2026년

ICH 가이드라인 교육

Training on ICH Guideline 2026

2026.10. 01.(Thu) – 10. 02.(Fri) I EL Tower(엘타워), Seoul

DAY 2 I 안전성 & 유효성 & 복합 교육

M14



이호준 (Hojoon Lee)

암젠 관찰연구센터 상무

Amgen, Center for Observational Research (CfOR), Senior Manager

이호준 박사는 현재 암젠 관찰연구센터 산하 일본·아시아태평양 데이터·분석센터의 역학 부문을 총괄하며, 일본 및 아시아·태평양 지역의 데이터 전략 수립과 근거 창출 체계 개발을 주도하고 있다.해당 지역의 데이터와 분석 역량을 바탕으로 질병 발생과 환자 규모를 추계하고, 임상개발 계획 수립과 약물감시 역학을 지원하는 한편, 실제임상근거의 지속적 창출을 위한 플랫폼과 운영 체계를 구축하고 있다. 이를 통해 지역 데이터가 세계적 차원의 근거 창출과 의사결정에 폭넓게 활용되도록 기여하고 있다.한양대학교 의과대학을 졸업한 후 존스홉킨스대학교 블룸버그 공중보건대학원에서 보건학 석사와 역학 박사 학위를 취득하였다. 이후 존스홉킨스대학교, 세계보건기구, 암젠 등 학계·국제기구·산업계에서 역학 연구, 질병 감시 및 공중보건 사업을 수행해 왔다. 주요 전문 분야는 실제임상자료를 활용한 관찰연구와 근거 창출 전략, 근거 기반 의사결정 지원, 의약품 개발 전 주기에 걸친 실제임상근거 활용이다.

Dr. Hojoon Lee currently serves as Head of JAPAC Data & Analytic Center Epidemiology, part of Amgen's Center for Observational Research. In this role, he leads the development of regional data strategies and evidence-generation systems across Japan and the Asia-Pacific region.Leveraging the region's data and analytics capabilities, he supports disease incidence and patient population forecasting, clinical development planning, and pharmacovigilance epidemiology. He also leads the development of platforms and operating models that enable the continuous generation of real-world evidence (RWE), helping ensure that regional data contribute to global evidence generation and decision-making.Dr. Lee earned his Doctor of Medicine (MD) degree from Hanyang University College of Medicine and his Master of Public Health (MPH) and Doctor of Public Health (DrPH) in Epidemiology from the Johns Hopkins Bloomberg School of Public Health. His career spans academia, international organizations, and the biopharmaceutical industry, with experience at Johns Hopkins University, the World Health Organization (WHO), and Amgen. Across these settings, he has contributed to epidemiologic research, disease surveillance, and public health initiatives. His areas of expertise include observational research, evidence-generation strategies using real-world data (RWD), evidence-informed decision-making, and the application of real-world evidence (RWE) across the drug development lifecycle.

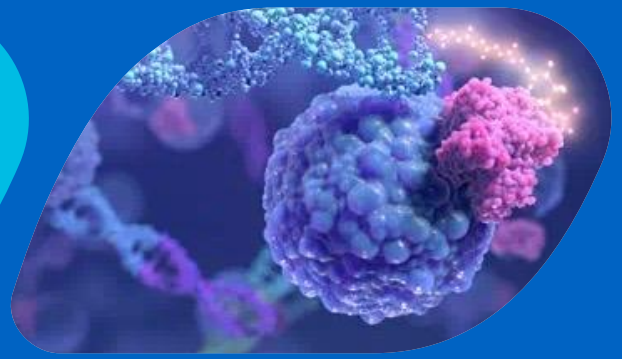
Program

ICH M14 가이드라인의 이해와 적용: 핵심 원칙, 실제 사례 및 향후 방향

Applying ICH M14: Practical Insights from Previous Studies

ICH M14 가이드라인은 의약품의 안전성 평가를 위해 실제임상자료(Real-World Data, RWD)를 활용하는 약물역학 연구의 계획, 설계 및 분석에 관한 일반 원칙을 제시한다. 본 강연에서는 가이드라인의 배경과 목적, 적용 범위를 소개하고, 연구 질문과 대상 인구집단의 정의, 데이터의 목적 적합성 평가, 적절한 연구설계와 비교군 선택, 교란 및 편향의 관리, 분석계획 수립, 결과 해석과 보고 등 연구 전 과정에서 고려해야 할 핵심 원칙을 살펴본다. 이어 실제 적용 사례를 통해 이러한 원칙이 연구 의사결정과 실행에 어떻게 반영되는지 설명하고, 적용 과정에서 직면한 주요 쟁점과 선택, 그리고 사례에서 얻은 교훈을 공유한다. 또한 지역별 데이터 환경과 분석 역량의 차이, 연구의 투명성과 재현성, 규제기관·산업계·학계·데이터 파트너 간 협력 등 향후 해결해야 할 과제를 논의한다.

ICH M14 provides general principles for the planning, design, and analysis of pharmacoepidemiological studies that use real-world data (RWD) to assess the safety of medicines. This presentation will introduce the background, objectives, and scope of the guideline and review key principles to consider throughout the study lifecycle. These include defining the research question and target population, assessing whether the data are fit for purpose, selecting an appropriate study design and comparator, addressing confounding and bias, developing the analysis plan, and interpreting and reporting study findings. A practical case example will then illustrate how these principles can be translated into study decisions and implementation, highlighting key challenges, decision points, and lessons learned. The presentation will also discuss areas requiring further attention, including regional differences in data environments and analytical capabilities, research transparency and reproducibility, and collaboration among regulatory authorities, industry, academia, and data partners.







Applying ICH M14: Practical Insights from Previous Studies

HOJOON LEE, MD, MPH, DRPH
AMGEN CENTER FOR OBSERVATIONAL RESEARCH

AMGEN

2026, Oct. 2

Disclaimer

- All information presented is based upon sources available publicly.
- The opinions expressed in this presentation and on the following slides are solely those of the presenter and not necessarily those of Amgen.
- Hojoon Lee is an employee of Amgen Korea and owns company stock.

Recap ICH M14

Objectives of ICH M14

- The purpose of this guideline is to recommend international standards for, and promote harmonization of, the general principles on planning, designing, analysing, and reporting of noninterventional studies that utilize fit-for-use (frequently referred to as fit-for-purpose) data for safety assessment of medicines (drugs, vaccines, and other biological products).

Objectives of ICH M14

- For safety assessment of medicines
- That utilize fit-for-use data
- To establish general principles on planning, designing, analysing, and reporting of noninterventional studies

ICH M14 conceptual framework

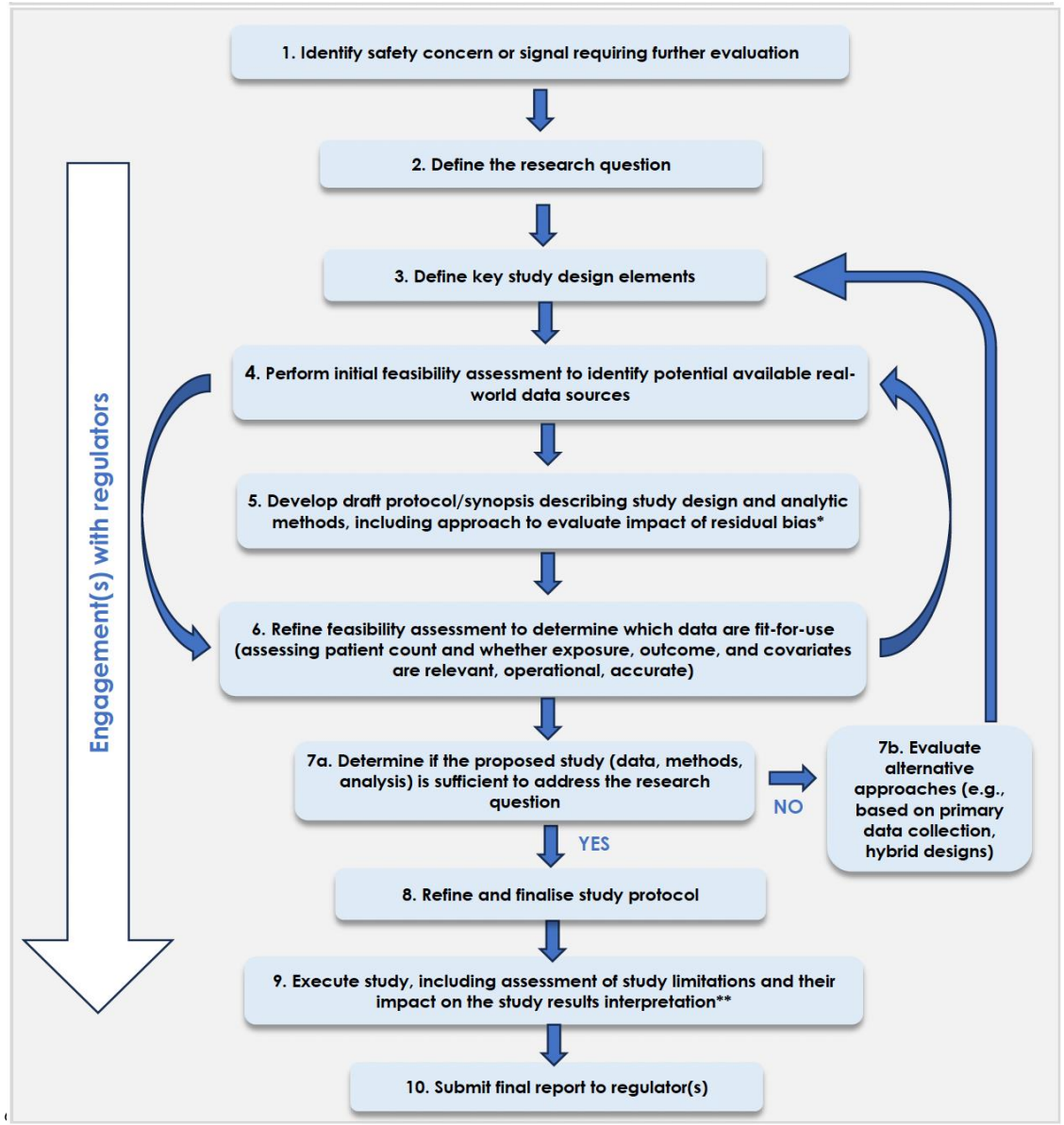
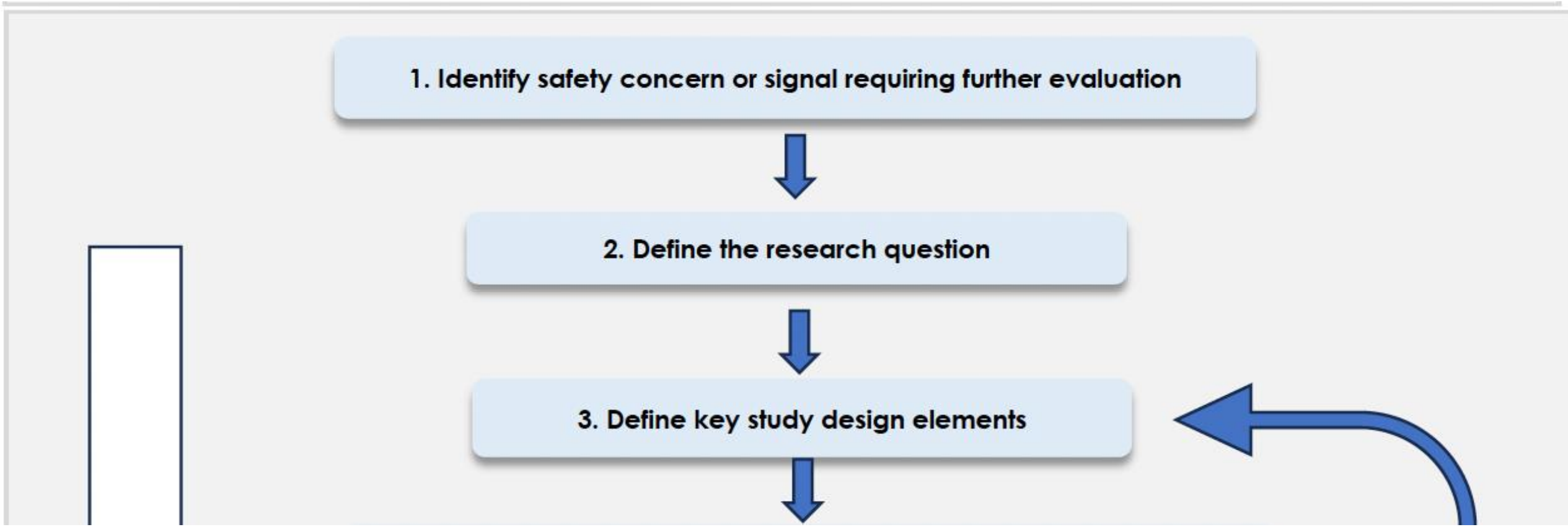
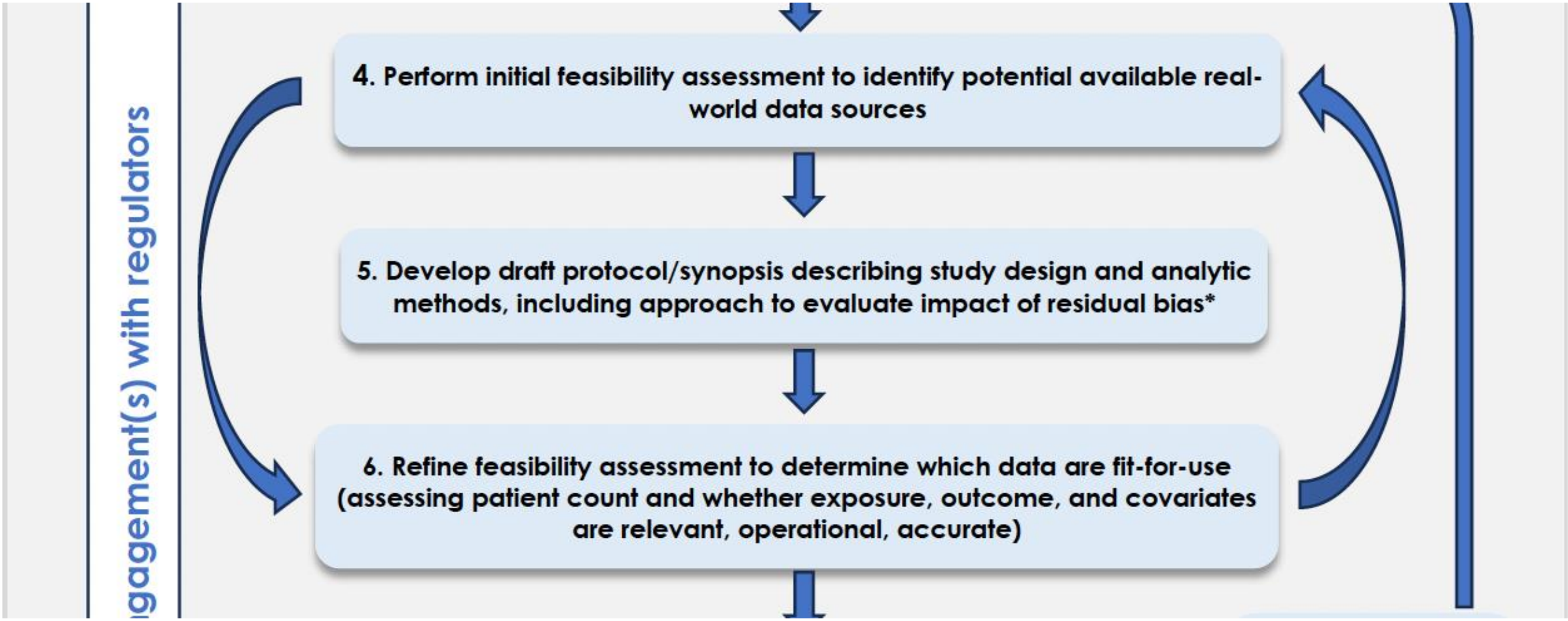


Figure 1. A conceptual framework for generating adequate evidence using fit-for-use real-world data to address regulatory questions on the safety of medicines

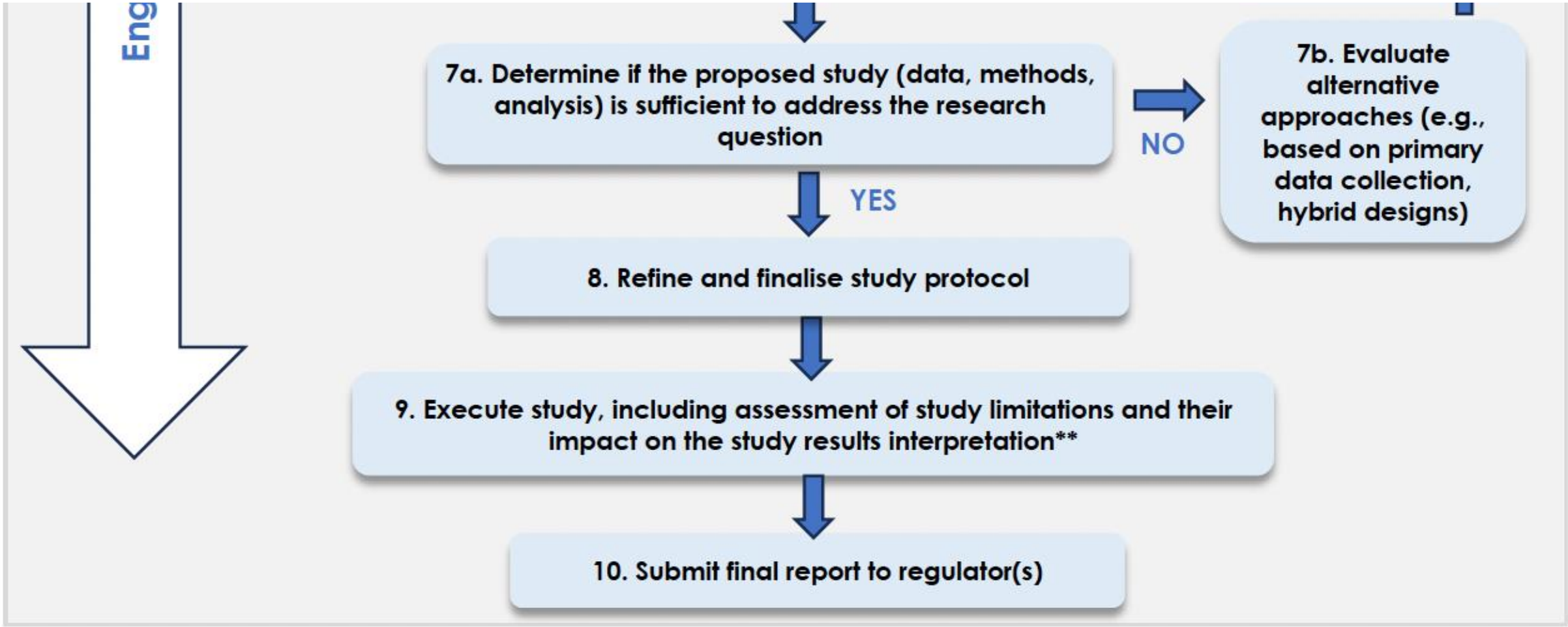
Study design and planning



Study design and planning

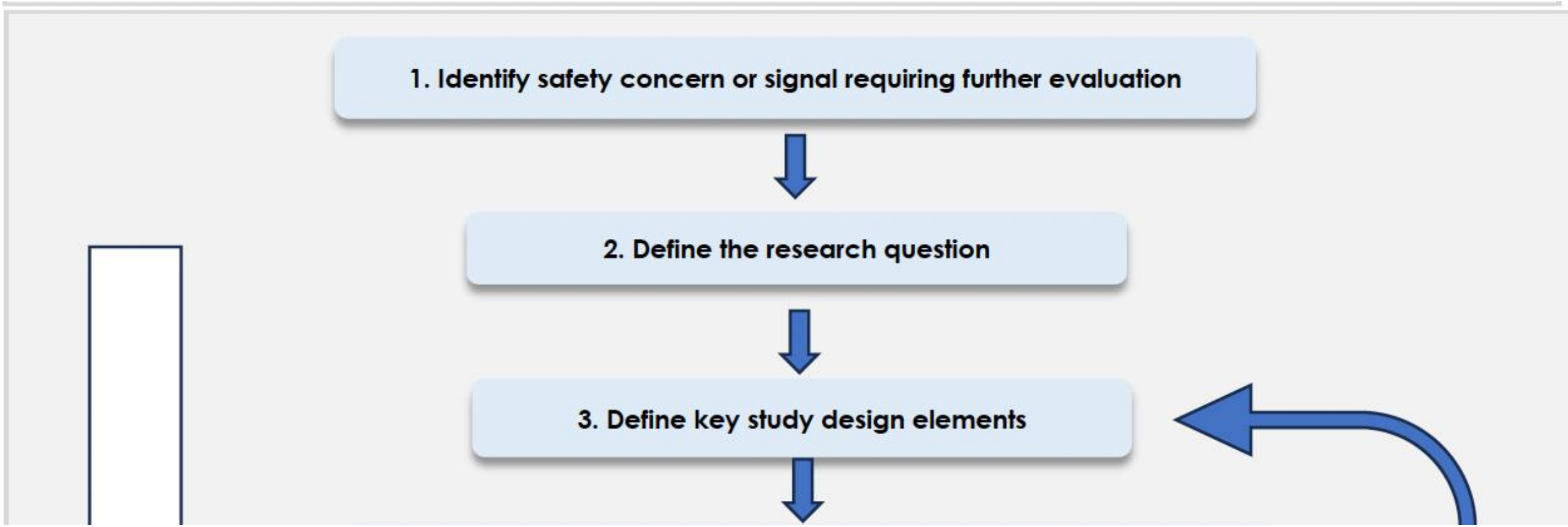


Analysis and reporting



Practical Insights from Previous Studies

Study design and planning



Postmarketing safety study of denosumab

Context – Denosumab approved for osteoporosis with high risk for fracture (2010) with Amgen commitment to conduct a 10-year study in the United States and European Union using RWD to describe incidence of Adverse Events of Special Interest

Robust feasibility assessment to inform design and interpretation "fit-for-purpose"

- Large datasets needed to assess rare events
- Validation to identify exposure, covariates, and endpoints
- Study design and analysis able to address confounding by indication



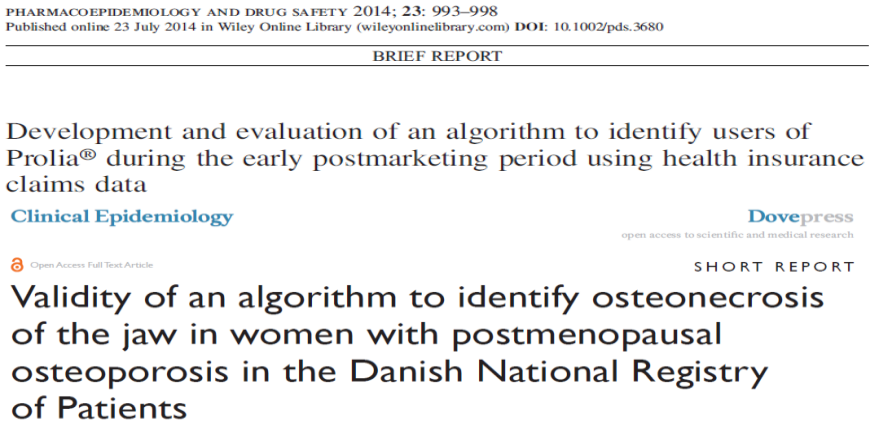
PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 1107–1114
Published online 15 July 2013 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3477

ORIGINAL REPORT

Design and methods of a postmarketing pharmacoepidemiology study assessing long-term safety of Prolia® (denosumab) for the treatment of postmenopausal osteoporosis‡

Fei Xue[1]*, Haijun Ma[2], Catherine Stehman-Breen[3], Christine Haller[4], Leonid Katz[3], Rachel B. Wagman[3], and Cathy W. Critchlow[1] for the Denosumab Global Safety Assessment Team†

[1]*Center for Observational Research, Amgen Inc., Thousand Oaks, CA, USA*



PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2014; **23**: 993–998
Published online 23 July 2014 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3680

BRIEF REPORT

Development and evaluation of an algorithm to identify users of Prolia® during the early postmarketing period using health insurance claims data

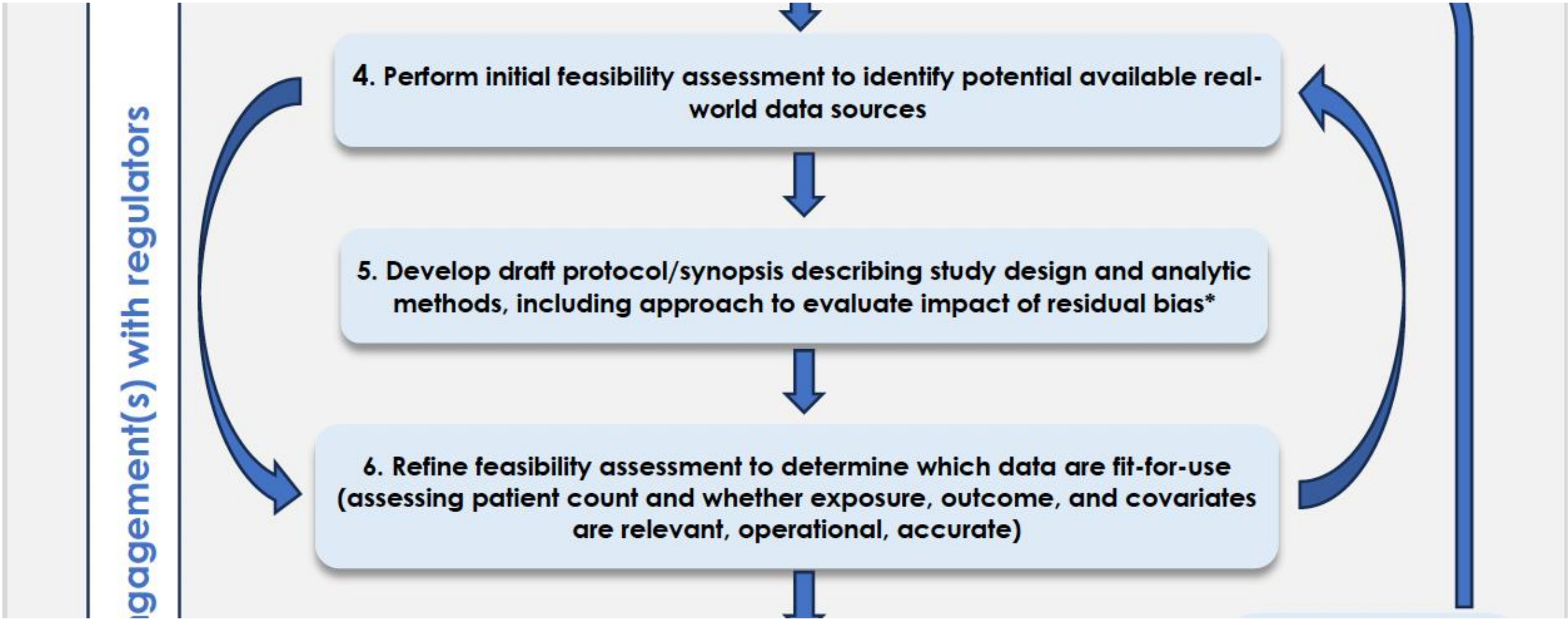
Clinical Epidemiology — Dovepress — open access to scientific and medical research

Open Access Full Text Article

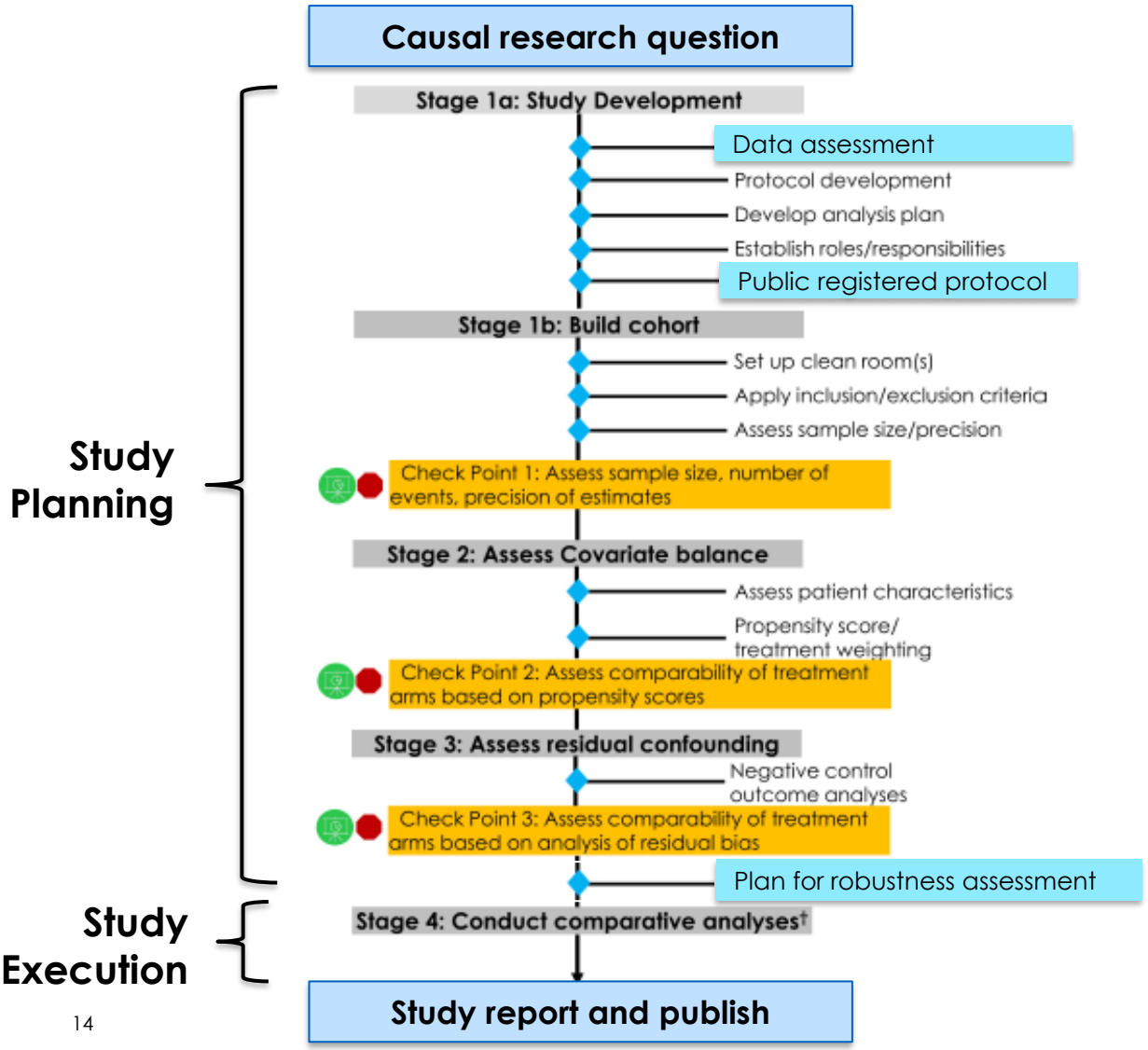
SHORT REPORT

Validity of an algorithm to identify osteonecrosis of the jaw in women with postmenopausal osteoporosis in the Danish National Registry of Patients

Study planning, analysis, and reporting



Stepwise process for comparative RWE



Step involved in the staging framework conducted by investigators

Check Point: Time when a decision is made to stop, continue, or revise the study

Results are shared with a review team (after Stages 1 through 3) or disseminated (after Stage 4)

† Only after all check points have been passed should the comparative analyses be conducted.

Received: 3 September 2023 | Revised: 29 January 2024 | Accepted: 30 January 2024
DOI: 10.1002/pds.5770

ORIGINAL ARTICLE

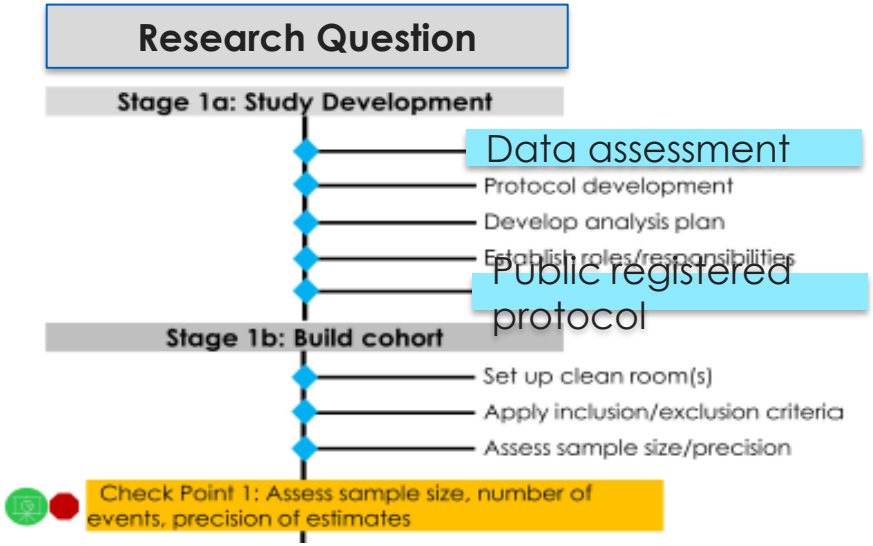
WILEY

Staging and clean room: Constructs designed to facilitate transparency and reduce bias in comparative analyses of real-world data

Paul Muntner[1] | Rohini K. Hernandez[2] | Shia T. Kent[2] | James E. Browning[2] | David T. Gilbertson[3] | Kathleen E. Hurwitz[4] | Susan S. Jick[5] | Edward C. Lai[6] | Timothy L. Lash[7] | Keri L. Monda[2] | Kenneth J. Rothman[8,9] | Brian D. Bradbury[2] | M. Alan Brookhart[10]

Pharmacoepidemiol Drug Saf. 2024;33:e5770.

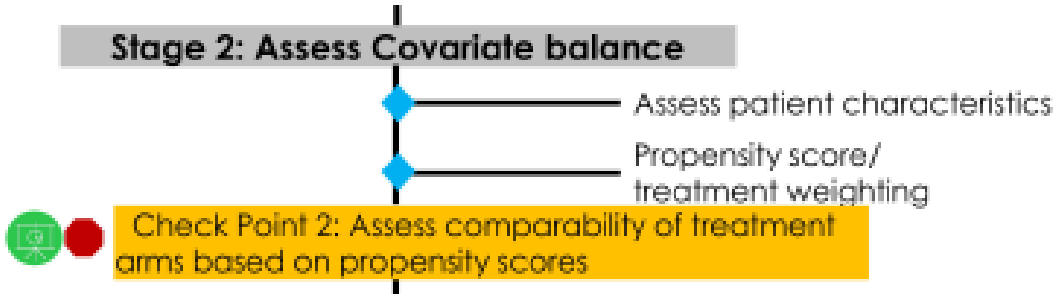
Checkpoint 1: Assess precision



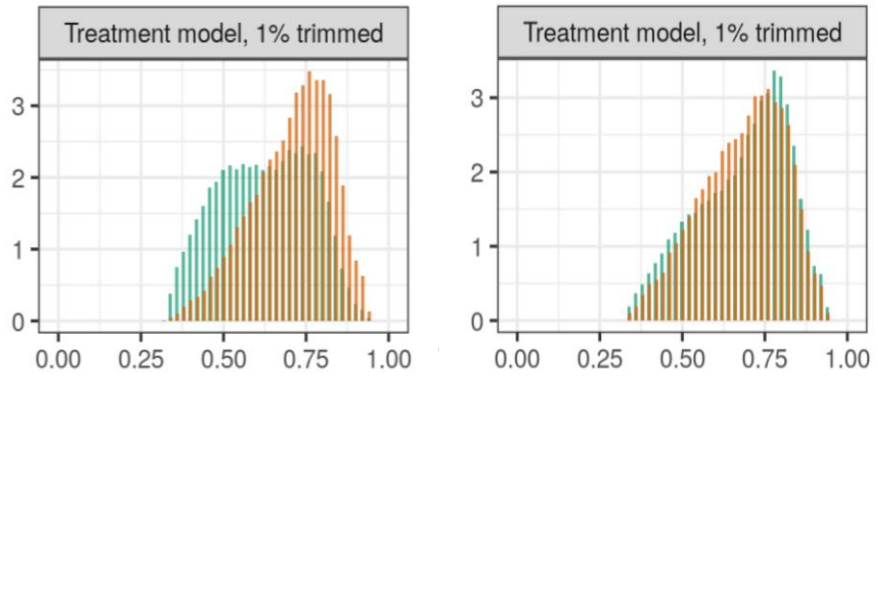
	Zoledronic Acid	Denosumab
Sample size	62,500	104,000
Follow-up (mean)	322 days	
Cardiovascular events (total)	715 events	
Cerebrovascular events (total)	505 events	

JBMR® Plus (WOA), Vol. 7, No. 10, October 2023, e10793.

Checkpoint 2: Assess cohort balance

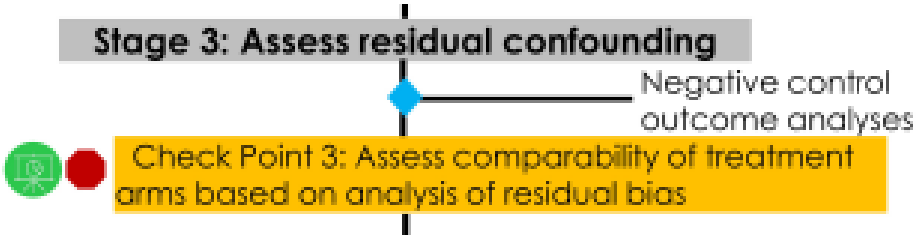


Before and after using propensity score modeling and treatment weighting



JBMR® Plus (WOA), Vol. 7, No. 10, October 2023, e10793.

Checkpoint 3: Assess unmeasured confounding



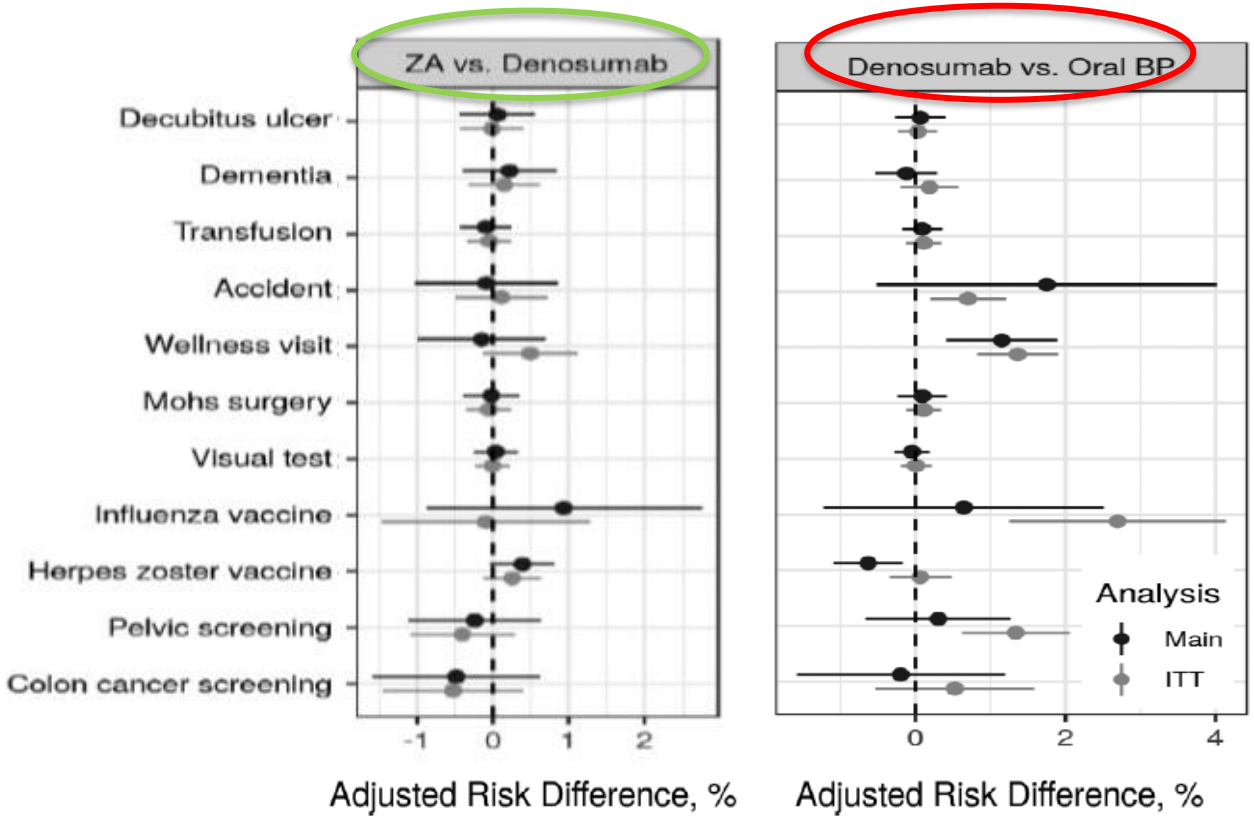
Negative control outcomes are:

- a precaution
- expectation of equivalence between cohorts
- to identify unmeasured confounding

Pragmatic considerations for negative control outcome studies to guide non-randomized comparative analyses: A narrative review

Sara N. Levintow[1,2] | Carrie M. Nielson[3] | Rohini K. Hernandez[3] | Alexander Breskin[1,2] | David Pritchard[2] | Timothy L. Lash[4] | Kenneth J. Rothman[5] | David Gilbertson[6] | Paul Muntner[7] | Cathy Critchlow[3] | M. Alan Brookhart[2,8] | Brian D. Bradbury[3]

Pharmacoepidemiol Drug Saf. 2023;32:599–606.



Checkpoint 3.2: Assess unmeasured confounding

Received: 12 August 2021 | Revised: 7 December 2021 | Accepted: 8 December 2021

DOI: 10.1002/pds.5396

ORIGINAL ARTICLE

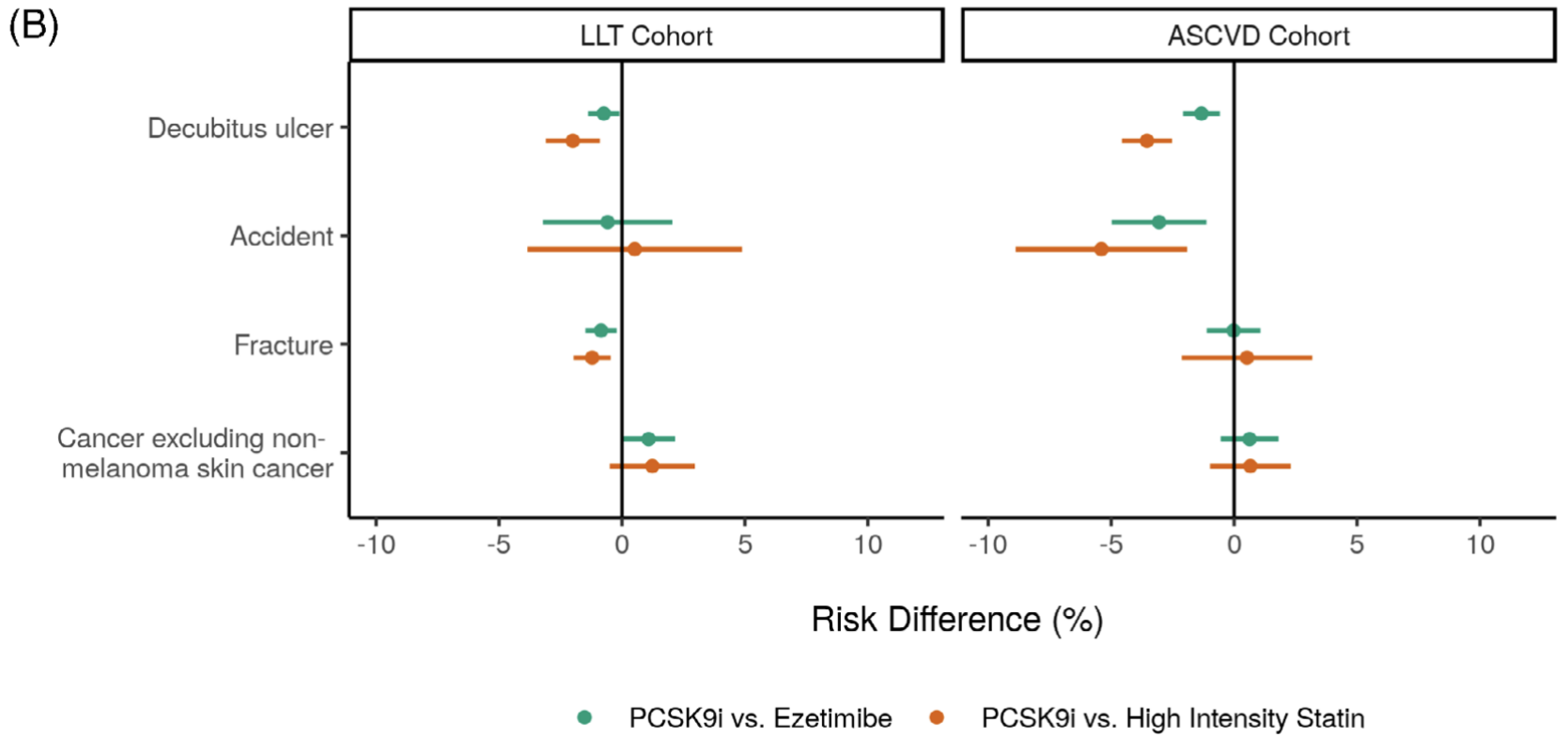
WILEY

Use of negative control outcomes to assess the comparability of patients initiating lipid-lowering therapies

Sara N. Levintow[1,2] | Kate K. Orroth[3] | Alexander Breskin[1,2] | Andrew S. Park[3] | Jose H. Flores-Arredondo[3] | Paul Dluzniewski[3] | Ann Marie Navar[4] | Henrik T. Sørensen[5] | M. Alan Brookhart[1,6]

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Checkpoint 3.2: Assess unmeasured confounding



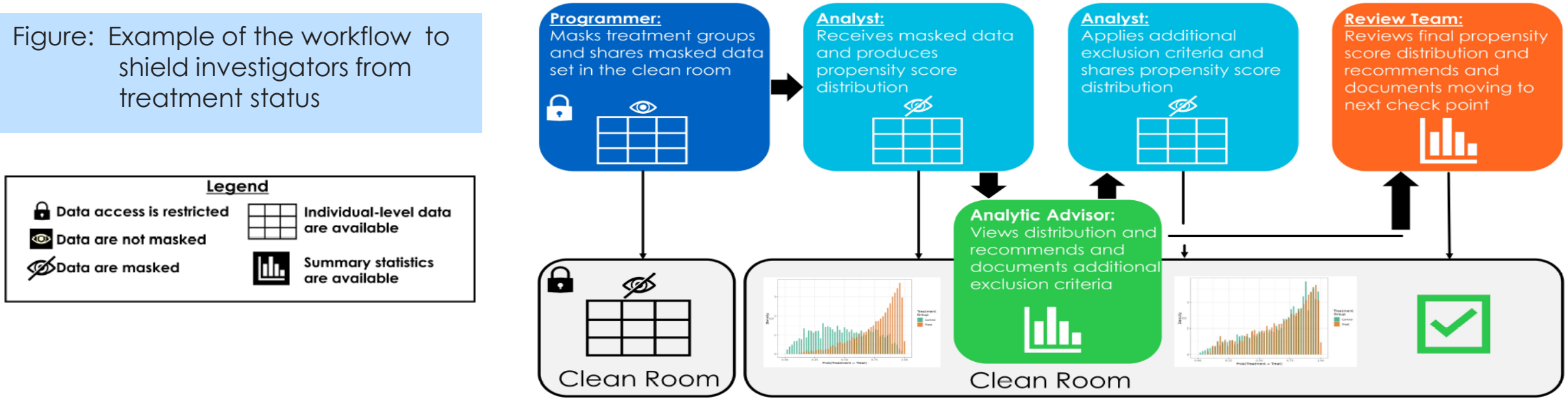
Conclusions: Observed associations suggest lower frailty and potentially greater health-seeking behaviors among PCSK9i initiators, particularly those with a recent ASCVD diagnosis, with the potential to bias real-world analyses of treatment effectiveness.

Transparency in study operations

To maintain study integrity, a workflow (e.g., clean room concept) can be created that:

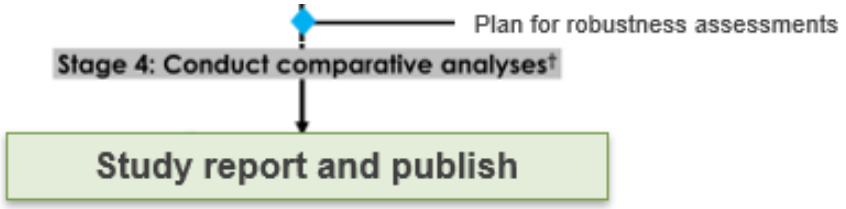
1) shields investigators from treatment status, hence not aware how their decisions affect the results
2) documents data access and changes via an audit trail and decision log

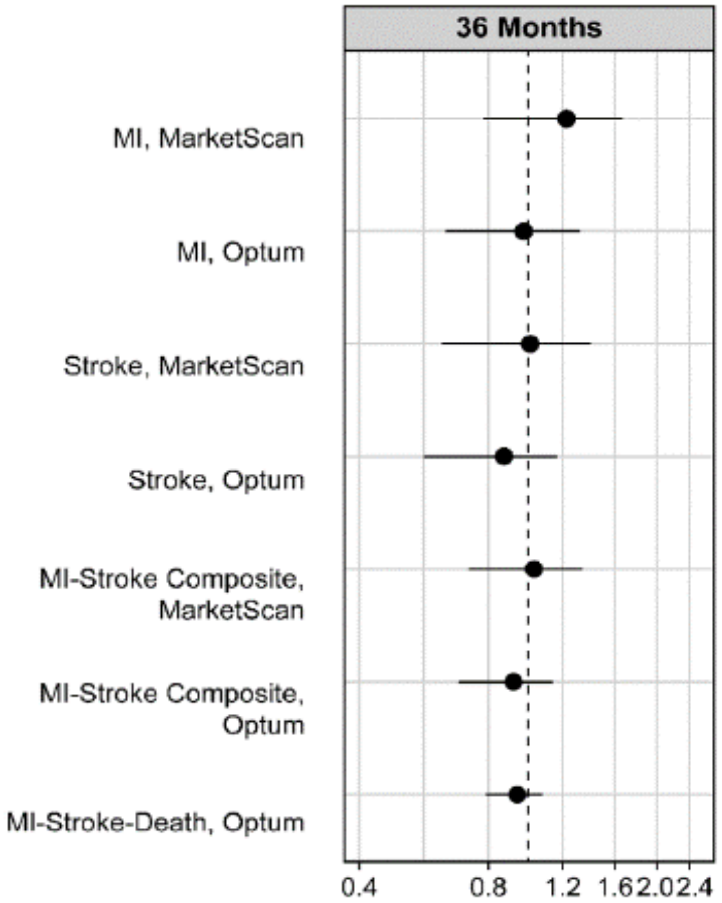
Figure: Example of the workflow to shield investigators from treatment status



JBMR® Plus (WOA), Vol. 7, No. 10, October 2023, e10793.

Study planning and execution





Robustness Assessment

- **Sensitivity analyses** to gauge influence of assumptions and design choices on study results
- **Quantitative bias analyses** to quantify residual uncertainties and magnitude of potential biases

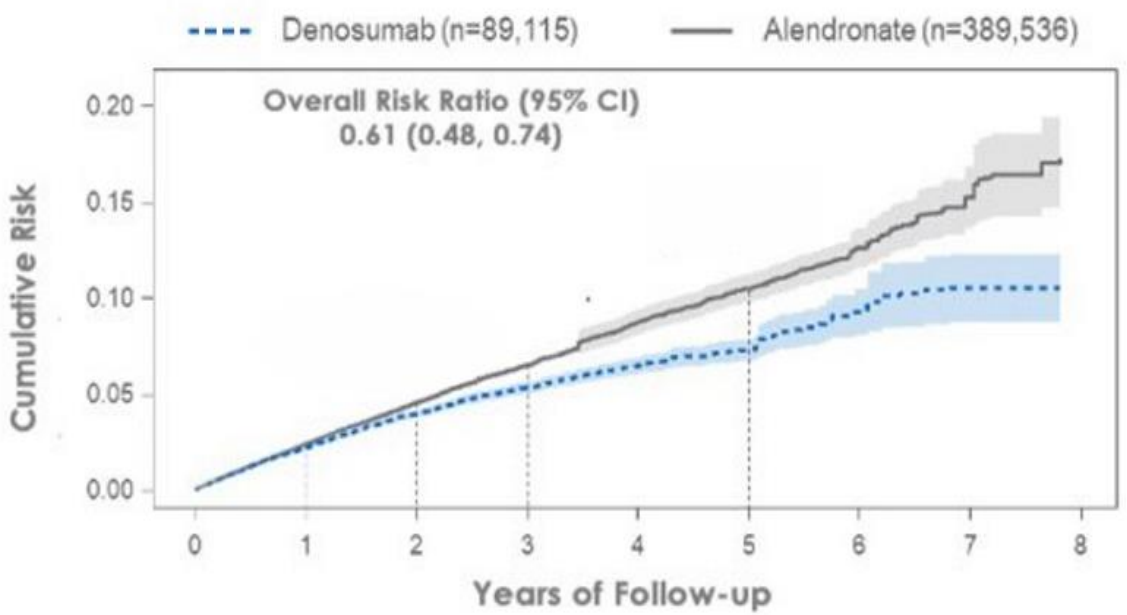
Results: Risk of cardiovascular and cerebrovascular events was NOT different between **denosumab vs. zoledronic acid**

JBMR® Plus (WOA), Vol. 7, No. 10, October 2023, e10793.

Effectiveness studies follow similar principles

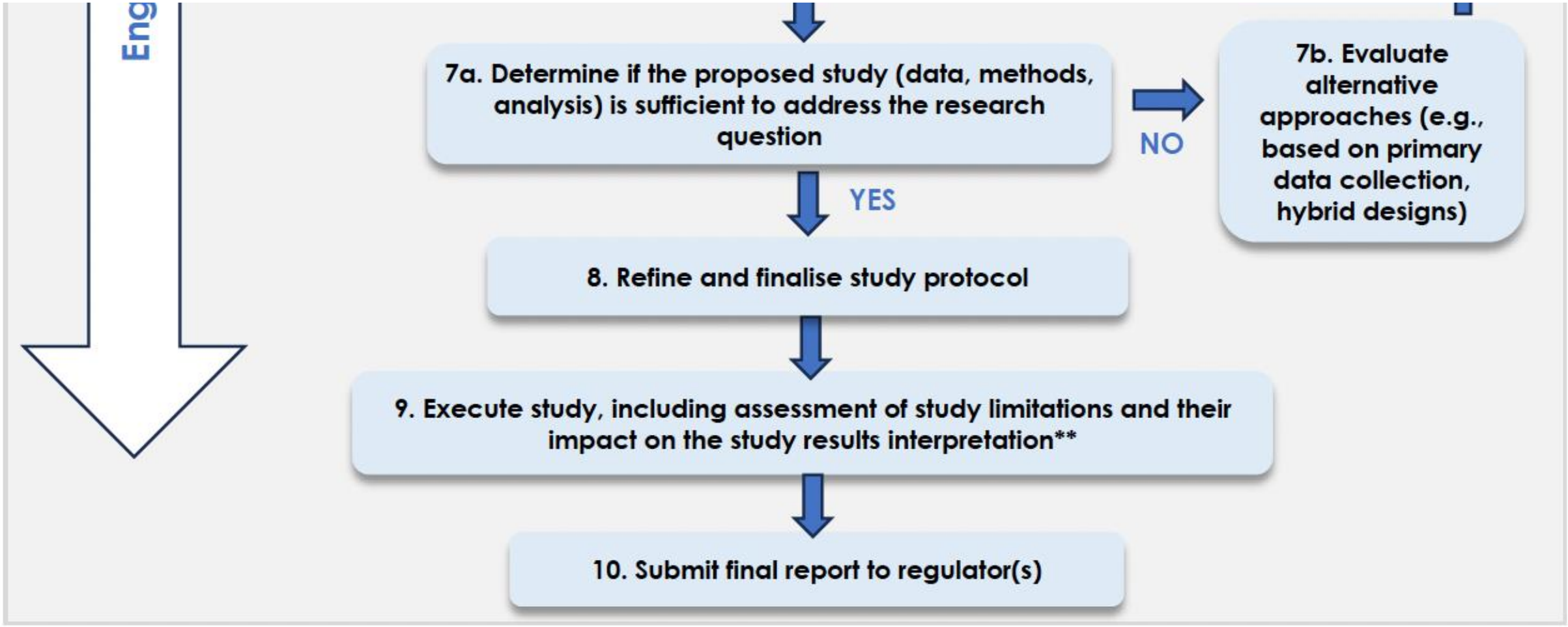
Study Design1

- Active comparator, new user design
- Medicare (n~478,000)
- Exposure: denosumab vs. alendronate
- Outcome: Osteoporotic fractures
- inverse probability of treatment and censoring weighting
- Negative controls2,3



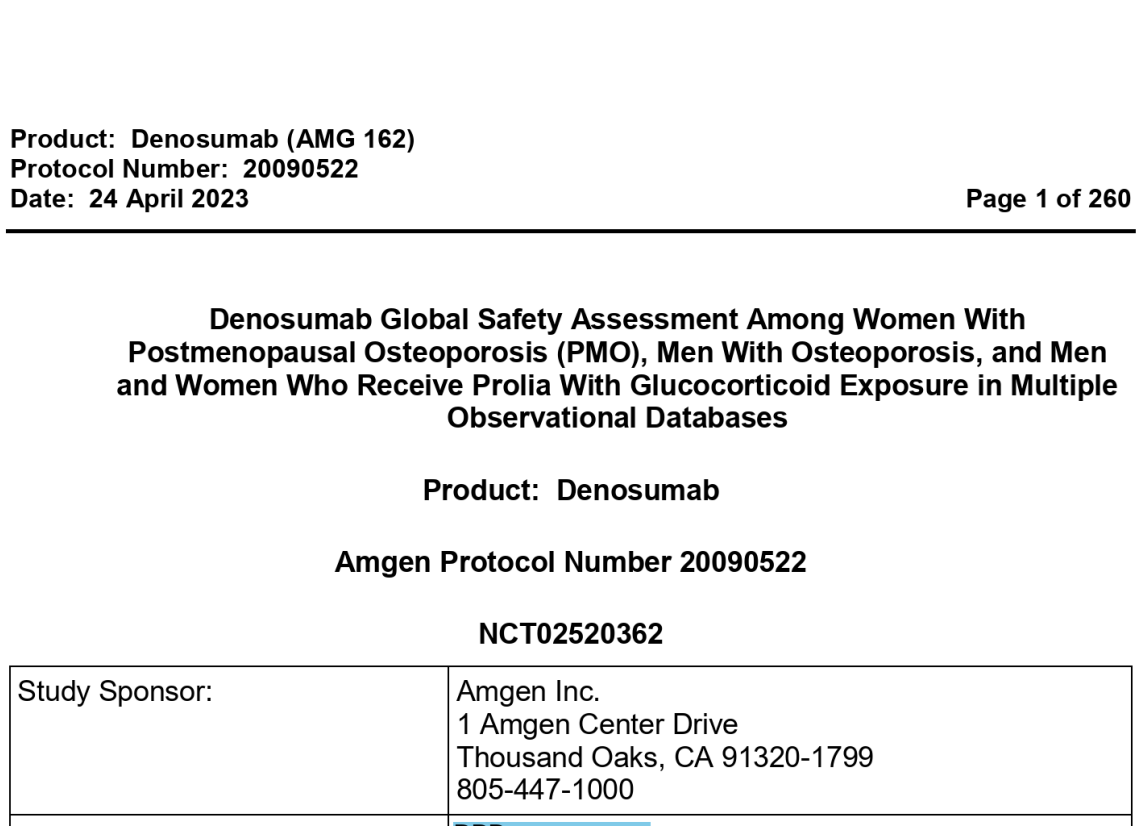
1Curtis et al., J Bone Mineral Res 2023; 2Kim et al., J Bone Miner Res 2023; 3Muntner et al., Pharmacoepidemiol & Drug Safety 2024

Analysis and reporting



Protocol refinement and finalization





Product: Denosumab (AMG 162)
Protocol Number: 20090522
Date: 24 April 2023

Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO), Men With Osteoporosis, and Men and Women Who Receive Prolia With Glucocorticoid Exposure in Multiple Observational Databases

Product: Denosumab

Amgen Protocol Number 20090522

NCT02520362

Study Sponsor:	Amgen Inc. 1 Amgen Center Drive Thousand Oaks, CA 91320-1799 805-447-1000

Study execution

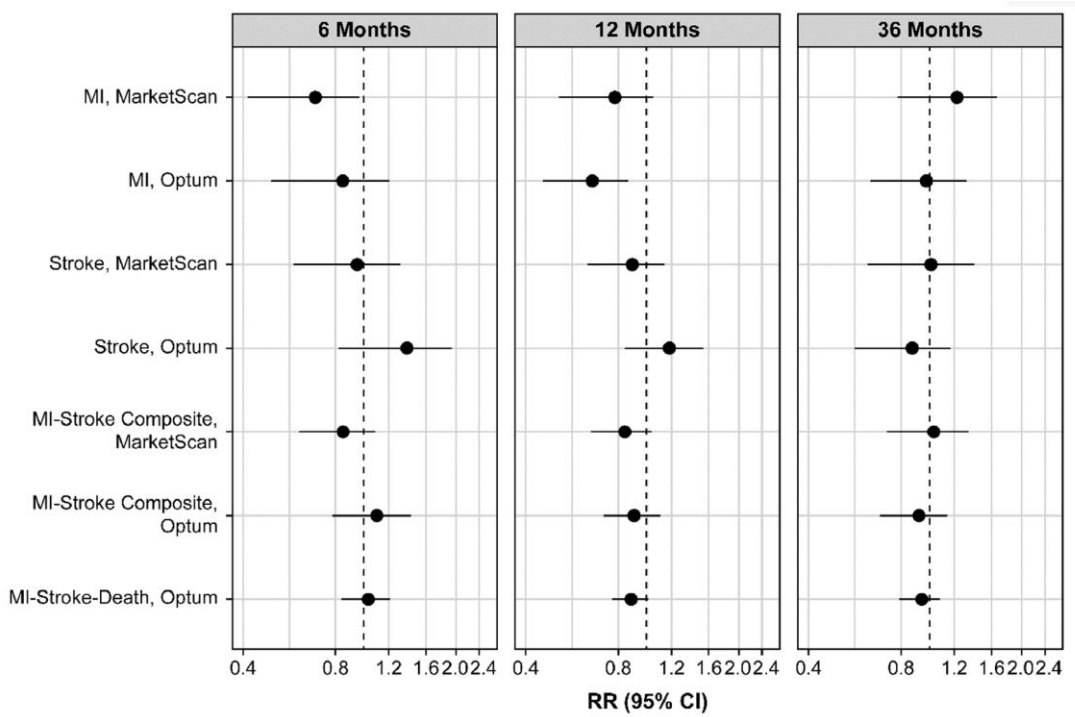
RESEARCH ARTICLE

JBMR PLUS Open Access ASBMR

Cardiovascular Safety in Postmenopausal Women and Men With Osteoporosis Treated With Denosumab and Zoledronic Acid: A Post-Authorization Safety Study

Leslie Spangler,[1] Carrie M. Nielson,[1] M. Alan Brookhart,[2,3] Rohini K. Hernandez,[1] Robert Kees Stad,[4] and Tzu-Chieh Lin[1]

[1]Center for Observational Research, Amgen Inc., Thousand Oaks, CA, USA
[2]NoviSci, Inc., Durham, NC, USA
[3]Department of Population Health Sciences, Duke University, Durham, NC, USA
[4]Research and Development, Amgen Inc. Europe GmbH, Rotkreuz, Switzerland



In these large samples of real-world US patients,
no increased risk in MI and stroke were identified for up to 36 months of treatment in denosumab users compared with zoledronic acid users.

AMGEN

Final report submission

Study results

Study results

20090522_ORSR_Abstract_13JUL2023_Redacted2.pdf

English (1.2 MB - PDF) View document

1. ABSTRACT

- **Title**

Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO), Men With Osteoporosis, and Men and Women Who Receive Prolia With Glucocorticoid Exposure in Multiple Observational Databases

Date: 13 July 2023

Name and affiliation of main author: [redacted] Amgen Inc.

- **Keywords**

US Medicare, postmenopausal osteoporosis, comparative safety analysis, risk ratio, cumulative risks.

THANK YOU

E2D(R1)



Yuan (Isaac) Meng

TJ 바이오제약 R&D 최고의학책임자(CMO)

TJ Biopharmaceutical R&D Chief Medical Officer

Yuan Meng은 2018년 TJBIO에 의학 부문 책임자(Head of Medical Office) 로 합류하여, 글로벌 규제 기준 준수를 보장하기 위해 회사의 의약품 안전성 시스템(medical safety systems) 및 연구개발(R&D) 품질보증 체계를 구축하고 지속적으로 개선해 왔습니다. 2024년부터는 최고의학책임자(Chief Medical Officer, CMO) 로서 TJBIO 파이프라인의 임상 개발 전략을 총괄하고 있으며, 복잡한 임상 개발 과제를 해결하기 위해 조직 역량 강화와 운영 우수성(Operational Excellence)을 이끌고 있습니다.Yuan Meng은 제약산업에서 25년의 경력을 보유하고 있으며, 이전에는 Johnson & Johnson에서 Cross-Sector Drug Safety Lead(전사적 의약품 안전성 책임자) 로 근무하며 중국 대륙 지역(Greater China)의 안전성 전략 및 약물감시(Pharmacovigilance) 운영을 총괄했습니다. 그는 산업계 경력을 Eli Lilly, Wyeth, Bristol-Myers Squibb 및 Pfizer에서 시작했습니다.제약업계에 진출하기 전에는 상하이 Ruijin Hospital(瑞金医院) 에서 임상 신경학 전문의로 진료와 교육 활동을 수행했습니다. 그는 Shanghai Medical University(현 푸단대학교 상하이 의과대학) 를 졸업했습니다.Meng 박사의 전문 분야는 임상 개발(clinical development), 약물감시(pharmacovigilance), 위해성 관리(risk management), 유익성-위해성 평가(benefit-risk assessment) 를 포함합니다. 현재 그는 ICH E2D(R1) 글로벌 전문가 실무그룹(Global Expert Working Group) 의 위원으로 활동하고 있으며, DIA China Advisory Council(중국 DIA 자문위원회) 의 핵심 구성원으로도 참여하고 있습니다.

Yuan Meng joined TJBIO in 2018 as Head of Medical Office, where he established and continues to refine the company's medical safety systems and R&D quality assurance frameworks to ensure compliance with global regulatory standards. Since 2024, as Chief Medical Officer, he has been leading the clinical development strategy for TJBIO's pipeline, driving team development and operational excellence to navigate complex clinical challenges.With 25 years of experience in the pharmaceutical industry, Yuan Meng previously served as the Cross-Sector Drug Safety Lead at Johnson & Johnson, overseeing safety strategy and pharmacovigilance operations in Greater China. He began his industry career at Eli Lilly, Wyeth, Bristol-Myers Squibb and Pfizer.Before joining the industry, Dr. Meng practiced and taught clinical neurology at Ruijin Hospital, Shanghai. He is a graduate of Shanghai Medical University (now Fudan University's Shanghai Medical College).Dr. Meng's expertise spans clinical development, pharmacovigilance, risk management, and benefit-risk assessment. He currently serves on the ICH E2D(R1) Global Expert Working Group and is a core member of the DIA China Advisory Council.

Program

ICH E2D(R1) 허가 후 안전성 데이터: 개별 이상사례 안전성 보고(ICSR)의 관리 및 보고를 위한 정의와 기준

E2D(R1) Post-Approval Safety Data: Definitions and Standards for Management and Reporting of Individual Case Safety Reports (ICSRs)

The ICH E2D guideline, first issued in 2003, has served as the foundational framework for post-approval individual case safety reporting. Over the past two decades, the pharmacovigilance landscape has transformed dramatically—new data sources such as social media, digital platforms, mobile health technologies, patient support programs, market research, and non-interventional studies have emerged or become increasingly prevalent. The 2003 guidance no longer adequately addressed these evolving realities.In response, ICH established the E2D(R1) Expert Working Group in 2019. Following extensive public consultation—with approximately 450 comments received on the 2024 draft—the revised guideline reached Step 4 in September 2025 and is now being implemented globally, with the EU effective date set for 18 March 2026.This presentation will examine the key changes introduced by E2D(R1): updated definitions of adverse events and adverse drug reactions, expanded guidance on solicited sources including organized data collection systems, new documentation requirements for activities not conducted according to a protocol, and clarified standards for good case management practices. Through practical examples, we will explore how these revisions impact day-to-day pharmacovigilance operations and why they are essential for maintaining robust post-market safety surveillance in today's data-rich environment.

ICH
harmonisation for better health

E2D(R1)

Post-Approval Safety Data: Definitions and Standards for Management and Reporting of Individual Case Safety Reports (ICSRs)

Step 4 document - to be implemented (September 2025)

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

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Background [continued]

- Original ICH E2D guideline was adopted in 2003
- New sources of post-market safety information have emerged (or are used more often) which vary in characteristics and contribution to post-market safety surveillance (e.g., patient support programs (PSPs) and social media)
- The definitions and regulatory guidance in the original ICH E2D document are no longer sufficient to provide guidance on current pharmacovigilance practices and needs
- ICH E2D(R1) EWG (Expert Working Group) established in 2019 to revise E2D to support appropriate post-market safety surveillance

Background [continued]

- E2D(R1) establishes a framework for current best practices of post-approval safety data management in a dynamic environment
- This updated guideline provides recommendations that are harmonized to the extent possible given differences in post-market safety reporting requirements among ICH regions
- Where applicable, this guideline notes where local and regional requirements may vary and, as such, marketing authorization holders (MAHs) should refer to the relevant regional and local regulatory authority's requirements
- These slides highlight only the significant updates and changes to the original 2003 E2D Guideline.
  Extensive editorial changes have been made throughout the document. Refer to the complete document for all changes and updates

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Post-Approval Safety Data: Definitions And Standards for Management and Reporting of Individual Case Safety Reports

1 **INTRODUCTION** *(updated)*

2 **DEFINITIONS AND TERMINOLOGY** *(updated)*

2.1 Basic Terms:
- 2.1.1 Adverse Event (AE) *(updated)*
- 2.1.2 Adverse Drug Reaction (ADR) *(updated)*
- 2.1.3 Serious AE/ADR *(updated)*
- 2.1.4 Unexpected AE/ADR *(updated)*
- 2.1.5 Other Observations *(new)*
- 2.1.6 Reporting Terminology *(new)*

2.2 Individual Case Safety Report (ICSR) including Minimum Criteria *(new)*

2.3 Expedited Report *(new)*

2.4 Primary Source *(new)*

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Post-Approval Safety Data: Definitions And Standards for Management and Reporting of Individual Case Safety Reports

2 **DEFINITIONS AND TERMINOLOGY (continued)**

2.5 Healthcare Professional (HCP) *(updated)*
2.6 Consumer *(updated)*
2.7 Digital Platform *(new)*
2.8 Organized Data Collection System (ODCS) *(new)*
2.9 Patient Support Program (PSP) *(new)*
2.10 Market Research Program (MRP) *(new)*

3 TYPES OF ICSRs *(new)*

3.1 Spontaneous Reports *(new)*
3.2 Solicited Reports *(new)*

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Post-Approval Safety Data: Definitions And Standards for Management and Reporting of Individual Case Safety Reports

4. **SOURCES OF ICSRs** *(updated)*
   - 4.1 Communications by HCPs and Consumers ***(new)***
   - 4.2 Literature *(updated)*
   - 4.3 Digital Platforms ***(new)***
     - 4.3.1 Digital platforms under the responsibility of the MAH ***(new)***
     - 4.3.2 Digital platforms not under the responsibility of the MAH ***(new)***
   - 4.4 Non-interventional Studies ***(new)***
     - 4.4.1 Non-interventional studies with primary data collection ***(new)***
     - 4.4.2 Non-interventional studies with secondary use of data ***(new)***
   - 4.5 Patient Support Programs ***(new)***
   - 4.6 Market Research Programs ***(new)***
   - 4.7 Regulatory Authorities ***(new)***
   - 4.8 Other Sources *(updated)*

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Post-Approval Safety Data: Definitions And Standards for Management and Reporting of Individual Case Safety Reports

5. STANDARDS FOR REPORTING *(updated)*

5.1 What Should Be Reported? *(updated)*

5.1.1 AEs/ADRs *(updated)*

5.1.2 Important Safety Findings ***(new)***

5.1.3 Other Observations *(updated)*

5.1.3.1 Lack of Efficacy or Lack of Effect *(updated)*

5.1.3.2 Overdose, abuse, misuse, medication error, occupational exposure *(updated)*

5.1.3.3 Exposure to medicinal products associated with pregnancy or breastfeeding (***new)***

5.1.3.4 Off-label use ***(new)***

5.2 Reporting Timeframes *(updated)*

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Post-Approval Safety Data: Definitions And Standards for Management and Reporting of Individual Case Safety Reports

6. GOOD CASE MANAGEMENT PRACTICES *(updated)*

6.1 Assessing Patient and Reporter Identifiability *(updated)*

6.2 The Role of Narratives *(updated)*

6.3 Clinical Case Evaluation *(updated)*

6.4 Follow-up Information *(updated)*

6.4.1 Other Observations ***(new)***

6.4.1.1 Overdose, abuse, misuse, medication error, occupational exposure ***(new)***

6.4.1.2 Exposure to medicinal products associated with pregnancy or breastfeeding-*(updated)*

6.5 Contractual Agreements *(updated)*

6.6 Duplicate Management ***(new)***

6.7 How to Report *(updated)*

Chapter 1 - Introduction

- The ICH E2D guideline was originally based on the contents of ICH E2A
- The introduction was updated to reflect the current focus of E2D: guidance on definitions and standards for post-approval individual case safety reporting, as well as good case management practices

Chapter 2 – Definitions and Terminology

- Key changes include:
  - New definitions **2.1.5 Other Observations** and **2.1.6 Reporting Terminology** have been added
  - New definition (2.2) was added for **Individual Case Safety Report (ICSR) including Minimum Criteria**
  - New definitions were added for **2.3 Expedited Report** and **2.4 Primary Source**

Chapter 2 – Definitions and Terminology (continued)

- New definitions have been provided for:

2.7 Digital Platform

2.8 Organised Data Collection System (ODCS)

2.9 Patient Support Program (PSP)

2.10 Market Research Program (MRP)

All of these were areas of specific focus for the revisions within ICH E2D(R1)

Chapter 3 – Types of ICSRs

The concepts of Spontaneous Reports and Solicited Reports were moved from section ‘Sources of ICSRs’ to new section ‘Types of ICSRs’ as they are report types rather than sources

- **Spontaneous Reports** are direct communications by an HCP or consumer to an MAH, regulatory authority or other organization that describe one or more AEs/ADRs in a patient who was exposed to one or more medicinal products and that was not gathered as part of an ODCS
- **Solicited Reports** are those derived from ODCS. For the purposes of reporting, solicited ICSRs are classified as ‘reports from study’ in E2B format and should have a causality assessment

Chapter 4.1 - Communications by HCPs and Consumers

- Includes guidance on the management of safety communications by HCPs and consumers to regulatory authorities or other Organisation (e.g., Regional Pharmacovigilance Center) and marketing authorisation holders (MAHs)

Chapter 4.2 - Reporting from Literature

- Updated recommendations on screening literature to improve harmonization
- Clarifies the start of the time clock for reporting literature ICSRs
- Clarifies expectations for reporting when the specific brand or trade name of the product is ambiguous or unknown
- Provides recommendations to include important findings from literature in Periodic Safety Reports, when applicable
- Provides helpful recommendation on classifying the Type of Report in ICH E2B for Literature ICSRs

Chapter 4.3 - Digital Platforms

- Replaces original E2D Section 3.1.3 Internet
- Defines what is meant by digital platforms as data source
- Provides description of MAH responsibilities depending on digital platform ownership
- No obligation for MAHs to screen external digital platforms
- Clarifies the start of the time clock for reporting
- **4.3.1 Digital Platforms under the MAH's responsibility**
  - MAHs should regularly screen digital platforms under their responsibility
  - Provides guidance on process for post-approval safety data management depending on nature of activity (i.e., spontaneous or solicited)

Chapter 4.3 - Digital Platforms [continued]

- **4.3.2 Digital platforms not under MAH's responsibility**
  - Provides guidance when accessing data on digital platform in context of Organized Data Collection System (ODCS)
  - Supports limiting the scope of screening for AEs/ADRs
  - Refers to a new value in E2B (ICSR reporting format) to identify cases from ODCS with source data from Digital Platforms
  - Provides guidance for managing AEs/ADRs identified on a digital platform outside the context of an ODCS

Chapter 4.4 – Non-interventional Studies

- Defines what is meant by non-interventional studies and describes primary data collection and secondary use of data
- Describes MAH responsibilities for review and reporting of AEs/ADRs depending on the type of data used (primary data collection versus secondary use of data)

Chapter 4.5 - Patient Support Programs (PSPs)

- PSPs are considered ODCSs
- PSPs include collection of medical information or program design is such that the program will likely receive medical information
- For the setup and conduct of PSPs, MAHs should have documentation in place as detailed in Section 2.8, ODCS
- Manage AEs/ADRs as solicited (i.e., study) reports
- Refers to new value in E2B (ICSR reporting format) to identify cases from PSPs

Chapter 4.6 - Market Research Programs (MRPs)

- MRPs are considered ODCSs
- For the setup and conduct of MRPs, MAHs should have documentation in place as detailed in Section 2.8, ODCS
- Manage AEs/ADRs as solicited (i.e., study) reports
- Refers to new value in E2B (ICSR reporting format) to identify cases from MRPs

Chapter 5.1 What Should be Reported?

- Updates reporting guidance to allow harmonization with current regional or local requirements with respect to seriousness, expectedness
- Added a new Section: **5.1.2 Important Safety Findings**

  Safety findings which do not qualify for ICSR reporting and which may lead to changes in the known risk-benefit balance of a medicinal product and/or impact on public health should be communicated as soon as possible to the regulatory authorities in accordance with regional or local requirements

Chapter 5.1.3 Other Observations

- Expanded section to clarify reporting obligations for several scenarios:
  - Lack of Efficacy or Lack of Effect
  - Overdose, abuse, misuse, medication error, occupational exposure
  - Exposure to medicinal products associated with pregnancy or breastfeeding
  - Off-label use

Results of public consultation

- Approximately 450 comments were received during public consultation. The EWG reviewed every comment received
- Numerous revisions were made to provide greater clarity
- Additionally, a new section for non-interventional studies was introduced to address primary data collection versus secondary use of data
- Practical coding examples to illustrate use of new E2B(R3) values will be provided as training material

Conclusions

- This revised Guideline provides updated guidance on post-approval safety data management by better reflecting current practices and sources of safety data

E14/S7B Q&A



Jean-Pierre Valentin

UCB, 벨기에 브레인르알뢰 비임상 안전성 평가, 초기 임상 개발 및 중개과학 수석 연구위원(펠로우), 전략 고문

UCB, Braine l'Alleud, BELGIUM, Non-Clinical Safety Evaluation, Early Clinical Development and Translational Science, Fellow, Strategic Advisor

Valentin 박사는 바이오의약품 산업에서 30년 이상의 경력을 보유한 제약과학자로, 여러 제약회사에서 과학 연구와 고위 리더십 역할을 두루 수행해 왔습니다. 그는 다수의 신약 후보물질 발굴에 기여했으며, 다양한 치료 분야에서 약 200개 화합물의 안전성 및 2차 약리학(secondary pharmacology) 평가를 총괄했습니다.Valentin 박사는 안전성약리학회(Safety Pharmacology Society)의 전 회장을 역임했으며, 현재 HESI Global, IQ-DruSafe, EFPIA-PDEG에서 리더십 역할을 맡고 있습니다. 지난 10여 년간 EFPIA 대표로 ICH E14/S7B 이행 실무그룹(Implementation Working Group)에 참여했으며, 글로벌 규제과학(regulatory science) 이니셔티브에도 활발히 기여해 왔습니다.또한 과학학회, 대학, 산업협회를 통해 연구자 교육과 멘토링에 지속적으로 헌신해 왔으며, 여러 건의 특허를 보유하고 있고 250편 이상의 과학 논문을 발표한 저자이기도 합니다.

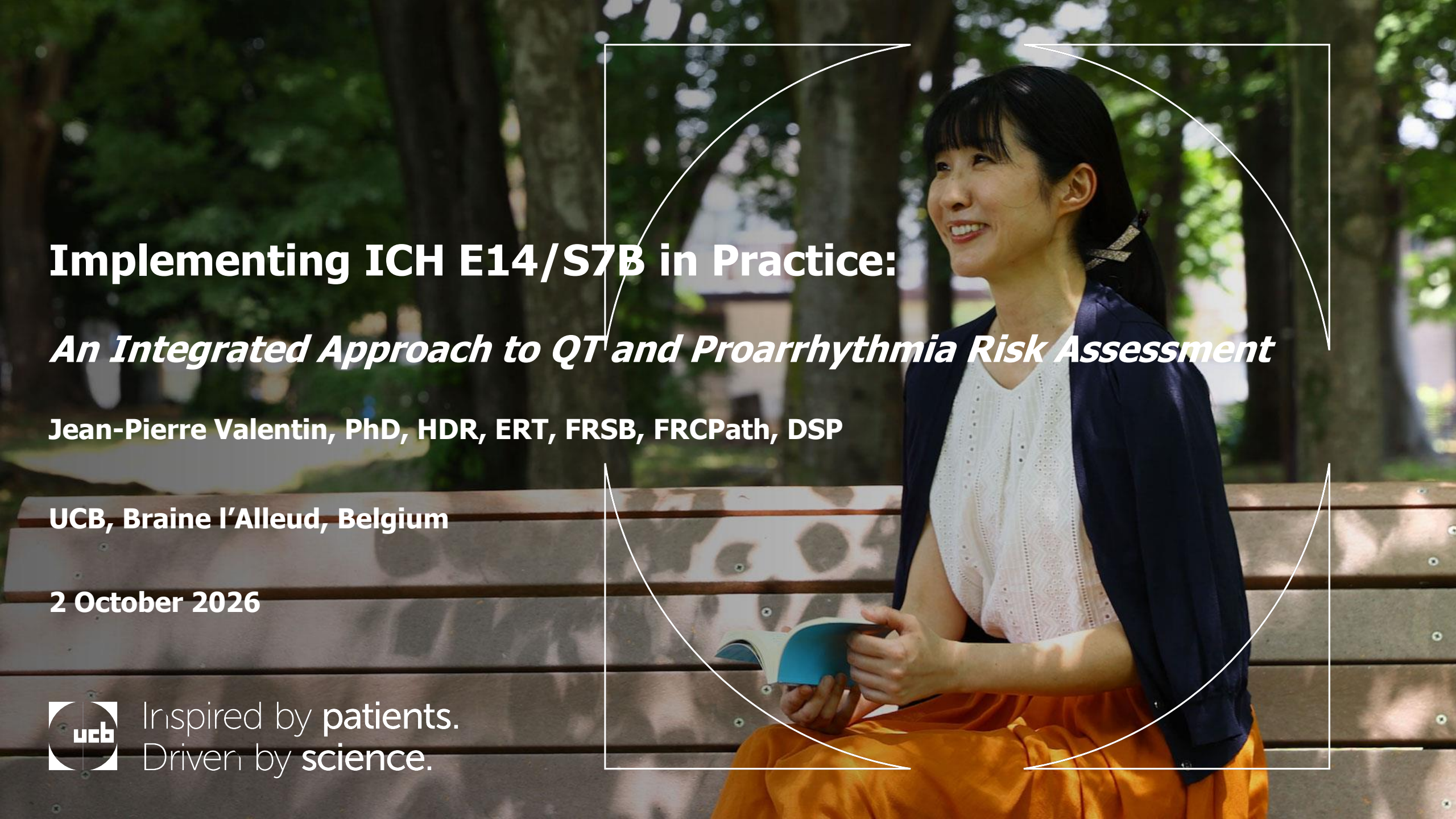
Dr Valentin is a pharmaceutical scientist with over 30 years of experience in the biopharmaceutical industry, spanning both scientific and senior leadership roles across several pharmaceutical companies. He has contributed to the discovery of numerous drug candidates and has overseen the safety and secondary pharmacology assessment of approximately 200 compounds across multiple therapeutic areas. Dr Valentin is a former President of the Safety Pharmacology Society and currently holds leadership roles within HESI Global, IQ-DruSafe, and EFPIA-PDEG. Over the past decade, he has represented EFPIA on the ICH E14/S7B Implementation Working Group and has been actively involved in global regulatory science initiatives. He has a longstanding commitment to training and mentoring through scientific societies, universities, and trade associations, and is the author of several patents and more than 250 scientific publications.

Program

ICH E14/S7B의 실제 적용: QT 및 부정맥 유발 위험 평가를 위한 통합적 접근

Implementing ICH E14/S7B in Practice: An Integrated Approach to QT and Proarrhythmia Risk Assessment

The implementation of ICH E14/S7B has transformed the assessment of proarrhythmic risk by enabling integrated interpretation of nonclinical and clinical data throughout drug development. Rather than relying on individual studies in isolation, the guideline promotes a weight-of-evidence approach that combines mechanistic understanding, exposure-response relationships, in vitro ion channel and human stem cell-derived cardiomyocyte assays, in vivo telemetry studies, and clinical ECG evaluation to support informed regulatory decision-making.This presentation will illustrate how the E14/S7B paradigm is applied in practice using representative case examples drawn from pharmaceutical development. Particular emphasis will be placed on study design, data interpretation, integration of evidence across disciplines, and the impact of these data on regulatory strategies, including situations where nonclinical findings may reduce the need for dedicated clinical QT studies. Practical lessons learned during implementation of the guideline across industry and regulatory interactions will be discussed, together with common challenges and opportunities to improve consistency of decision-making.Finally, the presentation will briefly consider how the collaborative experience gained through implementation of ICH E14/S7B may inform future evolution of safety pharmacology and broader ICH initiatives.



Implementing ICH E14/S7B in Practice:

An Integrated Approach to QT and Proarrhythmia Risk Assessment

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2 October 2026

Inspired by patients.
Driven by science.

Disclaimer



The views and opinions expressed are those of the sole author and do not necessarily represent the views, opinions and/or policies of his current employer.



The author is employed by a pharmaceutical company and may hold shares and/or stock options in the company.



The author declared no potential conflicts of interest with respect to the research, authorship, and/or communication of the data.

The author was a member of the ICH E14/S7B Implementation Working Group.

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Today's focus: implementing the 2026 E14/S7B Q&As

From scientific integration to modality-aware regulatory decisions

01

WHY INTEGRATION MATTERS

QT/QTc is an integrated phenotype

Why clinical and nonclinical evidence must be interpreted together

02

WHAT CHANGES IN 2026

A modality-aware and more flexible framework

Broader scope, qualified alternatives and greater study integration

03

HOW EVIDENCE SUPPORTS DECISIONS

E14 Q&As 5.1, 6.1 and 6.3

Different pathways, one evidentiary standard

04

APPLYING THE FRAMEWORK

Worked examples, uncertainty and lessons

From a clean hypothetical package to real-development complexity

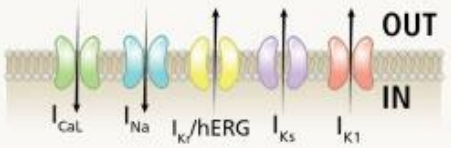
Primary emphasis: Practical implications of the August 2026 revision. *The 2022 foundation is assumed*

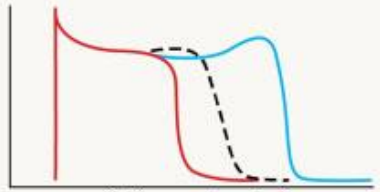
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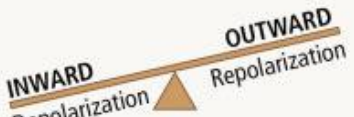
QT/QTc is an integrated phenotype, not a direct measure of proarrhythmic risk

Take-home: Regulatory interpretation requires integration of mechanism, exposure, assay performance, and complementary clinical and nonclinical evidence.

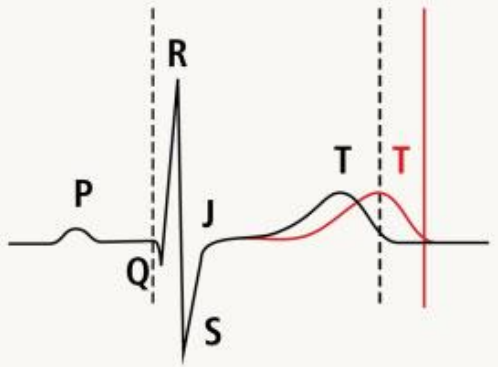
Direct Effects on Myocytes: Current & Action Potentials







- iKr/hERG block kinetics
- Multichannel block
- Channel expression/inactivation
- Intracellular accumulation
- Channel/receptor and second messenger cross talk



"Integrated" Effects on ECG:
Altered Ventricular Repolarization

Indirect Effects Through Physiology: Clinical Influences



Substrate
Sex/Age
Channel mutations
Structural heart disease

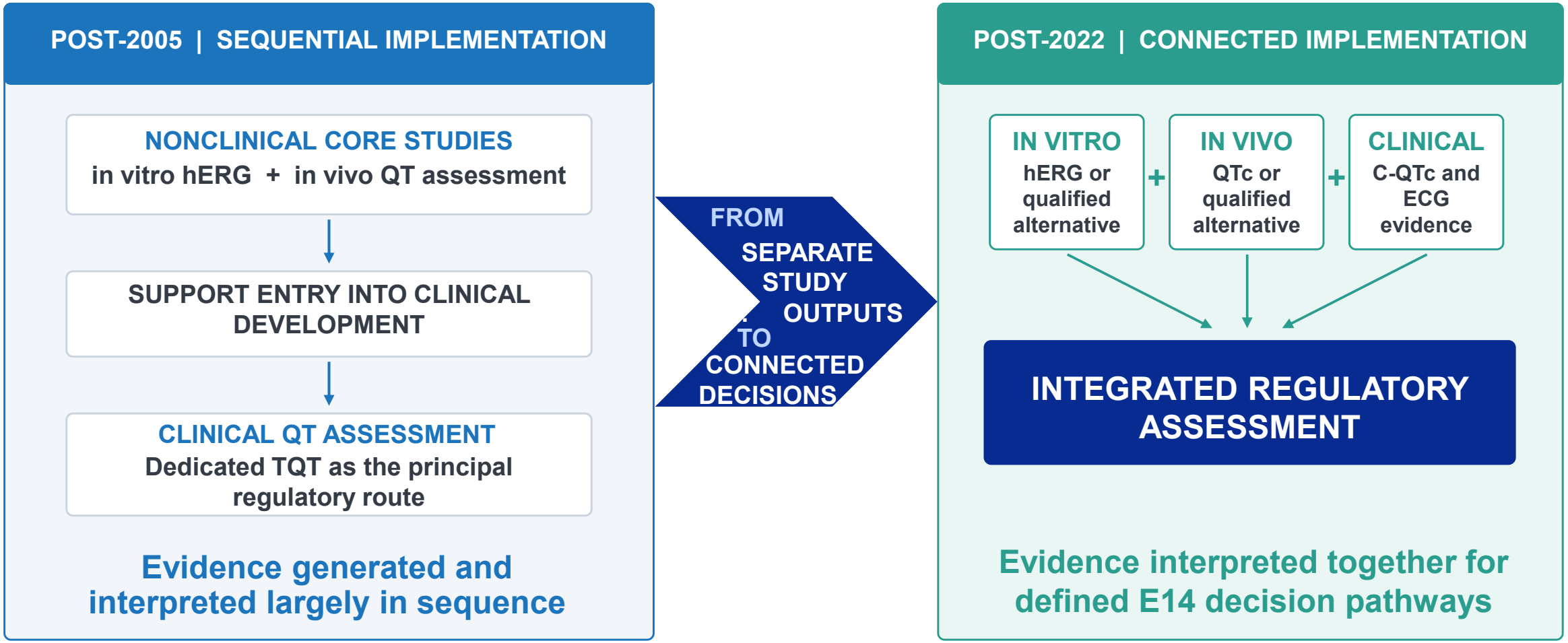
- Heart Rate/Hemodynamics
- Electrolytes
- Temperature
- Autonomic influences
- Drug-drug interactions
- Metabolites
- Disease

Adapted from Valentin et al. Challenges of Predicting Drug-Induced QTc Prolongation in Humans. Toxicological Sciences. 2022;187:3–24.

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From sequential testing to integrated regulatory decision-making

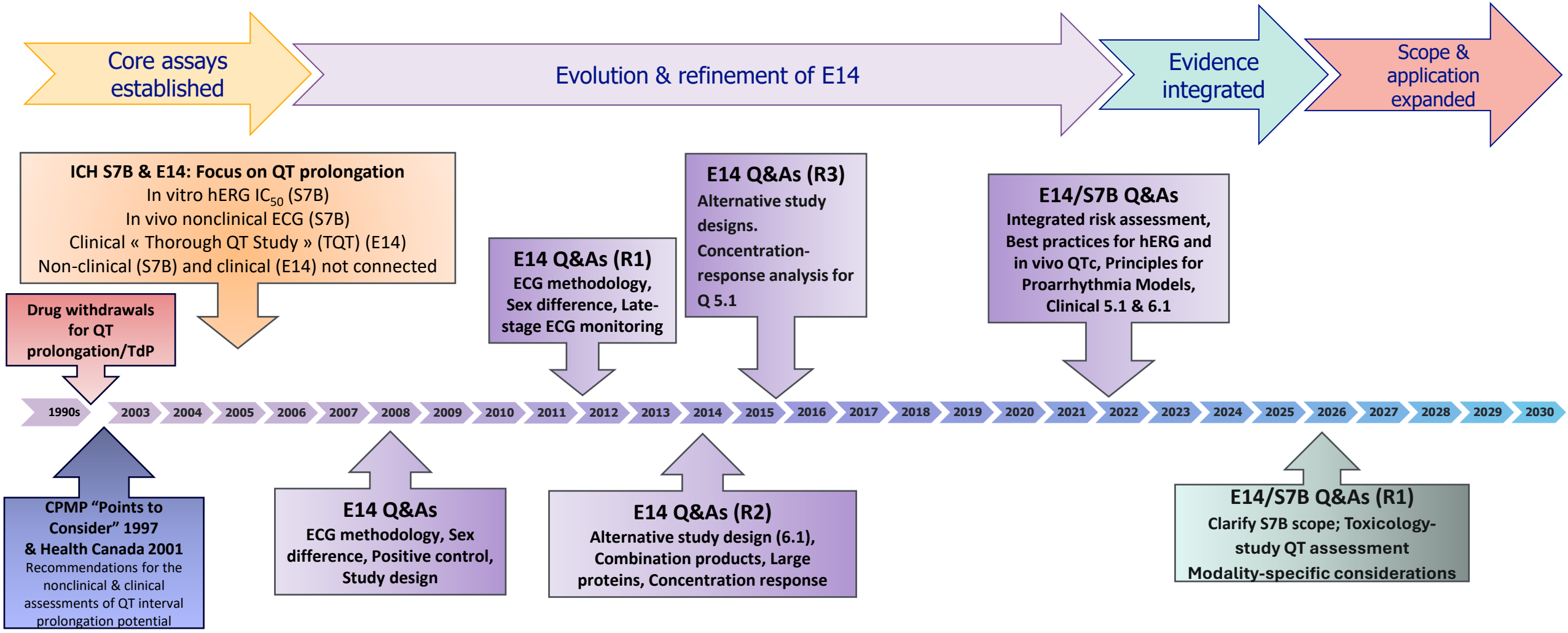
The evidence was complementary from the outset; its implementation was not always connected



Take-home: Integration changed how evidence is used: from separate study outputs to a connected assessment supporting defined regulatory decisions.

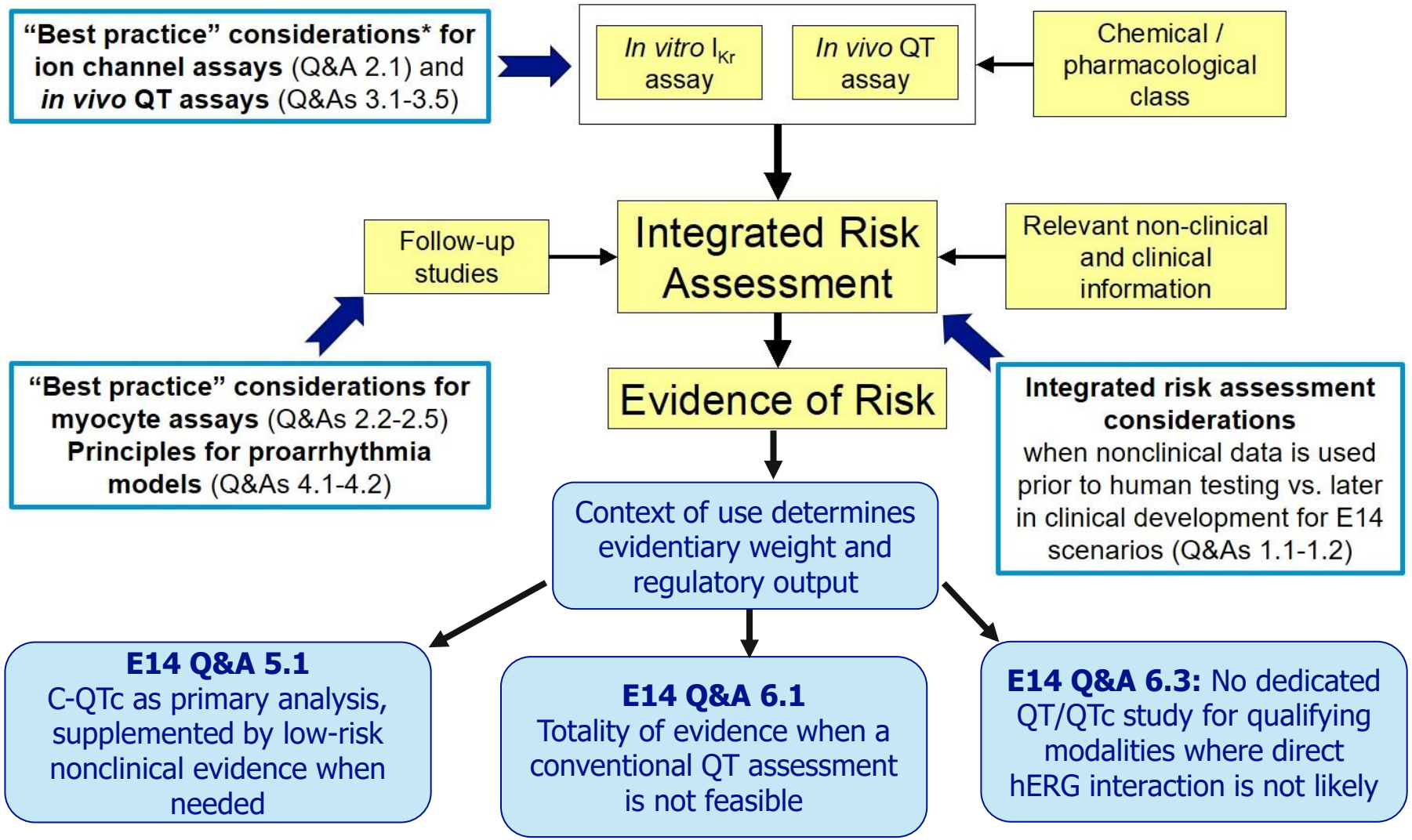
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E14/S7B evolution: from core studies to modality-aware integration



Take-home: 2022 established how evidence should be generated and integrated; 2026 expands where and how that framework can be applied.

From nonclinical integrated risk assessment to clinical regulatory decisions



Take-home: Integration is not the accumulation of negative studies. It is the weighted interpretation of clinical and nonclinical evidence according to quality, exposure, relevance and context of use

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What changes with the 2026 E14/S7B Q&As (R1)?

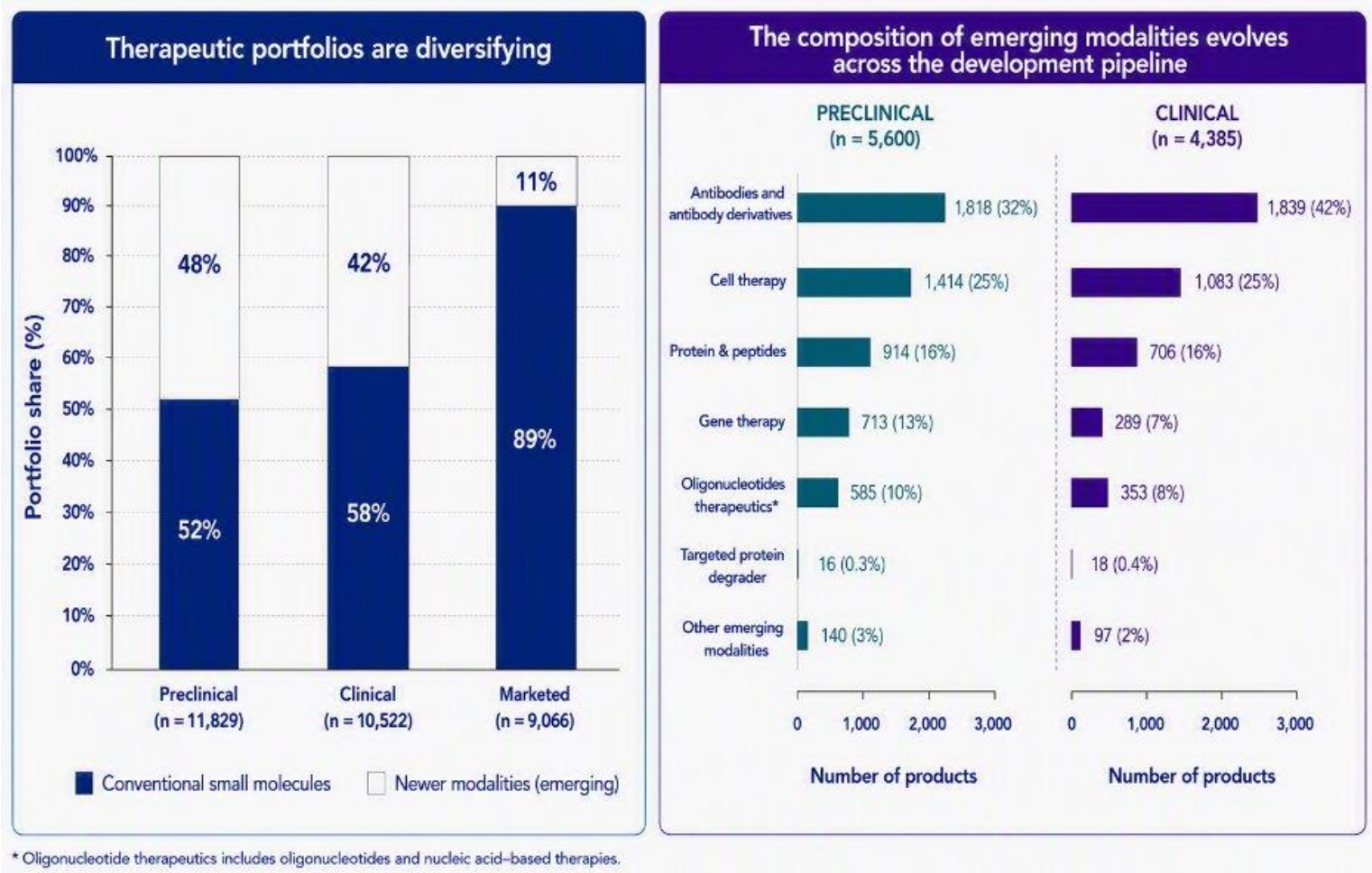
1. BROADER APPLICABILITY	2. MODALITY-AWARE STRATEGY	3. QUALIFIED ALTERNATIVE METHODS	4. GREATER INTEGRATED QTc ASSESSMENT	5. BROADER E14 PATHWAYS
• **Across therapeutic modalities** *Beyond a predominantly small-molecule paradigm*	• **Match testing to the likelihood of direct hERG interaction** *Likely | Unknown | Not likely*	• **Qualified alternative assays can serve as core components** *When appropriately qualified for the context of use*	• **Incorporate QTc assessment into general toxicology studies when feasible** *Comparable scientific and technical rigor*	• **Nonclinical evidence informs additional E14 decision pathways** *E14 Q&As 5.1 | 6.1 | 6.3*

Take-home: 2026 expands the flexibility of the framework, while preserving the evidentiary standards established in 2022.

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A diversifying therapeutic landscape requires a modality-aware testing strategy

- ***Portfolios are diversifying.***
- ***Modalities are changing.***
- ***Frameworks must evolve.***



* Oligonucleotide therapeutics includes oligonucleotides and nucleic acid–based therapies.

Take-home: Different modalities do not share the same biological plausibility for direct hERG interaction. So, which testing strategy is most informative for each modality?

Inspired by patients.
Driven by science.

Adapted from Rosenbrier Ribeiro et al., (2026). JPTM submitted

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Physicochemical properties associated with direct hERG interaction

Factor #1 of the ICH S7B Q&A 1.4 framework

PHYSICOCHEMICAL FEATURE	LIKELY PROFILE	UNKNOWN PROFILE*	NOT-LIKELY PROFILE
MODALITY EXAMPLE	Small molecules	Emerging or insufficiently characterised modalities, including novel delivery or intracellular-release properties	Monoclonal antibodies and large proteins
01 **Molecular size and conformational flexibility**	Low molecular weight; conformationally flexible	Size and conformation do not establish whether intracellular access is plausible	High molecular weight; ordered, folded and structurally complex
02 **Membrane permeability**	Passive diffusion and/or active uptake	Cellular uptake or intracellular release is uncertain or context-dependent	Minimal or absent permeability
03 **Hydrophobicity and aromaticity**	Greater lipophilicity; features compatible with hERG binding	Mixed, atypical or insufficiently characterised properties	Highly hydrophilic
04 **Charge characteristics**	Basic amine, positive charge or cationic functionality	Ionisation, formulation or delivery does not permit confident prediction	Highly negatively charged or polyanionic

Together, the four properties inform whether membrane permeability and interaction with intracellular hERG binding sites are biologically plausible.

Take-home: Physicochemical properties inform direct hERG interaction potential, but do not determine the final classification in isolation.

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Adapted from ICH E14/S7B Q&As(R1) Training Material, 2026. *Uncertain profile is the presenter's educational interpretation.

Three factors inform the classification and ICH S7B testing strategy

Physicochemical properties, mechanistic plausibility and accrued evidence are interpreted together

1 PHYSICOCHEMICAL PROPERTIES

Can the candidate cross the membrane & possess features associated with hERG inhibition?

- Size and conformation
- Membrane permeability
- Hydrophobicity and aromaticity
- Charge characteristics

2 MECHANISTIC PLAUSIBILITY

Can the modality directly access and inhibit hERG?

- Drug class or modality characteristics
- Prior association with direct hERG block
- Ability to access the intracellular central pore
- Strength of mechanistic understanding

3 ACCRUED EVIDENCE

What does the growing body of available evidence indicate?

- Peer-reviewed nonclinical and clinical datasets
- Public-domain evidence
- Sponsor-derived datasets
- Relevant class or modality experience

INTEGRATED ASSESSMENT • interpreted together, not scored independently => impact on ICH S7B strategy

LIKELY	UNKNOWN	NOT LIKELY *
Evidence supports the biological plausibility of direct hERG interaction	Available evidence is insufficient for confident classification	Evidence supports a low likelihood of direct hERG interaction
In vitro hERG + In vivo QTc assessment *or qualified alternatives*	***In vitro hERG + In vivo QTc assessment*** *or qualified alternatives*	***No in vitro hERG or in vivo QTc*** *for direct hERG-mediated effect*

Take-home: The ICH S7B strategy follows from the integrated interpretation of all three factors and the remaining uncertainty.

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Adapted from ICH E14/S7B Q&As(R1) Training Material, 2026, slides 5, 7, 8 and 10.

***"Not likely" applies specifically to direct hERG-mediated delayed repolarisation. Standard clinical safety ECG collection remains expected.**

What makes a nonclinical assessment informative?

A. In vitro evidence

Can the assay characterise relevant potency with confidence?

hERG or qualified alternative

- Best practice protocol
- Verified test concentrations
- Relevant controls and reference agents
- Quantitative potency and uncertainty
- Margin relative to high clinical exposure
- Parent and relevant metabolites considered

B. In vivo evidence

Could the study detect a relevant QTc effect at adequate exposure?

QTc assessment or qualified alternative

- Appropriate species and study design
- Relevant ECG recording periods
- Adequate parent and metabolite exposure
- Appropriate heart-rate correction
- Characterised assay sensitivity
- Interpretable PK–QTc relationship

C. Context of use

What regulatory decision must the evidence support?

Before FIH
Supports safe clinical entry

E14 Q&A 5.1
Supplements high-quality clinical C-QTc evidence

E14 Q&A 6.1
Supports a totality-of-evidence decision

In vivo sensitivity comparable to a dedicated clinical QT assessment

Result + Exposure + Sensitivity + Data quality + Context of use = Interpretability

TAKE-HOME : "No observed effect" is decision-relevant only when the assessment was capable of detecting a relevant effect at an appropriate exposure.

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Greater flexibility in evidence generation without compromising rigor

1. Qualified alternative assays

Can an alternative replace a conventional core component?

Qualification should address

- Defined context of use
- Relevant endpoint
- Appropriate reference agents
- Predictive performance and reproducibility
- Domain of applicability and limitations
- Characterisation of uncertainty

Human cardiomyocyte assays

Compare repolarisation effects with reference agents, analogous to the hERG safety-margin approach.

2. QTc assessment incorporated in general toxicology studies

Can the in vivo QTc assessment be incorporated rather than conducted separately?

The integrated assessment should retain:

- Pharmacologically and statistically sensitive ECG methodology & relevant recording periods
- Adequate parent and metabolite exposure
- Appropriate heart-rate correction and analysis
- Characterised assay sensitivity
- Management of confounding toxicity

ECG collection alone does not constitute an informative QTc assessment.

Two flexible approaches, one evidentiary standard

Qualified alternative or comparably rigorous integrated QTc assessment -> Decision-quality evidence for integrated E14/S7B assessment

Take-home: The 2026 revision expands how and where evidence may be generated, without lowering the evidentiary standard.

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How nonclinical evidence changes the clinical QT pathway

S7B Q&A 1.4 connects modality-aware nonclinical evidence to three different E14 scenarios

S7B Q&A 1.4 | Is direct hERG interaction likely, unknown, or not likely?

	E14 Q&A 5.1	E14 Q&A 6.1	E14 Q&A 6.3
STARTING POINT	**Informative clinical C-QTc, but insufficient exposure coverage**	**A conventional thorough QT assessment is not feasible**	**Direct hERG interaction is not likely for a qualifying modality**
NONCLINICAL ROLE	**SUPPLEMENTS** Low-risk integrated nonclinical evidence can close the remaining exposure gap	**CO-DRIVES** Sensitive in vivo QT and other S7B evidence contribute to the totality-of-evidence assessment	**SUPPORTS OMISSION** The S7B classification supports omission of dedicated QT/QTc testing
OUTCOME	**Supports the clinical C-QTc conclusion without a separate positive control**	**Supports a low likelihood of delayed-repolarisation risk based on the complete package**	**No dedicated QT/QTc study, unless other findings raise concern**

Take-home: Nonclinical evidence may supplement, co-drive, or support omission of a dedicated clinical QT pathway, depending on the scenario. Decision thresholds remain unchanged; the evidentiary routes are broader.

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Case study 1: nonclinical evidence closes a defined clinical exposure gap

Official hypothetical example under E14 Q&A 5.1

1 CLINICAL GAP

REASSURING C-QTc

3.3 ms

90% CI: 2.0 to 4.5 ms

BUT EXPOSURE REACHED ONLY

1.8-fold

versus the commonly sufficient 2-fold multiple

A defined exposure gap remains

2 NONCLINICAL BRIDGE

IN VITRO

95-fold

hERG safety margin

>51-fold reference threshold

Low-risk mechanistic evidence

IN VIVO

No QTc effect

at 2-fold exposure

10 ms minimal detectable difference

Exposure-relevant and sensitive

Both components address the remaining uncertainty

3 REGULATORY DECISION

EXPOSURE GAP

CLOSED

Clinical C-QTc

+

Low-risk in vitro + in vivo evidence

Supports the Q&A 5.1 conclusion without a separate positive control

Take-home: A defined clinical exposure gap can be closed when supplementary nonclinical evidence is decision-quality, exposure-relevant and concordant.

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Source: ICH E14 Q&A Training Material Examples Supplemental File, hypothetical Q&A 5.1 example.

Case study 2: reassuring evidence does not eliminate residual uncertainty

Anonymised real-development decision exercise

WHAT IS REASSURING?

CLINICAL	**No concentration-related QTc effect identified within observed exposures**
IN VITRO	**Substantial hERG safety margin**
IN VIVO	**No consistent dose-, time- or exposure-related QTc trend**

OVERALL DIRECTION: REASSURING

WHAT LIMITS INTERPRETATION?

CLINICAL ECG QUALITY	Not centrally read; 12-lead ECGs did not adequately cover Tmax
EXPOSURE COVERAGE	Conclusions limited to observed exposures; incomplete exposure & recording information
IN VIVO STUDY DESIGN	Parallel design and substantial QTc variability
EXTRAPOLATION	Simulations above observed exposure are not empirical evidence

OVERALL IMPACT: RESIDUAL UNCERTAINTY REMAINS

Take-home: Supportive but not decisive - The package is reassuring within observed exposures, but does not establish a definitive TQT waiver or coverage of higher exposures.

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Source: anonymised development example based on draft manuscript data; presenter interpretation.

Key lessons, future perspective and discussion

Implementing the 2026 ICH E14/S7B Q&As in practice

FOUR MESSAGES TO RETAIN

01	**Integrate for the decision**	Interpret clinical and nonclinical evidence according to context of use.
02	**Match testing to the modality**	Use physicochemical properties, mechanistic plausibility and accrued evidence together.
03	**Demand decision-quality evidence**	Exposure, sensitivity, data quality and uncertainty determine interpretability.
04	**Use flexibility without lowering rigor**	Qualified alternatives and integrated studies must remain fit for purpose.

LOOKING AHEAD

Generate → Share → Learn → Refine

Accrued evidence should refine modality classification and future testing strategies.

More flexible and modality aware, not less rigorous.
Decision-quality evidence remains the foundation of regulatory confidence.

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Sources and further reading

Regulatory documents and selected publications used in this presentation

REGULATORY DOCUMENTS

ICH E14/S7B Q&As (R1), Step 4 | 20 Aug 2026

Revised E14 Q&As 5.1, 6.1, 6.3 and S7B Q&As.

ICH E14/S7B Q&As (R1) Step 4 Presentation | 2026

Official overview and training slides for the revised framework.

ICH E14 Guideline | 2005

Clinical evaluation of QT/QTc prolongation and proarrhythmic potential.

ICH S7B Guideline | 2005

Nonclinical evaluation of delayed ventricular repolarisation.

ICH E14/S7B Training Material | March 2022

Foundation for integrated risk assessment and best-practice considerations.

KEY PUBLICATIONS

Valentin J-P et al. | Toxicological Sciences | 2022

Challenges of Predicting Drug-Induced QTc Prolongation in Humans.

Wu WW et al. | Clinical Pharmacology & Therapeutics | 2023

ICH S7B in vitro assays and QTc mechanisms for peptides and proteins.

Vargas HM et al. | J Pharmacol Toxicol Methods | 2008

Preclinical cardiovascular safety evaluation of biologics.

Vargas HM et al. | Expert Opin Drug Saf | 2013

Safety pharmacology strategy for biopharmaceuticals.

Fernandez D et al. | J Biol Chem | 2004

Physicochemical features of the hERG channel drug-binding site.

Delpy L et al. | J Pharmacokinet Pharmacodyn | 2025

Twenty years of progress in nonclinical QT and proarrhythmia assessment.

Acknowledgments: former ICH E14/S7B IWG colleagues, training-material contributors, scientific collaborators, and our South Korean hosts and participants.

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E14/S7B Q&A



임동석 (Dong-Seok Yim)

가톨릭대학교 의과대학 약리학교실 교수

College of Medicine, The Catholic University of Korea, Department of Pharmacology Professor

임동석은 서울대학교 의과대학에서 임상약리학으로 박사학위를 받은 후 가톨릭의대에서 재직 중이다. 신약임상개발, 계량약리학을 전공하고 있으며 제약바이오 연구인력 교육을 위해 설립된 (사)청람바이오아카데미의 이사장을 겸하고 있다.

Dong-Seok Yim received his Ph.D. in Clinical Pharmacology from Seoul National University College of Medicine and is currently a professor at the Catholic University of Korea College of Medicine. He specializes in clinical drug development and pharmacometrics, while also serving as Chairman of the Cheongram Bio Academy, an incorporated association established to educate pharmaceutical and biotech research personnel.

Program

ICH E14/S7B의 Q&A 추가에 따른 최근 적용사례

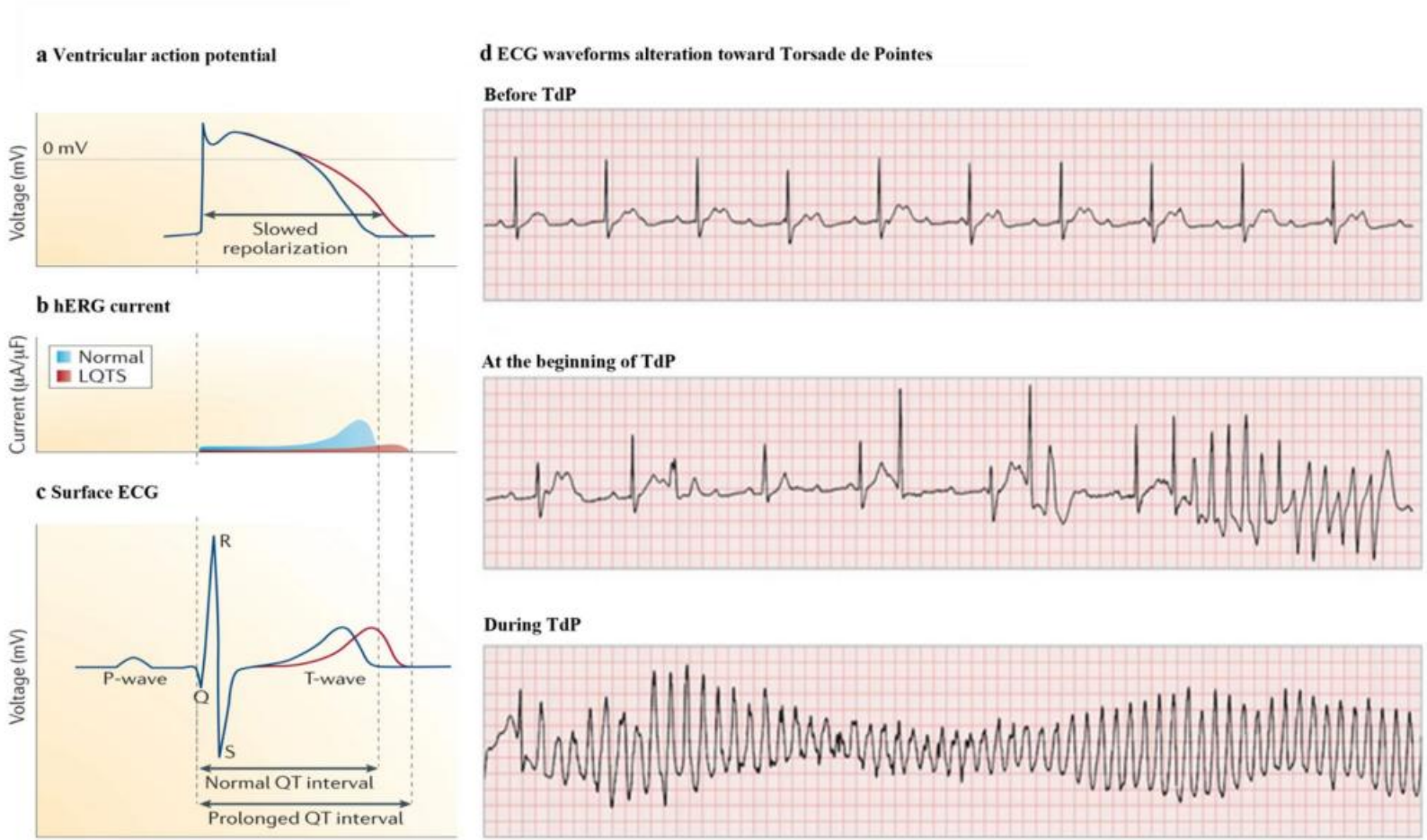
Cases of ICH E14/S7B의 Q&A

ICH E14/S7B는 1990년대의 약화사고로 인해 급히 발표된 이후, 시험비용의 부담과 false (+)의 문제로 개정에 대한 논의가 계속되었다. 2020년대에 FDA가 주도한 CiPA 프로젝트를 통하여 in vitro 연구결과를 단순한 스크리닝을 넘어 TQT 시험을 대체할 수 있는 근거로 쓸 수 있도록 하는 내용을 Q&A에 추가하게 되었다. 이번 강의에서는 2020년 이후 지금까지 ICH E14/S7B를 기존의 TQT 시험 외의 방법으로 탄력적으로 적용한 사례들을 통계치와 함께 제시하고자 한다.

Prompted by 1990s drug safety incidents, ICH E14/S7B was rapidly implemented, but faced ongoing calls for revision due to heavy testing costs and high false-positive rates. By the 2020s, the FDA-led CiPA initiative enabled regulatory Q&A updates allowing in vitro data to formally substitute for Thorough QT (TQT) studies rather than functioning solely as screening tools. This session highlights flexible, post-2020 applications of ICH E14/S7B using alternative methodologies alongside key statistical metrics.

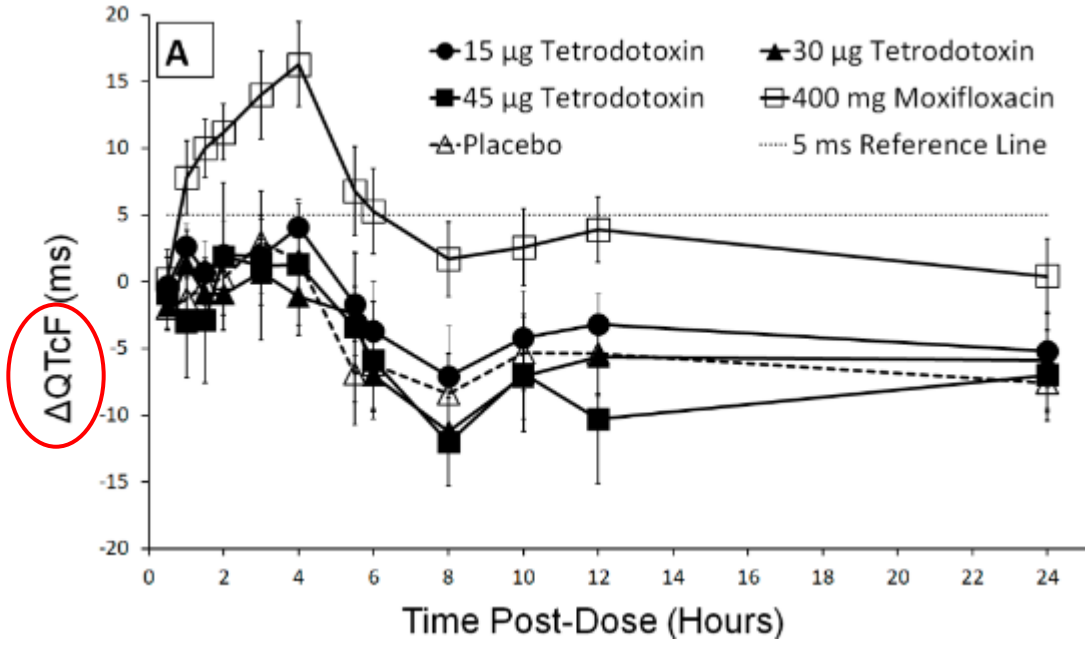
ICH E14 & S7B Q&A R1 Cases

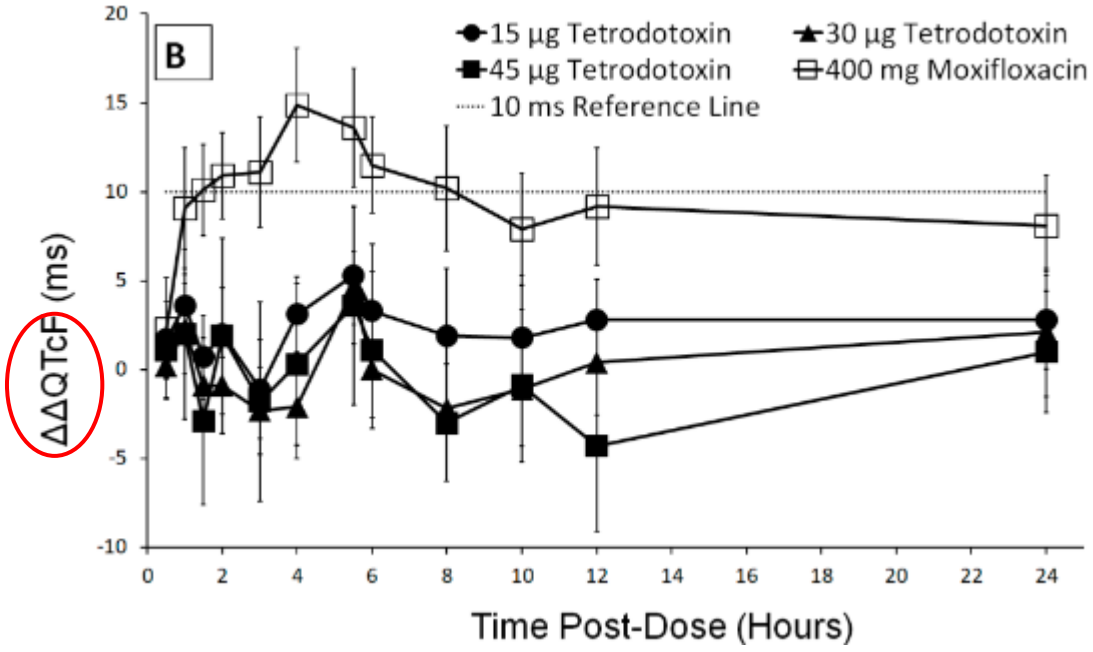
임 동석
가톨릭의대 약리학교실
(사) 청람바이오아카데미
㈜ AIMS 바이오사이언스


a Ventricular action potential
0 mV
Voltage (mV)
Slowed repolarization
b hERG current
Normal
LQTS
Current (μA/μF)
c Surface ECG
R
P-wave
Q
T-wave
S
Voltage (mV)
Normal QT interval
Prolonged QT interval
d ECG waveforms alteration toward Torsade de Pointes
Before TdP
At the beginning of TdP
During TdP

- TQT study methods by ICH E14

- ΔQTc: QTc after test drug – baseline QTc
- ΔΔQTc: ΔQTc after test drug - ΔQTc after placebo





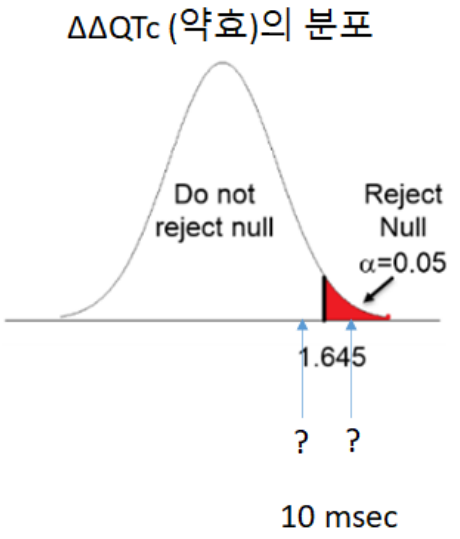
Toxins **2020**, *12*(8), 511; https://doi.org/10.3390/toxins12080511

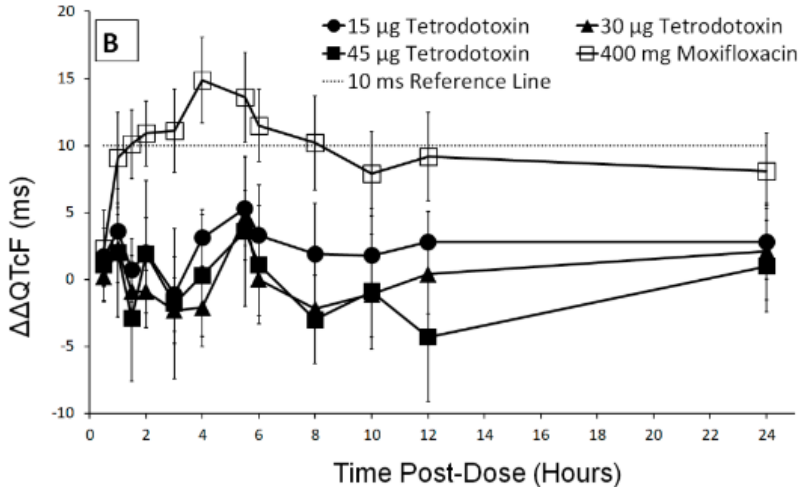
ICH E14 – Pressure for evolution since 2005

- Cost: 2~3 million $/study

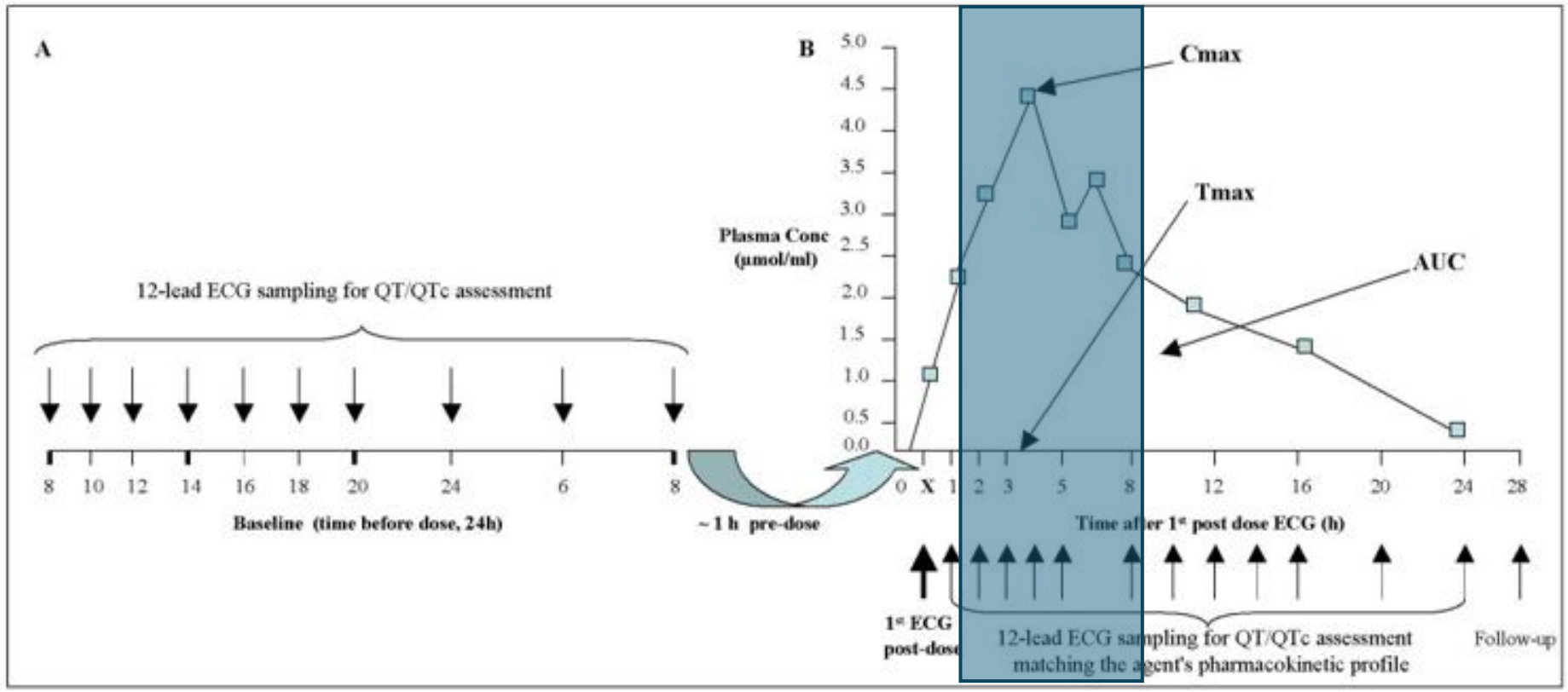
- Risk of false positive results
  - The more frequent ECG recording, the higher probability of finding time points of ΔΔQTc >10 ms

  - The one biggest ΔΔQTc >10 ms in all the measured ECGs
    - No concept of frequency or probability was considered.

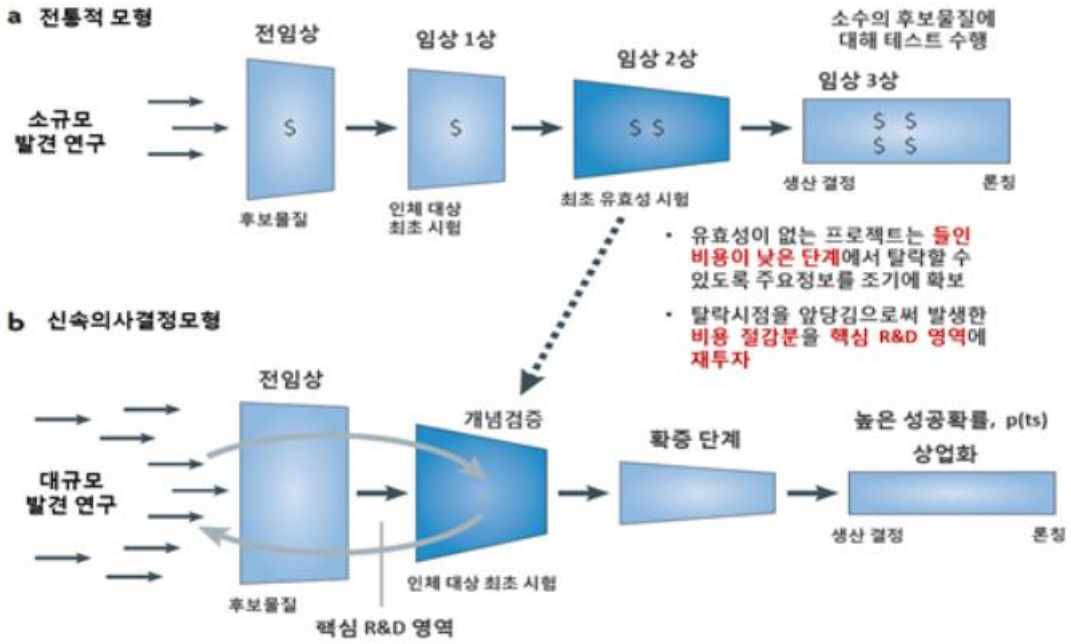




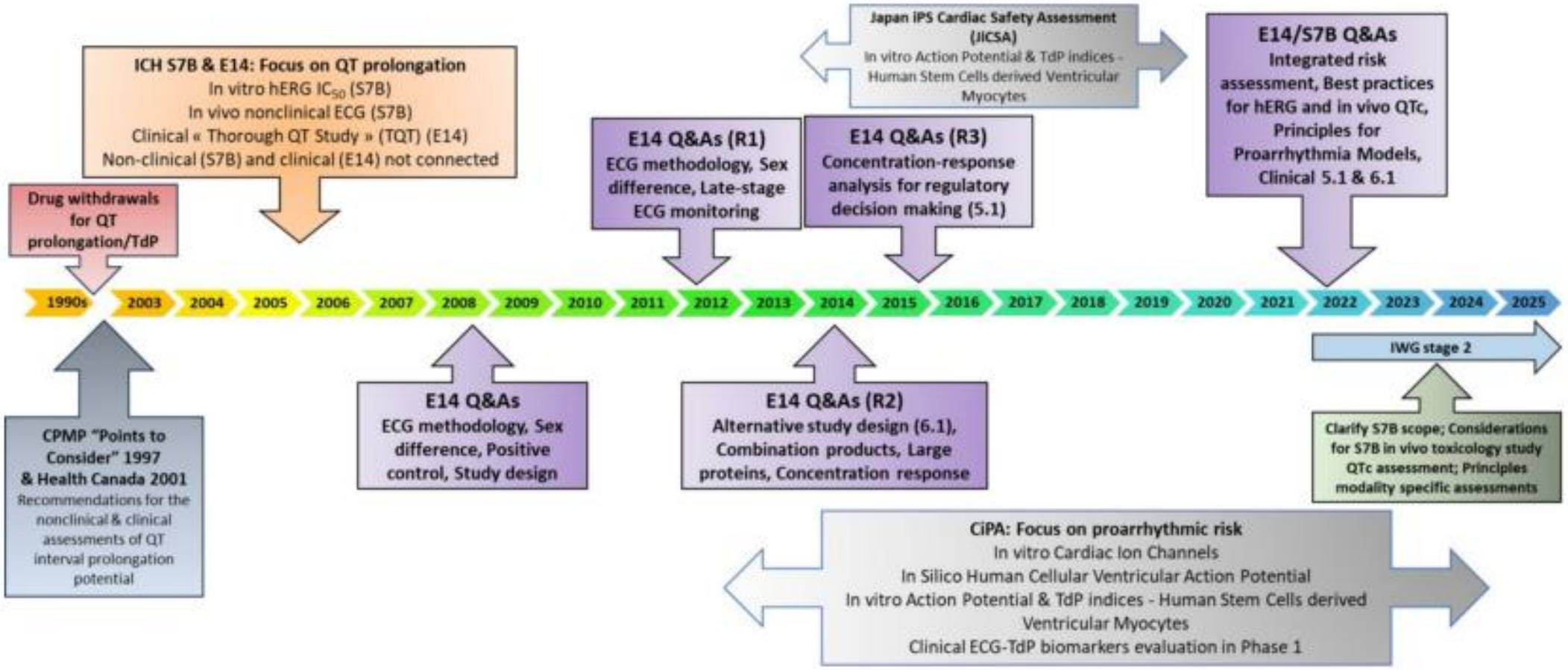
- False positive: 심전도를 자주 열심히 측정할수록 (+) 확률이 커짐!



- Timing issue of TQT study
  - therapeutic dose decided at the end of Phase II.
  - The supra-therapeutic dose to for a TQT study is thus decided at the end of Phase II.
    - Exposure in patients with hepatic or renal failure or with metabolic inhibitors.
  - Most of TQT studies to date have been conducted just prior to Phase III clinical development.
  - Notwithstanding “the fail early, fail cheaply” strategy.



Efforts to improve ICH E14



Journal of Pharmacokinetics and Pharmacodynamics (2025) 52:32

Motivation for New Approaches

- **Human QTc Studies**
  - One representative clinical assessment for cardiac safety related to proarrhythmia (TdP)
  - Imperfect biomarker to predict TdP
  - Thorough QT (TQT) study is the most expensive clinical pharmacology program
  - An alternative approach, concentration-QT (C-QT) is still requiring too strict conditions, e.g., 4 X higher concentrations than therapeutic concentrations without a positive control

→Thus utilizing preclinical data for integrated approach

ICH E14/S7B Q&A R1 (2026)
5. USE OF CONCENTRATION RESPONSE MODELING OF QTC DATA

Clinical exposure:

- Cmax,ss at maximum therapeutic dose

High clinical exposure:

- Cmax,ss at maximum therapeutic dose in organ impairment or DDI

Supratherapeutic dose:

- dose that provides exposures (mean Cmax) exceeding the high clinical scenario (x2)
- With this dose, (+) control not needed

Without supratherapeutic dose (from safety concerns etc)

- nonclinical integrated risk assessment can be used as supplementary evidence

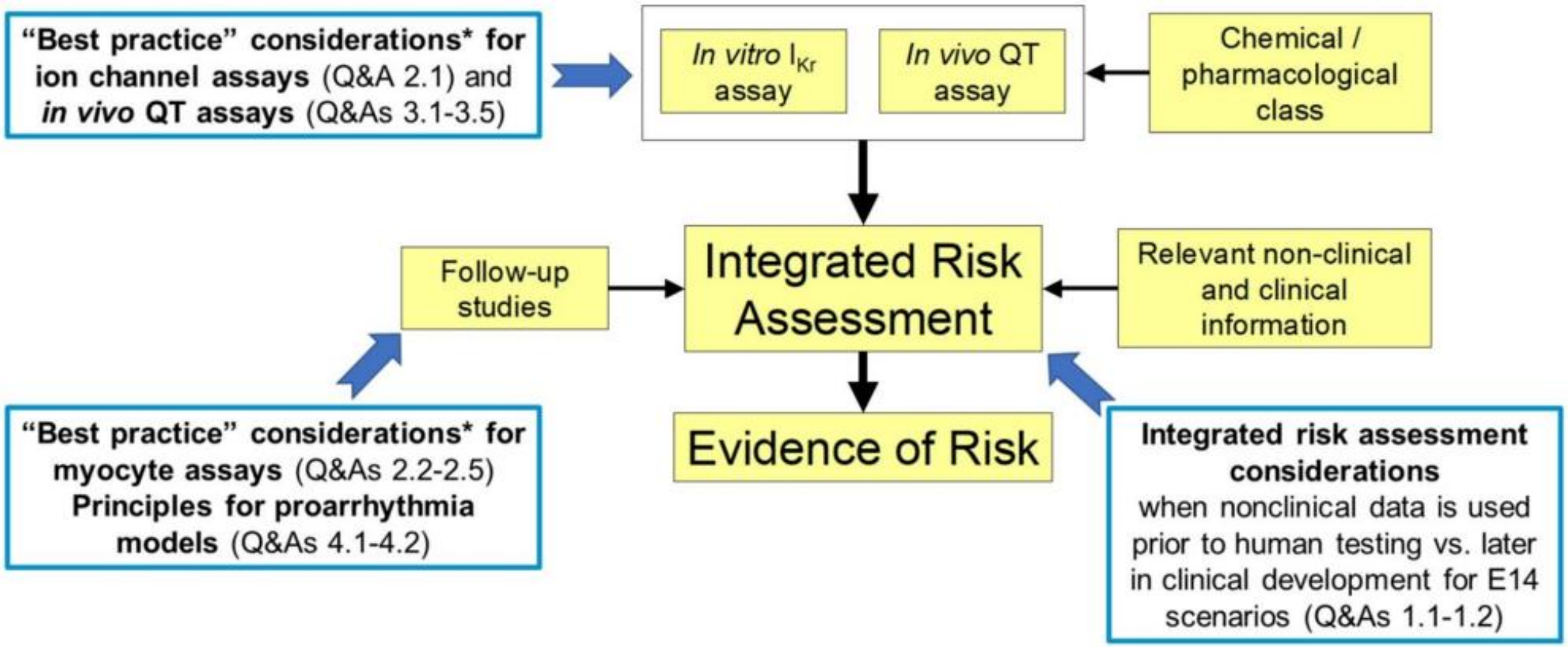
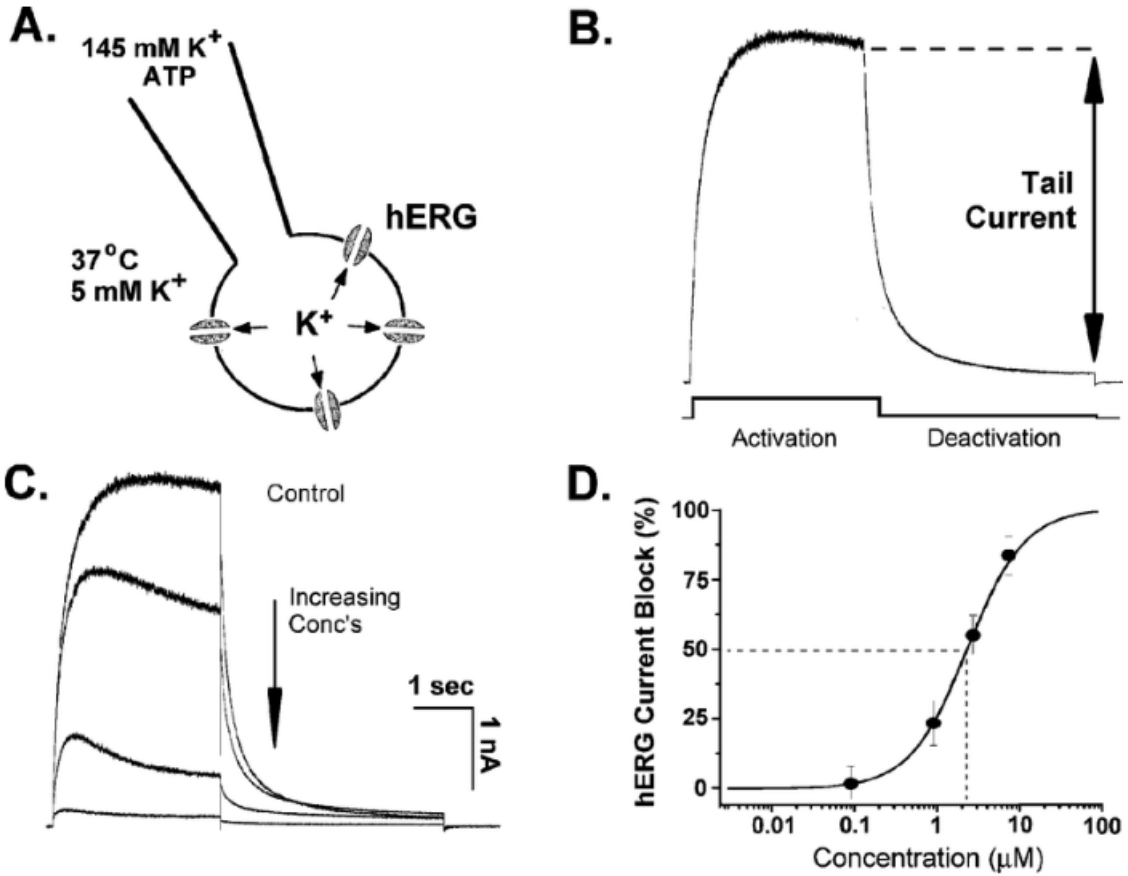


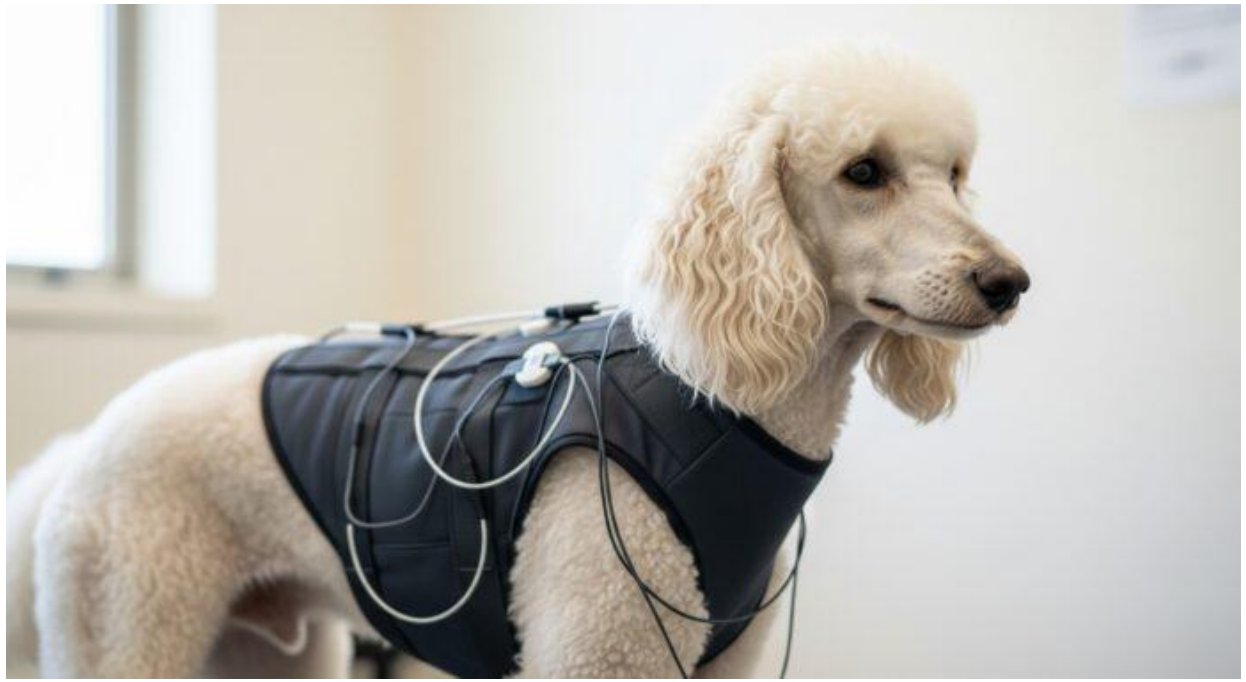
Fig. 4 Alignment of the 2022 S7B related Q&As in relation to the original 2005 S7B guideline.
Adapted from [2] and [4]. *The best practice considerations are not intended to impact a sponsor's screening activities. Some considerations only apply when using nonclinical data for clinical scenarios under E14 Q&As 5.1 and 6.1



—In vitro recordings of hERG current stably expressed in HEK- 293 cells. Panel A: patch clamp electrode attached to cell stably transfected with hERG channels. The cell maintains a high intracellular K + concentration compared to the extracellular solution. Panel B: Recording of voltage-dependent hERG current activated upon depolarization, and deactivated upon repolarization . The declining outward current upon repolarization is termed the tail current . Panel C: Recordings of hERG current under control conditions (upper most trace), and during exposure to increasing concentrations of a hERG blocking drug. Tail currents demonstrate a concentration-dependent reduction. Panel D: IC 50 values characterizing potency of hERG current block derived from Hill equation fit to experimental data.

In vitro hERG assay

10.1080/01926230500431376



Dog telemetry

https://ivcjournal.com/telemetry-vests-beyond-monitoring-to-calming-effects-in-dogs/

5.1 Example

- **Shows a data package for a hypothetical drug to support an integrated risk assessment**
- **Supporting tables:**
  - Table 1-A: Clinical QT Assessment
  - Table 1-B: *In vitro* hERG Assay Evaluation
    - Deviations from best practice
  - Table 1-C: *In vitro* Assay Results
    - Safety margin assessment using reference compounds
  - Table 1-D: *In Vivo* QT Assessment

<table>
<tr><td>QT assessment pathway</td><td>☑ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>High dose (250 mg x 1): 3.3 (90% CI 2.0, 4.5) ms at mean C_{max}; 1.8-fold the high clinical exposure
Therapeutic dose (50 mg QD): 1.7 (90% CI 1.2, 2.2) ms at mean C_{max}
➢ High clinical exposure was achieved, but a sufficient multiple (2x) was not obtained; therefore, a nonclinical integrated risk assessment can be used as supplementary evidence in lieu of positive control (see Table 1-A).</td></tr>
<tr><td>In vitro findings</td><td><table>
<tr><td></td><td>Safety Margin</td><td>Reference Drug Safety Margin</td><td>Best Practice Deviations</td></tr>
<tr><td>Parent</td><td>95x</td><td rowspan="2">51x</td><td>Met best practice</td></tr>
<tr><td>Metabolite 1 (9% of total drug exposure)</td><td>>3369x (5% block at 1000 µM)</td><td>No concentration verification - not expected to affect conclusion of hERG safety margin greater than reference.</td></tr>
</table>➢ hERG safety margin was higher than the threshold defined based on the safety margins computed under the same experimental protocol for a series of drugs known to cause TdP (see Tables 1-B and 1-C).</td></tr>
<tr><td>In vivo findings</td><td>No QTc prolongation in dogs at 2x the high clinical exposure in QTc study with minimal detectable difference of 10 ms.
➢ No QTc prolongation at exposures of parent compound that exceed high clinical exposures (see Table 1-D). Metabolite 1 not quantified in the in vivo study because it is 9% in humans and not hERG active.</td></tr>
<tr><td>Conclusion</td><td>• Integrated nonclinical assessment showed low risk for QTc prolongation at exposures exceeding the high clinical exposure scenario.
• The clinical and nonclinical assessments can be used as a substitute for a TQT study.</td></tr>
</table>

C-QTc study example

Concentration–Response Modeling of ECG Data From Early-Phase Clinical Studies as an Alternative Clinical and Regulatory Approach to Assessing QT Risk — Experience From the Development Program of Lemborexant

The Journal of Clinical Pharmacology
2017, 57(1) 96–104
© 2016, The American College of Clinical Pharmacology
DOI: 10.1002/jcph.785

Patricia J. Murphy, PhD[1], Sanae Yasuda, PhD[2], Kenya Nakai[2], Takashi Yoshinaga, PhD[2], Nancy Hall[1], Meijian Zhou, PhD[3], Jagadeesh Aluri[1], Bhaskar Rege, PhD[1], Margaret Moline, PhD[1], Jim Ferry, PhD[1], and Borje Darpo, MD, PhD[3,4]

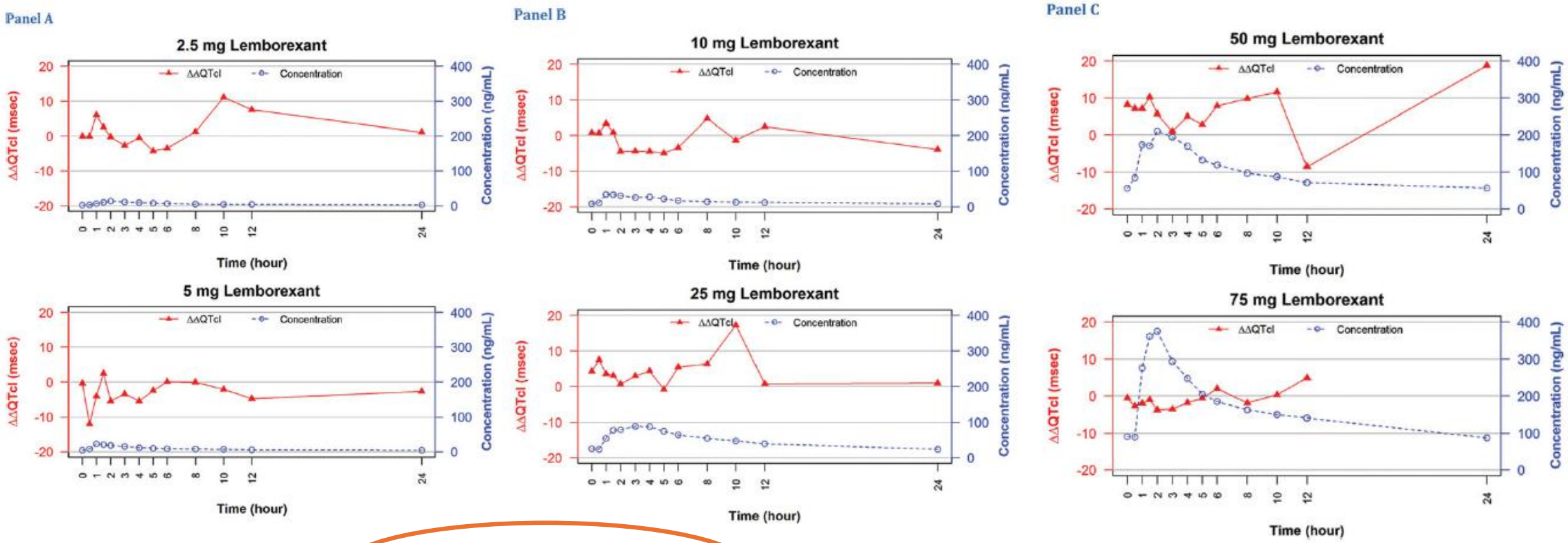
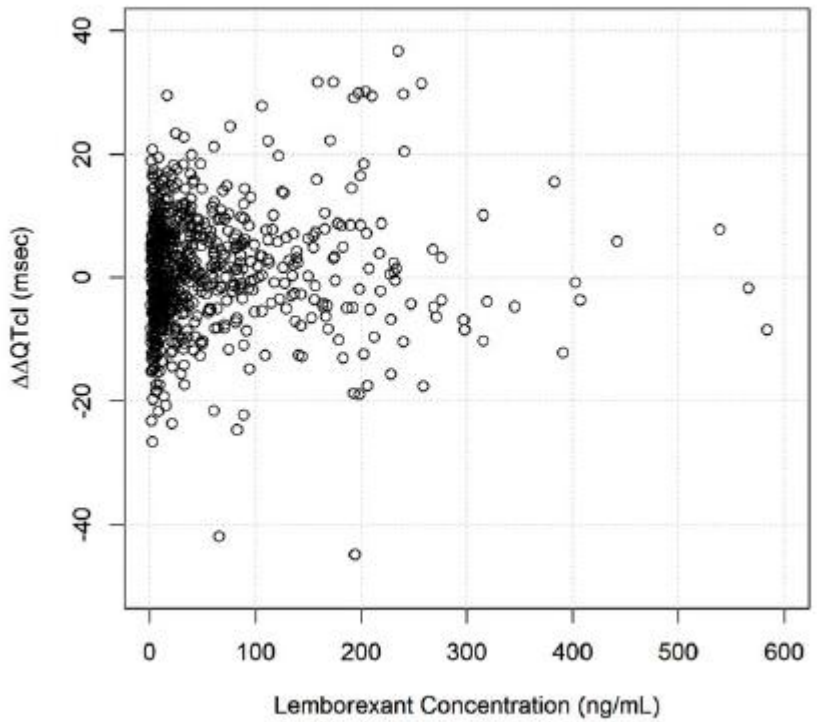


Figure 1. (A) Time course of placebo-corrected ΔQTcI (ΔΔQTcI) and lemborexant plasma concentrations for each dose group in the MAD study. Least-squares means ΔΔQTcI from the linear mixed modeling and mean lemborexant plasma levels are shown. (A) 2.5- and 5-mg dose groups; (B) 10- and 25-mg dose groups; (C) 25- and 75-mg dose groups.

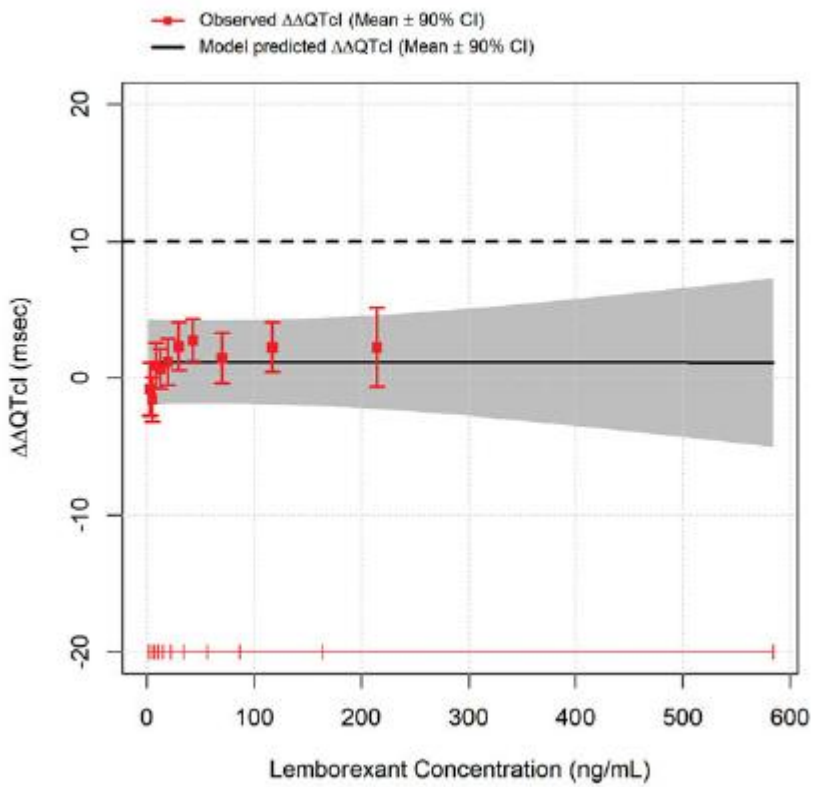
The Journal of Clinical Pharmacology
2017, 57(1) 96–104
© 2016, The American College of Clinical Pharmacology
DOI: 10.1002/jcph.785

$$\Delta\Delta QTcI_{ij} = Intercept_i + Subject_i + (slope_i + Subject_i) \cdot Conc_{ij} + \varepsilon_{ij},$$

Panel A



Panel B



Concentration–QTc Modeling to Support Clinical Development of Fezolinetant

Clinical Pharmacology in Drug Development 2026, 15(1) e1613
© 2025 The Author(s). *Clinical Pharmacology in Drug Development* published by Wiley Periodicals LLC on behalf of American College of Clinical Pharmacology.
DOI: 10.1002/cpdd.1613

Jace C. Nielsen[1], Masako Saito[2], Xuegong Wang[1], Megumi Iwai[2], Graeme L. Fraser[3,+], Steven Ramael[3,+], and Jiayin Huang[1,+]

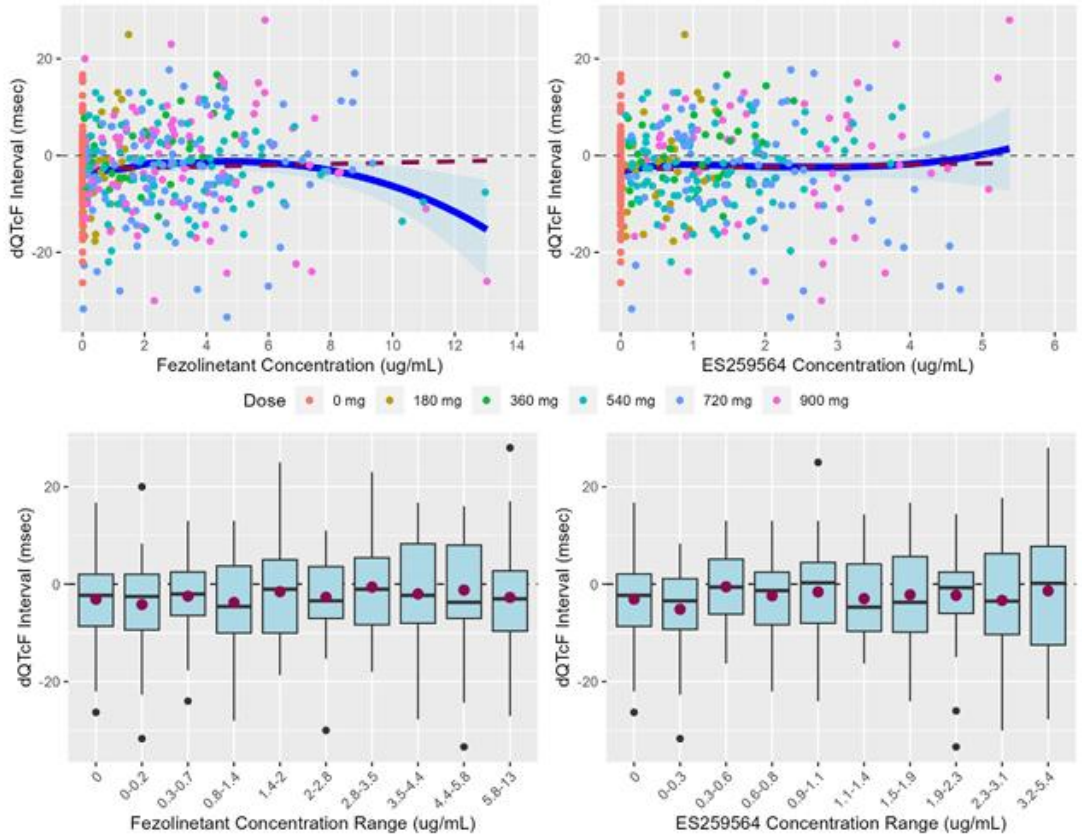
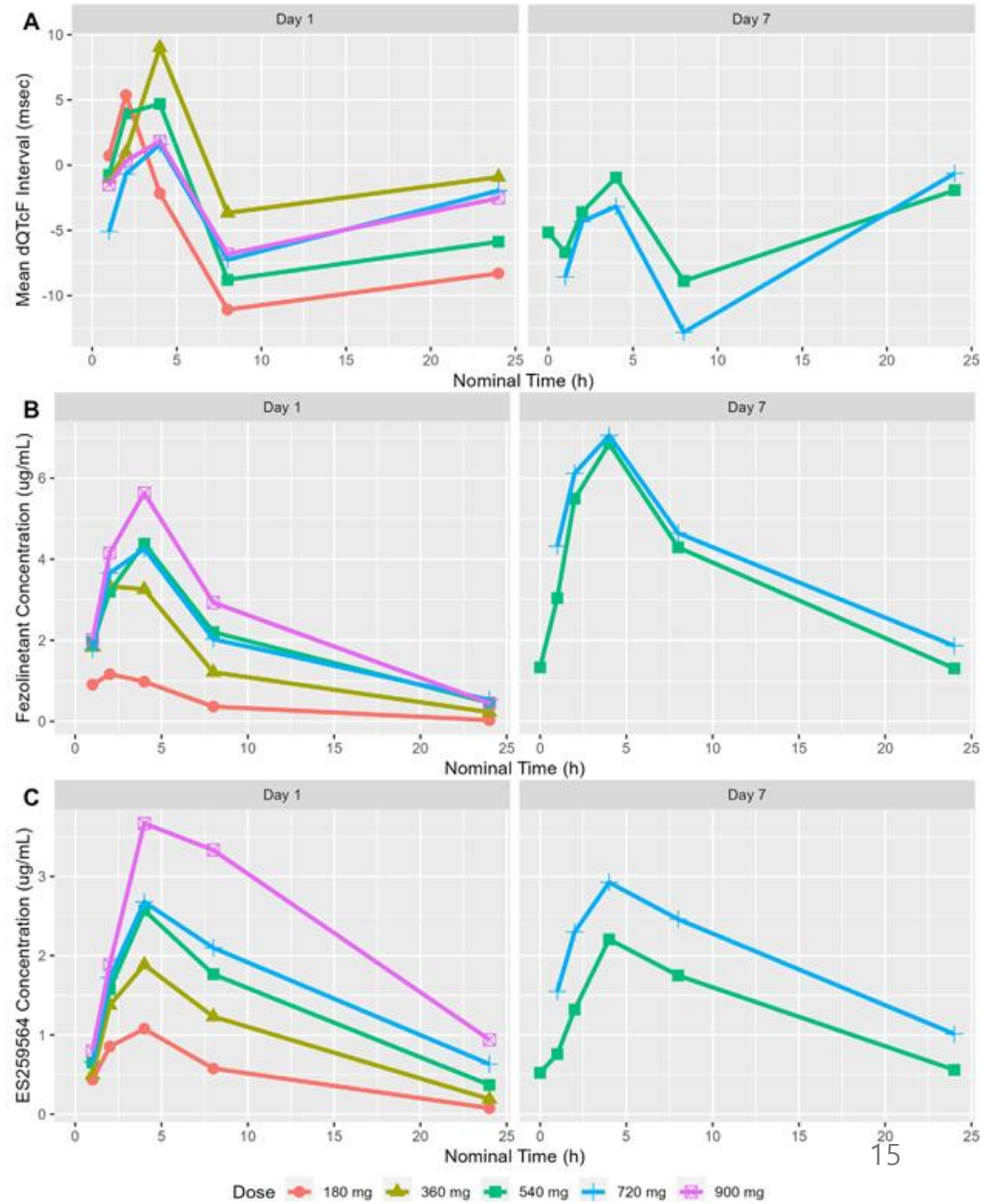


Figure 2. Linearity of PK/PD relationship.



- What was baseline?
- ΔQTc instead of ΔΔQTc
- "Predefined linear model"

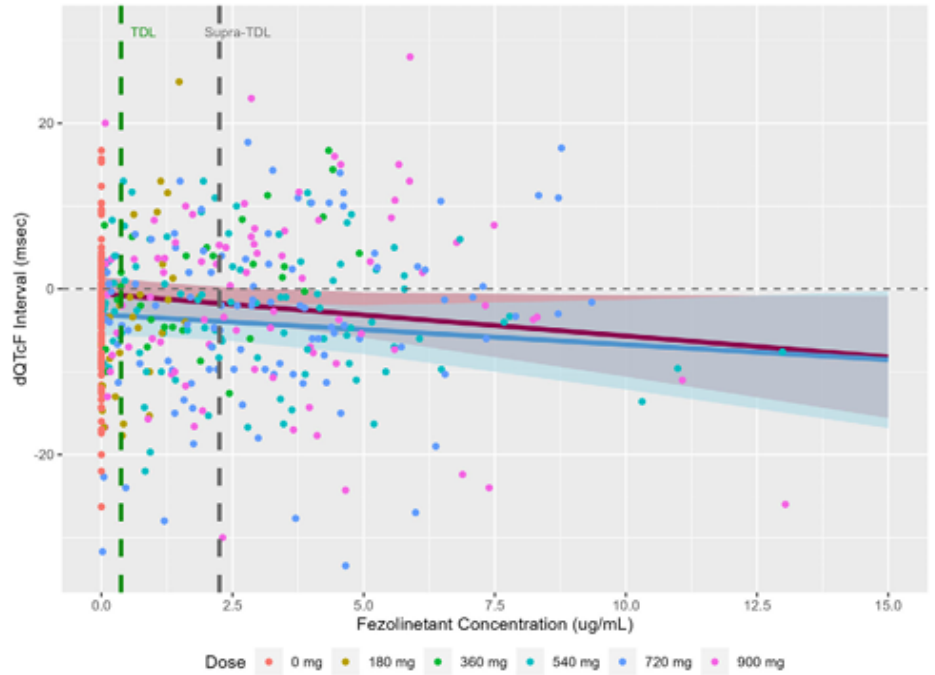


Figure 3. Concentration-QTcF plots for the Parent Model. Solid red line (pink shaded region) is the population mean model prediction (90% CI) for Day 1. Solid blue line (blue shaded region) is the population mean model prediction (90% CI) for Day 7. Colored symbols are the observed dQTcF intervals. Vertical dashed green line represents the concentration for the therapeutic dose level (TDL) and the vertical dashed grey line represents the concentration for the supra-therapeutic dose level.

$$dQTcF_{ijk} = (\theta_{int} + \eta_{int,i}) + \theta_{TRT} \cdot TRT_{ij} + \theta_{DAY} \cdot D7 + \theta_{rmean} \cdot (QTcF_{0,ij} - QTcF_{0,GM}) + \sum_{k=2}^{6} \theta_{NTIME(k)} \cdot NOMTIMEH_k + (\theta_{FEZO} + \theta_{D7_FEZO} + \eta_{FEZO,i}) \cdot Cp_{FEZO,ijk} + \varepsilon_{ijk}$$

$$dQTcF_{ijk} = (\theta_{int} + \eta_{int,i}) + \theta_{TRT} \cdot TRT_{ij} + \theta_{DAY} \cdot D7 + \theta_{rmean} \cdot (QTcF_{0,ij} - QTcF_{0,GM}) + \sum_{k=2}^{6} \theta_{NTIME(k)} \cdot NOMTIMEH_k + (\theta_{FEZO} + \theta_{D7_FEZO} + \eta_{FEZO,i}) \cdot Cp_{FEZO,ijk} + (\theta_{ES259564} + \theta_{D7_ES259564} + \eta_{ES259564,i}) \cdot Cp_{ES259564,ijk} + \varepsilon_{ijk}$$

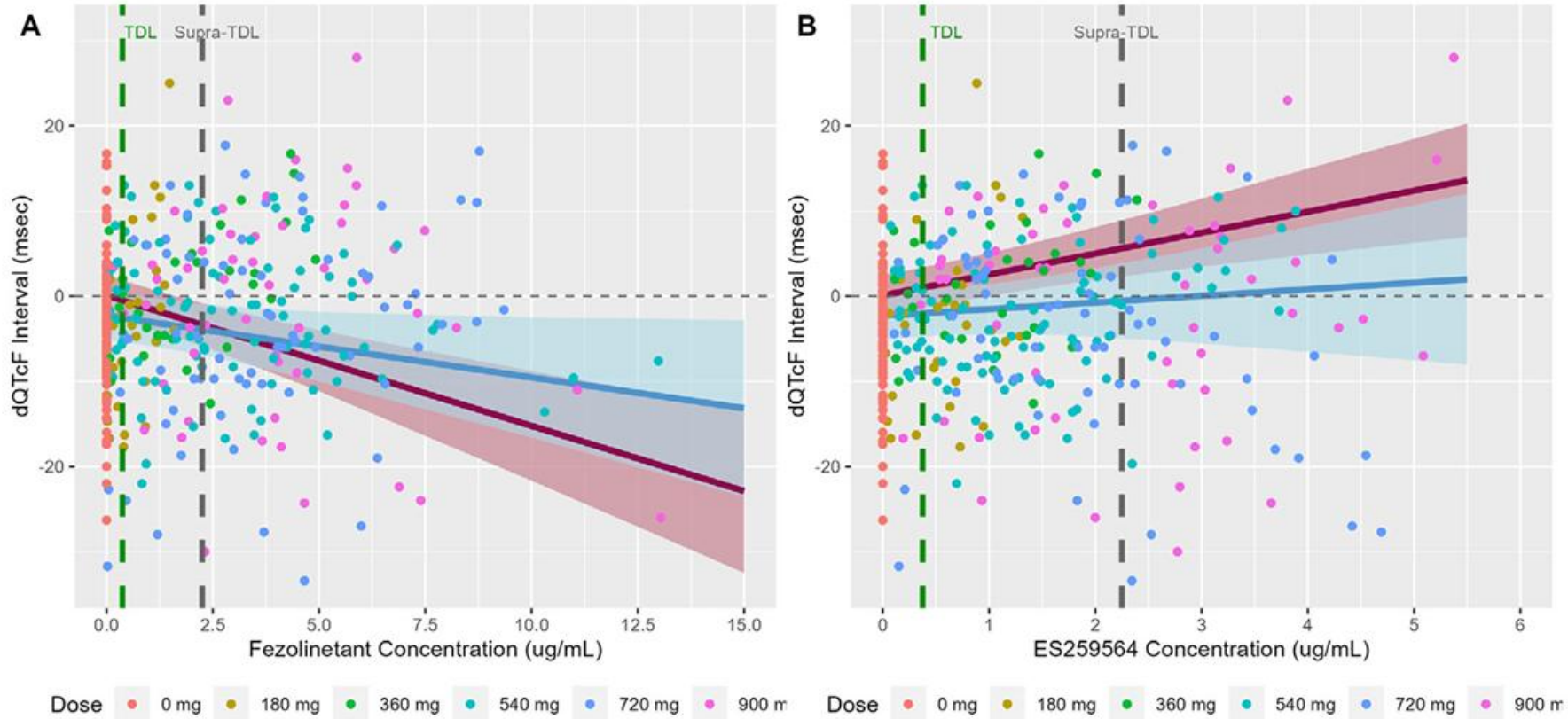
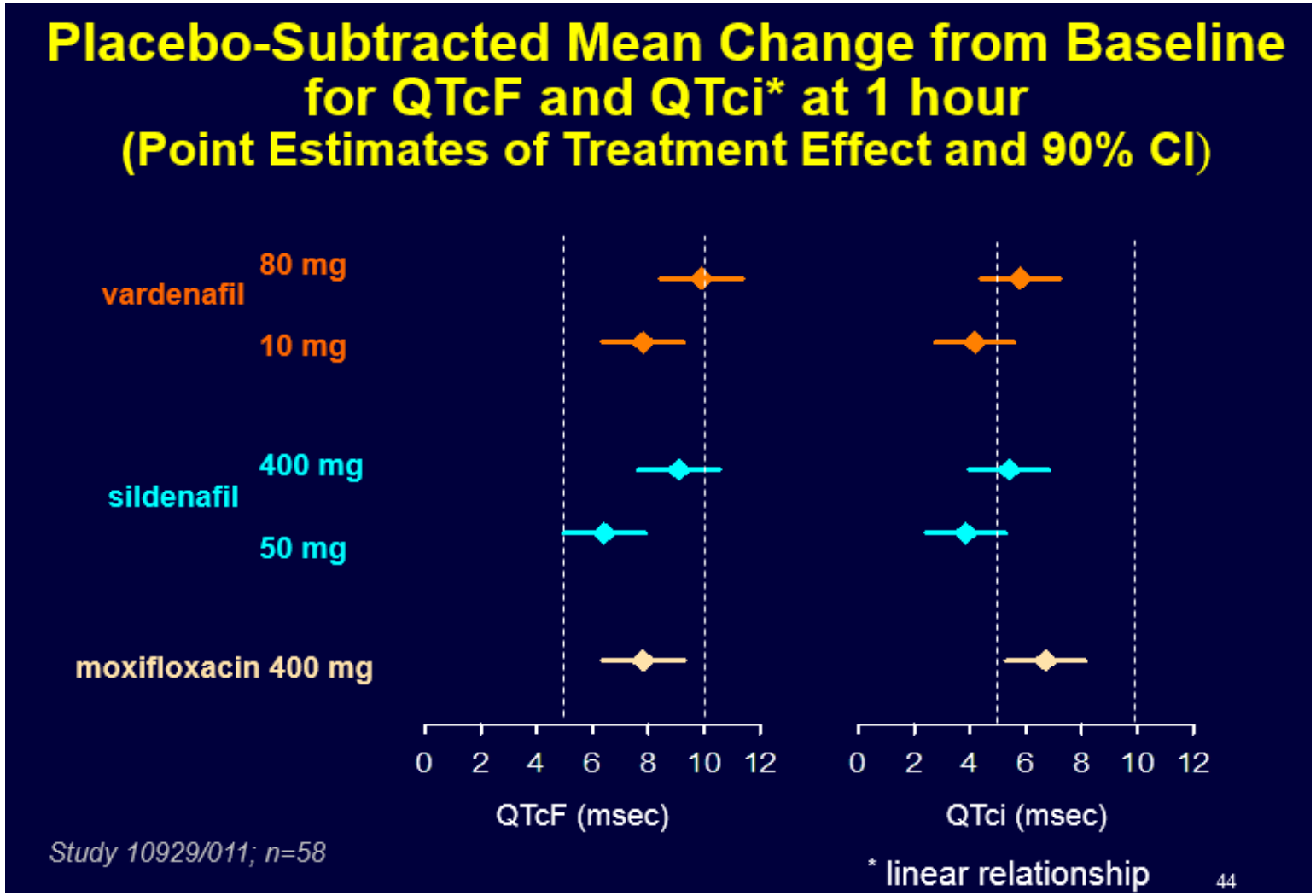


Figure 4. Concentration–QTcF plots for the Parent and Metabolite Model. Solid red line (pink shaded region) is the population mean model prediction (90% CI) for Day 1. Solid blue line (blue shaded region) is the population mean model prediction (90% CI) for Day 7. Colored symbols are the observed dQTcF intervals. Vertical dashed green line represents the concentration for the therapeutic dose level (TDL) and the vertical dashed grey line represents the concentration for the supra-therapeutic dose level.

FDA review example in 2002

• Vardenafil causes QT interval prolongation, however, the magnitude of prolongation observed is not likely of clinical concern. Committee members stated that this opinion was influenced by both (1) postmarketing AERS and WHO database results for a drug in the same class and (2) the shallow dose-QT/QTc response relationship for vardenafil.



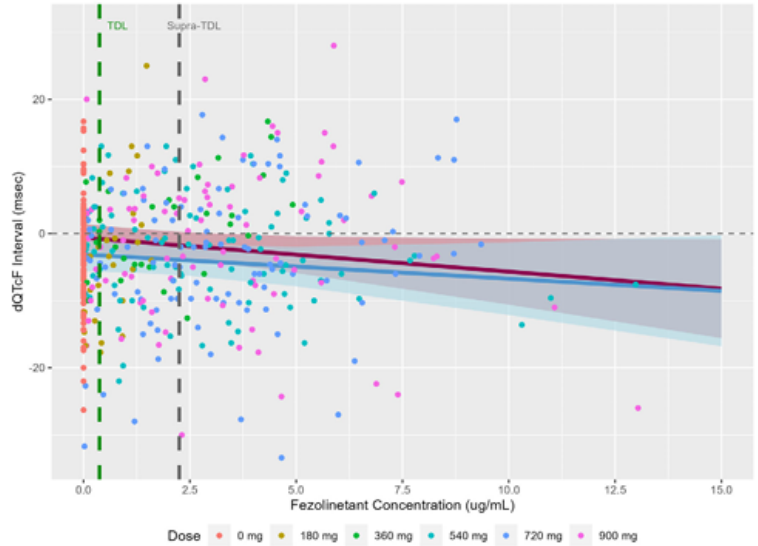


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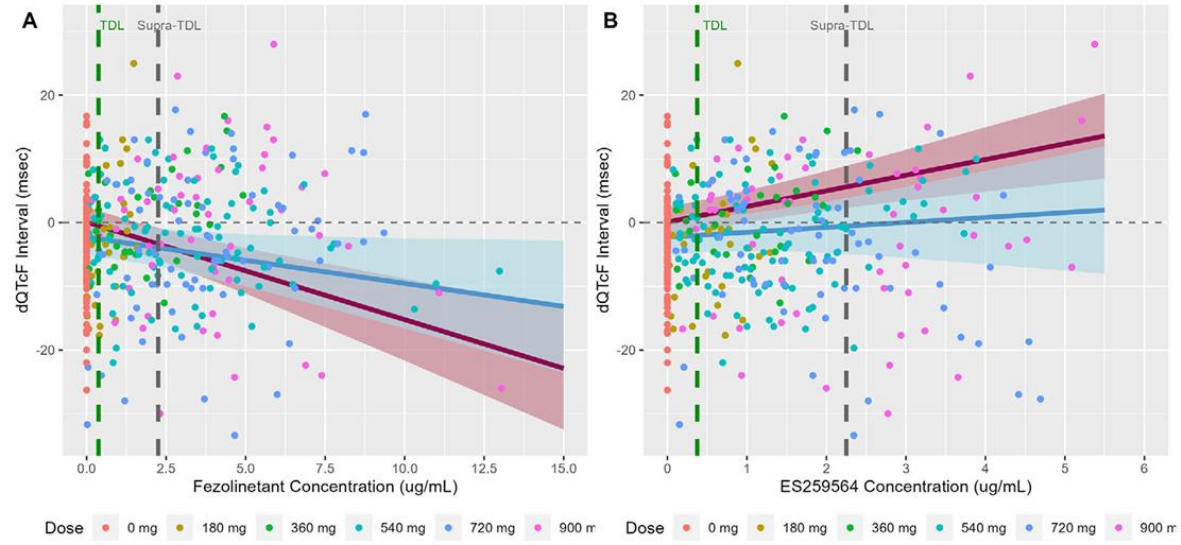


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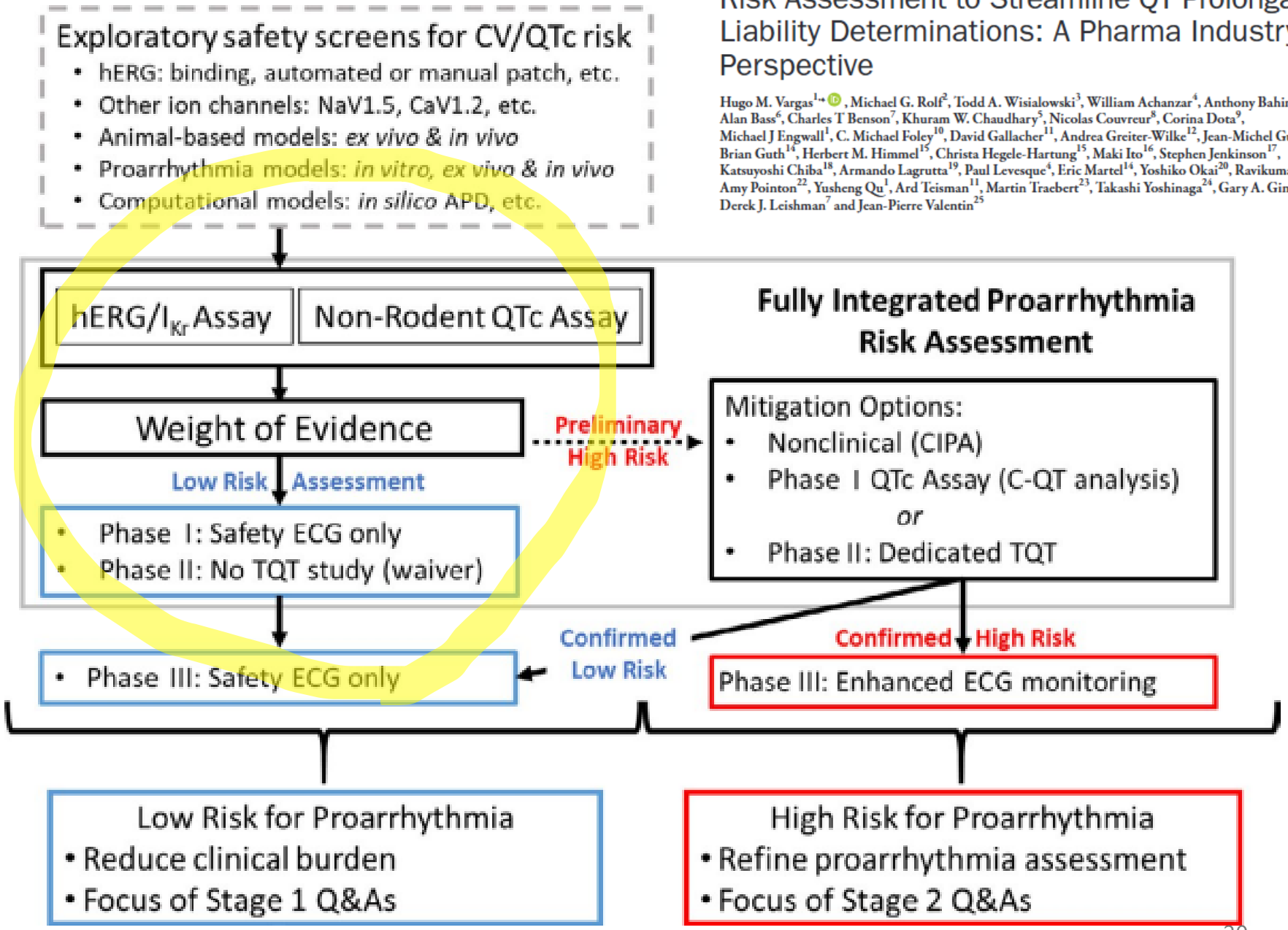
Table 2. Summary of ddQTcF Predictions for Relevant Concentrations From the Parent Model and the Parent and Metabolite Model

		Parent Model		Parent and Metabolite Model	
	Day	Prediction (ms)	Upper One-Sided 95% CI (ms)	Prediction (ms)	Upper One-Sided 95% CI (ms)
Therapeutic concentration (0.375 µg/mL)	1	2.0794	0.3276	1.4536	3.3483
	7	2.1337	0.3421	1.1251	3.1085
Highest clinical exposure (6-times therapeutic concentration) (2.25 µg/mL)	1	1.1287	−0.546	3.1875	5.4323
	7	1.4546	−0.5574	1.2162	4.8564
10-Times therapeutic concentration (3.75 µg/mL)	1	0.3681	−1.6262	4.5745	7.8686
	7	0.9114	−1.652	1.2890	7.0062

- Industry's view
  - Gap?

Time for a Fully Integrated Nonclinical–Clinical Risk Assessment to Streamline QT Prolongation Liability Determinations: A Pharma Industry Perspective

Hugo M. Vargas[1]*, Michael G. Rolf[2], Todd A. Wisialowski[3], William Achanzar[4], Anthony Bahinski[5], Alan Bass[6], Charles T Benson[7], Khuram W. Chaudhary[5], Nicolas Couvreur[8], Corina Dota[9], Michael J Engwall[1], C. Michael Foley[10], David Gallacher[11], Andrea Greiter-Wilke[12], Jean-Michel Guillon[13], Brian Guth[14], Herbert M. Himmel[15], Christa Hegele-Hartung[15], Maki Ito[16], Stephen Jenkinson[17], Katsuyoshi Chiba[18], Armando Lagrutta[19], Paul Levesque[4], Eric Martel[14], Yoshiko Okai[20], Ravikumar Peri[21], Amy Pointon[22], Yusheng Qu[1], Ard Teisman[11], Martin Traebert[23], Takashi Yoshinaga[24], Gary A. Gintant[10], Derek J. Leishman[7] and Jean-Pierre Valentin[25]



CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 109 NUMBER 2 | February 2021

Summary

To replace TQT studies (ICH E14, 2005),

- Cost & false (+) …

Integrated approaches using non-clinical data

- E14 / S7B Q & A R1
- Rather than TQT

M15



Shelly Wang

Gilead Sciences 임상약리과학부문 시니어 디렉터

Gilead Sciences, Clinical Pharmacology Sciences Senior Director

Shelly Wang은 Gilead Sciences에서 약물계량학(Pharmacometrics) 부문 Senior Director로 재직하고 있습니다.미국 서던캘리포니아대학교(University of Southern California)에서 의공학 박사학위를 취득했으며, Bristol-Myers Squibb에서 모델링 및 시뮬레이션 연구과학자로 경력을 시작했습니다. 이후 Metrum Research Group에서 Principal Scientist로 근무한 뒤, 2025년 Gilead Sciences에 합류했습니다.약물계량학 분야에서 19년의 제약산업 경력을 보유하고 있으며, 종양학, 면역과학 및 소아 분야에서 정량적 임상약리학 관련 임상 경험을 쌓아왔습니다.
Shelly Wang is a Senior Director of Pharmcometrics at Gilead Sciences.She earned her Ph.D. degree in Biomedical Engineering from the University of Southern California. Shelly startedher career at Bristol-Myers Squibb as a modeling and simulation research scientist, having worked at MetrumResearch Group as a principal scientist before joining Gilead Sciences in 2025. She brings 19 years ofpharmaceutical industry experience in the area of pharmacometrics. Shelly's clinical experience includesquantitative clinical pharmacology in oncology, immuno-science and pediatrics.

Program

ICH M15 가이드라인: 모델 기반 의약품 개발의 일반 원칙 및 실제 적용

ICH M15 Guideline: General Principles for Model-Informed Drug Development Practical Application

ICH M15 Guideline: General Principles for Model-Informed Drug Development

Practical Application

ICH Guideline Training

October 2026

Presented by Shelly Wang,
on behalf of IFPMA

IFPMA

Agenda

Introduction to the Guideline (10 min)

Practical Application (20 min)

Q&A (10 min)

Key Principles

Model-Informed Drug Development (MIDD):
the use of computational modeling and simulation (M&S) methods that can include and integrate nonclinical data, clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence.



MIDD evidence:
model outcomes that have been determined by application of the MIDD evidence assessment framework, including Model Evaluation, to be appropriate to inform the answer to the Question of Interest





Guideline Objectives and Scope

To provide general recommendations for planning, model evaluation, and documentation of MIDD evidence



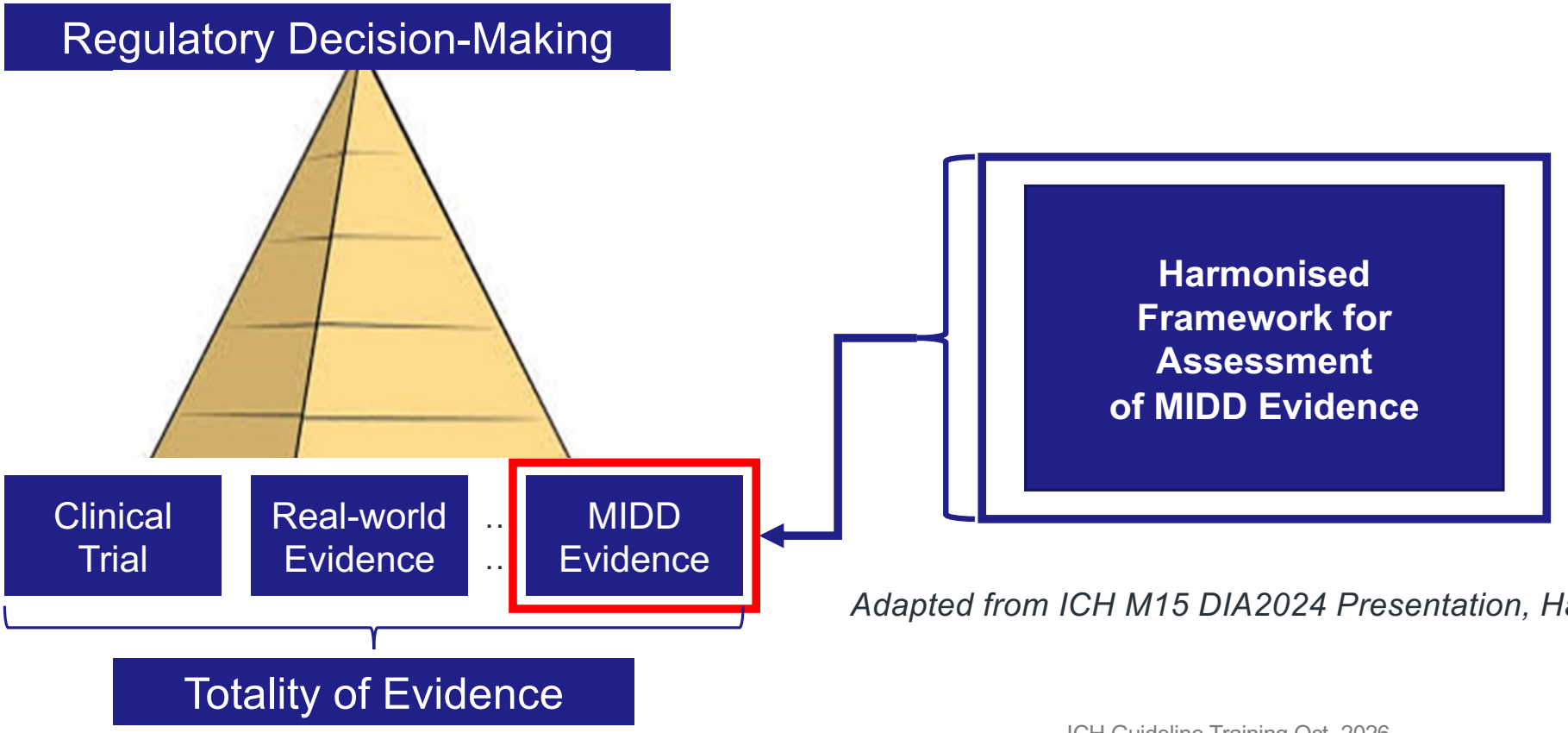
To establish a harmonized assessment framework (including associated terminology) for MIDD evidence



To facilitate a multidisciplinary understanding of MIDD and associated evidence generation



MIDD Evidence for Regulatory Decision-Making



Adapted from ICH M15 DIA2024 Presentation, Hao Zhu

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Background

M&S methods include but are not limited to the following

- Population pharmacokinetics
- Physiologically based pharmacokinetics and biopharmaceutics
- Dose-exposure-response
- Model-based meta-analysis

- Quantitative systems pharmacology and toxicology
- Agent-based models
- Disease progression models
- Artificial intelligence/machine learning

Scope

Applies to both current and emerging M&S methods and applications



Focuses on assessment of MIDD evidence and provides recommendations for related regulatory interactions, reporting, and submission



Does not include details regarding technical aspects of model development. Model development should follow the general recommendations outlined in this guideline.

Sequence of MIDD in Relation to the Relevant Guideline Sections

Stages	Planning and Regulatory Interaction		Implementation, Reporting, and Submission		
Sequence of Activities	**Key Assessment Elements**	**Additional Considerations for Interaction with Regulator and to Inform Decision-Making**	**Model Evaluation**	**Model Analysis Reporting**	**Documentation for Regulatory Interactions and Submissions**
	• Question of Interest • Context of Use • Model Influence • Consequence of Wrong Decision • Model Risk • Model Impact	• Appropriateness of Proposed MIDD • Technical Criteria for model evaluation and model outcomes[1] These should be documented (e.g., in a Model Analysis Plan [MAP]).	• Verification • Validation • Applicability assessment	• Model Analysis Report(s) (MAR)	• Regulatory documents, including + Outcome of MIDD Evidence Assessment + References to all relevant MAPs and MARs
Relevant Guideline Section	Section 2.1 and Appendix 1	Sections 2.2 and 4.1 and Appendix 1	Section 3	Section 4.2 and Appendix 2	Sections 2 and 4.3 and Appendix 1

Note: Terms used in this table are defined in relevant guideline sections.

[1] Results derived from M&S (i.e., via model-based predictions or simulations) and associated conclusions that are typically aligned to a Question of Interest.

Inform Decision-Making

Framework for Assessment of MIDD Evidence

Describes key concepts for assessment of MIDD evidence to inform decision-making, increase transparency, and provide an understanding of MIDD at the planning stage



These concepts are split into:



- Key Assessment Elements
- Additional Considerations for Interactions with Regulators to Inform Decision-Making



Table for Assessment of MIDD Evidence

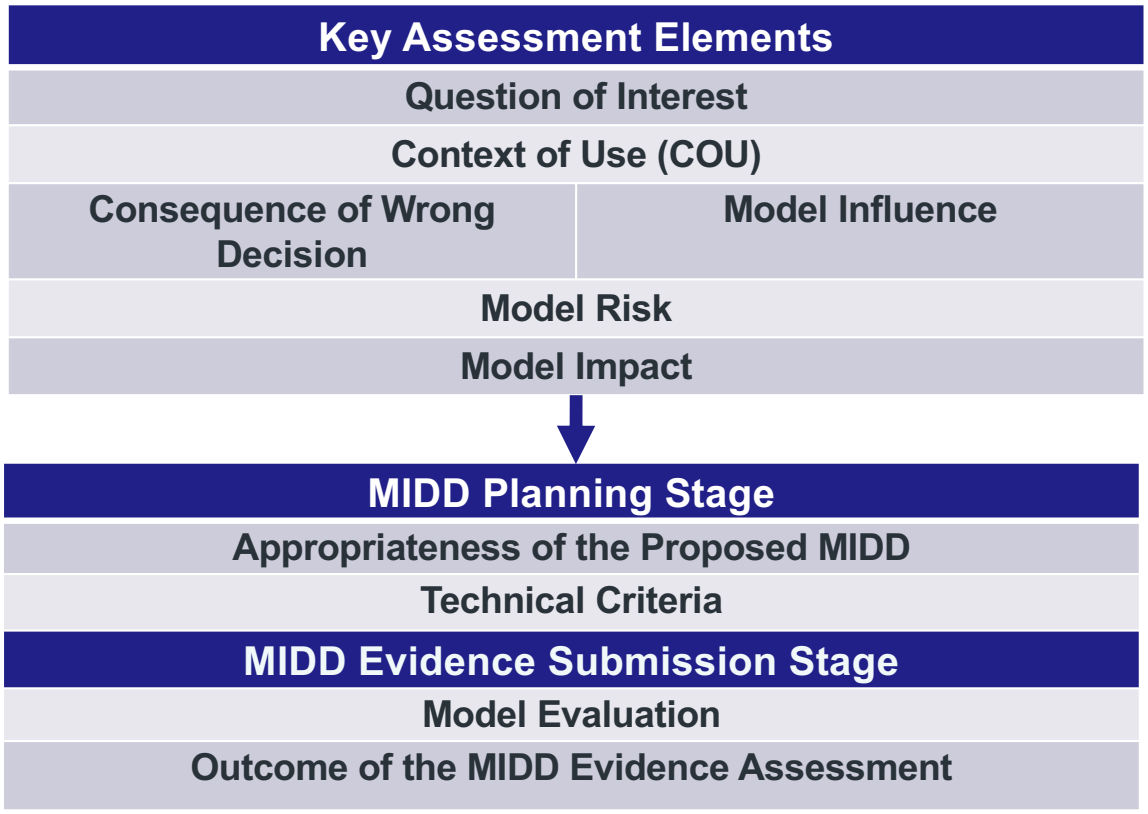
Item	Definition	Instruction	Entry
Key Assessment Elements			
Question of Interest[1]	The question that MIDD is intended to answer.	State the Question of Interest.	
Context of Use	A description of the model(s) and its specific role and scope to answer the Question of Interest.	Provide a concise, clear, and explicit description of the model, the data used to build the model, the specific role of the model outcomes, and the other data or evidence that will contribute to the answer to the Question of Interest.	
Model Influence	The intended weight of the model outcomes in decision-making considering the contribution of other relevant information.	Describe the Model Influence; rate it as low, medium, or high considering other relevant information (e.g., nonclinical and clinical) to inform decision-making; and justify the rating.	
Consequence of Wrong Decision	The consequences (e.g., with respect to patient safety and/or efficacy) if a wrong decision is made, based on all available information.	Describe the consequence of a wrong decision; rate it as low, medium, or high based on the severity of the consequences a wrong decision may have on patient safety and efficacy; and justify the rating.	
Model Risk[2]	The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.	Describe the risk; rate it as low, medium, or high based on the Model Influence rate and the Consequence of a Wrong Decision rate; and justify the rating.	
Model Impact	The contribution of the model outcomes in relation to current regulatory expectations or standards in answering the Question of Interest.	Describe the impact; rate it as low, medium, or high considering current regulatory expectations or standards; and justify the rating.	

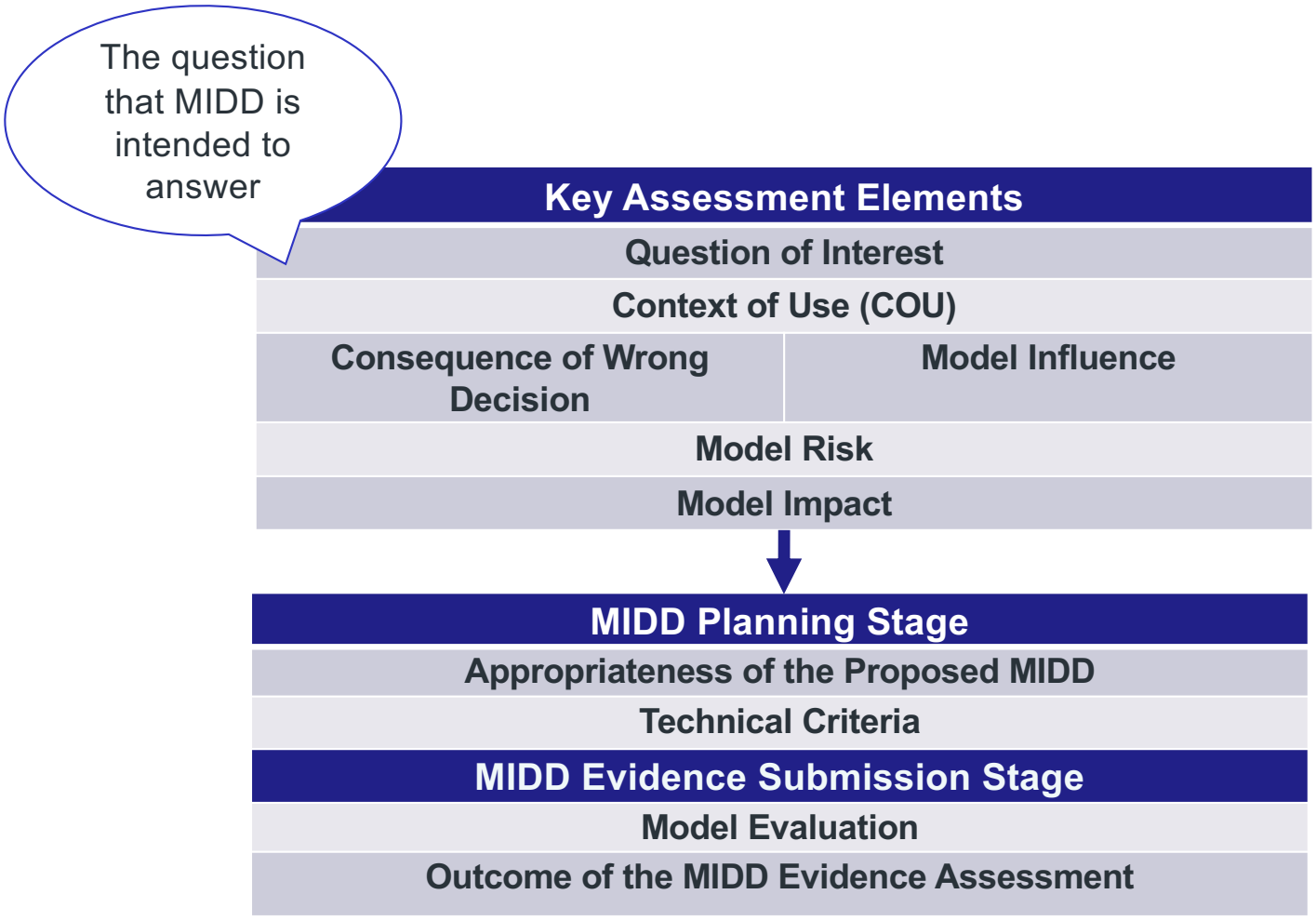
[1] If MIDD is planned to answer different Questions of Interest, it is recommended to use separate tables for each question.
[2] Model Risk should be interpreted in the context of answering a specific Question of Interest and is not to be perceived as a risk intrinsic to MIDD or M&S.

Item	Definition	Instruction	Entry
MIDD Planning Stage[3]			
Appropriateness of Proposed MIDD	The rationale for why the proposed MIDD is suitable to answer the Question of Interest and cover the related key assumptions and required data.	Include a description and justification sufficient to facilitate regulatory interaction on the appropriateness of the proposed MIDD to answer the Question of Interest.	
Technical Criteria	A summary and rationale of the key criteria for Model Evaluation and model outcomes to establish the acceptability of the model (e.g., using an acceptance standard such as bioequivalence acceptance limits).	Include a description of the Technical Criteria for the assessment of Model Evaluation and model outcome. This should include sufficient details on the relevant metric(s).	
MIDD Evidence Submission Stage			
Model Evaluation	A brief discussion of the key results and conclusions of the technical evaluation[4] of the model.	Describe the key results and how they compare to and fulfill the Technical Criteria and conclude on the acceptability of the model performance and model outcome, with details being provided in the appropriate regulatory documentation.	
Outcome of the MIDD Evidence Assessment[5]	A concise summary of the multidisciplinary assessment of the MIDD evidence to answer the Question of Interest.	Provide a multidisciplinary integrative assessment and conclusion for the acceptability of the MIDD evidence to contribute to the answer to the Question of Interest, referring to the MIDD assessment framework elements.	

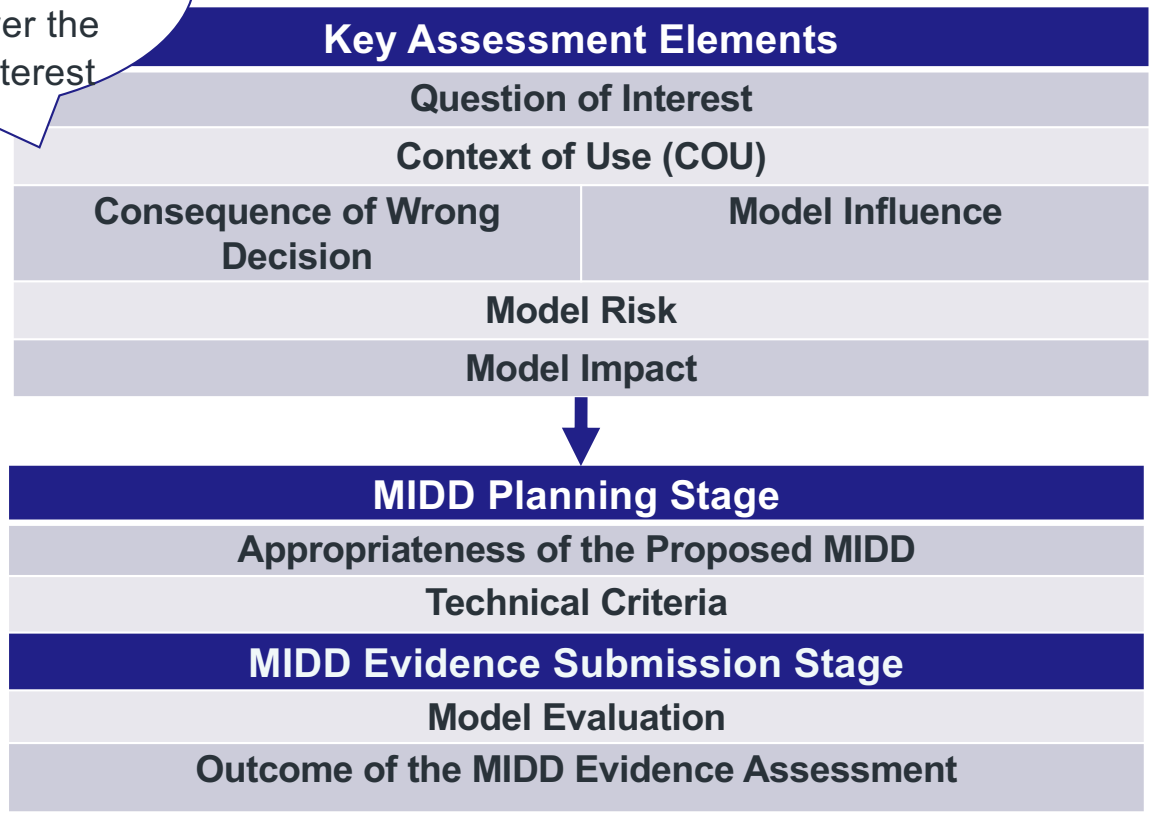
[3] These items should also be provided at the MIDD Evidence Submission Stage.
[4] Using the principles of Model Evaluation described in Section 3 of the draft guideline, with specific focus on Technical Criteria.
[5] "Assessment" in this context does not refer to any regulatory review activities or processes.

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Key Assessment Elements
Question of Interest
Context of Use (COU)
Consequence of Wrong Decision
Model Influence
Model Risk
Model Impact
MIDD Planning Stage
Appropriateness of the Proposed MIDD
Technical Criteria
MIDD Evidence Submission Stage
Model Evaluation
Outcome of the MIDD Evidence Assessment

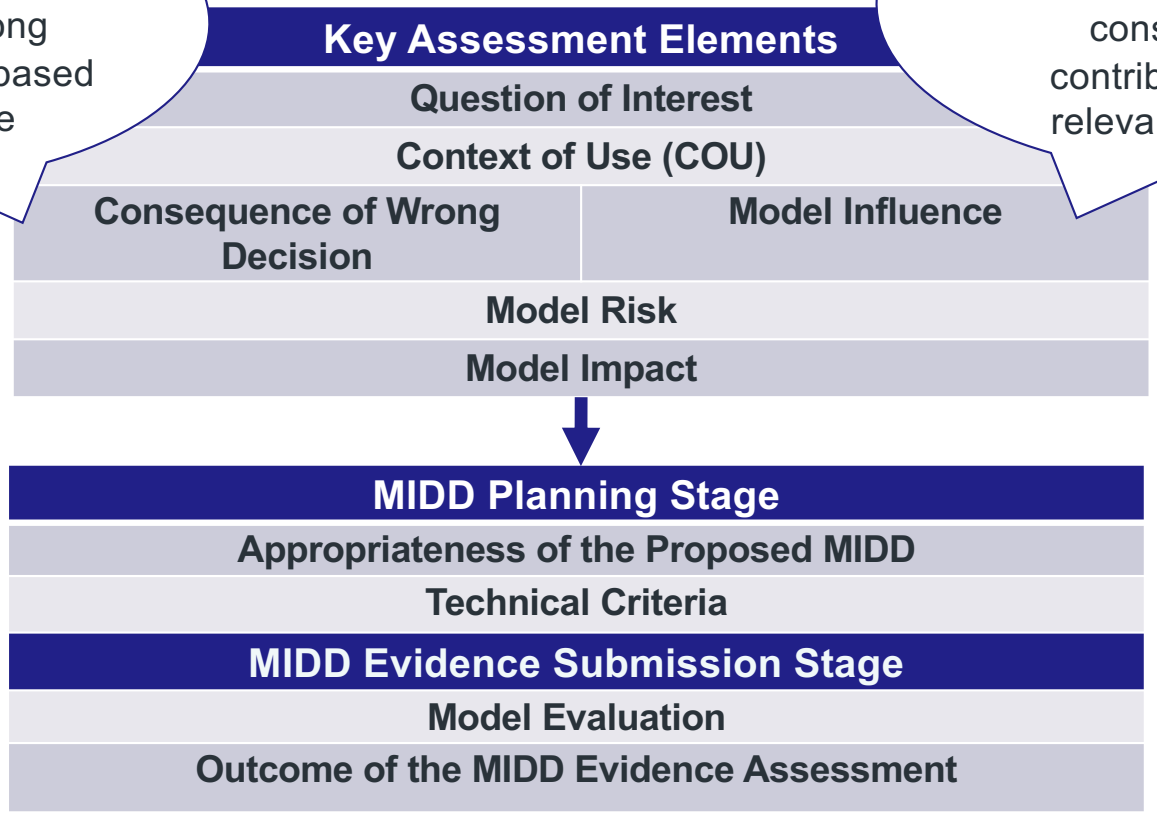

The question that MIDD is intended to answer
Key Assessment Elements
Question of Interest
Context of Use (COU)
Consequence of Wrong Decision
Model Influence
Model Risk
Model Impact
MIDD Planning Stage
Appropriateness of the Proposed MIDD
Technical Criteria
MIDD Evidence Submission Stage
Model Evaluation
Outcome of the MIDD Evidence Assessment

Description of the model(s) and its specific role and scope to answer the Question of Interest

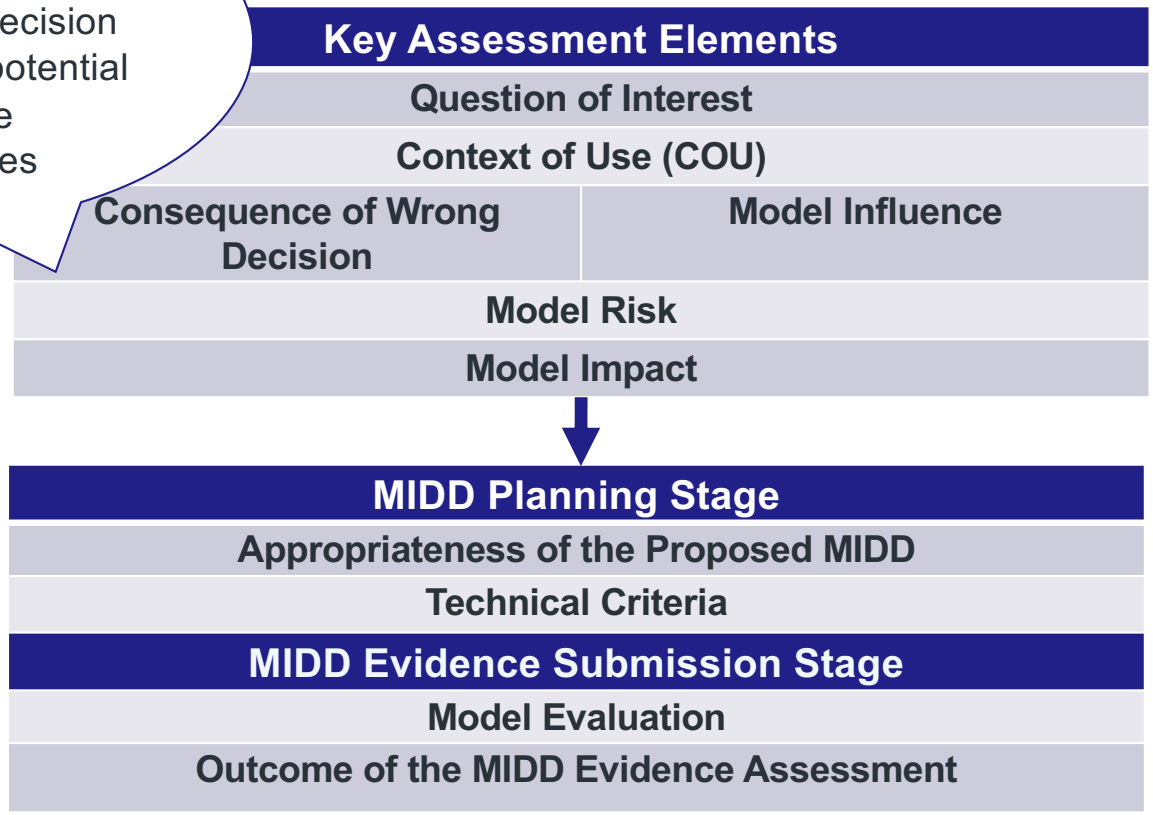


The consequences (e.g., with respect to patient safety and/or efficacy) if a wrong decision is made, based on all available information

The intended weight of the model outcomes in decision-making considering the contribution of other relevant information

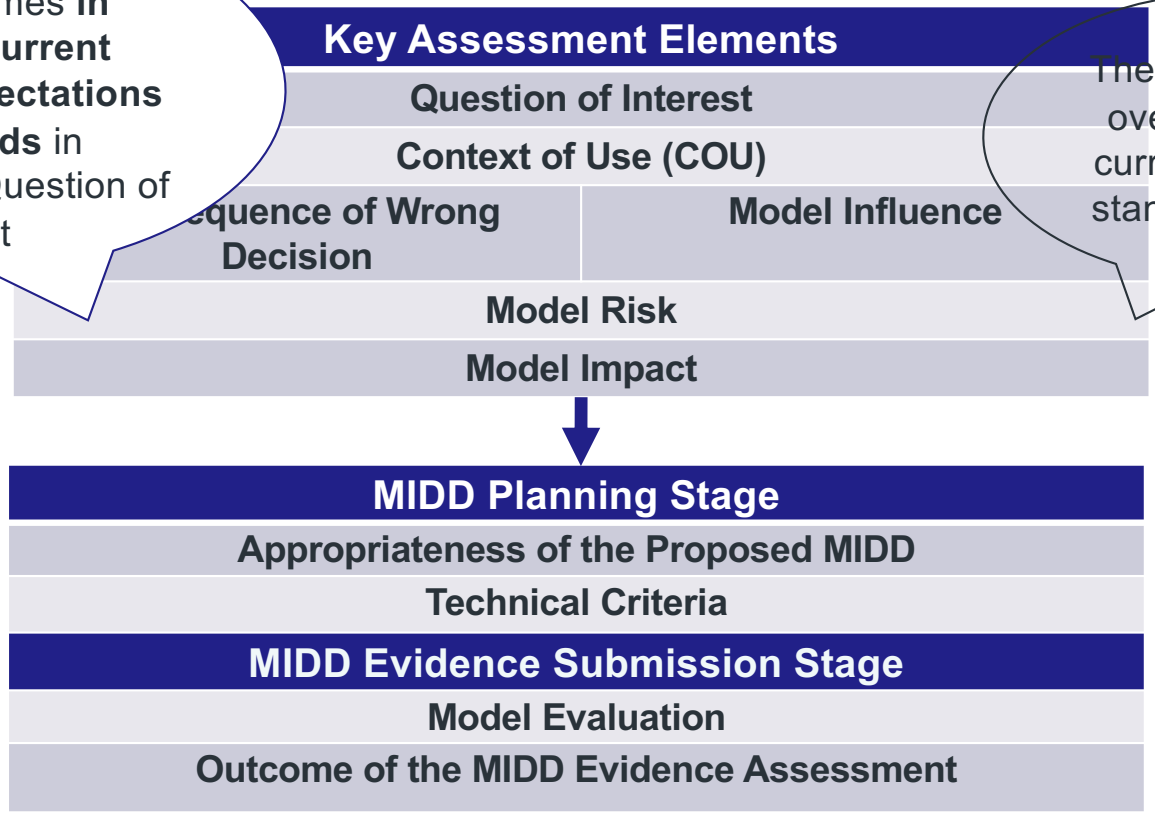


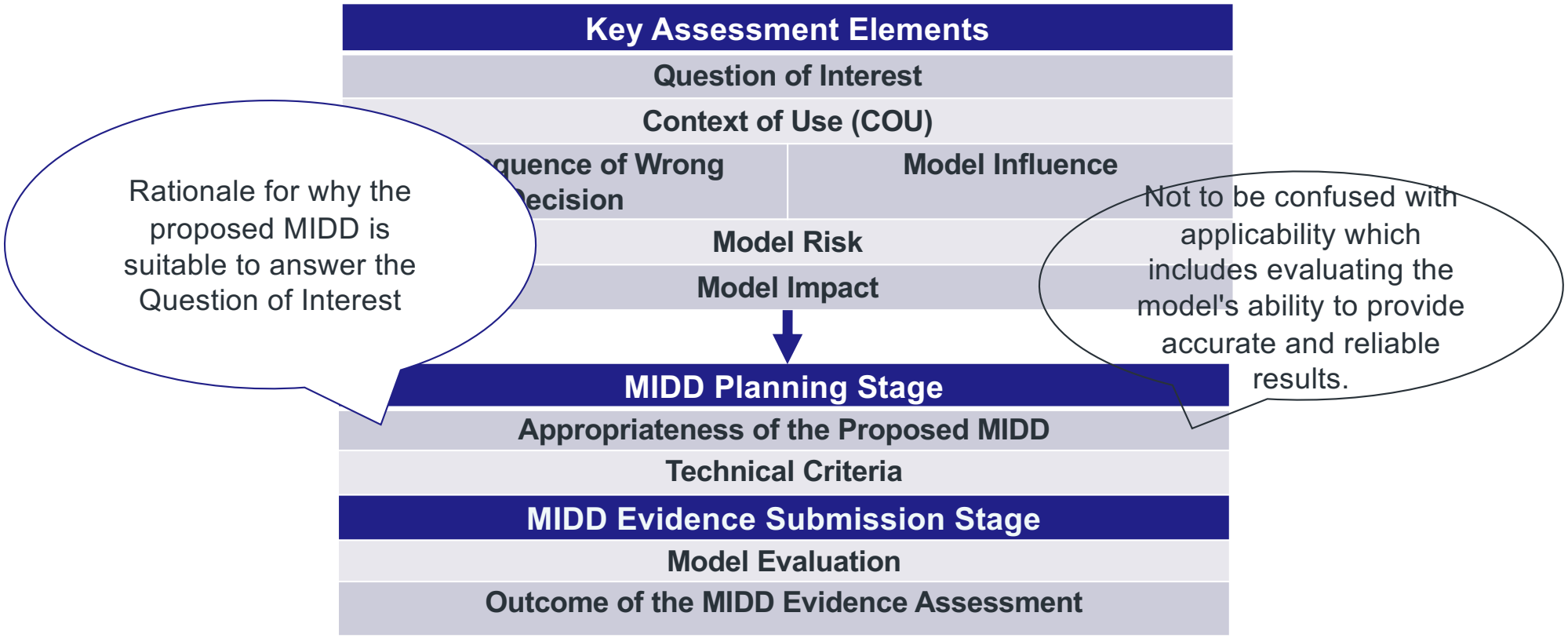
The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences

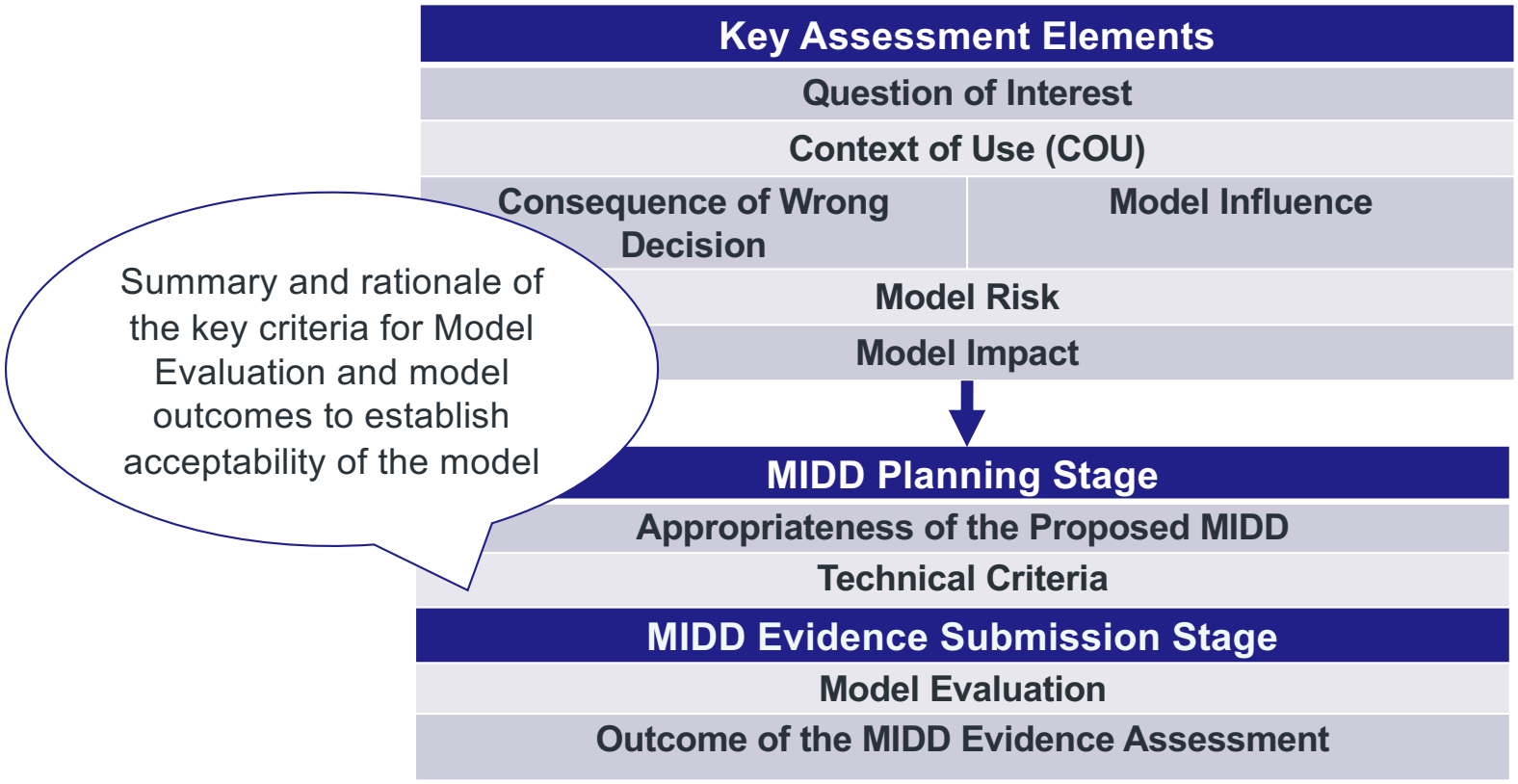


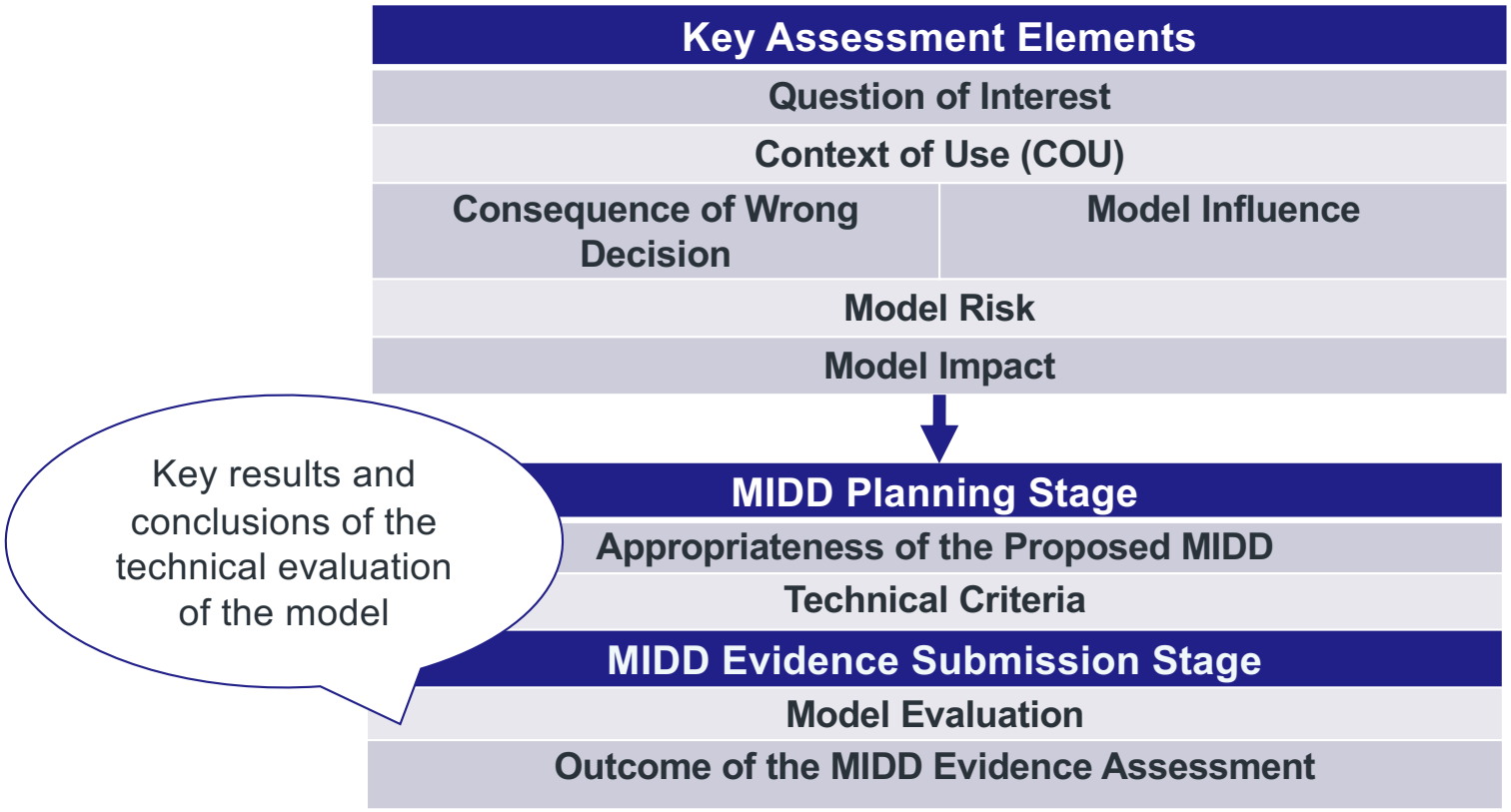
The contribution of the model outcomes **in relation to current regulatory expectations or standards** in answering the Question of Interest

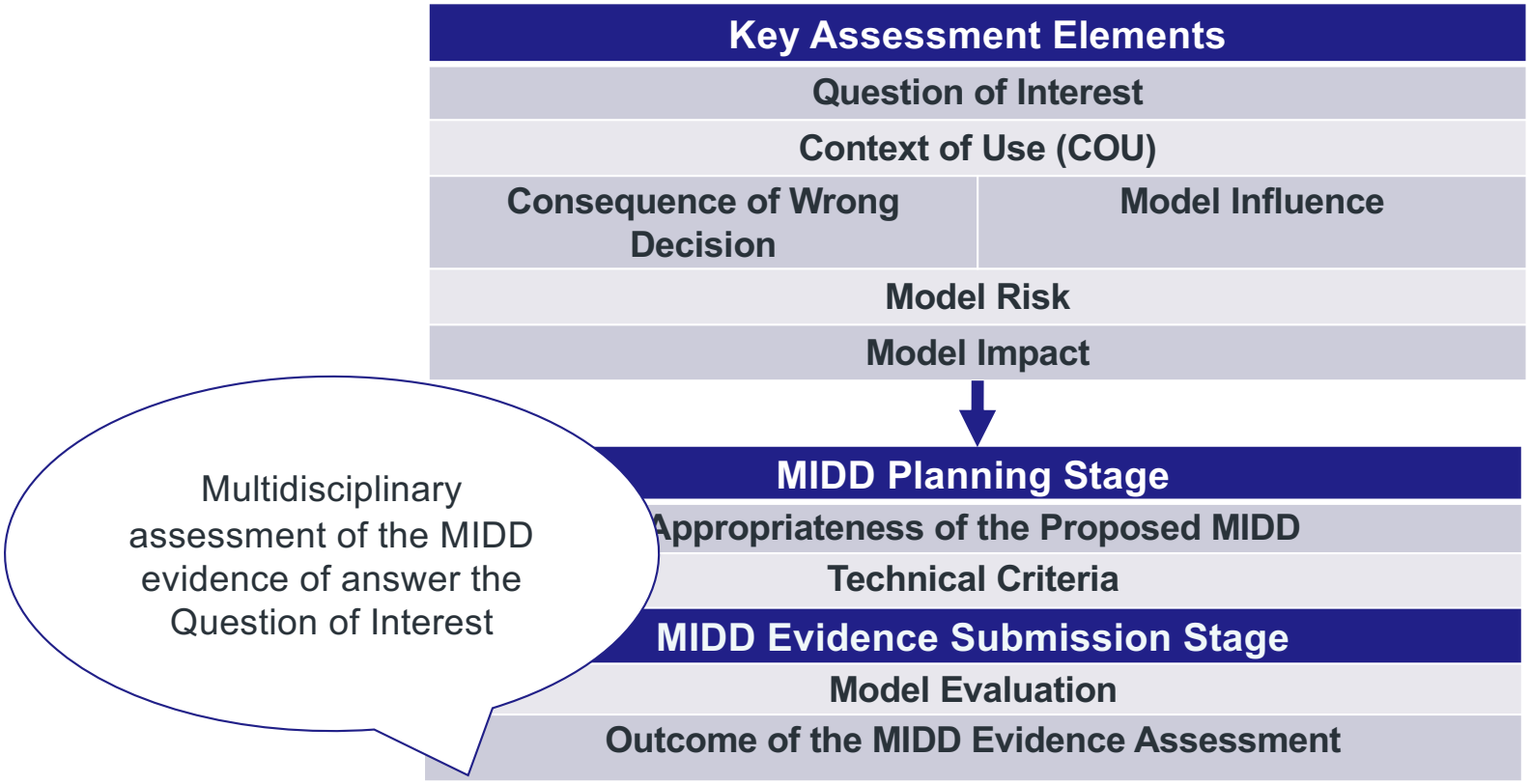
The rating change over time as the current regulatory standards change




Key Assessment Elements
Question of Interest
Context of Use (COU)
quence of Wrong
ecision
Model Influence
Model Risk
Model Impact
MIDD Planning Stage
Appropriateness of the Proposed MIDD
Technical Criteria
MIDD Evidence Submission Stage
Model Evaluation
Outcome of the MIDD Evidence Assessment
Rationale for why the proposed MIDD is suitable to answer the Question of Interest
Not to be confused with applicability which includes evaluating the model's ability to provide accurate and reliable results.


Key Assessment Elements
Question of Interest
Context of Use (COU)
Consequence of Wrong Decision
Model Influence
Model Risk
Model Impact
Summary and rationale of the key criteria for Model Evaluation and model outcomes to establish acceptability of the model
MIDD Planning Stage
Appropriateness of the Proposed MIDD
Technical Criteria
MIDD Evidence Submission Stage
Model Evaluation
Outcome of the MIDD Evidence Assessment


Key Assessment Elements
Question of Interest
Context of Use (COU)
Consequence of Wrong Decision
Model Influence
Model Risk
Model Impact
MIDD Planning Stage
Appropriateness of the Proposed MIDD
Technical Criteria
MIDD Evidence Submission Stage
Model Evaluation
Outcome of the MIDD Evidence Assessment
Key results and conclusions of the technical evaluation of the model


Key Assessment Elements
Question of Interest
Context of Use (COU)
Consequence of Wrong Decision
Model Influence
Model Risk
Model Impact
MIDD Planning Stage
Appropriateness of the Proposed MIDD
Technical Criteria
MIDD Evidence Submission Stage
Model Evaluation
Outcome of the MIDD Evidence Assessment
Multidisciplinary assessment of the MIDD evidence of answer the Question of Interest

Framework for Assessment of MIDD Evidence – Points to Remember

IFPMA

Intended to serve as a communication tool – no definite right or wrong way to fill it in



The ratings are intended to trigger a well-described justification for a specific item.



A high rating, e.g., high Model Risk, does not mean that the MIDD evidence will not be accepted, just that it needs more attention.

Scenario & example use of M15 – for Illustrative purposes

Use MIDD evidence to justify label change from weight-based to fixed dose for a monoclonal antibody previously approved to treat a life-threatening condition

Phase I–III studies conducted using body weight-based dosing across a large weight range providing:

- robust popPK (reviewed by health authorities with no concerns)
- relationship between exposure and efficacy (% of responders)
- identification of the exposure range where efficacy plateaus
- characterization of dose-exposure-safety
- a clear understanding of the between-subject variability

Safety established across full exposure range (3 times higher than the registered dose)

Additional real-world data with fixed dose is available, and clinical experience suggests fixed dosing would be more patient-centric

Key Assessment Elements

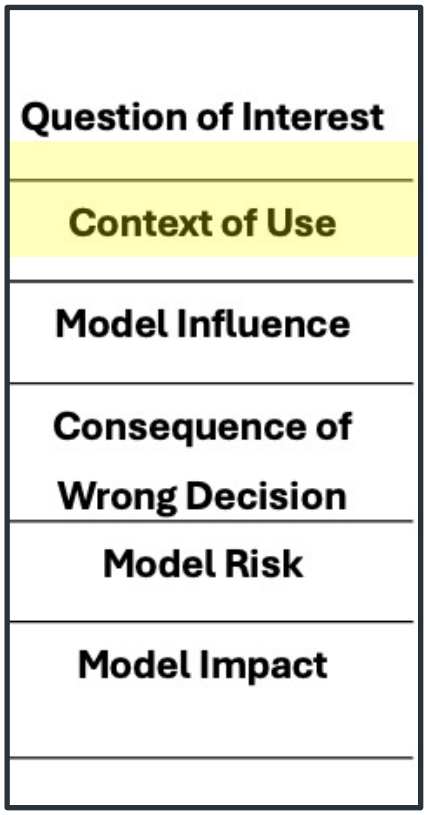
IFPMA

Question of Interest
Context of Use
Model Influence
Consequence of Wrong Decision
Model Risk
Model Impact

Definition	Instruction	Entry
The question that MIDD is intended to answer.	State the Question of Interest.	Could the approved body-weight-based dosing be replaced by a fixed dosing regimen while still providing a similar efficacy and safety profile?

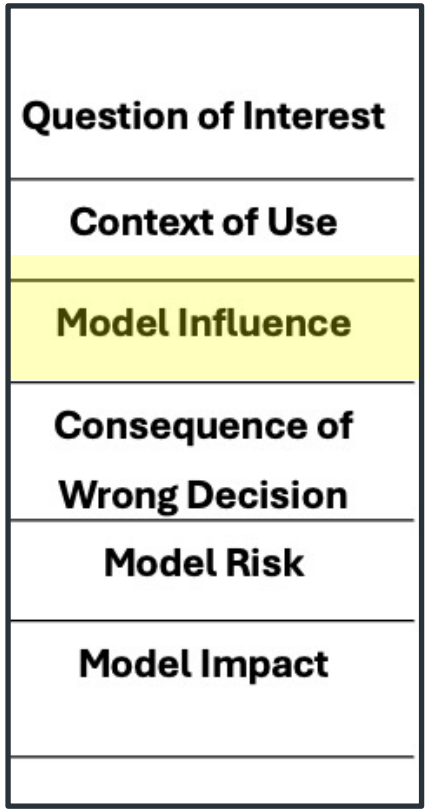
Key Assessment Elements

IFPMA



Definition	Instruction	Entry
A description of the model(s) and its specific role and scope to answer the Question of Interest.	Provide a concise, clear, and explicit description of the model, the data used to build the model, the specific role of the model outcomes, and the other data **or evidence that will contribute to the answer to the Question of Interest**.	**Strategy to address COU:** ▪ Previously developed PPK model will be **simulated** to identify fixed dose that generates exposure comparable to the approved body-weight-based dosing. **Additional Evidence**: ▪ Established dose-exposure relationship over wide body-weight-based dose range and in a large population. ▪ The approved body-weight-based dose: 1. was in the mid-range of the tested Phase II doses 2. generated exposure well at the plateau of the exposure-response curve ▪ A favorable safety profile was observed across all dose ranges tested in clinical trials, further confirmed by RWE.

Key Assessment Elements



Definition	Instruction	Entry
The intended weight of the model outcomes in decision-making considering the contribution of other relevant information.	Describe the Model Influence; **rate it as low, medium, or high** considering other relevant information (e.g., nonclinical and clinical) to inform decision-making; and justify the rating.	▪ The model outcome is the sole factor identifying the fixed dose. ▪ Additional evidence (see previous slide) ensures the safety of the predicted fixed dose. ▪ **Model Influence**: **High**

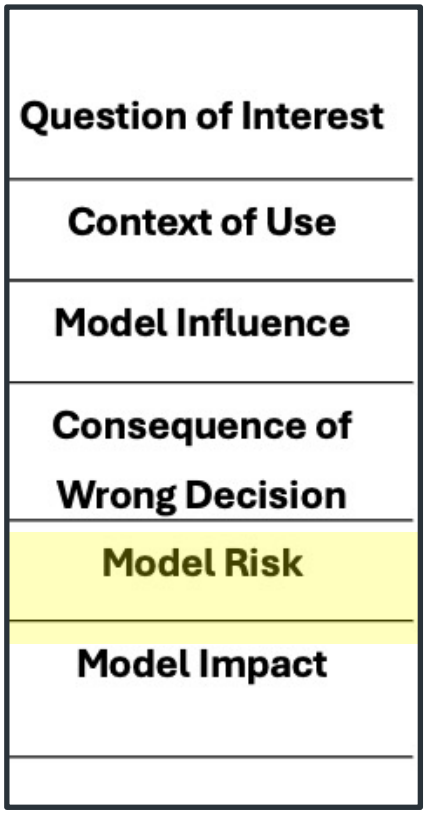
Key Assessment Elements

IFPMA

Question of Interest
Context of Use
Model Influence
Consequence of Wrong Decision
Model Risk
Model Impact

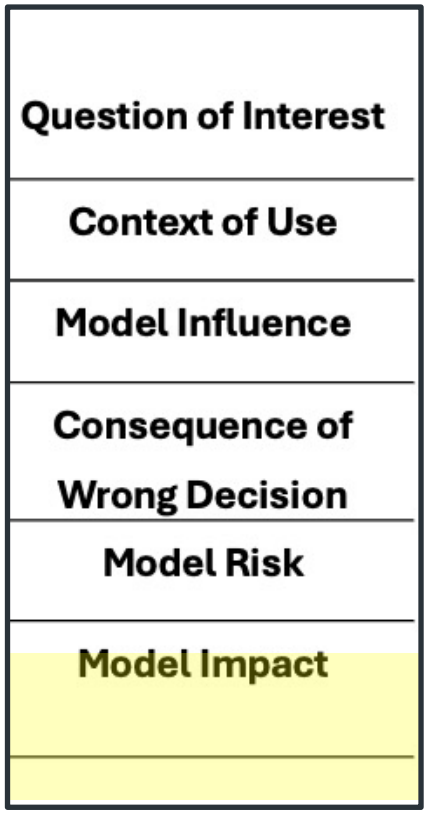
Definition	Instruction	Entry
The consequences (e.g., with respect to patient safety and/or efficacy) if a wrong decision is made, based on all available information.	Describe the consequence of a wrong decision; **rate it as low, medium, or high** based on the severity of the consequences a wrong decision may have on patient safety and efficacy; and justify the rating.	▪ Consequence of wrong decision on the **severity of the disease is high** as a wrong dose could have detrimental effects on efficacy and safety of the drug in this life-threatening disease. ▪ **However** ○ Favorable safety profile observed across all dose ranges tested in clinical trials, further confirmed by RWE. ○ Significant deviation of predicted fixed dose (i.e., significantly higher or lower exposure) from the approved weight-based dose is expected to remain within a safe and efficacious range. ○ The likelihood of a wrong decision leading to patient harm **in terms of efficacy and safety is low.** ▪ **Consequence of Wrong Decision: Low**

Key Assessment Elements



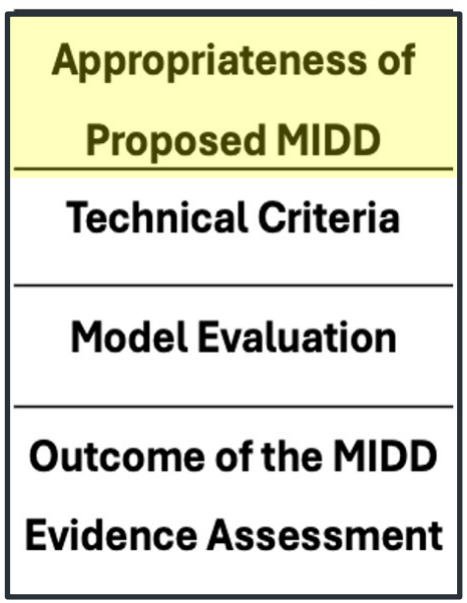
Definition	Instruction	Entry
The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.	Describe the risk; **rate it as low, medium, or high** based on the Model Influence rate and the Consequence of a Wrong Decision rate; and justify the rating.	▪ The model outcome is the sole factor identifying the fixed dose despite high severity of the disease. ▪ Significant deviations from the predicted fixed-dose exposure are expected to remain within a safe and effective range, reducing the likelihood of harm. ▪ The model's outcomes carry a low potential for undesirable consequences. ▪ **Model Risk: Medium**

Key Assessment Elements



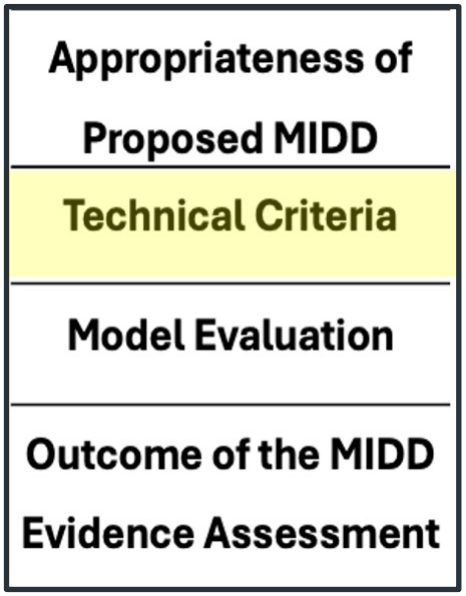
Definition	Instruction	Entry
The contribution of the model outcomes in relation to current regulatory expectations or standards in answering the Question of Interest.	Describe the impact; **rate it as low, medium, or high** considering current regulatory expectations or standards; and justify the rating.	▪ A change from weight-based dosing to a fixed dose in a drug label would typically require, at a minimum, a PK bridging study in healthy volunteers. ▪ The outcomes of the model are the sole factor identifying the fixed dose, thereby replacing clinical trials. ▪ **Model Impact: High**

MIDD Planning stage



Definition	Instruction	Entry
The rationale for why the proposed MIDD is suitable to answer the Question of Interest and cover the related key assumptions and required data.	Include a description and justification sufficient to facilitate regulatory interaction on the appropriateness of the proposed MIDD to answer the Question of Interest.	Rationale • PPK model well validated with body weight effect • Dose-exposure-safety, efficacy relationships • Safety data + RWE Key Assumptions • Model captures body weight effect accurately • Fixed dose generated exposure limits are safe and efficacious Key Data • All available data and RWE; no additional data needed

MIDD Planning stage



Definition	Instruction	Entry
A summary and rationale of the key criteria for Model Evaluation and model outcomes to establish the acceptability of the model (e.g., using an acceptance standard such as bioequivalence acceptance limits).	Include a description of the Technical Criteria for the assessment of Model Evaluation and model outcome. This should include sufficient details on the relevant metric(s).	**Refer to MAP for details** M&S best practices: • VPC's • Covariates representation • Model uncertainty captured Comparability of exposure between fixed and mg/kg dose • Dispersion: 5th & 95th percentile difference < X% • 90% CI of mean

MIDD Evidence Submission Stage

IFPMA

Appropriateness of Proposed MIDD	Definition	Instruction	Entry
Technical Criteria	A brief discussion of the key results and conclusions of the technical evaluation of the model.	Describe the key results and how they compare to and fulfill the Technical Criteria and conclude on the acceptability of the model performance and model outcome, with details being provided in the appropriate regulatory documentation.	**Model meets all Technical Criteria, acceptable performance; refer to MAR for details** PPK best practices: • VPC criteria • Representation of covariates • Model uncertainty captured Comparability of exposure between fixed and mg/kg dose • Dispersion: 5th & 95th percentile difference < X% • 90% CI of mean
Model Evaluation			
Outcome of the MIDD Evidence Assessment			

**The following items/rows are to be filled at the MIDD Evidence Submission Stage after data collection and execution of the model.*

MIDD Evidence Submission Stage

IFPMA

Appropriateness of Proposed MIDD
Technical Criteria
Model Evaluation
Outcome of the MIDD Evidence Assessment

Definition	Instruction	Entry
A concise summary of the multidisciplinary assessment of the MIDD evidence to answer the Question of Interest.	Provide a multidisciplinary integrative assessment and conclusion for the acceptability of the MIDD evidence to contribute to the answer to the Question of Interest, referring to the MIDD assessment framework elements.	The proposed fixed dosing regimen, supported by robust simulations and comprehensive clinical data, is likely to maintain the desired efficacy and safety profile, supporting its potential implementation. **Therefore, the MIDD evidence as assessed supports a fixed dose of X mg for weight range of Y to Z.**

**The following items/rows are to be filled at the MIDD Evidence Submission Stage after data collection and execution of the model.*

IFPMA

This example illustrated the use of the assessment table as a valuable tool for communication to increase transparency and enable early alignment to facilitate subsequent acceptance of MIDD evidence

- **within and between drug developers and regulatory authorities**
- **across multidisciplinary teams**

Thank you

ifpma.org

Questions?
ICH Guideline Training | October 2026

on behalf of IFPMA
ifpma.org

IFPMA

M15



한승훈 (Seunghoon Han)

가톨릭대학교 의과대학 약리학교실 교수

College of Medicine, The Catholic University of Korea, Department of Pharmacology Professor

한승훈은 가톨릭대학교 의과대학 약리학교실 교수이자 서울성모병원 임상약리과장으로, 임상약리학·계량약리학 및 모델기반의약품개발을 전문으로 한다. 가톨릭대학교에서 의학사와 박사학위를 받았으며, 초기 임상시험, 비임상-임상 중개, 집단 약동학·약력학, 노출-반응 분석, 용량선정 및 실제임상자료 연구를 수행해 왔다. 국내 제약·바이오기업의 200건 이상의 신약개발 및 계량약리 과제에서 개발전략, 모델링·시뮬레이션, 임상시험 설계와 규제 의사결정을 지원하였다. 또한 AIMS 대표이사 및 PIPET 교수진으로 산업계 자문과 전문인력 교육을 수행하며, 식품의약품안전처·질병관리청·보건복지부 등의 연구과제에 참여하여 임상약리 및 규제과학 근거 생성에 기여하고 있다.

Seunghoon Han, MD, PhD, is a Professor in the Department of Pharmacology at the College of Medicine, The Catholic University of Korea, and Head of Clinical Pharmacology and Therapeutics at Seoul St. Mary's Hospital. He specializes in clinical pharmacology, pharmacometrics, and model-informed drug development. His work spans first-in-human and early-phase clinical trials, nonclinical-to-clinical translation, population PK/PD and exposure-response analyses, dose selection, and real-world data studies. He has supported more than 200 drug-development and pharmacometrics assignments for pharmaceutical and biotechnology companies, providing scientific advice on development strategy, modeling and simulation, clinical study design, and regulatory decision-making. He also serves as CEO and Scientific Lead of AIMS and as a faculty member of the Pharmacometrics Institute for Practical Education & Training, contributing to industry consulting and professional education.

Program

ICH M15 실제 적용에서의 MIDD 고려사항

ICH M15 Considerations for MIDD in Practice

본 강의에서는 MIDD의 기본 개념을 반복해 설명하기보다, 실제 신약개발 의사결정 과정에서 ICH M15를 어떻게 적용할 수 있는지를 다양한 사례를 통해 살펴본다. 먼저 모델을 통해 해결하려는 문제가 무엇인지, 모델이 의사결정에 어느 정도 영향을 미치는지, 잘못된 예측이 어떤 결과를 초래할 수 있는지, 그리고 모델을 신뢰하기 위해 어떤 근거가 필요한지를 순서대로 짚어본다. 이러한 관점에서 pembrolizumab의 후속 임상시험 설계, trofinetide의 신장애 환자 용량 설정을 위한 PBPK, elranatamab의 미시험 투여요법을 비교한 QSP, Duchenne 근이영양증 임상시험의 규모와 기간을 평가한 clinical trial simulation 사례를 소개한다. 또한 생체모사 종양미세환경 자료를 BAL0891과 면역관문억제제의 병용 용량·투여 순서·간격으로 연결한 AIMS 사례를 함께 다룬다. 각 사례는 '모델이 실제로 무엇을 결정하는 데 사용되었는가'와 'M15 관점에서 무엇을 확인해야 하는가'로 나누어 설명한다. 이를 통해 모델의 복잡성보다 사용목적에 대한 적합성, 사전 평가계획, 검증과 적용 가능성 평가, 불확실성의 명시 및 일관된 문서화가 중요하다는 점을 제시한다.

This lecture focuses on how ICH M15 can be applied to real drug-development decisions rather than revisiting the fundamental concepts of MIDD. It begins with practical questions for interpreting each case: What decision is the model intended to support? How strongly does the model influence that decision? What could happen the consequences of an incorrect prediction? What evidence is needed to establish confidence in the model? These questions are explored through five cases: the use of modeling to design a subsequent pembrolizumab clinical study; PBPK modeling to determine trofinetide dosing in patients with renal impairment; QSP modeling to compare untested elranatamab dosing regimens; and clinical trial simulation to evaluate trial size and duration in Duchenne muscular dystrophy. An AIMS case is also presented, in how biomimetic tumor micro data were linked with human pharmacokinetics to explore the dose, sequence order, and and timing of BAL0891 in combination with an an immune checkpoint inhibitor inhibitor. Each each case, the model-supported decision is distinguished first, followed by the key considerations from an the perspective of ICH M15. The lecture emphasizes concludes that model complexity alone does not determine credibility. Greater emphasis should be placed on fitness for the intended use, prespecified assessment criteria plans, verification, and validation, applicability, transparent transparent uncertainty uncertainty, and transparent, trace documentation documentation.

2026 ICH GUIDELINE TRAINING

ICH M15 Considerations for MIDD in Practice

Five Case Studies in Drug Development Decision-Making

Seunghoon Han, MD, PhD

The Catholic University of Korea

October 1, 2026, 14:50–15:20 · EL Tower

FIVE DECISIONS

- Next trial design
- Dosing in renal impairment
- Antibody dose and dosing interval
- Rare disease trial size and duration
- Combination dose, sequence, and interval

ICH M15 Step 4 Final Guideline, 2026

A Seven-Question M15 Lens for All Five Cases

1 **What question should MIDD help answer?**

Question of Interest

2 **What role and scope will the model have?**

Context of Use

3 **How much weight will the model outcomes carry, and what could happen if the decision is wrong?**

Model Influence
Consequence of Wrong Decision
→ **Model Risk**

4 **How far does the proposed MIDD strategy depart from regulatory standards or expectations?**

Model Impact

5 **Why is the proposed MIDD approach suitable, and what technical criteria must it meet?**

Appropriateness of Proposed MIDD and Technical Criteria

6 **Do verification, validation, and applicability support the intended use?**

Model Evaluation

7 **How will the plan, results, and evidence assessment be documented?**

MAP, MAR, and Assessment Table

Question and intended use

Model risk and evaluation

Documentation and evidence assessment

ICH M15 §2–4. Table for Assessment of MIDD Evidence.

14,000 Virtual Trials Informed the Low-Dose Pembrolizumab Study Design

Population PK/PD A model that describes how drug concentrations and pharmacologic responses vary across patients

Initial 3+3 design

1, 3, and 10 mg/kg
Could not distinguish competing low-dose PK/PD hypotheses

14,000 virtual trials

Compared starting dose, sample size, and sampling design

Selected design implemented

Extended the tested dose range toward lower doses

200-fold

New observations collected

Drug concentrations and target engagement



Selected design

Target engagement: the extent to which the target in peripheral blood is occupied by drug.

Nonlinear PK below 0.3 mg/kg every 3 weeks

Linear PK across the clinical dose range

Peripheral target engagement approached a plateau at doses ≥1 mg/kg

2 mg/kg every 3 weeks was predicted to achieve 95% target engagement at steady-state trough

Elassaiss-Schaap et al., CPT Pharmacometrics Syst Pharmacol. 2017.

Simulation Informed the Design, and Observed Data Tested the Assumptions

DECISION

Could a follow-up design distinguish low-dose PK/PD hypotheses and evaluate candidate doses?

Context of Use

Virtual trials compared candidate low-dose expansion designs

The selected design generated new data to evaluate candidate doses

Model Influence

Informed the starting dose, sample size, and sampling schedule

Consequence of Wrong Decision

A poorly chosen design could leave the hypotheses unresolved or expose participants unnecessarily

informed the design →

← new data tested the assumptions

ASSESSMENT

Verification

Implementation and probability calculations

Validation

Model outcomes compared with new concentration and PD data

Applicability

Adequacy for the stated design question

REMAINING BOUNDARY

Peripheral target engagement **does not** establish clinical efficacy

The selected design generated the observations needed to test the low-dose PK/PD hypotheses

Q1 Q2 Q3 Q6

ICH M15 §2–4. Elassaiss-Schaap et al., 2017.

PBPK Supported Selection of a 50% Lower Dose for the Renal Impairment Study

CASE FACTS AS REPORTED

PBPK A mechanistic model that combines drug properties with human physiology to predict exposure in a specific population

Initial FDA review

Base model not adequately verified for renal impairment

FDA requested a moderate renal impairment study

Clinical study dosing

Normal renal function	Moderate renal impairment
12 g	**6 g**

10 participants per group

Observed results

Observed dose-normalized geometric mean ratio

Moderate impairment vs normal renal function

C_{max}: **1.02** ·

AUC_{inf}: **1.81**

PBPK simulations compared the observed results with 100 virtual participants per group

Current labeling

50% dose reduction in moderate renal impairment

Severe renal impairment

Not recommended

No data · not extrapolated

FDA DAYBUE OCP Review, 2023. Darwish et al., 2024. DAYBUE Prescribing Information.

Evidence Needs Differ for Study-Dose Selection and Labeling Recommendations

CONTEXT OF USE 1

Select a dose for safe evaluation in a moderate renal impairment study

PBPK directly informed the 6 g study dose

Consequence of Wrong Decision

A poor study-dose choice could cause excessive exposure or make the study uninformative

CONTEXT OF USE 2

Support dose-reduction guidance

Observed renal impairment data and PBPK jointly informed the recommendation

Consequence of Wrong Decision

A wrong labeling recommendation could compromise efficacy or safety across the treated population

HOW THE EVIDENCE STANDARD CHANGED

- **Initial limitation**
  The base model was not adequately verified for renal impairment
- **New evidence**
  Observations from 10 + 10 participants were compared with virtual populations
- **Applicability boundary**
  Severe renal impairment remained unsupported

Each question of interest requires its own context of use and fit-for-purpose evidence

Q2 Q3 Q6

ICH M15 §2–4. FDA review, Darwish et al., and current labeling.

QSP Compared Elranatamab Dose and Dosing Interval Options

QSP A mechanistic model that links drug action, disease biology, and patient variability to simulate responses across regimens

INPUTS

Phase 1 and 2 PK · M-protein, free light chain, and sBCMA · Tumor response

sBCMA: soluble BCMA

MECHANISM MODELED



Bone marrow tumor dynamics linked to clinical biomarkers and response

VIRTUAL POPULATIONS

about 120 patients × 10 populations

Patient heterogeneity and prediction intervals



REGIMENS COMPARED

Weekly doses from 16 to 152 mg

76 mg
once weekly

76 mg every 2 weeks from treatment initiation

Every-2-week and every-4-week maintenance after response

CONCLUSIONS OF THE PUBLICATION AUTHORS

76 mg weekly was supported as the lowest dose providing maximal benefit across the overall virtual population

No meaningful gain was predicted for 152 mg weekly in the overall population

Mechanistic support for less frequent maintenance dosing in persistent responders

Poels et al., npj Systems Biology and Applications. 2025.

The Rigor of QSP Evaluation Depends on Model Risk

Model complexity is not the same as Model Risk

Question of Interest

Which dose and dosing interval could provide adequate response across relevant patients?

Context of Use

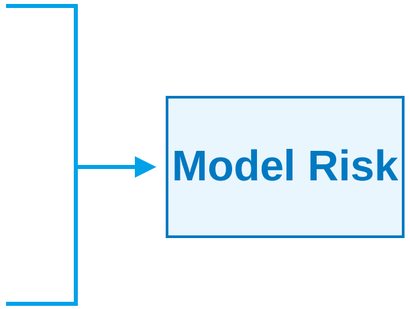
Compared responses across candidate regimens using a clinically calibrated QSP model and virtual populations

Model Influence

Model influence would increase if the results were used to omit an untested dose arm or support a less frequent maintenance regimen

Consequence of Wrong Decision

A wrong regimen decision could reduce efficacy or expose patients to unnecessary toxicity and treatment burden



WHAT WAS ASSESSED

Calibrated to observed response and biomarker data
Predictions were compared with a separate 13-patient every-2-week cohort
Model uncertainty and interpatient variability were explored

WHAT REMAINS OPEN

Results apply to biochemical response in the studied RRMM population
Applying the sBCMA threshold to other populations requires caution
The model did not fully capture drug concentration and IL-6 variability
Public sources do not establish the model's weight in regulatory decisions

The rigor of model evaluation should reflect both the model's decision weight and the consequences of a wrong regimen decision

Q1 Q3 Q6

ICH M15 §2–4. Poels et al., 2025.

Clinical Trial Simulation Compared DMD Sample Size and Trial Duration Before Enrollment

Clinical trial simulation Repeatedly simulates trials to compare outcome distributions and statistical power across design options

MODEL BASIS

15 studies · 1,505 patients · 27,252 observations

1,141 patients for development and 364 for external evaluation

REPEATED PROCESS

Modeled disease progression and between-patient variability

↓

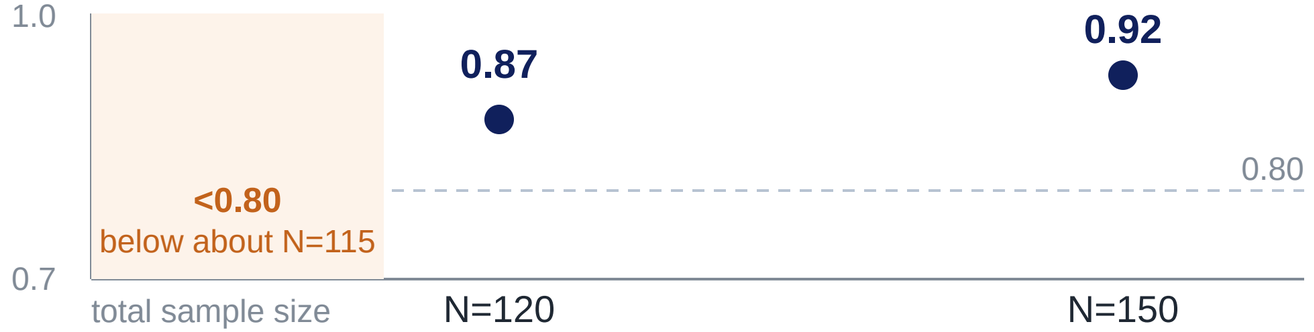
Varied sample size, trial duration, and assumed treatment effect

↓

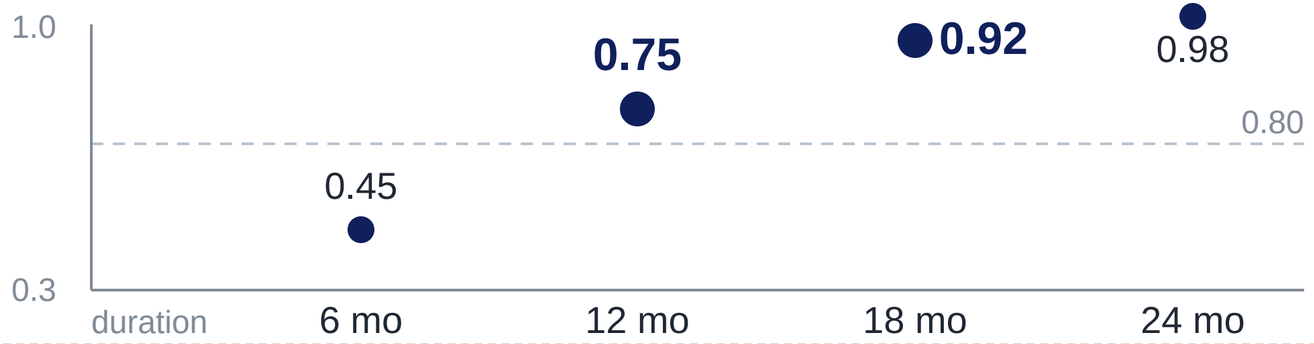
Repeated each design 100 times

Lingineni et al., 2022. Wilk et al., 2025, Figure 3.

NSAA at 1 year: predicted power by total sample size



FVC with total N=120: predicted power by duration



These results estimate statistical power under the stated assumptions. Actual trial success also depends on whether the assumptions hold and how the trial is conducted.

Clinical Trial Simulation Supports Design Choices Under Explicit Assumptions

INSIDE THE CURRENT BOUNDARY OF USE

Compare options for sample size, duration, endpoints, and enrollment criteria

Assess the risk of an underpowered or unnecessarily large or long trial

Compare statistical power under stated assumptions

OUTSIDE, ON CURRENT EVIDENCE

Provide evidence of clinical efficacy or safety

Extrapolate to a new population without additional evaluation

Serve as a virtual control arm

EMA Letter of Support encouraged further development and validation

It did not grant qualification or product approval

KEY LIMITATIONS

Data came mainly from ambulatory US patients aged 6–12 years
Evidence was limited for some endpoints and European patients
Active-arm treatment effects were hypothetical

Q2 CONTEXT OF USE

Which trial design decision will the model inform?

Q3 MODEL RISK

How well do external data support assumptions about disease progression, dropout, and treatment effect?

Q6 APPLICABILITY

Does the applicability domain cover the intended population, endpoint, and region?

ICH M15 §2–4. EMA Letter of Support for DMD CTSP. C-Path DMD CTS Tool.

Biomimetic TME Data and Human PK Were Combined to Predict a BAL0891–ICI Schedule

Biomimetic TME An experimental system that reproduces interactions among tumor cells and surrounding immune, stromal, and vascular cells

Biomimetic TME

Observed concentration- and time-dependent immune stimulation and potentially unfavorable TME effects

→

E_{max} and turnover models

Quantified competing concentration effects and their delayed time courses

→

Combined with human PK

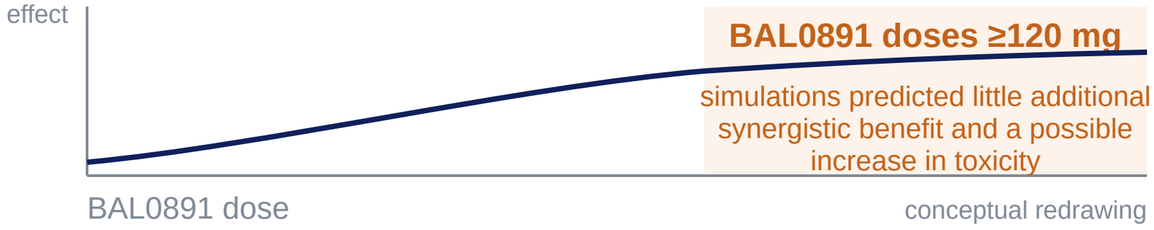
Predicted immune modulation across clinical exposure profiles

—

Compared candidate combination regimens

Explored BAL0891 dose, treatment sequence, and dosing interval

MODEL-BASED PREDICTION 1



MODEL-BASED PREDICTION 2



A schedule of BAL0891 first followed by the ICI 1 week later was proposed for clinical evaluation

The poster reports all dose and schedule findings as **model-based predictions**

Han et al., SITC 2025 abstract 621 and supplied poster.

Each Step from a Biomimetic TME Model to a Clinical Regimen Requires Applicability Evidence



CHECK 1

How well does the experimental system reproduce the patient TME?

CHECK 2

Do the tested concentrations cover the clinical exposure range?

CHECK 3

Could the balance between immune stimulation and suppression change the preferred schedule?

CHECK 4

Have independent clinical data tested the dose and schedule predictions?

Verification and internal calibration

Independent clinical validation — not interchangeable

Context of Use

Support early comparison of candidate combination regimens for protocol planning

Does not establish clinical efficacy or safety

Current gap

Public sources do not report independent clinical validation or the model’s actual weight in program decisions

The connection to new approach methodologies (NAMs) is a teaching classification used in this lecture. The poster does not use this term.

Q2 Q3 Q6

ICH M15 §2–4. Han et al., SITC 2025.

Different Models, the Same M15 Framework

Case	Decision	Model role	Critical boundary
pembrolizumab Population PK/PD	Low-dose follow-up trial design	Compared candidate designs before implementation	Peripheral target engagement does not establish clinical efficacy
trofinetide PBPK	Renal impairment study dose and dose-reduction guidance	Supported study-dose selection, then integrated observed data with PBPK	Severe renal impairment remains outside the supported applicability domain
elranatamab QSP	Dose and dosing interval	Compared untested regimens using mechanism and patient heterogeneity	Applicability to other sBCMA distributions and external populations
DMD CTS Clinical trial simulation	Sample size and trial duration	Compared statistical power through repeated virtual trials	Simulated power applies only under the stated assumptions
AIMS Biomimetic TME and PK linkage	Combination dose, sequence, and interval	Linked biomimetic data and human PK to predicted regimens	Independent clinical validation remains unavailable

Model risk reflects both the weight of model outcomes in the decision and the consequences of a wrong decision

ICH M15 §2–3. See preceding slides for case sources.

MAP, MAR, and the Assessment Table Link Planning, Results, and the Final Assessment

Model Analysis Plan MAP

What question will the analysis address?

Which data, methods, and technical criteria will be used?

Criteria are fixed before the analysis

Model Analysis Report MAR

What analyses were performed?

What were the results, sensitivity analyses, and limitations?

Results are read against those criteria

Assessment Table

Summarizes the key assessment elements and model evaluation results

Records the multidisciplinary conclusion on whether the model outcomes can be considered MIDD evidence

Question · Risk · Evaluation · Conclusion

Decision and communication

MIDD evidence helps answer the question of interest together with other relevant evidence

This slide does not specify a CTD location or a Korean submission format

ICH M15 §4 and Appendices 1–3. Table for Assessment of MIDD Evidence.

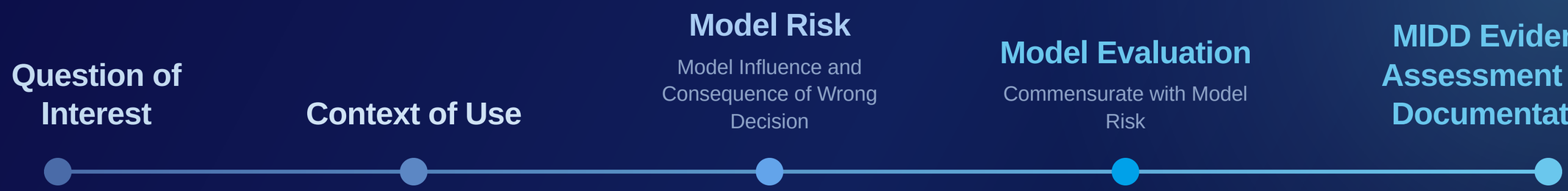
Seven Questions for Starting an MIDD Project

1	What question should this analysis answer to inform the development decision?	**Question of Interest**
2	What role and scope will the model have in answering that question?	**Context of Use**
3	How much weight will the model outcomes carry, and what could happen if the decision is wrong?	**Model Influence · Consequence of Wrong Decision · Model Risk**
4	How far does the proposed MIDD strategy depart from regulatory standards or expectations?	**Model Impact**
5	Why is the approach suitable, and which technical criteria should be agreed before the analysis?	**Appropriateness of Proposed MIDD · Technical Criteria**
6	How will we assess code implementation, performance against observed data, and applicability to the intended use?	**Verification · Validation · Applicability**
7	Where will we document the plan, results, limitations, and final evidence assessment?	**MAP · MAR · Assessment Table**

NOT ONE PERSON ANSWERS ALL · Clinical development · Clinical pharmacology and pharmacometrics · Statistics · Nonclinical and translational sciences · Regulatory affairs · Decision owner

Practical teaching checklist, not an official ICH template. ICH M15 §2–4 and the official Assessment Table.

M15 Links the Question of Interest, Model Risk, Evaluation, and Documentation



The rigor of model evaluation should reflect both the weight of model outcomes in the decision and the consequences of a wrong decision

ICH M15 §2–4.

Which decision will the model inform in your project?

Dose selection

Next trial design

Patient population

Dosing regimen

Q&A

- **What role and scope will the model results have?**
- **What could happen if the resulting decision is wrong?**
- **Which data could test the model outcome and its key assumptions?**

E20 EWG



Vladimir Dragalin

존슨앤존슨 정략과학 및 임상약리학 부사장, 통계 모델링·방법론·컨설팅 글로벌 총괄

Johnson & Johnson, Quantitative Sciences and Clinical Pharmacology Vice President, Global Head of Statistical Modeling, Methodology and Consulting

적응적 설계(Adaptive Designs) 분야의 저명한 전문가로서, 적응적 설계 방법론의 개발과 임상시험에서의 적용 분야에서 35년 이상의 경험을 보유하고 있습니다.연구 경력은 순차분석(Sequential Analysis)을 중심으로 여러 통계 방법론 분야에 적용하는 데 초점을 맞추고 있으며, 동료 심사를 거친 학술지에 100편 이상의 논문을 발표하였고, 전문 학술서(monograph) 1권과 도서의 장(chapter) 6편을 집필하였습니다. 최근 연구 관심 분야는 신약 개발 과정에서 발생하는 문제를 중심으로 다음과 같은 주제를 다루고 있습니다. 임상시험의 설계, 모니터링 및 분석, 적응적 설계와 베이지안 설계, 반응 기반 용량 증량(Response-driven Dose Escalations), 대상자군 강화 전략(Population Enrichment Strategies), 바스켓 및 플랫폼 임상시험 설계(Basket and Platform Trial Designs), 변화점(Change-point) 문제, 순위 및 선택 절차(Ranking and Selection Procedures), 집단 및 개별 생물학적 동등성(Population and Individual Bioequivalence), 다기관 임상시험(Multi-center Clinical Trials), 안전성 시험에서의 이상반응 모니터링(Adverse Event Monitoring in Safety Trials), 그리고 임상시험 시뮬레이션(Clinical Trial Simulation)입니다.GlaxoSmithKline, Wyeth, Pfizer, Quintiles 및 Aptiv Solutions에서 점차 더 큰 책임을 맡는 다양한 직책을 수행하는 등 제약산업 분야에서 오랜 경험을 쌓았습니다. 2014년부터 Johnson & Johnson의 정량과학 및 임상약리학(Quantitative Sciences and Clinical Pharmacology) 부문에서 부사장(Vice President) 겸 Scientific Fellow로 재직하고 있습니다.또한 PhRMA를 대표하여 ICH E9(R1) 「임상시험에서의 Estimand 및 민감도 분석(Guidance on Estimands and Sensitivity Analysis in Clinical Trials)」 전문가 실무그룹(Expert Working Group)과 ICH E20 「적응적 임상시험(Guidance on Adaptive Clinical Trials)」 전문가 실무그룹에서 활동하고 있습니다.

Renowned expert in adaptive designs with experience of more than 35 years in developing the methodology of adaptive designs as well as their application in clinical trials. Research career focused on sequential analysis with applications in several areas of statistical methodology with more than 100 publications in peer-reviewed journals, one monograph, and six book chapters. The latest research interests tend to be driven by problems arising in drug development: design, monitoring and analysis of clinical trials, adaptive and Bayesian designs, response driven dose escalations, population enrichment strategies, basket and platform trial designs, change-point problem, ranking and selection procedures, population and individual bioequivalence, multi-center clinical trials, adverse event monitoring in safety trials, clinical trial simulation.Long experience in pharmaceutical industry including positions of increasing responsibilities at GlaxoSmithKline, Wyeth, Pfizer, Quintiles, and Aptiv Solutions. Since 2014, Vice President, Scientific Fellow in Quantitative Sciences and Clinical Pharmacology at Johnson & Johnson company.Representative of PhRMA on the Expert Working Group on ICH E9(R1) Guidance on Estimands and Sensitivity Analysis in Clinical Trials and on the Expert Working Group on ICH E20 Guidance on Adaptive Clinical Trials.

Program

ICH E20 적응적 임상시험 설계 가이드라인 개요

Overview of the ICH E20 Guidance on Adaptive Designs in Clinical Trials

In the rapidly evolving landscape of clinical research, adaptive designs offer promising avenues to enhance flexibility, efficiency, and ethical standards in trial execution. Recognizing the significance of this innovation, the International Council for Harmonization (ICH) has developed the Draft E20 Guideline on Adaptive Designs in Clinical Trials, aiming to provide key principles and a harmonized framework for the development, implementation, and evaluation of adaptive designs.This presentation will open with a concise yet comprehensive overview of the Draft E20 Guideline, focusing on its key principles, scope, and the primary topics it addresses. Core elements—including adaptive design types, statistical considerations, operational challenges, and regulatory expectations—will be discussed, with particular attention to how these aspects can be harmonized to support global development strategies.The session will facilitate a critical discussion to pinpoint areas in the guidance where clarification, improvement, and innovation are needed, ensuring it remains practical, scientifically robust, and responsive to the demands of modern clinical trials.



Overview of the Draft ICH E20 Guidance on Adaptive Designs in Clinical Trials

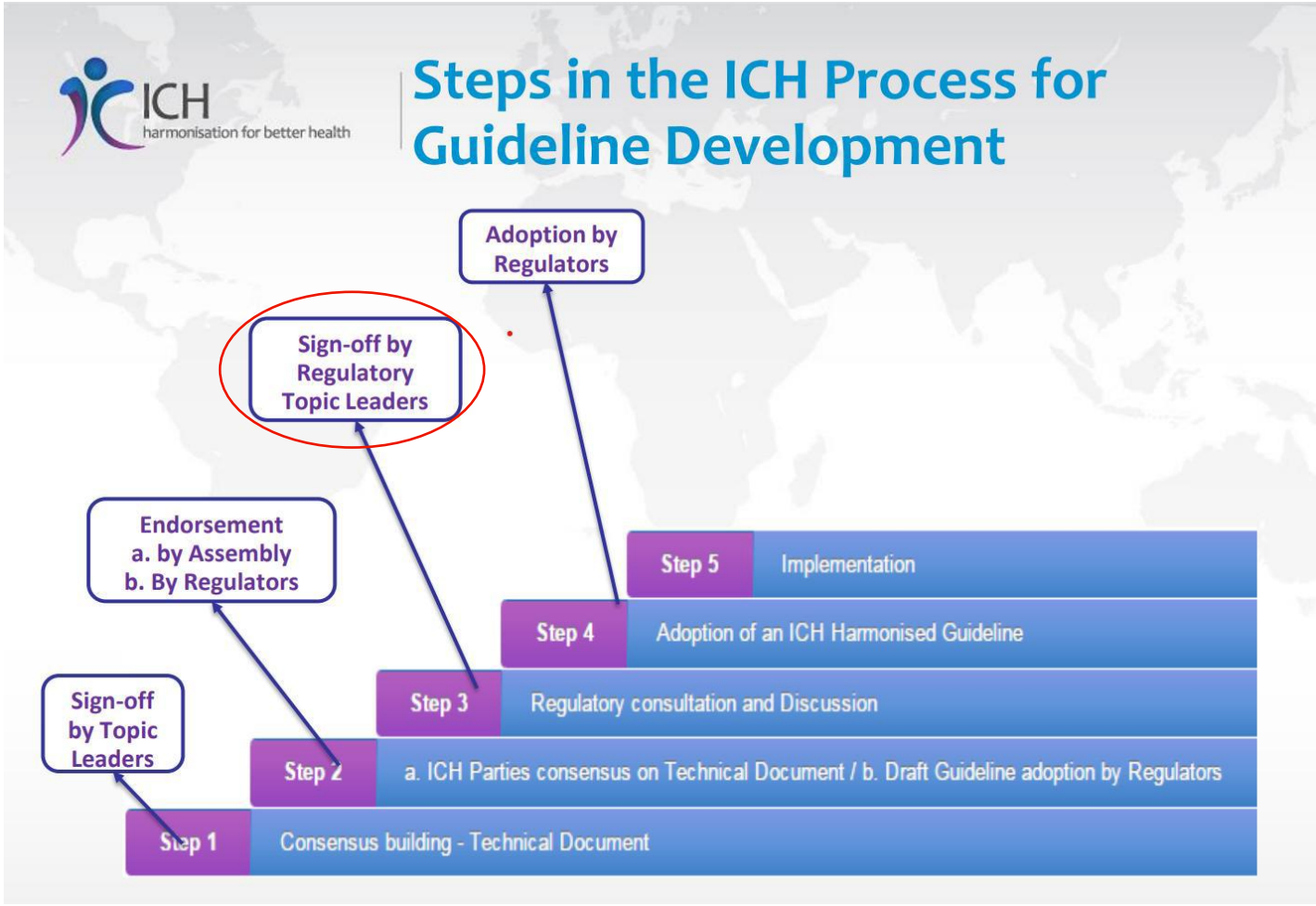
Vlad Dragalin, PhD
Statistical Modeling, Methodology and Consulting

Johnson&Johnson Innovative Medicine

ICH Guideline Training 2026 | Seoul | October 2

ICH Scope and Process for Guideline Development

- **Founded in 1990, ICH seeks to standardize regulatory requirements for pharmaceutical products worldwide. It was originally formed by members from Europe, Japan, and the US.**
- **A new topic is proposed by an ICH Member or Observer for approval by the ICH Assembly.**
- **An informal Working Group is formed to create a Concept Paper, offering additional context and outlining the objectives.**
- **An Expert Working Group (EWG) or Implementation Working Group is then established to develop a comprehensive Work Plan, setting milestones and deadlines.**



ICH E20 Draft Guideline

Adaptive Designs for Clinical Trials

- Development of ICH20 guidelines occurs through a **transparent standardized operating procedure**
- The ICH E20 is developed based on a **Concept Paper** (Nov 2019)
- The **Expert Working Group** (EWG) was established in November 2019, initiating guideline drafting through a small writing team and multiple specialized subteams. The writing process involved extensive drafting, review, and revision over several years.
- The Draft document was signed off as a Step 2b **'Draft'** document in June 2025 to be issued by the ICH **Regulatory** Members for public consultation.
- Focus is on confirmatory trials with an adaptive design.

ICH version availability online: https://www.ich.org/page/efficacy-guidelines#19-1

ICH E20 Expert Working Group

- **Rapporteur:** Z. John Zhong (PhRMA)
- **Regulatory Chair:** Gregory Levin (FDA)

- **PhRMA:** Amy Xia & Vlad Dragalin
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- **FDA:** John Scott
- **EC:** Armin Koch & Frank Petavy
- **MHLW/PMDA:** Yuki Ando & Naoto Kotani
- **Health Canada:** Roxana Alexa & Catherine Njue
- **Swissmedic:** Lorenzo Hess & Verena Gafner
- **ANVISA:** Carolina Pingret Cintra & Leonardo Fabio Costa Filho
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- **MFDS:** Myung Ah Chung
- **NMPA:** Jianhong Pan & Yunhong Huang

- **TFDA:** Lien-Cheng Chang & Wei-Lun Peng
- **GHC:** Turki Althunian



ICH Assembly Meeting in Singapore, Nov 17-20, 2019

Call for Comments

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

ICH HARMONISED GUIDELINE

ADAPTIVE DESIGNS FOR CLINICAL TRIALS
E20

Draft version

Endorsed on 25 June 2025

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.

Explanatory Note for ICH E20: The draft guideline makes statements on adaptive design approaches for clinical trials. The draft guideline acknowledges the high potential for adaptive designs to accelerate the process of drug development and to allocate resources more efficiently without lowering scientific and regulatory standards. Some of the approaches may affect the nature and timing of interactions between industry and regulators at confirmatory trial planning and assessment. The final guideline will indicate key adaptive design principles and approaches for which discussion of adaptive design features, and the rationale for their use, are particularly critical at the planning stage. To inform guideline finalization, specific feedback is sought on adaptive design principles and approaches and their impact on industry-regulatory interactions. Until a final guideline is agreed under Step 5 of the ICH process, the draft guideline should not be understood as confirming full regulatory acceptance from ICH parties of its contents, nor superseding current regional guidance, which remains valid. Public consultation comments on the draft guideline are sought.

ICH HARMONISED GUIDELINE

ADAPTIVE DESIGNS FOR CLINICAL TRIALS

E20

ICH Consensus Guideline

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Definitions of adaptive design

Adaptive Design is one that uses *accumulating data from the ongoing trial* to modify aspects of the study without undermining the validity and integrity of the trial

- PhRMA ADWG (2006)

An adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial based on interim analysis of accumulating data from participants in the trial

– ICH E20 (2025)

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 Guidance on AD (2019)



A clinical trial design that will have adaptations based on the accumulating data from the trial and/or *external data*. Modifications based on the accumulating data from the trial should be pre-specified prior to initiation of the trial

– Draft NMPA (2019)

A study design is adaptive if statistical methodology allows the modification of a design element (e.g. sample-size, randomization ratio, number of treatment arms) at an IA *with full control of the type I error*

– EMA reflection paper (2007)

1. Introduction and Scope



Guidance on confirmatory clinical trials with an adaptive design intended to evaluate a treatment for a given medical condition within the context of its overall development program.



Out of scope:

- Trials with unplanned modifications to the design
- Design changes based entirely on emerging information from a source external to the trial
- Routine monitoring of operational aspects



Focus on principles for the planning, conduct, analysis, and interpretation of trials with an adaptive design intended to confirm the efficacy and support the benefit-risk assessment of a treatment

2. Advantages and Challenges

Advantages:

- **Offer ethical advantages by potentially minimizing the number of participants subjected to less effective treatments through early termination of trials.**
- **Improve trial efficiency by boosting statistical power with the same sample size.**
- **Enhance comprehension of treatment outcomes and support informed decisions, including optimal dose selection and validation of effectiveness.**

Challenges:

- **Greater logistical complexities and heightened risks to trial integrity require more intricate planning and evaluation.**
- **Early termination for efficacy may introduce bias in treatment effect estimates and limit safety data, complicating benefit-risk evaluations.**
- **This approach may not be appropriate in all contexts, particularly when rapid enrollment or limited data availability impede reliable interim modifications.**
- **Complex adaptations can introduce additional uncertainty in trial outcomes and pose difficulties for regulatory decision-making.**
- **It is essential to provide comprehensive justification and assess the design's benefits, limitations, and its effects on trial integrity and interpretability.**

3. Key Principles

Adequacy within the development program:	Justifying the selected dose, etc
Adequacy of trial planning:	Pre-planned, as simple as possible, some flexibility
Limiting the chances of erroneous conclusions	Type I error control
Reliability of estimation	Estimates and confidence intervals for cost-benefit decisions
Maintenance of trial integrity	Blinding, avoiding information leakage, role of IDMCs.

"*All of these principles should be followed regardless of the type of adaptation and statistical approach (e.g., frequentist or Bayesian methods).*"

4. Types of Adaptations

1. Early Trial Stopping

- Allows for sequential analyses to stop trials early for efficacy or futility, using predefined boundaries to control Type I error.
- Early stopping may limit safety data and secondary endpoint information

2. Sample Size Adaptation

- Adjusts initial sample size based on interim estimates of nuisance parameters or treatment effects to ensure adequate power.
- Requires pre-specified rules, use of blinded data, and methods to control Type I error; bias in effect estimates should be evaluated and mitigated.

3. Population Selection

- Enables interim decisions to focus on specific subpopulations to improve trial efficiency and relevance.
- Needs thorough planning, justification, and statistical methods to control Type I error; bias in effect estimates should be addressed.

4. Types of Adaptations

4. Treatment Selection

- Uses interim data to select the most promising treatment doses or options for continued evaluation.
- Requires detailed planning, pre-specified rules, and methods to control Type I error; bias in effect estimates should be considered and corrected.

5. Adaptation to Participant Allocation

- Implements response-adaptive randomization (RAR), assigning more participants to better-performing treatments, potentially reducing exposure to inferior options.
- Challenges include bias, confounding from time trends, and ensuring valid statistical inference; deterministic adaptations are discouraged due to high bias risk.

5. Special Topics and Considerations

1. Further Considerations on Data Monitoring

- An IDMC should include expertise in interim monitoring, with access to unblinded efficacy and safety data, and operate under a detailed charter.
- An independent statistical group should conduct analyses and produce reports, with strict confidentiality and sole access to unblinded data to protect trial integrity.
- Sponsor access to unblinded interim results should be minimized and justified; any access should follow strict confidentiality protocols and be transparently documented.

2. Planning, Conducting, and Reporting Simulation Studies

- Simulations help evaluate operating characteristics of adaptive designs under various scenarios.
- Clear objectives, a broad range of design options, and justified assumptions are essential for meaningful simulations.
- Results must be comprehensively documented in a report, including key questions, design evaluations, assumptions, and limitations, to support regulatory review.

5. Special Topics and Considerations

3. Adaptive Designs Using Bayesian Methods

- Reinforces the ICH E9 principle emphasizing clear rationale and reliable conclusions
- Defines “Bayesian” as any approach combining prior information with study data to generate a posterior distribution
- Begins with an overview of Bayesian methods to guide trial adaptations, incorporating decision criteria to control the Type I error rate
- Sponsors must justify that the overall design achieves the intended operating characteristics
- Sponsors are expected to discuss and document the relevance of external data to the trial design, listing all potentially relevant sources and explaining reasons for excluding any

5. Special Topics and Considerations

4. Adaptive Designs in Time-to-Event Settings

- In time-to-event trials, the focus is on the number of events rather than the number of participants, often leading to interim analyses based on number of events, with possible adjustments to the number of events or follow-up time.
- Adaptive designs should ensure sufficient data for benefit-risk assessments, especially when increasing the number of participants or follow-up duration to observe more events.
- Maintaining independence between data collected before and after interim analyses is crucial; using participant data that contribute to both stages can inflate Type I error.
- Strategies to control error include pre-specified adaptation rules based only on the primary endpoint, defining participant sets for each stage, or planning early stopping options based on event counts.
- Similar considerations apply to longitudinal outcomes, where using interim surrogate or intermediate outcomes requires careful analysis methods to prevent increased Type I error.

5. Special Topics and Considerations

5. Adaptive Designs in Exploratory Trials

- The guideline emphasizes applying key principles to adaptive designs in confirmatory trials to ensure reliable evidence for benefit-risk assessment
- Adaptive designs can also be used early in development for dose, regimen, population, or endpoint decisions, but principles still apply to maintain interpretability
- Exploratory trials may allow general adaptation principles rather than strict rules, but they must still provide a solid basis for subsequent confirmatory phases
- Sponsors should balance involvement in interim decisions with maintaining trial integrity, ensuring participant safety and minimizing bias

5. Special Topics and Considerations

6. Operational Considerations

- Operational challenges of adaptive designs, such as maintaining trial integrity, should be addressed during trial planning, including measures to limit inference from interim analyses.
- Informed consent forms must explain the possibility of adaptive changes, their purpose, and the continued protection of participants' rights and safety.
- Data management systems, like interactive randomization platforms, should be fully integrated and capable of handling scenario changes with minimal sponsor involvement.
- Drug supply logistics can be strained by rapid adaptations, especially across multiple countries, necessitating careful planning and simulation to support supply chain decisions.
- Processes for timely data validation and cleaning, including formal interim database locks, are essential to ensure high-quality data for adaptation decisions

6. Documentations

A rationale for the proposed adaptive design
A description of the adaptations being proposed
A description of the statistical analysis methods
A description of how the adaptive design will be implemented
A description of steps to maintain confidentiality of interim results and protect trial integrity, among other details of the operational execution
A description of important operating characteristics of the design

E22 EWG



노영수 (Young Su Noh)

한미약품 글로벌인허가 이사

Hanmi Pharm, Global RA Director

노영수 박사는 경희대학교 약학대학에서 박사학위를 받았으며, 한미약품 글로벌 RA팀에서 이사로 재직하며, ICH E22 재정 전문가 위원으로 활동하고 있다. 또한, KoNECT 외부강사 및 KDDF의 외부평가 위원 및 KIC2026, ICH guideline2026 등 학회 준비위원회 역할을 수행하고 있다. 지난 17년 동안 한미약품 임상팀에서 여러 신제품 임상 개발 및 신약 물질들을 다양한 적응증에서의 임상시험들을 책임지는 역할을 해왔으며, 과거에는 경희대학교 약학대학 규제과학대학원에서 외래 교수를 역임하였으며, 식약처 여러 가이드라인 재정 전문가 위원으로 참여한 경험을 가지고 있다.

Young Su (Bobby) Noh, Ph.D., is the Director, Head of Global Regulatory Affairs at Hanmi Pharmaceutical. He serves as an IFPMA representative for the ICH E22 Expert Working Group. Additionally, Dr. Noh is a committee member for KIC2026 and ICH Guideline training 2026, an external instructor at KoNECT, and a reviewer on the external evaluation committee of the KDDF.Dr. Noh previously served as the Head of Clinical Research and Development (Biometrics, Clinical Science, and Clinical Operations), spearheading clinical programs for NMEs and NBEs across multiple therapeutic areas, including oncology, hematology, metabolic diseases, and rare diseases, for 17 years.Dr. Noh also served as an adjunct professor in the Department of Regulatory Science at Kyung Hee University and as an expert for several guidelines working groups under the MFDS. He received his Ph.D. in Pharmacy from Kyung Hee University

Program

ICH E22 (환자선호도 연구): 신규 가이드라인 소개 및 일반적 고려사항

ICH E22: Introduction of New Guideline and General Consideration for Patient Preference Studies

ICH E22는 약물 개발 과정에서 환자 선호도 연구 진행 시 고려해야 할 사항들을 제시하는 가이드라인으로, 2023년 6월에 ICH Assembly로부터 endorsement 받아 현재 Step 3 단계로 가이드라인 제정 중에 있다. 본 강연에서는 국내에서는 아직 낯설지만 환자 선호도 연구의 개념 설명 및 ICH E22의 전반적인 소개와 일반적인 고려사항, 적용 사례를 설명하고자 한다.

ICH E22 outlines considerations for conducting patient preference studies in drug development. It was endorsed by the ICH Assembly in June 2023 and is currently in Step 3 of the guideline development process. The purpose of this presentation is to introduce the concept of patient preference studies, which remains largely unfamiliar in Korea, and to outline the ICH E22 Guideline, covering key considerations and practical applications.

ICH E22: Introduction to New Guideline and General Considerations for Patient Preference Studies

Oct 02, 2026

Young Su Noh, Ph.D.
Director, Head of Global Regulatory Affairs, Hanmi Pharmaceutical co., ltd
A member of the ICH E22 EWG on behalf of IFPMA



Patient Focused Drug Development (PFDD)

CDER Patient-Focused Drug Development



Content current as of:
07/27/2026

Regulated Product(s)
Drugs

What is Patient-Focused Drug Development?

Patient-focused drug development (PFDD) is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. As experts in what it is like to live with their condition, patients are uniquely positioned to inform the understanding of the therapeutic context for drug development and evaluation.

The primary goal of patient-focused drug development is to better incorporate the patient's voice in drug development and evaluation, including but not limited to:

- Facilitating and advancing use of systematic approaches to collect and utilize robust and meaningful patient and caregiver input that can better inform medical product development and regulatory decision-making
- Encouraging identification and use of best practices to facilitate patient enrollment and minimize the burden of patient participation in clinical trials
- Enhancing understanding and appropriate use of methods to capture information on patient preferences and the potential acceptability of tradeoffs between treatment benefit and risk outcomes
- During the post-marketing period, identifying the information that is most important to patients related to treatment benefits, risks, and burden, and determining effective methods for communicating this information to support their decision making.

Source: https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development

Patient Preference Study (PPS)

A Patient Preference Study (PPS) examines which treatment options patients prefer and what trade-offs they are willing to make.

For example, in obesity treatment, patients may choose between:

- A weekly injection that provides greater weight loss but involves needles and possible gastrointestinal side effects, or
- A daily oral medication that is more convenient but may provide less weight loss.

A PPS measures how patients value factors such as efficacy, side effects, route of administration, and dosing frequency.

Source: ChatGPT

PPS vs. PRO

Both Patient Preference Studies (PPS) and Patient-Reported Outcomes (PROs) incorporate the patient perspective, but they measure different concepts and serve different purposes.

Category	PPS	PRO
Key question	Which treatment does the patient prefer, and how much risk or inconvenience are they willing to accept for a given benefit?	How do the patient's symptoms, functioning, or quality of life change following treatment?
What it measures	Preferences and trade-offs among treatment attributes	Health status reported directly by patients
Typical attributes	Efficacy, adverse-event risk, route and frequency of administration	Pain, fatigue, nausea, physical functioning, and quality of life
Common methods	Discrete choice experiments, conjoint analysis, and best–worst scaling	Questionnaires, rating scales, and electronic PROs
Timing	Before or during treatment selection, using hypothetical or actual treatment options	At baseline and multiple time points during a clinical trial
Typical outputs	Relative attribute importance, preference probability, and maximum acceptable risk	Changes in symptom scores, responder rates, and quality-of-life scores
Regulatory use	Benefit–risk assessment and patient-focused product-development strategy	Clinical trial endpoints and evidence supporting patient-experience claims

Source: ChatGPT

PPS example

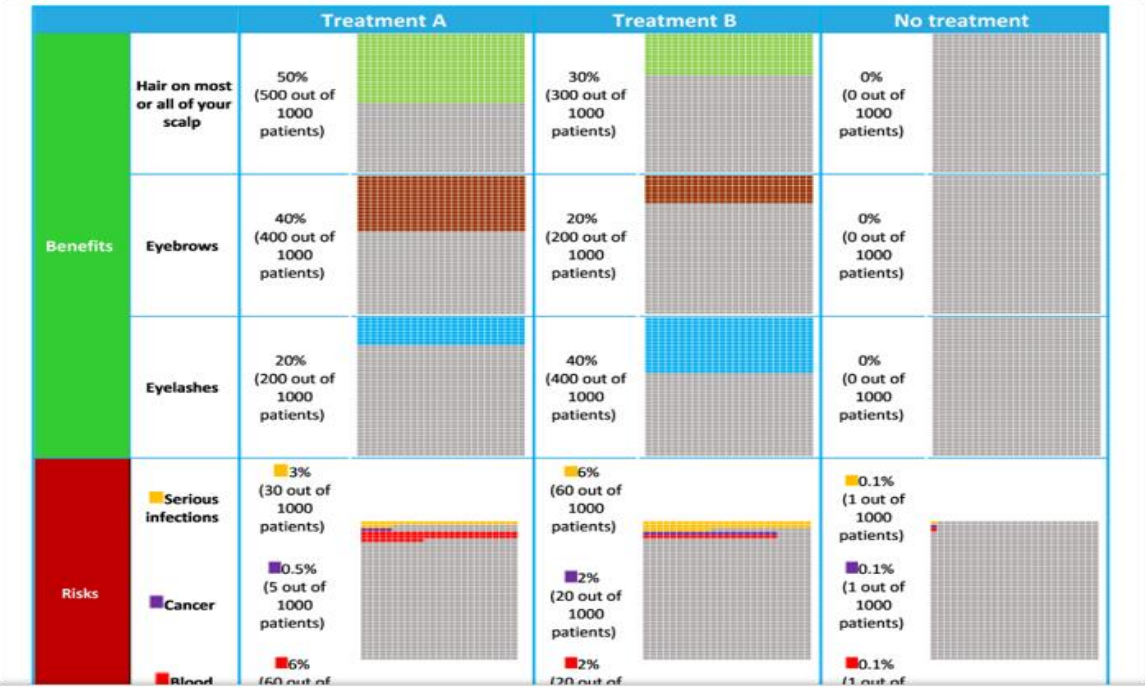
Example: Treatment preferences of adults and adolescents with alopecia areata (AA): A discrete choice experiment (Tervonen et al. 2024)

The most important attribute was the probability of achieving hair regrowth on most or all the scalp.

Patients with AA were willing to accept substantial risks to obtain an effective treatment.

For a 20% increase in the probability of 80%-100% scalp hair regrowth they accepted a **3-year risk of**:

- **Serious infection = 7.4%** (5.5-9.3);
- **Cancer= 2.5%** (1.9-3.1);
- **Blood clots = 9.3%** (6.4-12.2).



Given the high value patients with severe AA placed on scalp hair regrowth in the patient preference studies in adults and adolescents, the net B/R for ritlecitinib 50 mg, compared to no treatment, is considered positive from the patient's perspective.

Litfulo; INN-ritlecitinib

Use of Patient Preference Studies in Drug Development

A **Patient Preference Study (PPS)** systematically evaluates how patients value and choose among treatment benefits, risks, modes of administration, and treatment burdens. In drug development, PPS findings can inform development, clinical, regulatory, and market-access strategies.

Development Stage	Application of PPS
Early development	Identify unmet needs and treatment attributes that matter most to patients
Target Product Profile	Define target efficacy, acceptable safety risks, route of administration, and dosing frequency
Clinical trial design	Select patient-relevant endpoints and determine the minimum meaningful level of benefit
Protocol development	Optimize visit schedules, assessments, administration methods, and participant burden
Benefit–risk assessment	Quantify the risks patients are willing to accept for additional treatment benefits
Regulatory and reimbursement strategy	Provide complementary patient-perspective evidence to regulators and HTA bodies
Post-marketing phase	Evaluate preferences, treatment adherence, and persistence in real-world settings

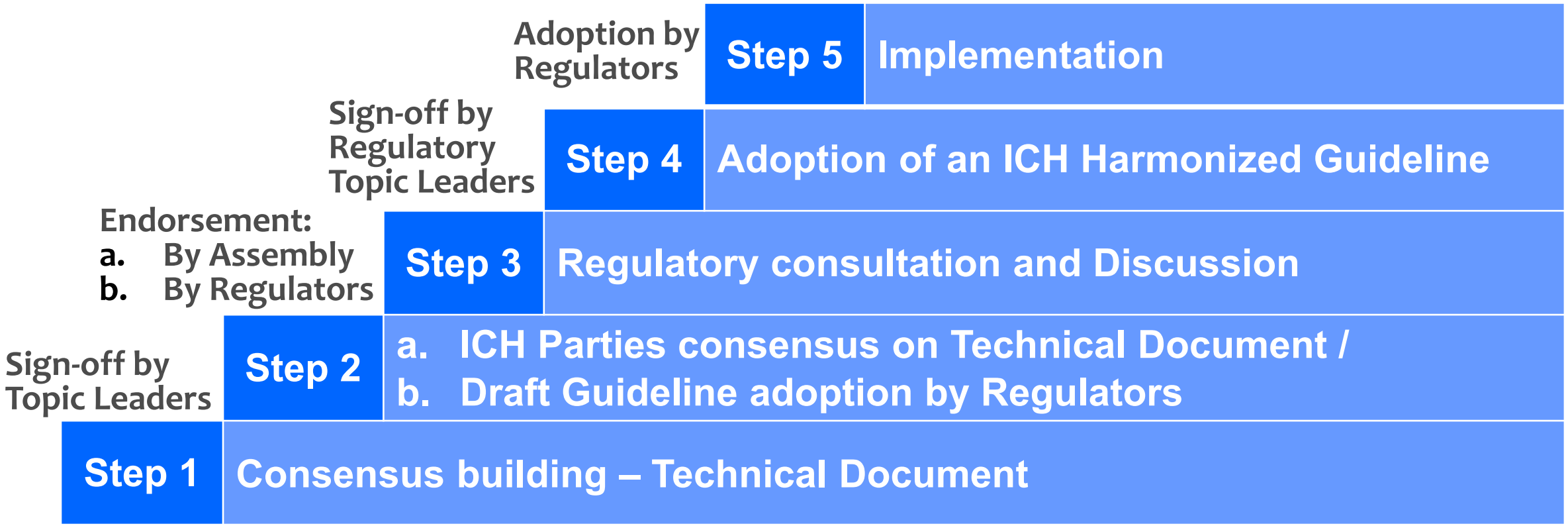
Draft Guideline

Background

- ✓ The E22 technical document has been signed off as a Step 2 document (19 November 2025) to be issued by the ICH Regulatory Members for public consultation
- ✓ This document was developed based on a Concept Paper (2 June 2024) and a Business Plan (19 August 2024)
- ✓ Public consultation have been conducted for stakeholders to provide scientific, operational, and implementation input that can directly influence the final ICH guideline (February ~ April 2026)
- ✓ Anticipating finalization as a Step 4 document to be implemented in the local regional regulatory system: December 2026

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

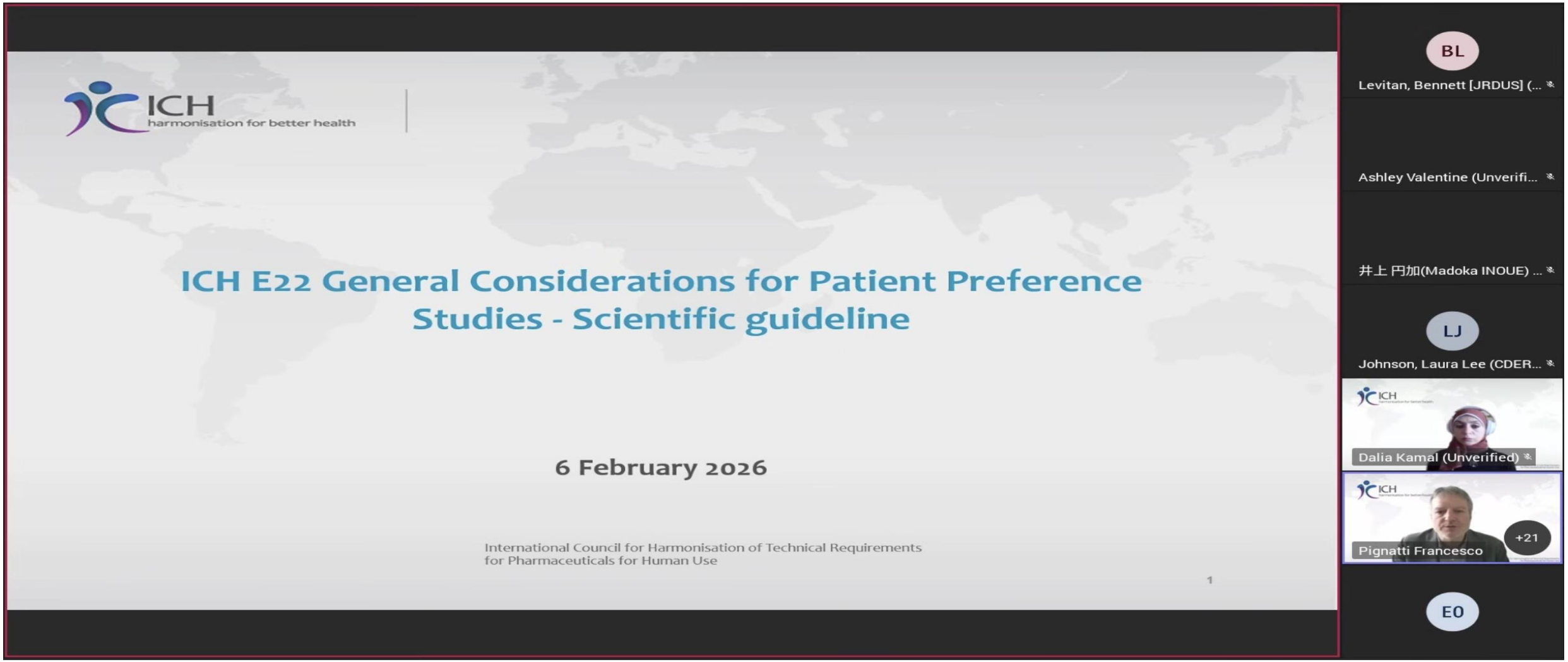
ICH Guideline Development Pathway (Step overview)



https://www.ich.org/page/formal-ich-procedure

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

Stakeholder Engagement_Draft ICH Guideline E22



https://youtube.com/watch?v=3sO6VIJXKOc

Key Principles

- ✓ Patients who have experience or knowledge of a disease and its treatments provide relevant perspectives
- ✓ Understanding these qualitative and quantitative insights is important for various aspects of drug development, such as identifying unmet needs, designing clinical studies, and interpreting results
- ✓ PPS may be considered together with the efficacy and safety information in the benefit-risk assessment of drugs and related regulatory submissions

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

Guideline Objectives

- ✓ To outline general considerations about the use, design, conduct, analysis, and submission of PPS aimed at informing drug development, regulatory submission and evaluation, drug approvals, and maintenance of such approvals

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

Scope Of The Guideline

- ✓ The focus of the E22 guideline is on patient preference studies using stated-preference methods (studies where patients are asked to state their choice through surveys or interviews)
- ✓ The E22 guideline may be applicable to similar and potentially useful studies (e.g., caregiver or revealed- preference studies), but these are outside the scope
- ✓ The placement of PPS data in labelling is considered a regional matter outside the scope of the E22 guideline

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

Summary Of Guideline Content

Table Of Contents Of The E22 Guideline

1. Introduction
2. General Principles
3. PPS in Drug Development and Post-marketing Evaluations
4. Recommendations and Practical Considerations for PPS

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

- ✓ PPS aim to assess the relative desirability or acceptability of actual or potential health interventions, or their characteristics and outcomes (e.g., efficacy and safety outcomes)
- ✓ The qualitative and quantitative insights provided by PPS may be informative for various aspects of drug development, such as identifying unmet needs, designing clinical studies, and interpreting results
- ✓ Note: The information provided by PPS does not replace the information provided by efficacy and safety studies

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

2.1 Protection Of Study Participants

- ✓ Principles applicable to other types of studies involving human subjects, such as ethical conduct, compliance with the protocol, and protection of personal data, are applicable to PPS as well
- ✓ PPS participants should be protected in accordance with the applicable regulatory and legal requirements

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

2.2 Patient Input In The Development Of PPS

Patient input is valuable throughout the development, including:

- ✓ Identifying the use for a PPS
- ✓ Identifying feasibility challenges in the conduct of a PPS
- ✓ Designing a PPS; developing PPS protocols; selecting attributes and levels

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

2.3-2.4 Preliminary Research And De Novo Work

- ✓ Thorough preliminary research ensures that all relevant information is identified and included in the PPS design
- ✓ De novo work may not always be justified aiming to avoid unnecessary burden on the patient community

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2.5-2.6 Global Applicability And Early Consideration And Planning

- ✓ In some circumstances, PPS conducted in other region(s) may be informative
- ✓ The degree of applicability of PPS results from other region(s) should be evaluated and justified
- ✓ The applicant may find this topic useful to discuss prospectively with the relevant regulatory authorities
- ✓ Beginning as early as possible, the usefulness of PPS should be considered systematically throughout drug development

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2.7-2.8 Quality Standards And Ensuring Multidisciplinary Expertise

- ✓ PPS are expected to follow the principles of good study design and conduct, including study documents such as informed consent forms, protocol, analysis plan, etc.
- ✓ Study design and statistical analysis should be pre-specified
- ✓ It may be useful to pre-register protocols using a registry, a comparable platform, or other formal mechanisms to enhance research credibility and transparency
- ✓ The conduct of PPS should align with the principles of the “quality by design” approach to ensure the generation of reliable and meaningful results, using a risk-proportionate approach (see ICH E8)
- ✓ PPS should be undertaken by a cross-functional study team with the relevant PPS methodology and clinical expertise

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3.1 Types Of PPS

- ✓ Available methodologies can be classified as
  - Qualitative studies (narrative information)
  - Quantitative studies (statistical estimation)
  - Mixed methods approaches

- ✓ Qualitative research produce insights for the design of Quantitative PPS
- ✓ Quantitative PPS can be used, for example, to estimate the degree to which patients state they are willing to make trade-offs among different attributes
  - Attributes: The characteristics and outcomes of health interventions (e.g., efficacy and safety outcomes)

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3.2 How Might PPS Inform Drug Development And Evaluation

- ✓ During early stage of development, for example:
  - Informing about unmet needs, and patients' willingness to participate in clinical studies
  - Informing the choice of endpoints for clinical trials
- ✓ At a later stage, for example:
  - Informing the interpretation of the trial results (trade-offs among attributes or if benefits outweigh the risks) or development of risk-mitigation strategies
- ✓ PPS may also help describe preference heterogeneity (the distribution of preferences within a population or between subgroups)

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4. Recommendations And Practical Considerations

- ✓ Many methods are available for designing PPS
  - External resources may offer relevant insights and supplementary information
- ✓ It is up to the applicant to explain how the results of PPS are intended to support their regulatory submission
- ✓ Applicants to regulatory authorities are ultimately responsible for all aspects of studies submitted to regulatory authorities

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

4.1 Research Objective And Research Question

- ✓ The research question(s) should align with the research objective(s), which drive the methods chosen

- ✓ Objective: What the PPS is intended to inform
  - For example, informing benefit-risk assessment

- ✓ Questions: Related to the answers needed to address objective
  - For example, what are the levels of acceptable risks in exchange for benefit?

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

4.2 Study Design And Method Selection

- ✓ The choice of method can depend on several factors, including the research question(s), the patient population, and the number of attributes or scenarios to be assessed
  - A PPS is not limited to one method and can include both quantitative and qualitative approaches
- ✓ PPS should follow internationally recognised scientific standards and recommended practices
- ✓ Researchers are encouraged to refer to published literature for more information on the methods available, and the respective strengths and limitations

Source: ICH E22 Presentation Step 2 Guideline 2025 1211.pdf

4.3-4.4 Study Sample And Sample Size

- ✓ The PPS sample should be guided by the research objective(s) and question(s)
- ✓ A sample that is representative of the target population of the regulatory submission may minimise generalisability/applicability issues
- ✓ There are different types of recruitment strategies; researchers should justify the recruitment strategy and describe potential bias
- ✓ The sample size for PPS varies based on research question(s), type of method, and complexity of the study (e.g., number of attributes and levels)

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4.5 Attributes And Levels

- ✓ Particular attention should be paid to the attributes and levels when designing the instrument
- ✓ Attributes included should be relevant for the patients, research objective, and question(s)
  - Including irrelevant attributes might increase burden
  - Omitting relevant attributes may limit the usefulness of the results
  - The range of attribute levels should cover the values expected in clinical studies (treatment and control groups)
- ✓ Patient engagement in the attribute selection is encouraged

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4.6 Instrument Design

- ✓ Instruments (e.g., interview guides, surveys) should be clear, comprehensible, and relevant; potential bias should be minimised

- ✓ Appropriate consideration should be given to, e.g.,
  - Numeracy; complexity; translations in multilingual studies; description of attribute levels; minimising cognitive bias

- ✓ Implementing quality checks
  - Data quality checks are a critical aspect of PPS, which may highlight potential data and study limitations
  - Important issues highlighted by quality checks should be addressed

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4.6 Pretesting And Piloting

- ✓ Pretesting and piloting an instrument serve different purposes, and both are essential steps in developing the instrument
  - Pretesting: Initial evaluation to identify any issues with comprehension or interpretation
  - Piloting: Testing under study conditions to identify issues of feasibility, data quality, or logistics

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4.7 Analysis Plan

- ✓ The analysis, as detailed in the pre-specified analysis plan, should address the research objective and question(s) and follow recommended practices
- ✓ In some situations, such as quantitative benefit-risk analysis, data from quantitative PPS may be combined with clinical data
- ✓ The analysis plan should specify all primary and exploratory analyses, and handling the outcome of quality checks, as appropriate

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4.8 Submission To The Common Technical Document (CTD)

- ✓ PPS can be listed in CTD 2.5.1 “Product Development Rationale”
- ✓ The PPS report should be included in CTD 5.3.5.4 “Other Clinical Study Reports”
  - The PPS report can be based on the structure of clinical study reports (ICH E3R1), adapted as appropriate
- ✓ If applicable, PPS results can be included in Benefits and Risks Conclusions along with a critical assessment of the PPS (CTD 2.5.6)
  - PPS results and/or quantitative benefit-risk analyses can be included in the appendix to the Clinical Overview (CTD 2.5.6.5; see ICH M4E for details)

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Conclusions

- ✓ E22 general considerations provide guidance when considering the need for PPS, and to ensure that PPS are based on sound methodology and produce rigorous results

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Thank you!