If so, risk-benefit assessment can be done in high precision and accuracy. VICRORY trial induced big-discussion in early termination.



After discussion

- The IRR(internal rate of return) may be telling us that we, humans, should choose to become wealthy by other means.
- We humans may think that the basic medicines have been prepared by now except some disease area, such as cancer, central nerve system areas, and rare diseases would be in that category.
- However, they are difficult to develop, and the lack of efficacy in confirmatory trials may result in zero investment up to that point.
- Pharmaceutical development may have been reached a high-risk area for companies.
- Nevertheless, change may be necessary if humanity wants to use companies to obtain new medicines at the same rate as before.

After discussion

- It would be possible for the government or administration to conduct confirmatory trial as their own trial through a public agency, and it would also be possible to make drug prices a social burden. it can reduce expected risk for drug development.
- Alternatively, access to new drugs might be made more gradual to extend the patent period.
- Utilization of RWD would be an option. If efficacy is suggested by surrogate endpoints, then providing the product to medical settings under controlled conditions and validating its usefulness by RWD may be an option.
- At that point, the method for obtaining RWD itself would need to be rethought. If, as a society, we allow validation by RWD, we should routinely obtain the data necessary to do so.

After discussion

- Increasing the efficiency of drug development is always an available option.
- It is important not to continue to vaguely use traditional study designs, but to continue to look for ways to increase efficiency.
- In clinical trials, integrity is paramount.
- Losing it would render the trial useless. It is the mission of biostatisticians to seek the highest efficiency while ensuring integrity.