June 5, 2024 Hyatt Centric Downtown Minneapolis

MedTech Event: EU MDR Regulatory Updates and Best Practices for Evidence Management

DistillerSR 3Aware AKRA TEAM

Status of EU MDR 2017/745 and Key Learnings from initial EU MDR Certification

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EU MDR CE Mark

Update from the European Regulatory Landscape

Minneapolis, June 2024

Dr. Bassil Akra
CEO – AKRA TEAM

AKRA TEAM

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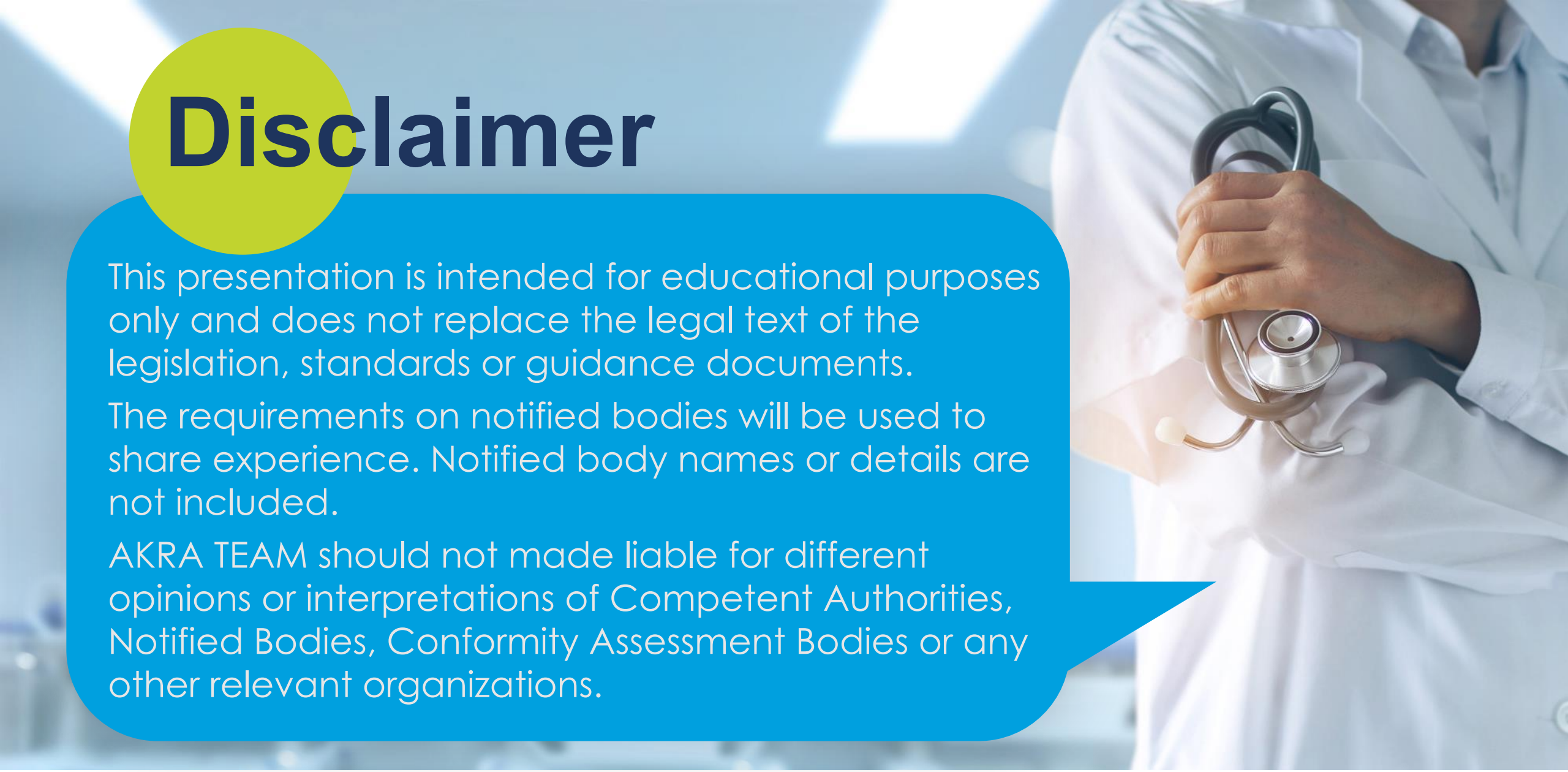

This presentation is intended for educational purposes only and does not replace the legal text of the legislation, standards or guidance documents.

The requirements on notified bodies will be used to share experience. Notified body names or details are not included.

AKRA TEAM should not made liable for different opinions or interpretations of Competent Authorities, Notified Bodies, Conformity Assessment Bodies or any other relevant organizations.

Implementation of the MDR

Extension of Transition Provisions per MDR Art. 120

Regulation 2023/607 15 March 2023

Applies only to devices that

- that do not present any unacceptable risk to health and safety
- that have not undergone significant changes in design or intended purpose AND
- for which the manufacturers have already undertaken the necessary steps to launch the certification process under the MDR
  - Adaptation of QMS to MDR
  - Application for conformity assessment by a NB before a certain deadline

Extension of the transitional period in Art. 120 (3)

- 2027 for class III and Implantable class IIb
- 2028 for class IIa, IIb and class I devices

Manufacturer Extension of the validity of certificates issued under MDD /AIMDD Confirmation Letter - Not a Requirement!

if needed for legal or practical reasons (e.g., third country markets access)

Removal of the „sell off“ provision in MDR and IVDR (Devices must be placed lawfully on the market)

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49 MDR Notified Bodies (NB) in comparison to more than 86 under the Directives (AIMDD/MDD)

Search options

Country: All countries

Body type: All types

Notification status: Active

Legislation: Regulation (EU) 2017/745 on m

Procedure / article or annex: All procedures

Products: All products

Horizontal technical competence: All competences

Search results (46)

Showing results 1 - 30

NOTIFICATION STATUS: Active

LEGISLATION: Regulation (EU) 2017/745 on medical devices

Items per page: 30

Body type	Body Name	Country
NB 0476	KIWA CERMET ITALIA S.P.A.	Italy
NB 1434	POLSKIE CENTRUM BADAN I CERTYFIKACJI S.A.	Poland
NB 0546	CERTIQUALITY S.r.l.	Italy
NB 1370	BUREAU VERITAS ITALIA S.P.A.	Italy
NB 1282	ENTE CERTIFICAZIONE MACCHINE SRL	Italy
NB 0426	ITALCERT SRL	Italy
NB 0477	Eurofins Product Testing Italy S.r.l.	Italy
NB 0425	ICIM S.P.A.	Italy
NB 0373	ISTITUTO SUPERIORE DI SANITA'	Italy

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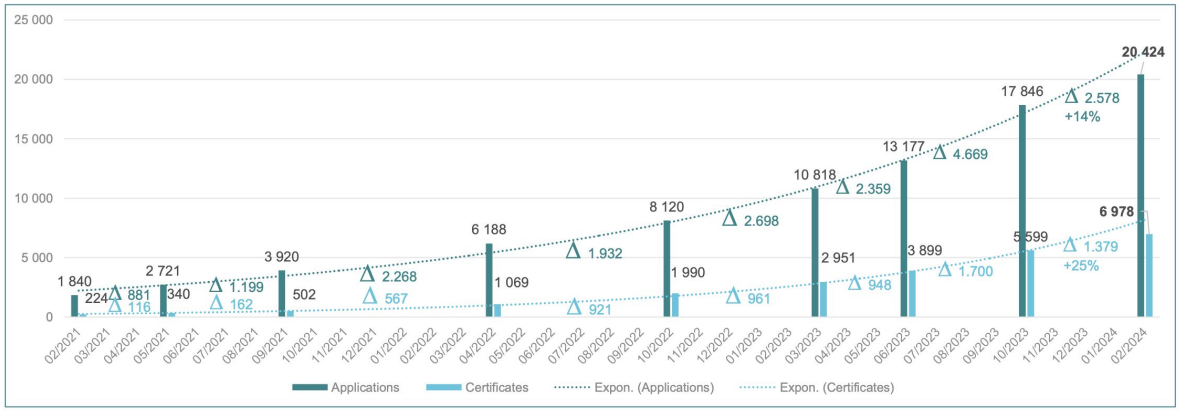
MDR applications filed and certificates issued (sum of Annexes)

MD

Ⓜ

February 2024
MDR Applications:
Total number of applications filed by Annex Ⓜ: 20.424*
MDR Certificates:
Total number of certificates by Annex Ⓜ: 6.978



Notes: February 2024: Designated NBs for MD: 43; NBs that included Annex XVI products in the numbers provided: 20

* The data shown comes from the medium data set Ⓜ – except for 2 NBs where the total number of applications filed was derived from the small data set Ⓢ since they could not provide the data per Annex.

- Δ (Delta) = Difference in MDR Applications / MDR Certificates from one survey to the next one
- **Applications filed**: This number includes **all applications filed (syn. lodged) so far** according to MDR Annex VII section 4.3 (from the day when the designation became valid, i.e. one day after publication in the Single Market Compliance Space to the date of the survey up to 29/02/2024), i.e.: applications with issued certificates, applications without decisions on the outcome of the conformity assessment activities, applications that were eventually refused or withdrawn by the manufacturer (including transferred applications), applications lodged for changes of existing MDR certificates. Pre-application activities are not included. One application can correspond to more than one certificate.
- **Certificates issued:** This number includes **certificates issued so far** (from designation up 29/02/2024) under the MDR.

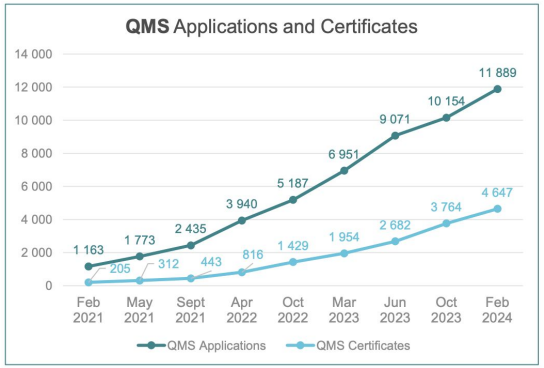
MDR applications and certificates by type (QMS vs Product) – survey comparison

MD

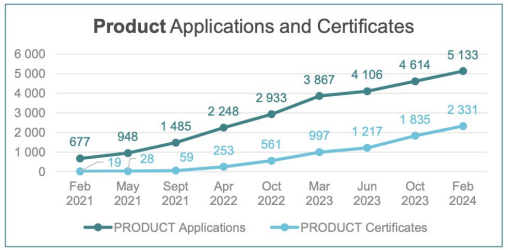
Ⓜ

February 2024
MDR Applications: 20.424*
MDR Certificates: 6.978

* The data shown comes from the medium data set (applications and certificates by Annex: Two NBs could not provide the application information by Annex; hence the total number of applications is higher - see number in the small data set).



Note QMS Applications and Certificates: This relates to Annex IX Chapter I or Annex XI Part A according to MDR.



Note PRODUCT Applications and Certificates: This relates to Annex IX Chapter II, Annex X or Annex XI Part B according to MDR.

Total number of applications lodged for changes received for already MDR issued certificates: 2.535

European Commission

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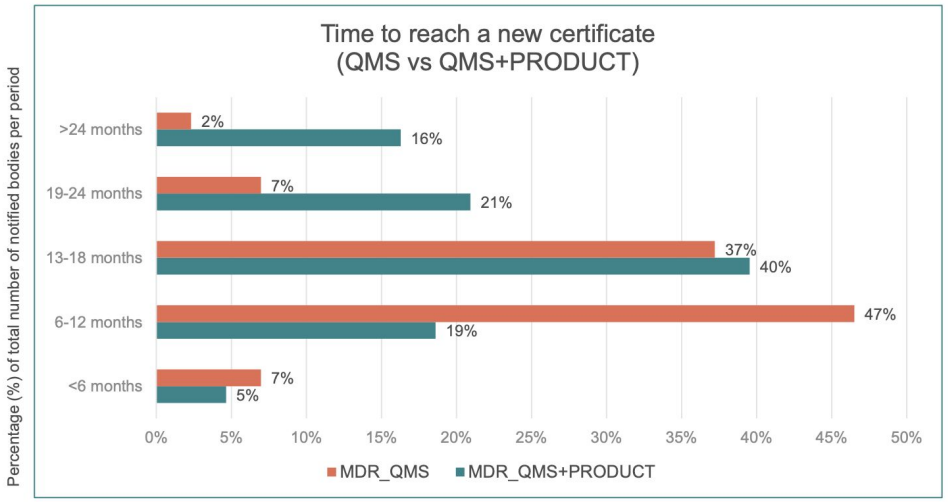
Duration and Predictability

Time to reach a new certificate (QMS vs QMS+PRODUCT)

MD



February 2024
MDR Applications: 20.424*
MDR Certificates: 6.978

MDR QMS certificates:

- For 47% of NBs: 6-12 months to issue a new QMS certificate
- For 46% of NBs: ≥ 13 months (max: 24 months)

MDR QMS+PRODUCT certificates: longer time

- For 40% of NBs: 13-18 months to issue a new product certificate
- For 77% of NBs: ≥ 13 months

Notes:

* The data shown comes from the medium data set Ⓜ – except for 2 NBs where the total number of applications filed was derived from the small data set Ⓢ since they could not provide the data per Annex.

- This indicator shows the time to reach issuance of a new EC certificate (from written agreement signed to issuance) under MDR.
- Some NBs have not issued a certificate yet, so the indicated time frame is an estimation.
- One NB stated that time from agreement to certificate varies a lot.
- One NB stated to observe time periods to be increasing.

European Commission

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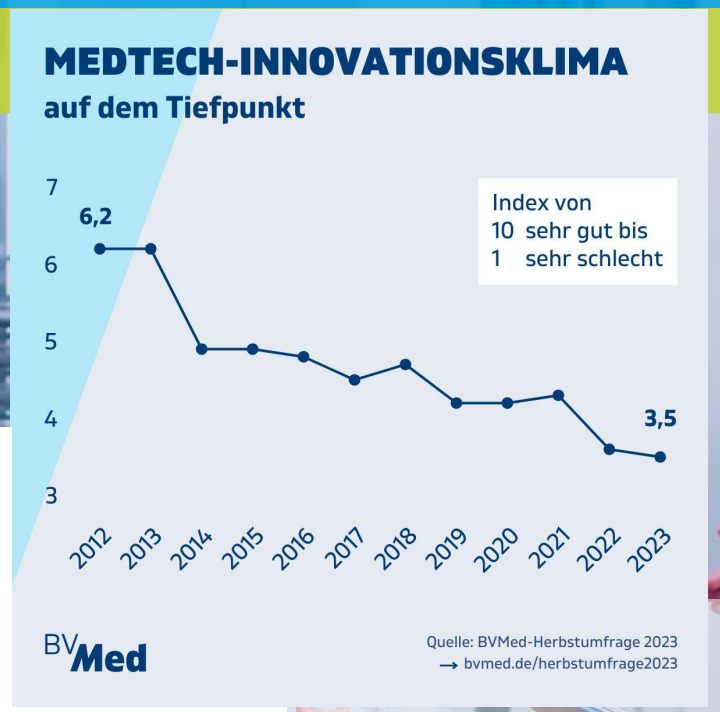
Innovation in the Union Market



Political Measures to ensure a more sustainable future plan

Germany is taking the lead on pushing politically towards a systematic revision of the EU Regulation to keep EU Attractive for Innovative Manufacturers.

BVMed Die Stimme der deutschen MedTech-Branche

VDGH Verband der Diagnostica-Industrie

Summary BVMed and VDGH White Paper on the Future Development of the MDR and IVDR

In cooperation with Erik Vollebregt – Axon Lawyers

BVMed and VDGH have drafted a white paper that discusses the consequences of the underperforming regulatory system for healthcare, innovation and the position of the CE mark for medical devices and IVDs internationally. The white paper proposes several solutions, grouped by the following categories:

- Measures to supplement the current regulatory system set out under the MDR and IVDR;
- Measures to increase efficiency and implement principles of good administration;
- Reform of the current five-year certification cycle;
- Increased international cooperation and regulatory reliance; and
- Centralisation of responsibility and policy within the regulatory system.

from diagnosis to cure

Press Releases

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You are here : Homepage » Latest press releases » MedTech Europe welcomes the adoption of amended transitional provisions of the Medical Devices Regulations and calls for continued work to address outstanding implementation challenges

PRESS RELEASE | NEW MEDTECH REGULATIONS

MedTech Europe welcomes the adoption of amended transitional provisions of the Medical Devices Regulations and calls for continued work to address outstanding implementation challenges

Posted on 07.03.2023

Brussels, 7 March 2023 – MedTech Europe welcomes the adoption of the European Commission's Proposal to amend the transitional provisions of the EU Medical Devices Regulation (MDR) and the *In Vitro* Diagnostic Medical Devices Regulation (IVDR). The amendment will help mitigate the immediate risk that medical devices across all areas of medicine, which are still on the EU market, would no longer be available after May 2024.

"The amendment of the Medical Devices Regulations' transitional provisions is a needed step forward to help ensure that more medic-

TEAM NB — The European Association for Medical devices of Notified Bodies

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December 2023

18 DEC 2023 — Team-NB Lifetime MD position paper

Thanks to the work of the task force, Team-NB members [...]

14 DEC 2023 — Annex XVI guidances

MDCG endorsed at their meeting of December 12th, 2023 the [...]

08 DEC 2023 — IVDR Technical Documentation Training for

06 DEC 2023 — Designation of EU reference laboratories

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Was it a good plan?

26 May 2021

27 May 2024

European Commission | English | Search

Public Health

Home > Study supporting the monitoring of availability of medical devices on the EU market

Study supporting the monitoring of availability of medical devices on the EU market

The European Commission's Directorate-General for Health and Food Safety (DG SANTE) - through the European Health and Digital Executive Agency (HaDEA) - has commissioned a "Study supporting the monitoring of availability of medical devices on the EU market". The study started in December 2022 and will be running for 36 months (December 2025). The study has been contracted to a consortium led by the Austrian National Public Health Institute (Gesundheit Österreich GmbH/GÖG), in collaboration with Areté and Civic Consulting.

In the context of the study, a dashboard has been developed. **The dashboard** presents an overview of the data gathered from different stakeholders. In addition, comparable data from previous surveys of notified bodies conducted by the European Commission have been integrated in the dashboard.

EY

About this survey

Feedback period: 13 December 2023 - 31 January 2024

Topic: Regulatory governance and innovation in the field of medical devices and in vitro diagnostic medical devices

Target audience: All types of actors and stakeholders are invited to contribute through the online questionnaire. This includes but is not limited to: Competent Authorities, Notified Bodies, economic operators (especially SMEs) and their representatives, as well as patient and professional organisations, and other sectorial interested parties.

Why we are consulting The current regulatory framework for medical devices and in vitro diagnostic medical devices in the EU includes two Regulations adopted in April 2017: Regulation (EU) 2017/745 on medical devices (MDR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR). The Regulations established a regulatory governance system encompassing structures, processes and coordination methods by means of which the key actors (European Commission, National Competent Authorities, Notified Bodies and economic operators) aim to ensure the MDR's and IVDR's practical application.

The key aim of the European Commission is to identify the key benefits and challenges of the current governance structure in the medical devices sector and its impact on innovation, with a view to informing possible adaptations to further optimise the system in short, medium and long term. In light of this, the European Commission's Directorate-General for Health and Food Safety (DG SANTE) and the European Health and Digital Executive Agency (HaDEA) have appointed the consultancy firm Ernst and Young (EY Consulting, De Kleetlaan 2, 1831 Diegem, Belgium) to carry out the "Study on Regulatory Governance and Innovation in the field of Medical Devices", scheduled to be completed in late 2024.

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Monitoring the Availability of Medical Devices and In Vitro Diagnostic Medical Devices in the

European Commission

Gesundheit Österreich GmbH

Areté The Agri-food Intelligence Company

CIVIC CONSULTING

Latest update of data
20.12.2023

Select stakeholder

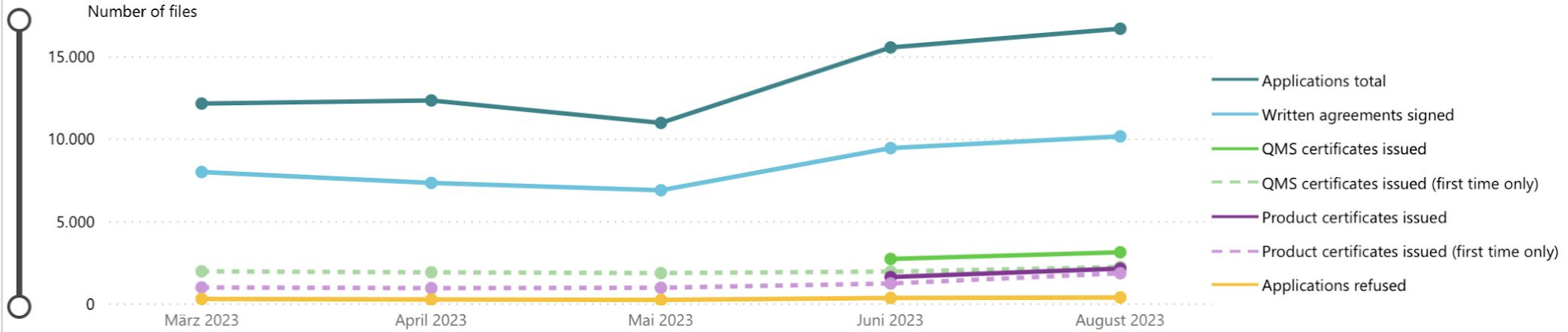
Notified Bodies (NBs)

Select figure

Ⓢ Overview indicators (MDR)

Ⓢ Overview indicators (MDR)

Compare: Total valid MDD/AIMDD certificates: 22.793 (10/22)



Please hover over the dots in the figure to see detailed numbers.

ⓘ How to interpret: Detailed information on displayed figure

This figure displays an overview of the (main) indicators on applications and certifications for medical devices under the MDR for the surveys performed. Notified bodies reported on how many written agreements they have signed, how many applications from economic operators have been refused, how many QMS and product certificates they have issued as well as how many certification applications have been received in total. Note that these data are collected within the small dataset (every (two) months) and are displayed and updated accordingly.

Select all, one or several of these indicators by clicking on the black buttons. For a selected indicator its definition and detailed information are shown in the infobox below.

Alle auswählen	Applications total	Written agreements signed	QMS certificates issued	QMS certificates issued (first time only)	Product certificates issued	Product certificates issued (first time only)	Applications refused

https://app.powerbi.com/view?r=eyJrIjoiN2YwMTEwM2UtYjQwMS00MjBiLWEyZjAtYjJlMGZjM2NhZDdiliwidCI6ImIyNGM4YjA2LTUyMmMtNDZmZS05MDgwLTcwOTI2ZjhkZGRiMSIsImMiOjh9

EU Parliament and Council voted in April and May 2024 positively for the following amendment

Text

Document information

Procedure

Internal procedure

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Text

EUROPEAN COMMISSION

Brussels, 23.1.2024

COM(2024) 43 final

2024/0021(COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards a gradual roll-out of Eudamed, information obligation in case of interruption of supply and the transitional provisions for certain in vitro diagnostic medical devices

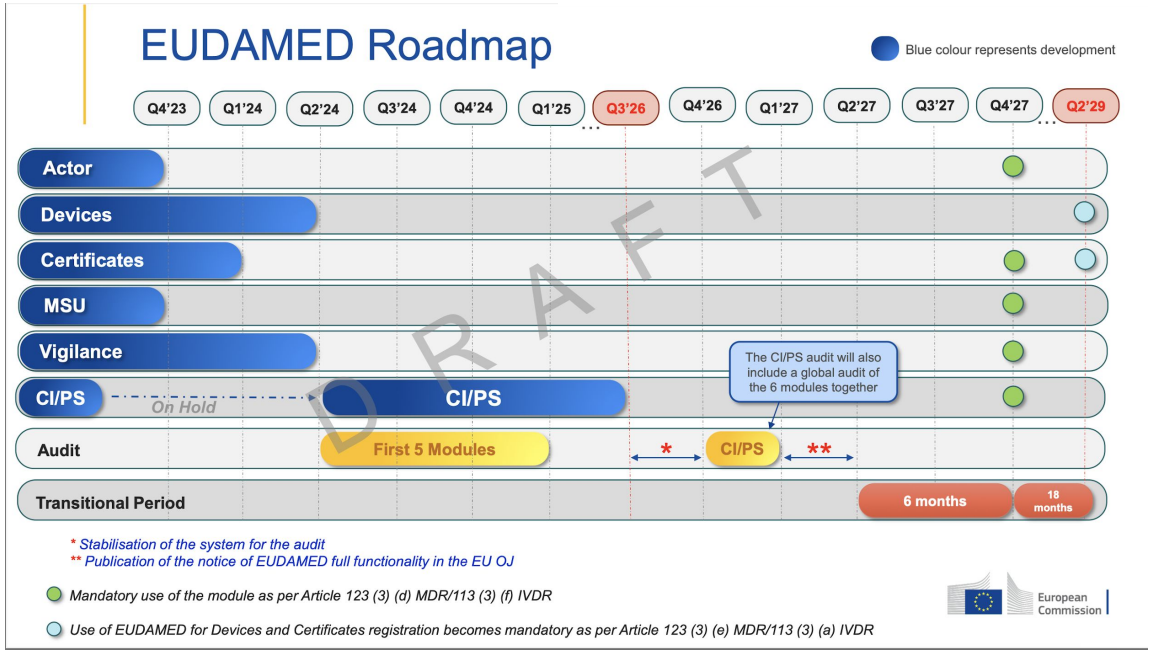
(Text with EEA relevance)

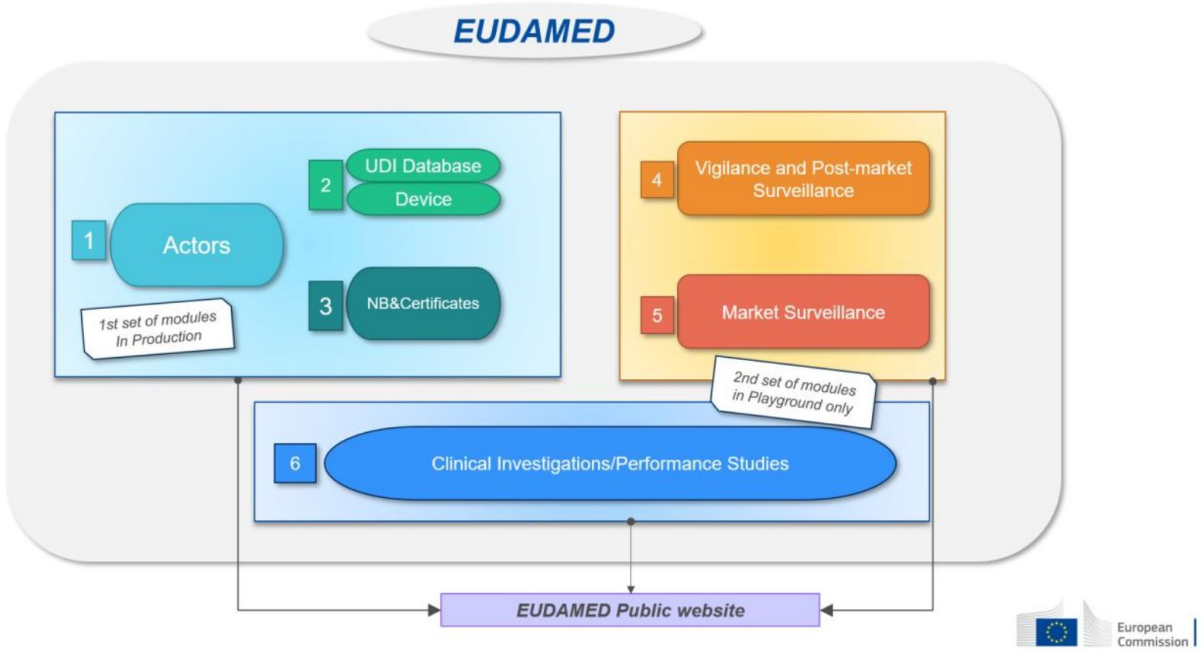
Additional Amendments - Plan for IVD and EUDAMED

This proposal for targeted amendments addresses two urgent issues. Firstly, it aims to further extend the transitional period for certain IVDs to mitigate the risk of shortages of these products, especially of high-risk IVDs, which are used, for example, to test for infections in blood or organ donations or for blood grouping for transfusions.

Secondly, the proposal aims to enable a gradual roll-out of the electronic systems integrated into the European database on medical devices ('Eudamed') that are finalised, instead of deferring the mandatory use of Eudamed until the last of the six

Potential Shortages
IVD-Extension
EUDAMED Roll-Out





Key Learnings from initial EU MDR Certification

EU MDR Updates and Best Practices for Evidence Management

June 5th, 2024

Matthias Fink
Senior Clinical Consultant

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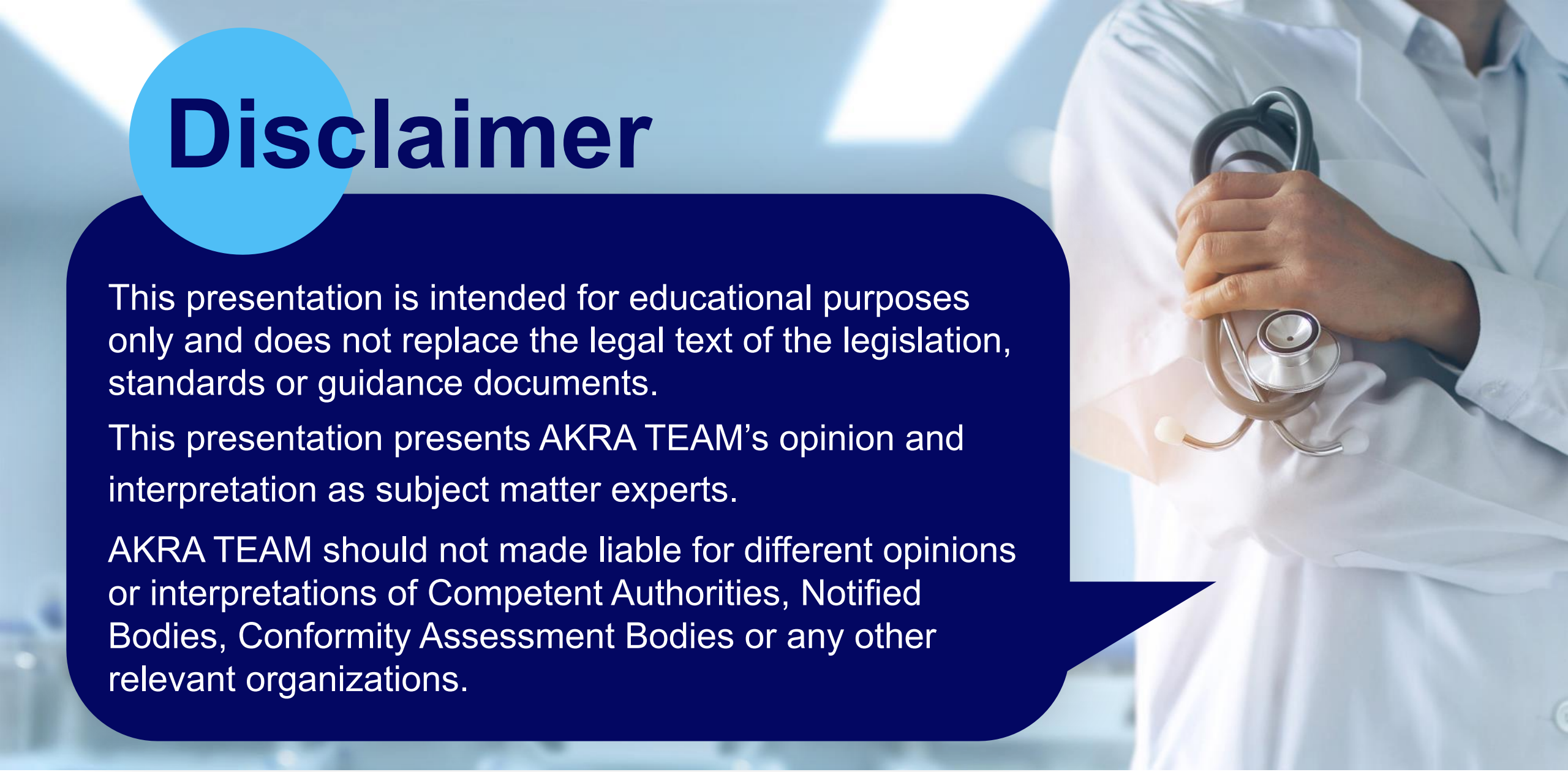

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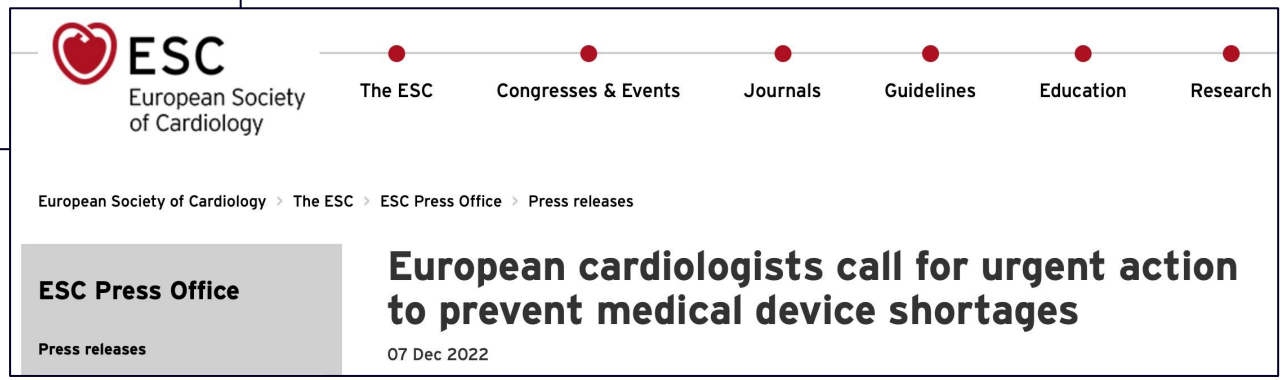
Challenges seen by a Consultant

- 49 NBs and 27 National Competent Authorities
- > 100 MDCG Guidance Documents
- Learning Curve Notified Bodies
- Learning Curve Manufacturers
- Political and Public Pressure

https://testlabsuk.com/blog/list-of-notified-bodies-map-of-europe/

Public Opinion



Better Alignment between Notified Bodies?

- **MDCG 2020-13**
- Joint events at regulatory conferences and meetings
- Alignment between Team-NB members on clinical topics
- Mandatory Clinical Evaluation Consultation Procedure

JUNE 5, 2024 I HYATT CENTRIC DOWNTOWN MINNEAPOLIS
MedTech Event: EU MDR Regulatory Updates and Best Practices for Evidence Management

TEAM NB
The European Association for Medical devices of Notified Bodies

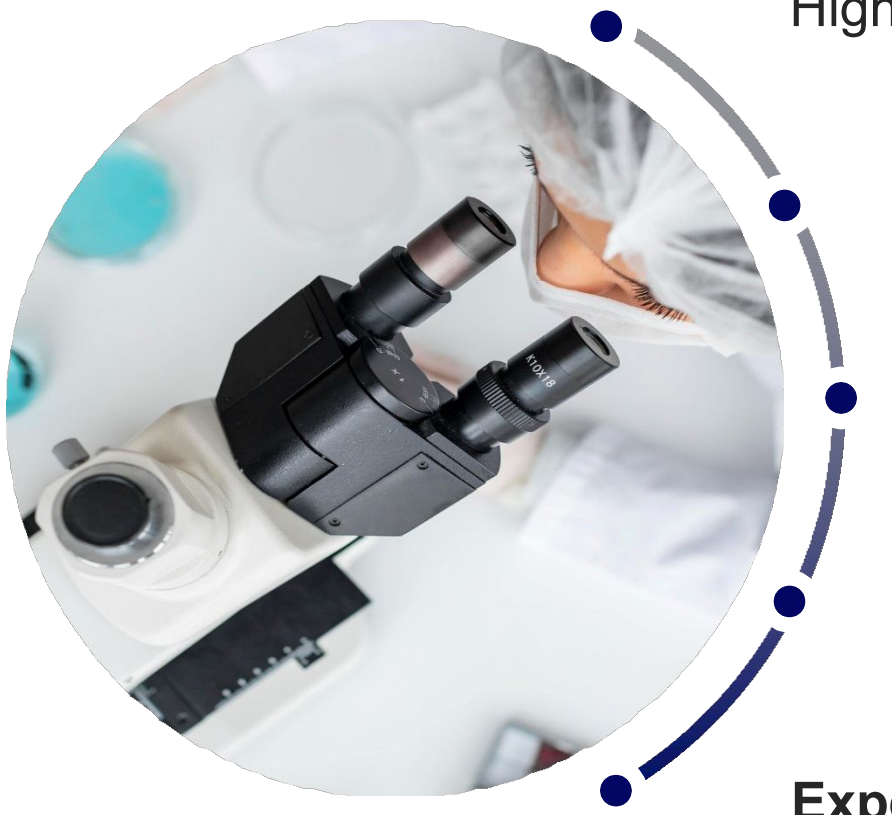
osma
Orthopaedic Surgical Manufacturers Association

What is new with clinical data under the MDR? Interactive panel session with Notified Bodies

Session Leader: Matthias Fink, MD – Akra Team Inc.
Presenter: Richard G. Holborow – BSI
Presenter: Christoph Ziskoven, MD – TÜV Rheinland LGA Products GmbH
Presenter: Ulrich Nitsche, MD – TÜV SÜD Product Service GmbH

Devices (includes Medical Devices and In Vitro Diagnostics)

Clinical Evaluation Challenges



Higher scrutiny of clinical data for certain medical devices
Definition of key safety and performance endpoints

Insufficient clinical data for legacy devices

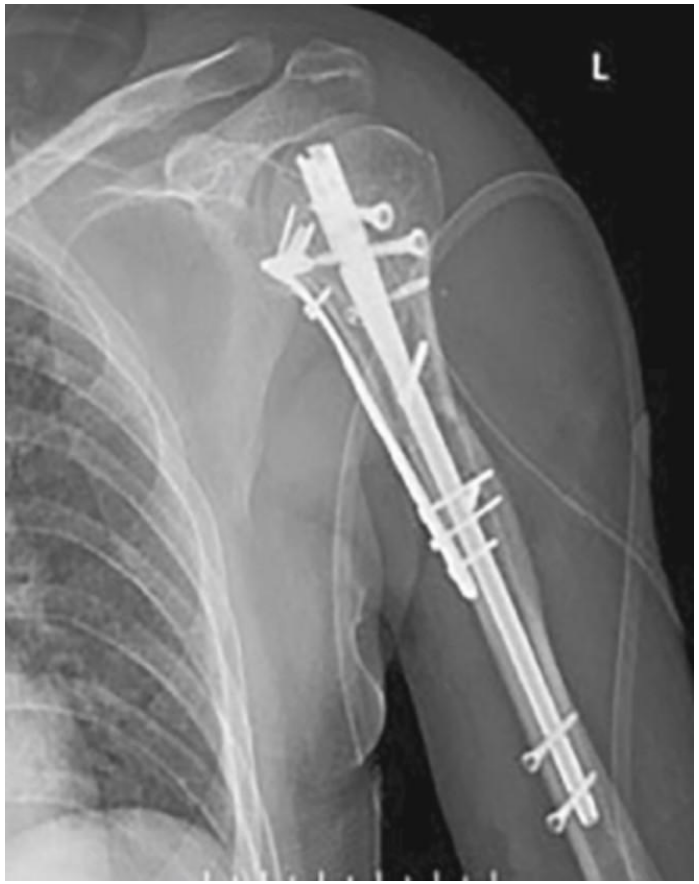
Definition of lifetime of a medical device

Expectations on clinical evidence differ between NBs

Higher Scrutiny for Class IIb Implantable Devices

Annex IX; not applicable for devices listed in Art, 61.6(b)

> 4.4. The notified body shall review the clinical evidence presented by the manufacturer in the clinical evaluation report and the related clinical evaluation that was conducted. The notified body shall employ device reviewers with sufficient clinical expertise and, if necessary, use external clinical experts with direct and current experience relating to the device in question or the clinical condition in which it is utilised, for the purposes of that review.



Additional Challenges:

- **Up-classification** of all partial and total joint prostheses and most spinal implants
- Most **IIb legacy orthopedic** devices are now reviewed by a **Clinical Reviewer**
- **Higher focus on the clinical data** compared to assessments under the Directives

Safety and Performance Acceptance Criteria

MDR, Annex XIV, 1.1(a)

to plan…manufacturers shall: an indicative list and **specification of parameters** to be used to determine, **based on the state of the art** in medicine, the **acceptability of the benefit-risk ratio**

Challenges

- Limited number of publications on similar devices
- Heterogeneity of study designs
- Definition of key safety and performance endpoints
- Calculation of acceptance criteria
- Selected endpoints are challenged by NBs

SOTA Acceptance Criteria – Challenges

Safety Endpoint

Infection Rate

- 0.5 – 18.7% based on 9 publications on similar devices
- Acceptance criteria <18.7% would be challenged by NB

PubMed®

Embase®

NIH U.S. National Library of Medicine

ClinicalTrials.gov

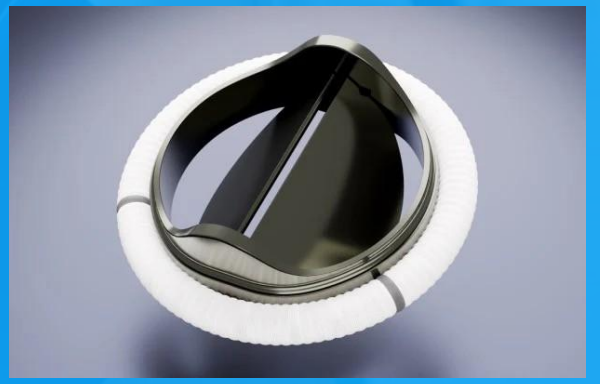
- ► More **detailed analysis** required
- ► **Outlier(s) should be removed**
- ► **Data gaps** between the subject device and the SOTA endpoints must be addressed in a **specific PMCF activity**

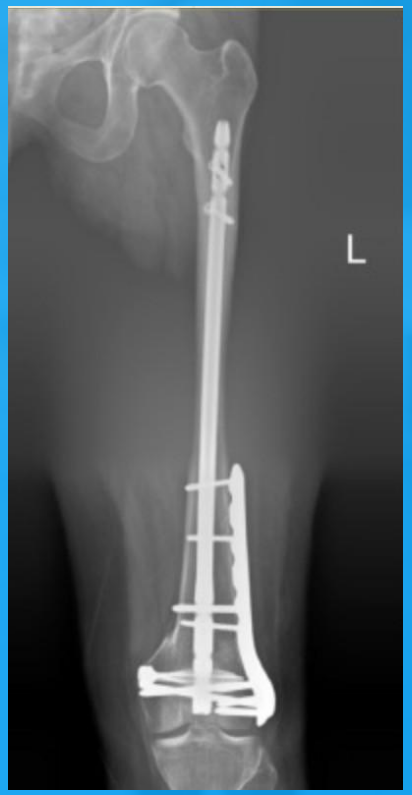
Clinical Evidence over the Device Lifetime

GSPR 6

The **characteristics and performance of a device shall not be adversely affected** to such a degree that the health or safety of the patient … are compromised **during the lifetime of the device, as indicated by the manufacturer**, …

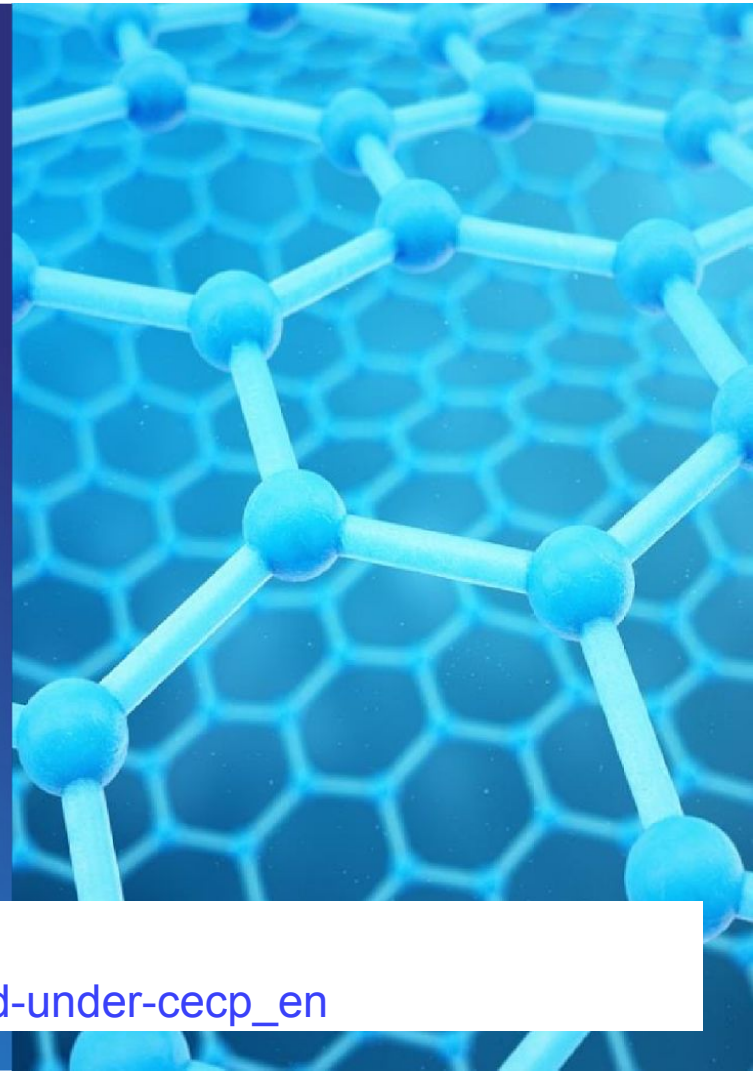
- Definition of the device lifetime
- Team-NB PP on Lifetime:
  "Unlimited lifetime or undefined lifetime is practically impossible to claim and **lifetime is expected to be defined in quantitative terms** of number of years…"
- Expectations by NB to collect specific PMCF data over the full lifetime
- RWE and Registries do not always include all key safety and performance endpoints





Summary of relevant findings by the Expert Panels

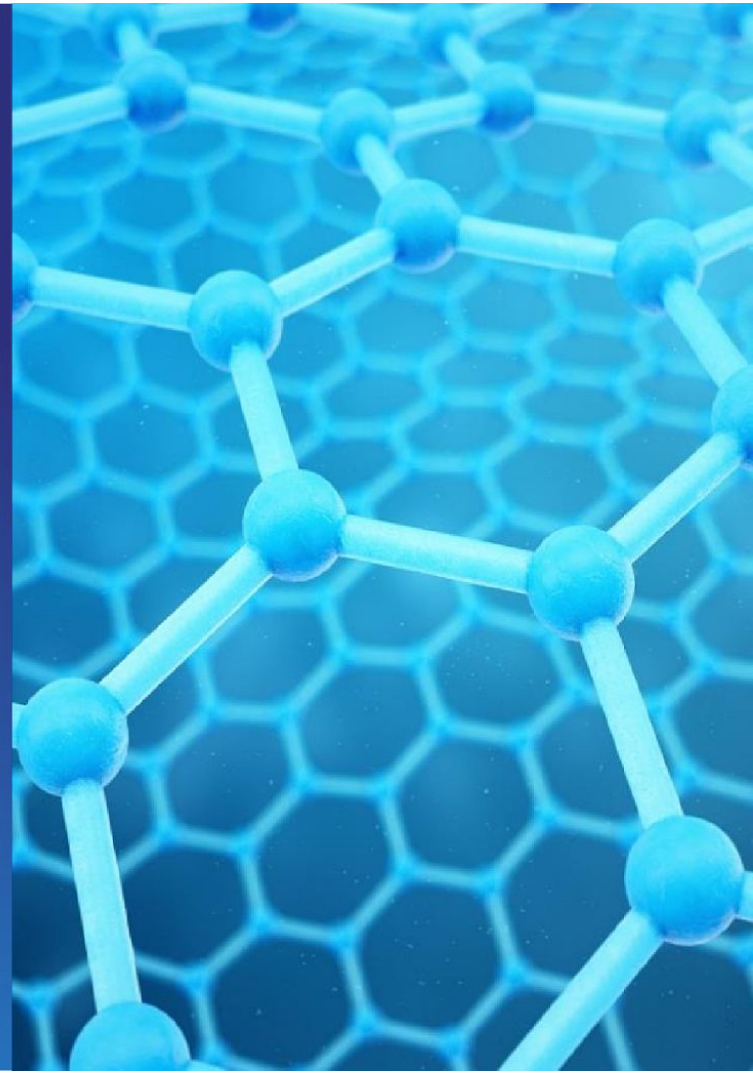
- CEAR could be presented in amore structured way
- Relevant published information not included in manufacturers' documentation and CEAR
- Methodology for literature reviews was found inadequate (e.g., biased or incomplete)
- Positive benefit-risk assessment of NB could not be followed



Published Scientific Opinions
https://health.ec.europa.eu/medical-devices-expert-panels/experts/list-opinions-provided-under-cecp_en

Summary of relevant findings by the Expert Panels

- Concerns regarding the study design and level of evidence
- Insufficient Clinical Data
  - Data transferability between indications
  - (Clinically) worst-case indication not covered
  - Number of patients too small
  - Lifetime not sufficiently addressed
  - Not all available data sources (e.g. registries) considered



Medtronic
Engineering the extraordinary

Key Learnings from Initial EU MDR Certification

June 5, 2024

Rita Guzzetta

Current deadlines

The new deadlines depending on the class of device:

- Class I devices (sterile, measuring, reusable surgical devices): until December 31, 2028
- Class IIb devices (non-implantable): until December 31, 2028
- Class IIb implantable devices: until December 31, 2027
- Class III devices (most): until December 31, 2027
- Class III custom-made implantable devices: until May 26, 2026

Additionally, the “sell-off” period, which allowed products certified under the previous directives (MDD/IVDD) to be sold until May 27, 2025, has been removed.
This change means that these products can continue to be sold until they are depleted from distributors' warehouses

EU MDR 2017/745

Overview

Stricter pre-market control/more tech doc requirements

Enhanced post-market surveillance

Increased transparency & traceability

Device Types

Including new & up classified

Key learnings

- Varying interpretations among reviewers and NB's; everyone is learning
- Plan resources for periodic document updates (CERs, PSURs, Risk Management)
- Bottleneck is not resolved, another may be coming
- Pace of innovation has slowed
- Global Regulatory Alignment: The stringent requirements of the EU MDR are influencing other regions to adopt similar regulatory frameworks

Long-term strategic planning

Where do we go from here?

Develop a centralized system for tech docs, post-market surveillance and regulatory updates

Companies that invest can gain competitive advantage

Prioritize diligence

Keep in tune with evolving regulatory landscape

Upcoming changes

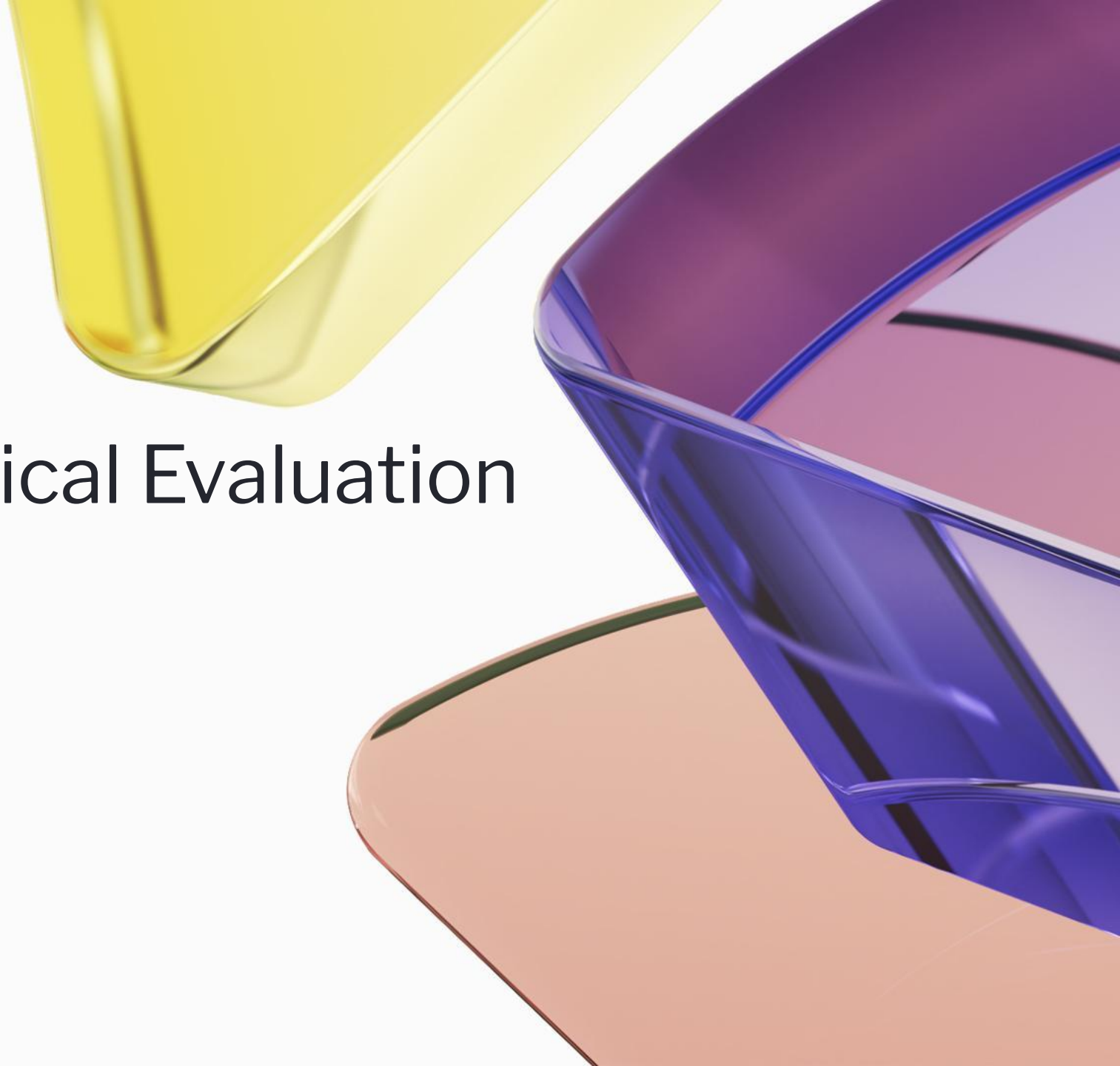
Guidance documents, evolving best practices

NB Update: Clinical Evaluation Assessment Process

Richard Holborow
Global Head of Clinical Compliance
at BSI Notified Body (NL) &
BSI Approved Body (UK)

Gretchen Adams
Technical Director
at DEKRA Product
Testing & Certification

Nunung Nur Rahmah
Head of Internal Clinical Team
at DEKRA Product
Testing & Certification



State of Play – Clinical Evaluation

MDR & UKCA

Rich Holborow
Head of Clinical Compliance
05.06.2024

Clinical Evaluation - Hot Topics

The Medical Devices Regulation (MDR) and the United Kingdom Conformity Assessment (UKCA) situation continues to have an impact in the area of clinical evaluation …

Orphan Devices

- Continued attention on the availability of medical devices for paeditric and rare diseases .
- UKCA and MDR reporting issues on availability

Certificates With Conditions

- MDR and IVDR both support the use of certificates with conditions.
- Drive to ensure that devices where collection of clinical data is impractical that certificates with conditions may help support continued access to the market.

Innovation

- There are reports that the launch of innovation is being favoured in other geographic regions because of the implementation of the MDR.
- MDR recital (1) encourages innovation in a safe environment.

Orphan Devices

Definition of an Orphan Device

Currently under consultation □

Market Shortages

Medical societies and health authorities are reporting some shortages in the UK and EU of devices for paediatric and rare diseases,. The difficulty remains trying to establish what is being discontinued for commercial reasons and what is actually being impacted by the regulation.

Draft Guidance

Both the UK and EU are looking at producing guidance/pathways for orphan devices to ensure continued availability. Legislative changes approved for EU manufacturers to provide 6 months' notice before removing a device from the market.

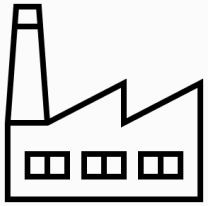
- the device is specifically intended to benefit patients in the treatment, diagnosis, or prevention of a disease or condition that presents in not more than 12,000 individuals in the European Union per year; and at least one of the following criteria are met:
  - there is insufficiency of available alternative options for the treatment or management of this disease/condition, or
  - the device will offer an option that will provide an expected or probable clinical benefit compared to available alternatives or state of the art for the treatment/management of this disease/condition, taking into account both device and patient population-specific factors.

Extrapolated from the population estimate criteria for Humanitarian Use Device (HUD) designation established by the U.S. Food and Drug Administration (FDA) and calculated on the basis of an EU population of 447 million.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-use-device-hud-designations

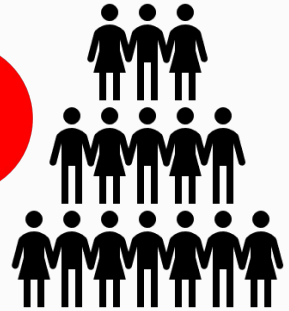
The proposed EU Solution...

1



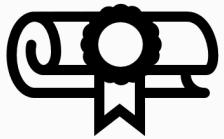
The Manufacturer needs to determine whether the device meets the definition of ‘orphan device’ . The manufacturer may approach the EU expert panels for an opinion ahead of the conformity assessment.

2



The EU expert panels will provide an opinion on whether a device meets the definition and may provide some expectations on the typical ‘sufficient’ evidence expected to be obtained for both the conformity assessment and post market considerations. The Notified body may also engage with the expert panels if they disagree with a manufacturer who claims their device is an orphan device but has not consulted the opinion of the EU expert panels ahead of the conformity assessment.

3



Notified body will consider the opinion as part of the conformity assessment and expectations that certificates may be issued with specific conditions relating to the collection of clinical data in the post market phase to further support the benefit/risk profile of the device in this small population.

Certificates with Conditions

*In combination with the possibility for notified bodies to **issue certificates under conditions**[13] or combined with the requirement to carry out PMCF / PMPF studies*[14]*, this action will increase the necessary flexibility to apply the reinforced clinical evidence requirements to devices that have a demonstrable track record of safety. (Point 17)*

4.8 The notified body shall have documented procedures for decision-making including as regards the allocation of responsibilities for the issuance, suspension, restriction and withdrawal of certificates. Those procedures shall include the notification requirements laid down in Chapter V of this Regulation. The procedures shall allow the notified body in question to:

- decide, based on the results of its assessment of the clinical evaluation and risk management, whether the post-market surveillance plan, including the *PMCF plan, is adequate*,
- decide on *specific milestones* for further review by the notified body of the up to date clinical evaluation,
- decide whether *specific conditions or provisions* need to be defined for the certification,

Annex VII Section 4.8

Certificates under conditions

BSI has a history under the medical device directive of issuing certificates under conditions. This has been primarily used to ensure safe market release of novel devices with a Post Market Clinical Follow-up (PMCF) commitment, ensuring that patients who receive a device are either enrolled into a PMCF study or registry and there are strict reporting requirements expected of the manufacturer to the notified body dates of the MDR.

Novelty/Innovation

These are situations where a device type is first to market and is completely new technology, it is difficult to ascertain the longer term risk associated with devices, so closer surveillance may be required by requesting a certificate is issued under conditions.

Orphan Devices

There are situations where it may be impossible to gather large statistically valid volumes of evidence because the device is used in rare circumstances Issuing certificates with conditions in these circumstances can ensure that data obtained in the post market phase can verify that the device is indeed safe and effective

Unmet medical need

There may be situations where there are breakthrough products for unmet medical need that may have strong early evidence but limited in volume. Certificates with conditions can enable these devices to get to market early to treat patients but with the added benefit of closer surveillance when there is limited evidence.

Certificates under conditions

The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose

(article 61 (1))

- Conditional certification is not a method that should be used to support devices where clinical data is possible to be obtained in a pre-market setting. Article 61 (1) clarifies the need for the manufacturer to have sufficient data.

- Conditional certification is typically considered when:

  - There is a limitation to be able to collect sufficient data in the pre-market space. e.g. orphan devices
  - There is a high level of novelty associated with unknown long-term risks
  - Breakthrough products to support an unmet medical need.

Innovation

Council Directive 90/385/EEC (3) and Council Directive 93/42/EEC (4) constitute the Union regulatory framework for medical devices, other than in vitro diagnostic medical devices. However, a fundamental revision of those Directives is needed to establish a ***robust, transparent, predictable and sustainable regulatory framework for medical devices*** *which ensures a high level of safety and health* ***whilst supporting innovation****. (Opening Statement)*

Innovation

Innovation is important to patients. It ensures that opportunities are explored to help minimise risk and support performance improvements . Innovation can also help by exploring new opportunities or approaches to disease diagnosis or management.

Some aspects of innovation may be novel. What is meant by Novelty?

"*Novelty typically means that there is a lack of experience in regard to the safety and performance of the device or specific features of the device or related clinical procedure, and there are no similar devices or insufficient experience with similar devices to enable straightforward appraisal of its future real-world safety and performance.*"

2020/C259/09Criterion 1 - Commission guidance for the medical device expert panels.

MEDDEV 2.7/1 rev 4 Updates (Note: to be MDCG Guidance 2024-XX)

Clarity on terms a definitions used within MDR

Use of Clinical Data coming from **Extra EU Clinical Investigations**

Use of retrospective clinical studies

Clarifications on PMCF e.g. when a PMCF study is required

Use of clinical data from PMCF and PMS activities

Appraisal methodology in line with MDCG 2020-6

Demonstration of indirect clinical benefit

Phase 1 Developments

- Acceptance that this guidance needs to be aligned to MDR clinical evaluation assessment
- Updates are to be delivered in 2 phases
- This work is being led by Italian CAs in a closed group and should be out for consultation soon.
- Primary focus is on the orphan devices taskforce.

Hierarchy of clinical evidence (Core-MD)

Proof of Sufficient clinical evidence

Application of article 61.10

Evaluation of WET per article 61 (6) (b)

Using State of the art data to support clinical evaluation

Use of Surrogate Endpoints

Clinical Evaluation of Orphan devices

Clinical Evaluation of AI devices

Phase 2 Developments

EU MDR- Clinical Data

Gretchen Adams, Technical Director
Nunung Nur Rahmah M.D, Ph.D.

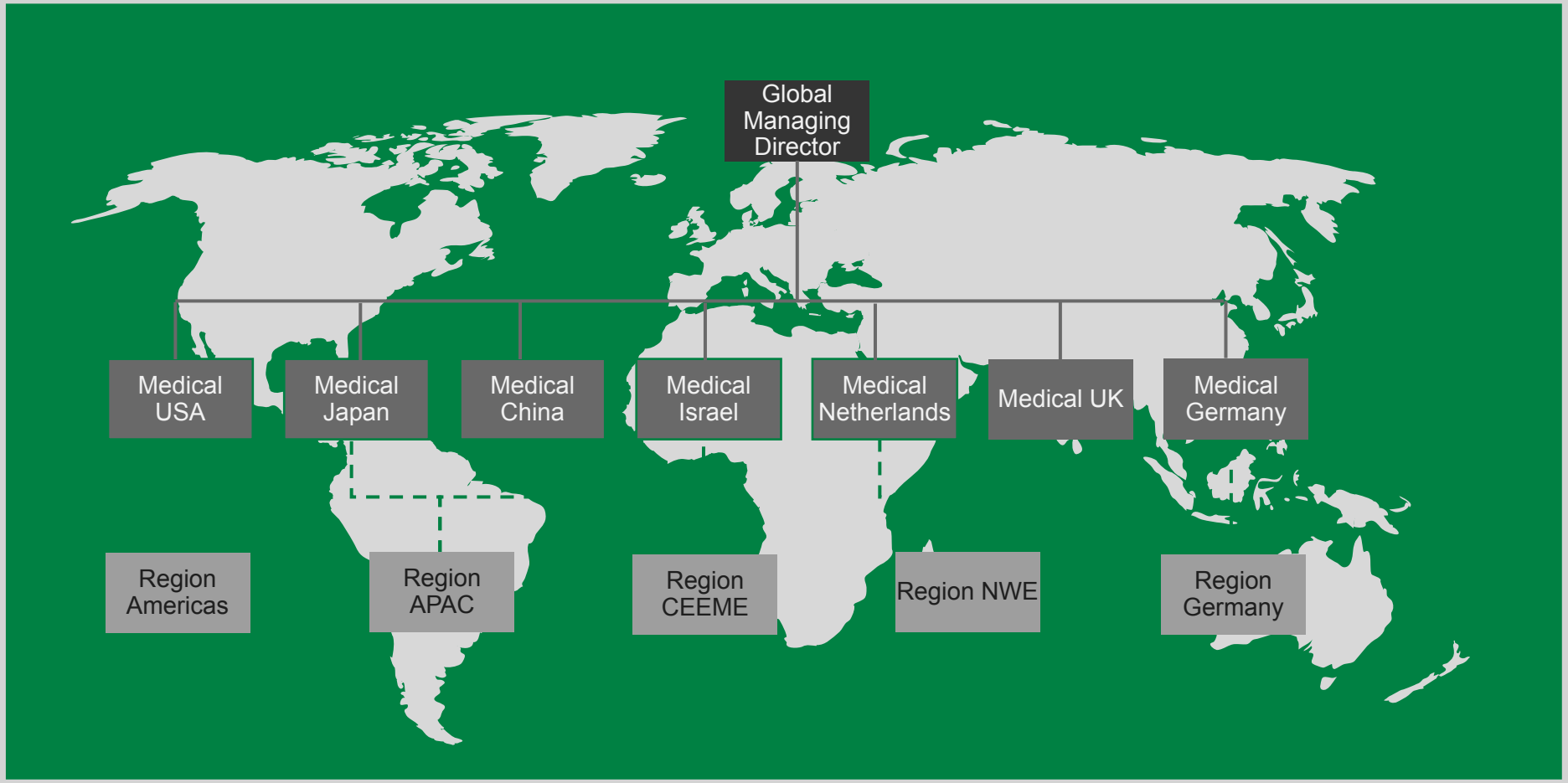
June 2024

About DEKRA

Introduction

- Established in 1925, DEKRA is a global leader in **testing, inspection and certification** in numerous technology fields and industry sectors
- DEKRA's mission is to be the global partner for a **safe, secure, sustainable world**
- **More than 48,000 employees** in 60 countries
- Revenue of ~ 4.1 Billion EUR (2023)
- **DEKRA** offers various specialty services to **healthcare manufacturers** globally

Global Medical Organization



Scope

- NB CE0344 for MDR and IVDR
- ISO 13485 RvA
- MDSAP
- TCP
- UK CAB
- ISO 13485 UKAS
- ISO 13485 SAC
- ISO 13485 DAkkS

Progress on MDR

EC 8th notified bodies survey on certifications and applications 17 May 2024

- 43 Notified Bodies now designated for Medical Devices
- To date >20K MDR Applications filed and almost 7K Certificates issued
- Reports of incomplete submissions remain high at intake review:
  - 77% of NB report submissions < 50% complete
- Time for QMS Certificate: 50% NB report time is greater than 13 months (up to 24 months)
- Longer Time for QMS + TD Certificate: 40% NB indicate 13-18 months, the rest report longer times

MDR Clinical Data Review Progress

+MDCG Guidance related to clinical data (22 for Clinical Data and PMS/Vigilance)

+ Clinical Expert Panel Pilot Program

+Promotion of communication between NB/Mfg via Structured Dialogue

+Resource gaps

-MDR Submission completeness

-MDD Extension impact on MDR focus

Clinical Expert Panel Review “Experience”

- To date only 10 opinions are published (7 from Dutch NoBo)
  - Class III implantables

- Reviews by the Expert Panel meet defined timelines
- Option to decline review due to low level of novelty

- Lack of opportunities for communication with Reviewers remains a challenge for the Notified Bodies

- Experience with conformity assessments with devices that participated in the pilot program just starting

Clinical data composed from sources relevant for the life cycle of the device and using defined and methodologically sound methods

Clinical data evaluated against requirements of MDR-including identification of gaps

PMS/PMCF Planning is state of the art and addresses any gaps identified in the clinical data

MDR Article 61(p4, 6) requires CI for Class III devices and implantable devices with exceptions

- Expectations for legacy devices is expected to be more focused on experience in the market (MDCG 2020-6)
- Other sources are acceptable for devices with indirect clinical benefit (MDCG 2020-6)
- Gaps should be identified per Annex XVI part A, 1(b) via Literature Review (MEDDEV 2.7.1/Rev4 A4)

Class III and Implantable Legacy devices

Results of high quality CI covering all device variants, indications, patient populations, duration of treatment effect, etc.

Results of high quality CI with some gaps

Outcomes from high quality clinical data collection systems such as registries

Outcomes from studies with potential methodological flaws but where data can still be quantified and acceptably justified

Generally not considered high quality sources

- SoA based on clinical data from similar devices
- Complaints and vigilance due to limitations in reporting
- Simulated use/animal cadaveric testing

MDR Article 61(10)

Allows demonstration of conformity with GSPRs for Clinical Data to be deemed not appropriate and conformity with GSPRs based on results of non-clinical testing methods (performance evaluation, bench testing, preclinical evaluation) to be sufficient – not for Class III and Implantables

Integrating AI for Regulatory-Compliant Literature Reviews: Trends & Forecast

Peter O'Blenis
CEO at DistillerSR

Artificial intelligence, or AI, is technology that enables computers and machines to simulate human intelligence and problem-solving capabilities.

AI in Literature Reviews

Rerank I Deduplication I Check For Screening Errors I AI Screening

- 2009 – Deterministic AI for reference screening
- 2010 – NLP-powered duplication
- 2016 – Deterministic classifiers trained on expert datasets
- 2018 – Named Entity Recognition
- 2023 – LLM summarization and feature identification, data extraction

ARTICLE

Classifying Biomedical Abstracts Using Committees of Classifiers and Collective Ranking Techniques

Authors: Alexandre Kouznetsov, Stan Matwin, Diana Inkpen, Amir H. Razavi, Oana Frunza, Morvarid Sehatkar, Leanne Seaward, Peter O'Blenis Authors Info & Claims

Canadian AI '09: Proceedings of the 22nd Canadian Conference on Artificial Intelligence: Advances in Artificial Intelligence • May 2009 • Pages 224–228 • https://doi.org/10.1007/978-3-642-01818-3_29

Published: 15 May 2009 Publication History

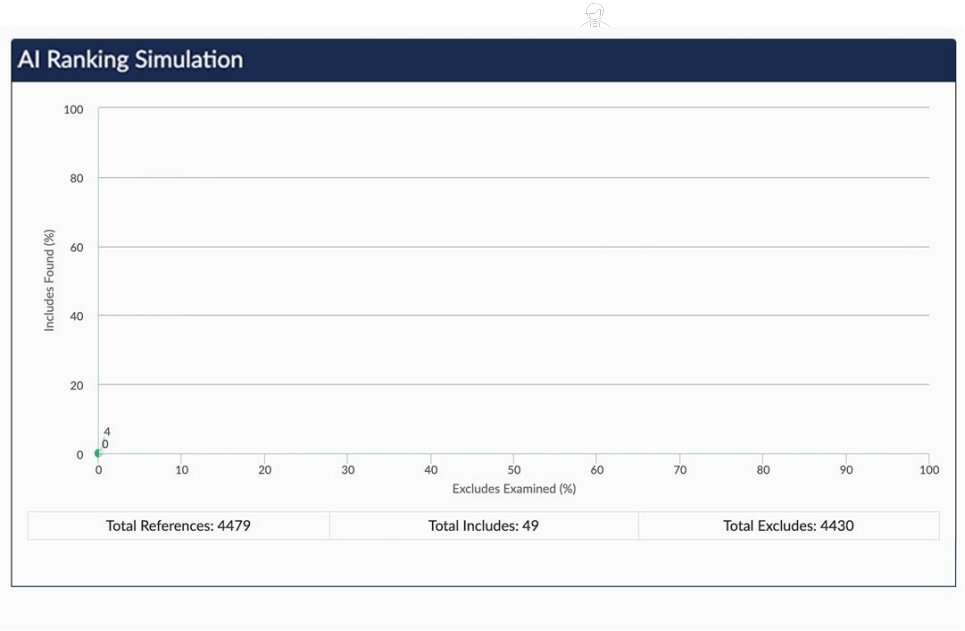
Deterministic AI for Screening

Rerank for Screening

Automatic Training

Autonomously trains on human screening choices as reviewers identify relevant and irrelevant references. Learns to recognize relevant references/studies and then continuously reprioritizes them based on relevance scores **reducing time to literature review completion by as much as 70%**

AI ReRank Simulation



The diagonal line represents traditional screening methods while the green line represents the time saved with continuous AI reprioritization

Business Value

- Faster Screening
- Quality Control
- Low CPU load
- Trained on domain-specific data

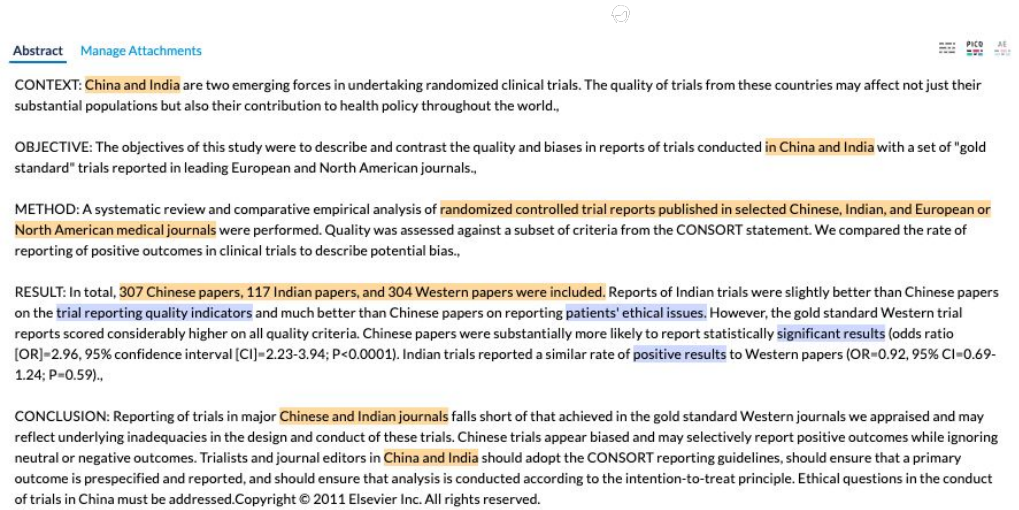
Named Entity Recognition

Examples: BioELECTRA, SciBERT

Open Models

Deterministic AI using open models. Pre-trained on domain-specific datasets to for Named Entity Recognition / Classification

PICO Element Detection



Abstract Manage Attachments

CONTEXT: China and India are two emerging forces in undertaking randomized clinical trials. The quality of trials from these countries may affect not just their substantial populations but also their contribution to health policy throughout the world.,

OBJECTIVE: The objectives of this study were to describe and contrast the quality and biases in reports of trials conducted in China and India with a set of "gold standard" trials reported in leading European and North American journals.,

METHOD: A systematic review and comparative empirical analysis of randomized controlled trial reports published in selected Chinese, Indian, and European or North American medical journals were performed. Quality was assessed against a subset of criteria from the CONSORT statement. We compared the rate of reporting of positive outcomes in clinical trials to describe potential bias.,

RESULT: In total, 307 Chinese papers, 117 Indian papers, and 304 Western papers were included. Reports of Indian trials were slightly better than Chinese papers on the trial reporting quality indicators and much better than Chinese papers on reporting patients' ethical issues. However, the gold standard Western trial reports scored considerably higher on all quality criteria. Chinese papers were substantially more likely to report statistically significant results (odds ratio [OR]=2.96, 95% confidence interval [CI]=2.23-3.94; P<0.0001). Indian trials reported a similar rate of positive results to Western papers (OR=0.92, 95% CI=0.69-1.24; P=0.59).,

CONCLUSION: Reporting of trials in major Chinese and Indian journals falls short of that achieved in the gold standard Western journals we appraised and may reflect underlying inadequacies in the design and conduct of these trials. Chinese trials appear biased and may selectively report positive outcomes while ignoring neutral or negative outcomes. Trialists and journal editors in China and India should adopt the CONSORT reporting guidelines, should ensure that a primary outcome is prespecified and reported, and should ensure that analysis is conducted according to the intention-to-treat principle. Ethical questions in the conduct of trials in China must be addressed.

Elements of interest automatically located in scientific texts for rapid user identification/extraction

Business Value

- Faster reviews
- Quality Control
- Efficient, cost effective

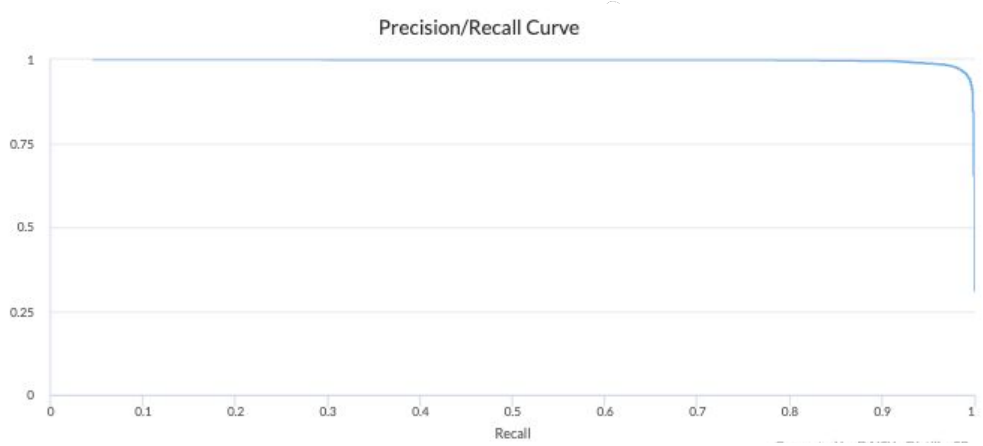
Deterministic AI for Labeling

User-Generated Deterministic Classifiers

AI Screening and Categorisation

Meta-data collected during a review is used to train domain-specific deterministic classifiers **AI Classifiers can then be used to automatically label references, identify key elements in a paper, or serve as a second reviewer**. Predictable and consistent outcomes, explainability and, if required, streamlined human-in-the loop validation.

AI Classifiers



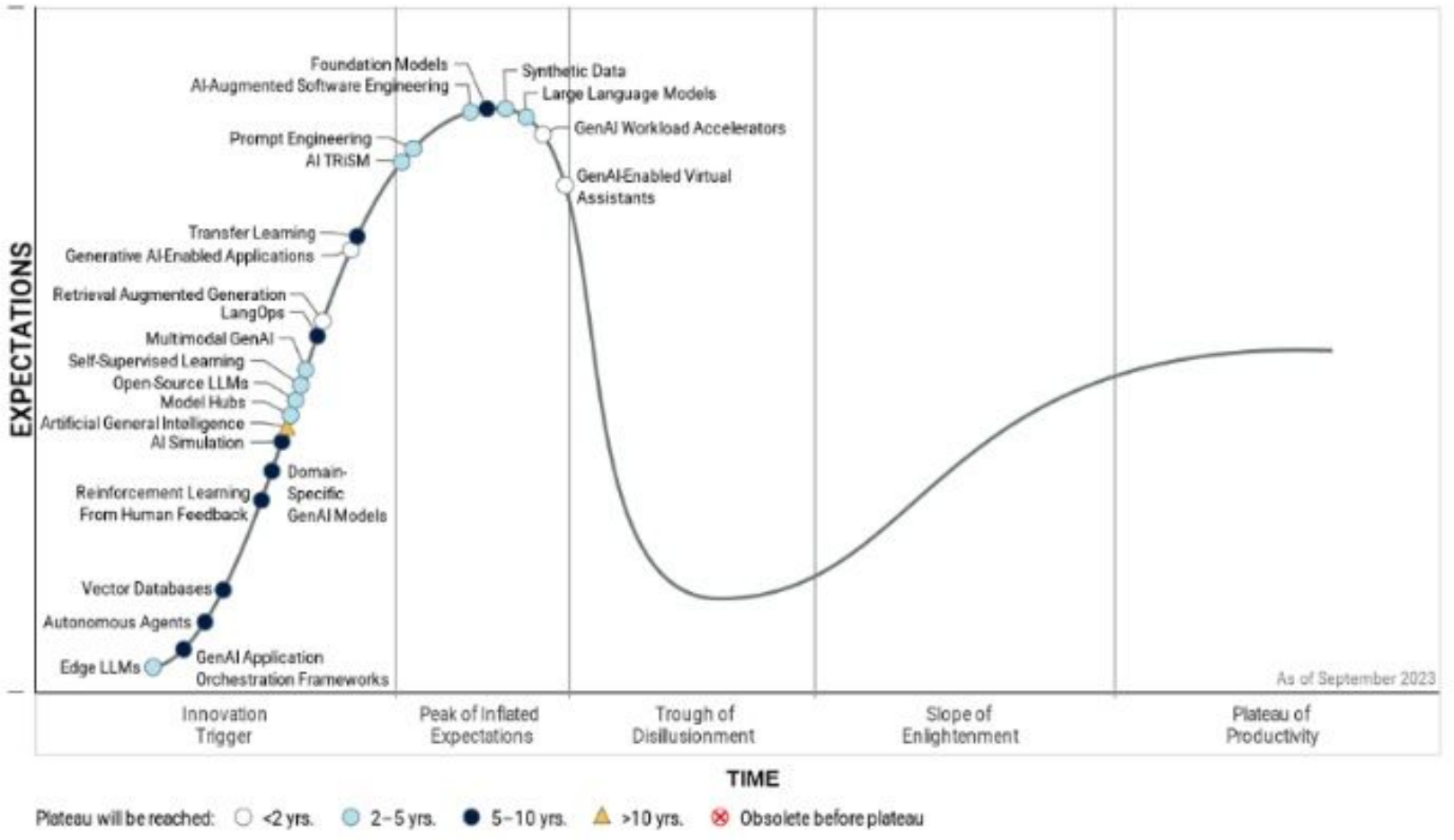
AI Classifiers can be trained and deployed across all relevant reviews, across the enterprise. Trained on clean, high quality domain specific data.

Business Value

- Faster classification and data extraction
- Quality. AI as a second reviewer
- Trained on domain-specific data
- Low cost training

Generative AI

Large Language Models



Gartner

Generative AI

Large Language Models

OpenAI putting 'shiny products' above safety, says departing researcher

Jan Leike, a key safety researcher at firm behind ChatGPT, quit days after launch of its latest AI model, GPT-4o

Generative AI

Large Language Models

In Play Today

- Summarization of available evidence
- Assisted extraction of Meta-Data
- Insights generation
- Drafting of document elements

Current Limitations/Considerations

- Human-in-the-Loop
- Training Data
- Domain-Specific Models
- CPU power/costs
- Copyright
- Data privacy
- Transparency/reproducibility

Business Value

Accelerated review preparation

Quality Control

Insight generation

Scientifically Validated AI For Literatures Review

"Implementing AI Vertical use cases - Scenario 1".
Stefano Cagnonia, Vieri Emilianib, Gianfranco Lombardoa, Wynand Alkemac, Carlijn Hooijmansd, Leiden (NL) d Radboud University Medical Center, Nijmegen (NL) e EcoMole s.r.o., Prague (CZ) f University of Edinburgh, Edinburgh (UK) g Charité University Hospital, Berlin (DE)

"Error rates of human reviewers during abstract screening in systematic reviews".
Zhen WangID 1,2*, Tarek NayfehID 2, Jennifer Tetzlaff3, Peter O'BlenisID 3, Mohammad Hassan Murad1,2

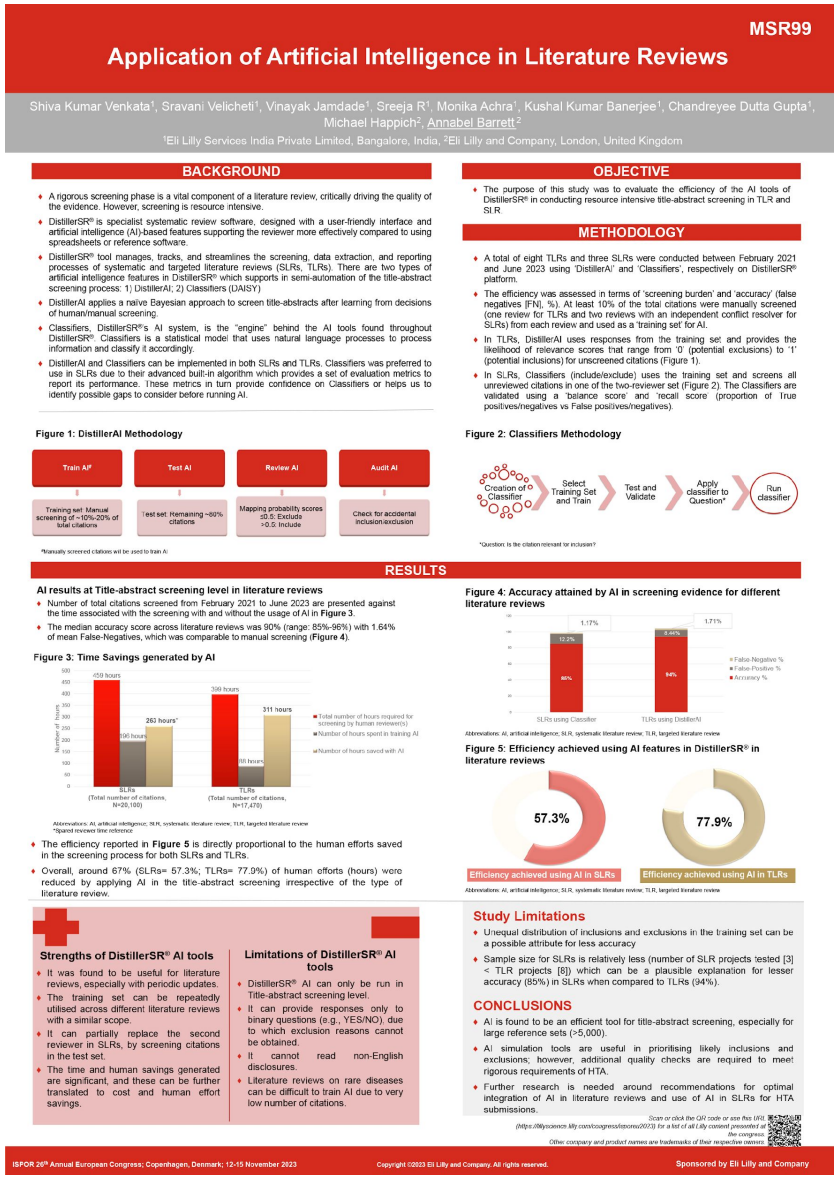
"Guidance for using artificial intelligence for title and abstract screening while conducting knowledge syntheses.".
C Hamel, M Hersi, SE Kelly, AC Tricco, S Straus, G Wells, B Pham, B Hutton 2021

"An evaluation of DistillerSR's machine learning-based prioritization tool for title/abstract screening - impact on reviewer-relevant outcomes.".
C Hamel, SE Kelly, K Thavorn, DB Rice, GA Wells, B Hutton 2020

"Evaluating the efficacy of artificial intelligence tools for the automation of systematic reviews in cancer research: A systematic review.".
X Yao, MV Kumar, E Su, A Flores Miranda, A Saha, J Sussman 2023

"Application of Artificial Intelligence in Literature Reviews ".
Shiva Kumar Venkata1 , Sravani Velicheti1 , Vinayak Jamdade 1 , Sreeja R1 , Monika Achra 1 , Kushal Kumar Banerjee 1 , Chandreyee Dutta Gupta 1 , Michael Happich 2 , Annabel Barrett 2 1Eli Lilly Services India Private Limited, Bangalore, India, 2Eli Lilly and Company, London, United Kingdom

"Using an artificial intelligence tool can be as accurate as human assessors in level one screening for a systematic review.".
JK Burns, C Etherington, O Cheng, Beiyin, S Root 2021



MSR99

Application of Artificial Intelligence in Literature Reviews

Shiva Kumar Venkata[1], Sravani Velicheti[1], Vinayak Jamdade[1], Sreeja R[1], Monika Achra[1], Kushal Kumar Banerjee[1], Chandreyee Dutta Gupta[1], Michael Happich[2], Annabel Barrett[2]
[1]Eli Lilly Services India Private Limited, Bangalore, India, [2]Eli Lilly and Company, London, United Kingdom

BACKGROUND

- A rigorous screening phase is a vital component of a literature review, critically driving the quality of the evidence. However, screening is resource intensive.
- DistillerSR® is specialist systematic review software, designed with a user-friendly interface and artificial intelligence (AI)-based features supporting the reviewer more effectively compared to using spreadsheets or reference software.
- DistillerSR® tool manages, tracks, and streamlines the screening, data extraction, and reporting processes of systematic and targeted literature reviews (SLRs, TLRs). There are two types of artificial intelligence features in DistillerSR® which supports in semi-automation of the title-abstract screening process: 1) DistillerAI; 2) Classifiers (DAISY)
- DistillerAI applies a naïve Bayesian approach to screen title-abstracts after learning from decisions of human/manual screening.
- Classifiers, DistillerSR®'s AI system, is the "engine" behind the AI tools found throughout DistillerSR®. Classifiers is a statistical model that uses natural language processes to process information and classify it accordingly.
- DistillerAI and Classifiers can be implemented in both SLRs and TLRs. Classifiers was preferred to use in SLRs due to their advanced built-in algorithm which provides a set of evaluation metrics to report its performance. These metrics in turn provide confidence on Classifiers or helps us to identify possible gaps to consider before running AI.

Figure 1: DistillerAI Methodology

*Manually screened citations will be used to train AI

OBJECTIVE

- The purpose of this study was to evaluate the efficiency of the AI tools of DistillerSR® in conducting resource intensive title-abstract screening in TLR and SLR.

METHODOLOGY

- A total of eight TLRs and three SLRs were conducted between February 2021 and June 2023 using 'DistillerAI' and 'Classifiers', respectively on DistillerSR® platform.
- The efficiency was assessed in terms of 'screening burden' and 'accuracy' (false negatives [FN], %). At least 10% of the total citations were manually screened (one review for TLRs and two reviews with an independent conflict resolver for SLRs) from each review and used as a 'training set' for AI.
- In TLRs, DistillerAI uses responses from the training set and provides the likelihood of relevance scores that range from '0' (potential exclusions) to '1' (potential inclusions) for unscreened citations (Figure 1).
- In SLRs, Classifiers (include/exclude) uses the training set and screens all unreviewed citations in one of the two-reviewer set (Figure 2). The Classifiers are validated using a 'balance score' and 'recall score (proportion of True positives/negatives vs False positives/negatives).

Figure 2: Classifiers Methodology

*Question: Is the citation relevant for inclusion?

RESULTS

AI results at Title-abstract screening level in literature reviews

- Number of total citations screened from February 2021 to June 2023 are presented against the time associated with the screening with and without the usage of AI in **Figure 3**.
- The median accuracy score across literature reviews was 90% (range: 85%-96%) with 1.64% of mean False-Negatives, which was comparable to manual screening (**Figure 4**).

Figure 3: Time Savings generated by AI

Abbreviations: AI, artificial intelligence; SLR, systematic literature review; TLR, targeted literature review
*Spared reviewer time reference

- The efficiency reported in **Figure 5** is directly proportional to the human efforts saved in the screening process for both SLRs and TLRs.
- Overall, around 67% (SLRs= 57.3%; TLRs= 77.0%) of human efforts (hours) were reduced by applying AI in the title-abstract screening irrespective of the type of literature review.

Figure 4: Accuracy attained by AI in screening evidence for different literature reviews

Abbreviations: AI, artificial intelligence; SLR, systematic literature review; TLR, targeted literature review

Figure 5: Efficiency achieved using AI features in DistillerSR® in literature reviews

Abbreviations: AI, artificial intelligence; SLR, systematic literature review; TLR, targeted literature review

Strengths of DistillerSR® AI tools

- It was found to be useful for literature reviews, especially with periodic updates.
- The training set can be repeatedly utilised across different literature reviews with a similar scope.
- It can partially replace the second reviewer in SLRs, by screening citations in the test set.
- The time and human savings generated are significant, and these can be further translated to cost and human effort savings.

Limitations of DistillerSR® AI tools

- DistillerSR® AI can only be run in Title-abstract screening level.
- It can provide responses only to binary questions (e.g., YES/NO), due to which exclusion reasons cannot be obtained.
- It cannot read non-English disclosures.
- Literature reviews on rare diseases can be difficult to train AI due to very low number of citations.

Study Limitations

- Unequal distribution of inclusions and exclusions in the training set can be a possible attribute for less accuracy
- Sample size for SLRs is relatively less (number of SLR projects tested [3] < TLR projects [8]) which can be a plausible explanation for lesser accuracy (85%) in SLRs when compared to TLRs (94%).

CONCLUSIONS

- AI is found to be an efficient tool for title-abstract screening, especially for large reference sets (>5,000).
- AI simulation tools are useful in prioritising likely inclusions and exclusions; however, additional quality checks are required to meet rigorous requirements of HTA.
- Further research is needed around recommendations for optimal integration of AI in literature reviews and use of AI in SLRs for HTA submissions.

Scan or click the QR code or see this URL (https://lillyscience.lilly.com/congress/isporeu2023) for a list of all Lilly content presented at the congress

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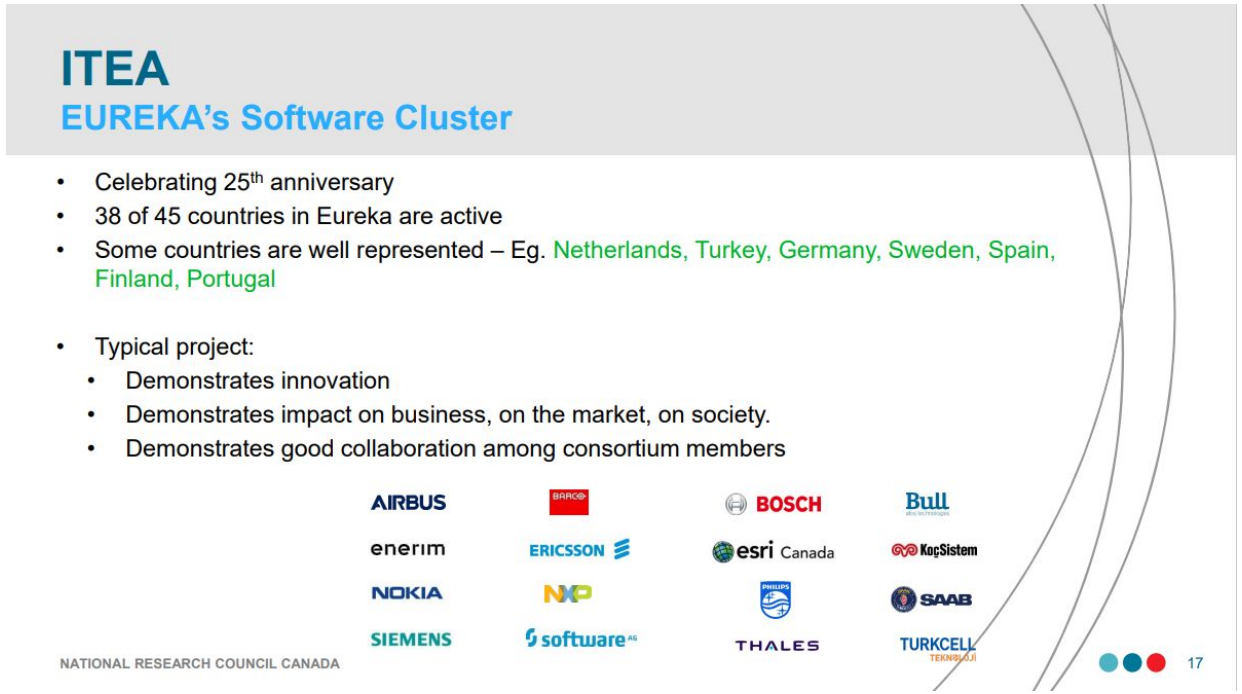
ISPOR 26th Annual European Congress; Copenhagen, Denmark; 12-15 November 2023

Sponsored by Eli Lilly and Company

ITEA – International Co-innovation Project

Project: Automating Full Text Data Extraction from Scientific Publications Using Generative AI



PHILIPS

BIOTRONIK

LUMC

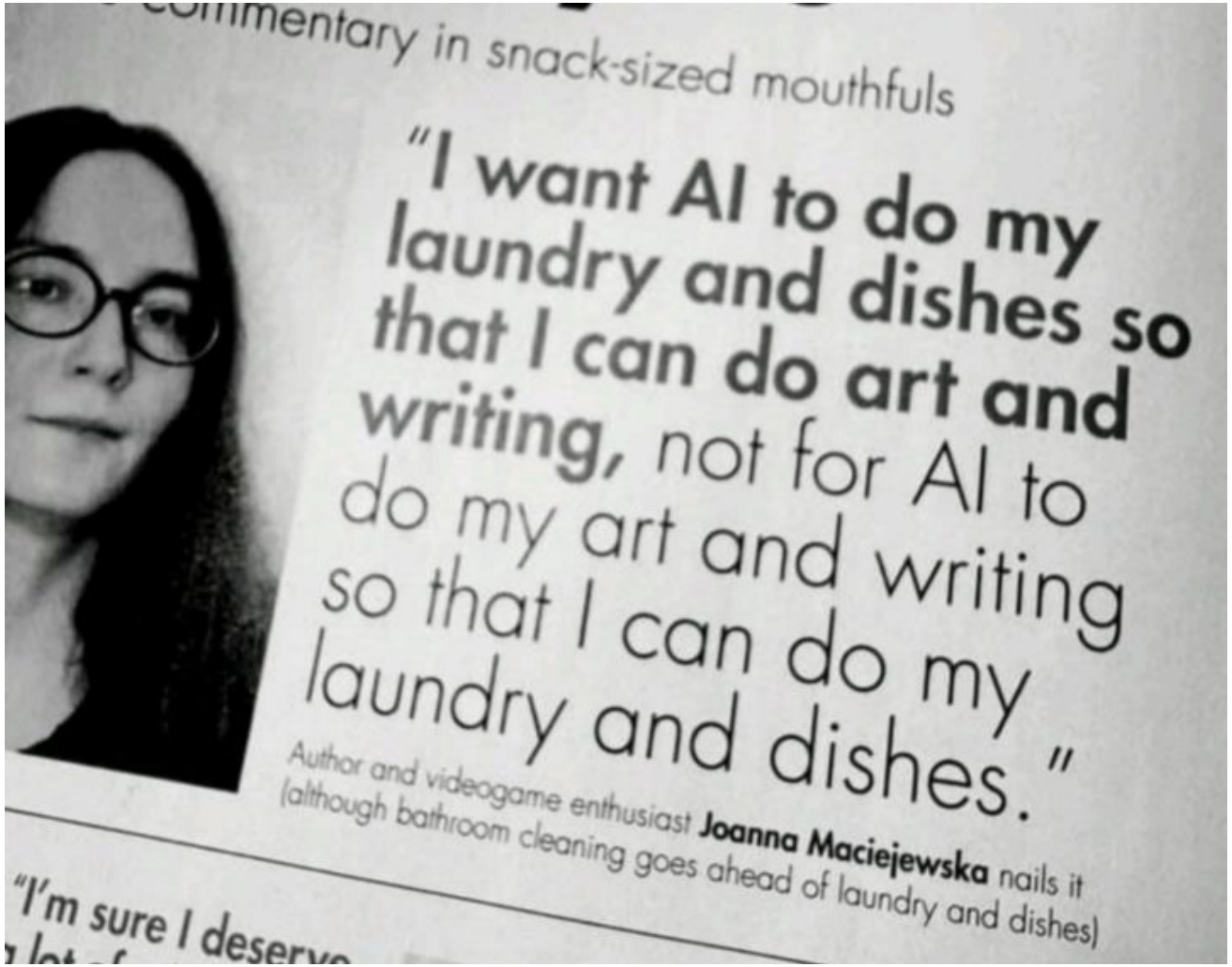
Adelphi

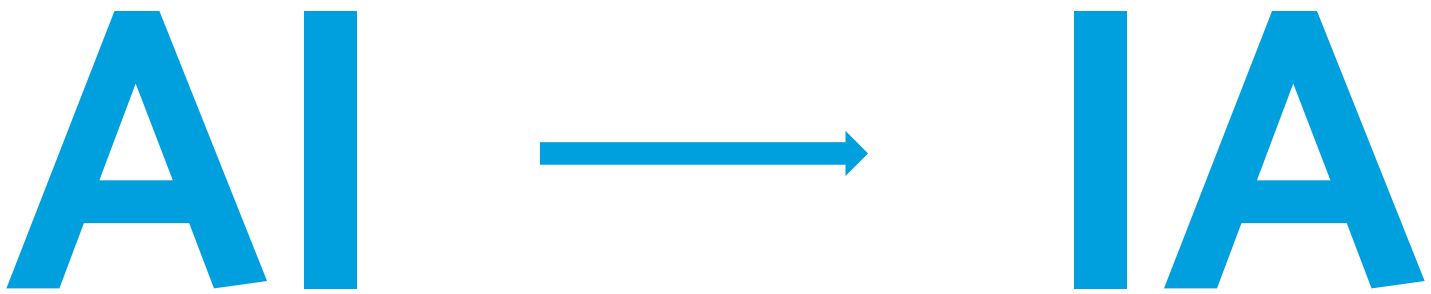
synerscope

ÖSSUR
LIFE WITHOUT LIMITATIONS

Generative AI

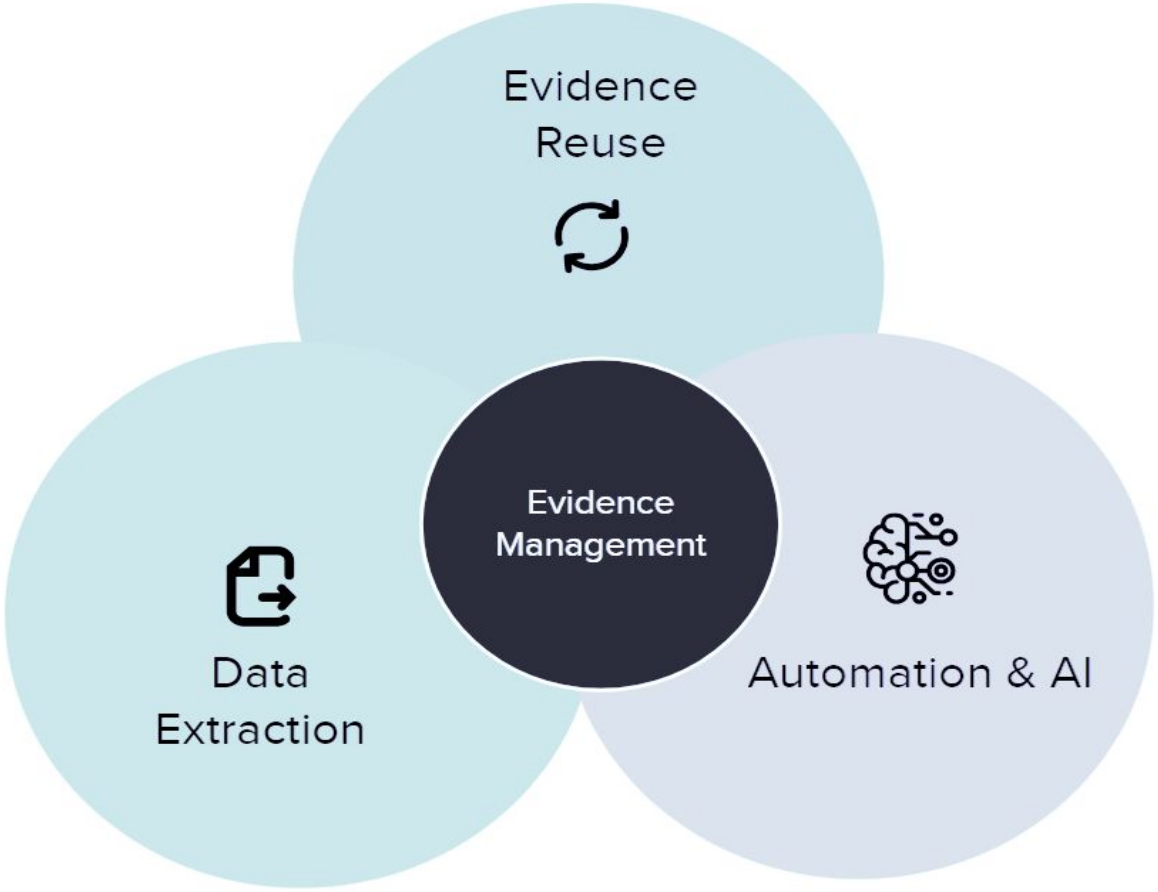
Large Language Models





Intelligent automation (IA)–artificial intelligence (AI), business process management (BPM) and robotic process automation (RPA)–to streamline and scale decision-making across organizations.

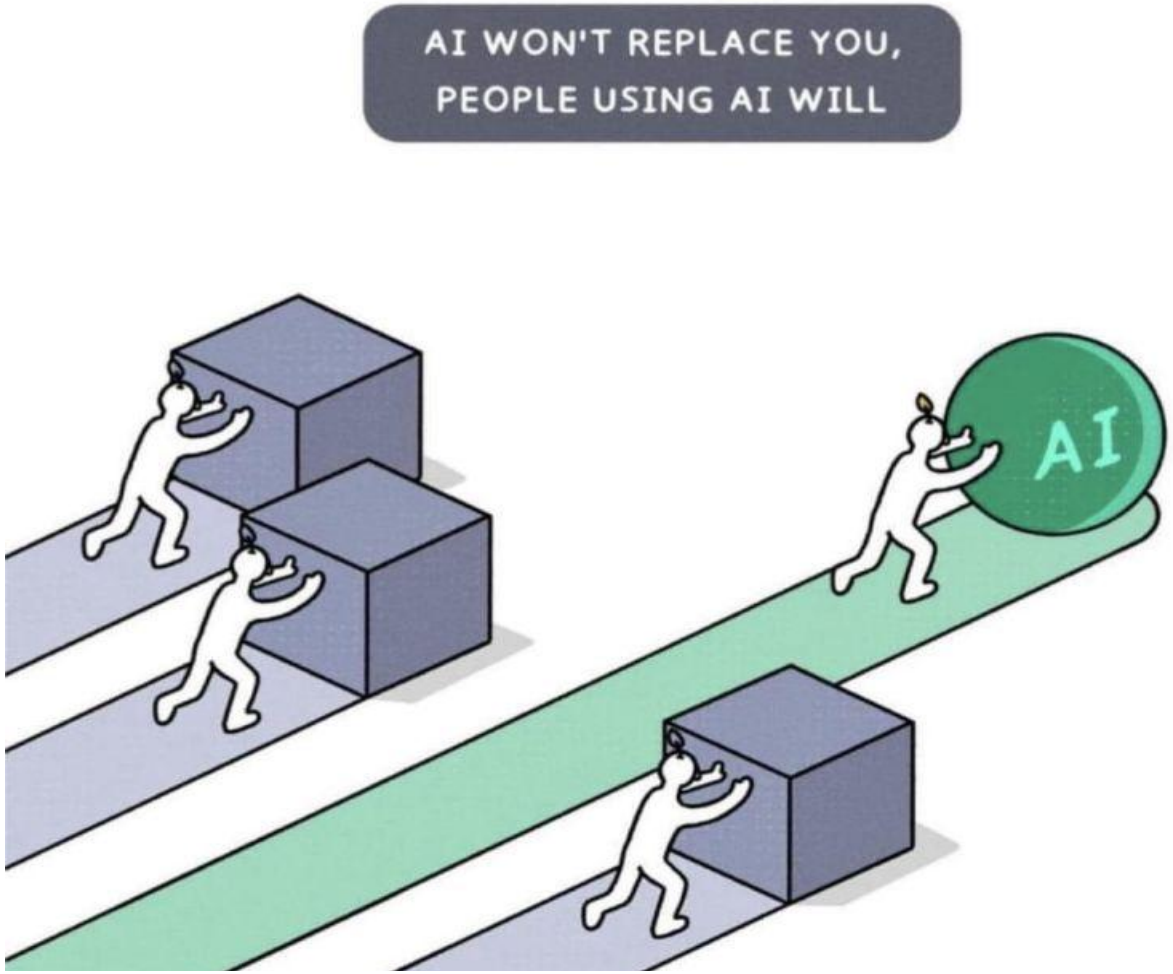
IA and Evidence Management: Three Pillars



AI in Literature Reviews

Considerations

- How will you integrate AI into your processes?
- Are your teams already using it?
- Do you have the technical resources to conduct your own R&D?
- Build vs Buy
- Domain specific models
- Training Data
- Validation
- Bias in models
- Quality due to researcher fatigue
- Policies and Guidelines
- Copyright
- Data Security



Best Practices for RWE in EU and US Markets

Amelia Hufford,
Co-founder and SVP, Clinical and Regulatory Science Operations at 3Aware

Wendy Pierce, Phd,
Senior Clinical Research Program Manager, Peripheral Vascular Health at Medtronic

What is RWD and RWE?

Real World Data (RWD) is defined as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- Electronic Health Records
- Product & Disease Registries
- Medical Claims & Billing data
- Patient generated data e.g. in home-use settings
- Wearables & Mobile Technology

Real World Evidence (RWE) is defined as the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.

FDA Guidance, *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*, August 2017

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DistillerSR AKRA TEAM 3Aware

Medtronic
Engineering the extraordinary

Use of RWE for EU MDR PMCF

Best Practices for RWE in EU & US Markets

Wendy Pierce, PhD, PMP
3Aware | DistillerSR | AKRA Team | MedTech Event
June 5th, 2024

Agenda

1. Utilization of RWE
2. Supporting Guidance for RWD
3. Challenges of RWD
4. Assessing RWD Source

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Utilization of RWE

Regulatory Decisions

- Premarket Authorization
  - Indication expansion
  - Line extensions
- Post Market Surveillance
  - Ongoing surveillance

Product Development

- Supplement preclinical data
- Support new Marketing Claims
- Inform clinical trial design

Publications & Presentations

- Enhance Awareness
- Education

Health Economics

- Reimbursement
- Economic Analysis

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Why choose RWD?

To meet the EU MDR objectives, RWD is a good option as part of cumulative body of evidence for Clinical Evaluation. Offers practical advantages and representative data.

Practicality: Confirm safety & performance in a cost efficient and timely manner, which is not practical with investigations.

Representation: Illustrative of actual clinical use e.g. procedural outcomes, device usage, human factors like experience, infrastructure setting.

Practicality: Difficult to ethically justify randomization or no treatment for rare or deadly diseases. Costly and time-consuming to recruit for such diseases.

Representation: Exposure to larger populations & subgroups, increasing heterogeneity to mitigate narrow scope & selection bias in investigations.

Practicality: Offer insights for devices with limited premarket clinical evidence or uncommon use e.g. orphan & supportive devices, device iterations, pediatric use.

Representation: Inform on new benefits or emerging risk profiles, Unknown Side effects, Misuse or Off-label use.

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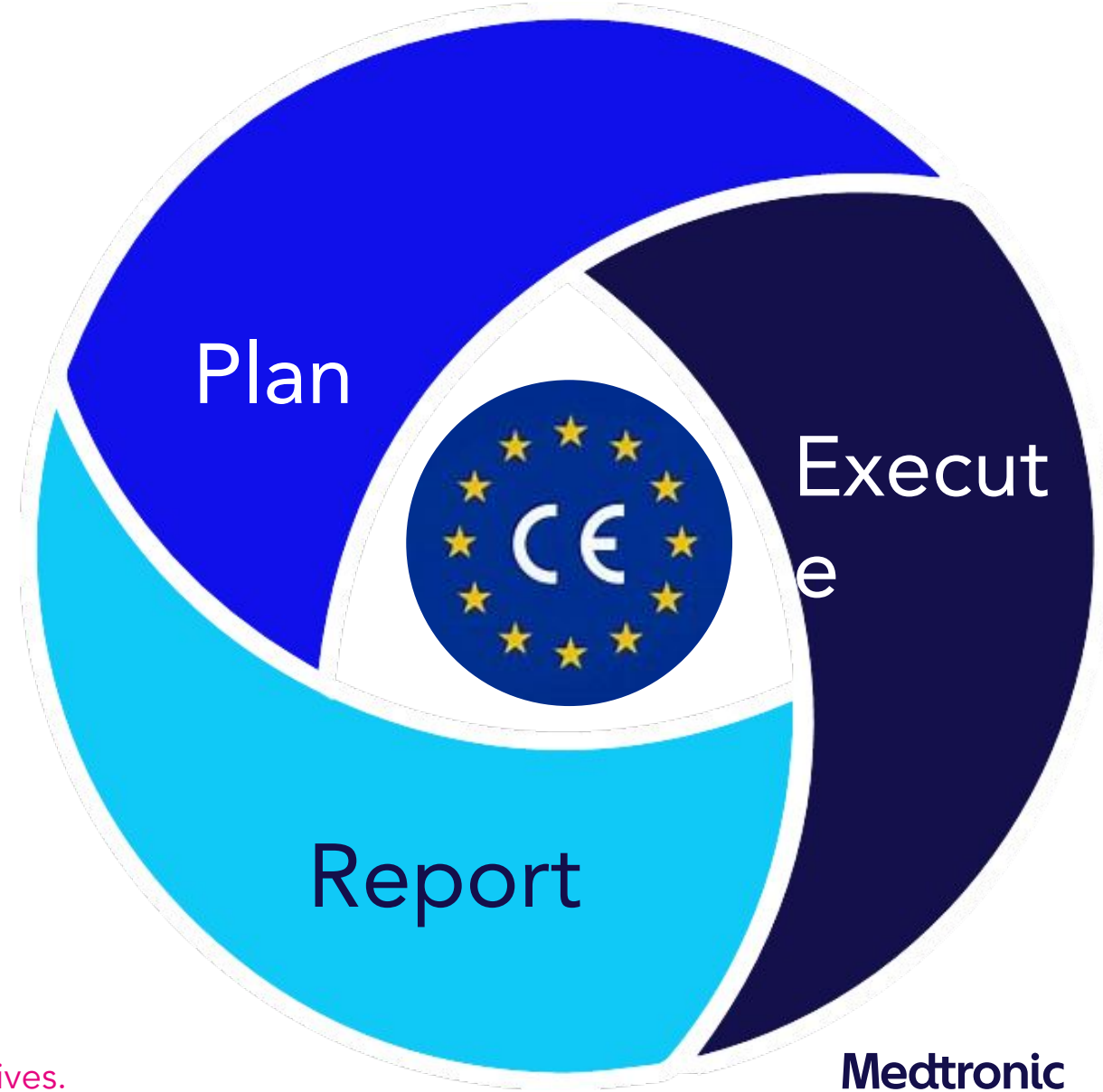
Clinical Evaluation Cycle

Post Market Clinical Follow-Up (PMCF)

PMCF shall be understood to be a continuous process that updates the clinical evaluation and shall be addressed in the manufacturer's post-market surveillance plan. When conducting PMCF, the manufacturer must proactively collect clinical data from the use in or on humans of a device which bears CE marking and is placed on the market or put into service within its intended purpose as referred to in the relevant conformity assessment procedure, with the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and detection of emerging risks on the basis of factual evidence.

MDR Text, Annex XIV Part B (5)



Under MDR, manufacturers are expected to commit to PMCF.
RWD/E is a source for actual clinical use to support these objectives.

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No explicit guidance but there are extrapolations or call-outs for RWD/E. Guidance outlined for PMCF data.

Supporting Guidance under EU MDR

MEDDEV 2.12/2 Rev 2

- Describes the design and methodologies that should be considered, as well as how obtained study data should be analyzed and utilized to provide clinical evidence for medical devices
- "Manufacturer should consider the data available from clinical investigations, PMCF studies, registries or other systematic studies ….."
- Systematically identify aspects during post-market surveillance e.g. in PMCF Studies including "estimation of residual risks and uncertainties or unanswered questions (such as rare complications, uncertainties regarding, long-term performance, safety under wide-spread use)"

MDR Text, Annex XIV Part B (5)

- Manufacturers are expected to "proactively collect and evaluate clinical data from the use in or on humans of a device which bears the CE marking…"
- Emphasis on long-term clinical data with "the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and detection of emerging risks on the basis of factual evidence."

MDCG Guidance 2020-7

Activities related to PMCF:

- "Planned RWE analyses could be indicated in this section, together with a summary of the plan including the design, sample size, the endpoints, and analysis population."
- " RWD from which these analyses are based on should be of sufficient quality and come from reliable sources."

MDCG Guidance 2020-6

- Provides hierarchy of data & evidence which includes registries and high-quality surveys.
- Indirect clinical benefits may be demonstrable by other evidence such as RWD e.g. registries, information deriving from insurance database records, etc."

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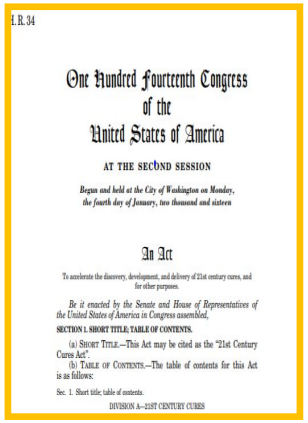
United States Regulatory Activity for Real World Evidence

December 2016



H.R. 34

One Hundred Fourteenth Congress of the United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Monday, the fourth day of January, two thousand and sixteen

An Act

To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "21st Century Cures Act".

(b) TABLE OF CONTENTS.—The table of contents for this Act is as follows:

Sec. 1. Short title; table of contents.

DIVISION A—21ST CENTURY CURES

21st Century Cures

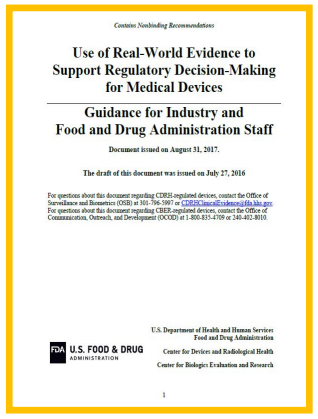
Accelerate medical product development and approvals

FDA shall establish an RWE Program to support:

(1)Approval of new indication for a drug approved under section 505(c)

(2)Satisfy post-approval study requirements for drugs

August 2017



Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHOfficeofEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

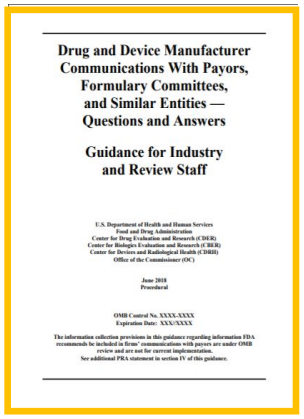
FDA RWE Guidance For Medical Devices

FDA RWE Guidance for medical devices

Expanded indication, post-market surveillance, post-approval studies, control group, supplementary data

RWD must have sufficient quality to support regulatory use case

June 2018



Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities — Questions and Answers

Guidance for Industry and Review Staff

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of the Commissioner (OC)

June 2018
Procedural

OMB Control No. XXXX-XXXX
Expiration Date: XXX/XXXX

The information collection provisions in this guidance regarding information FDA recommends be included in firms' communications with payors are under OMB review and are not for current implementation. See additional PRA statement in section IV of this guidance.

FDA Communication

FDA discusses what is considered "competent and reliable scientific evidence" to support health care economic information, and states that it will look to existing good research practices of various professional

December 2018

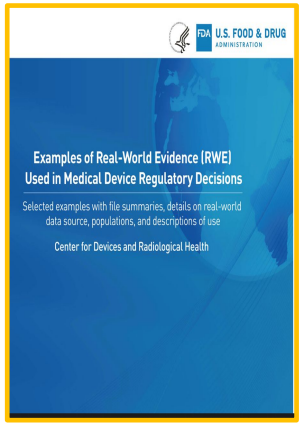
FDA RWE Evidence

In response to 21st Century Cures (RWE Program for drugs)

Describes priority areas, remaining challenges and potential pilot opportunities

Defines RWE, RWD, and outlines FDA thinking on assessing fit for purpose and application

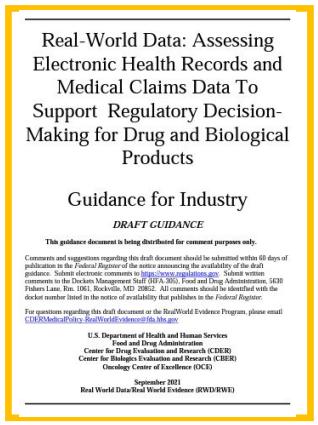
March 2021



FDA Examples of RWE for Med Device Reg Sub

Most common examples were to supplement PMS or indication expansion with sources from registries and admin claims. Less common examples were EHR retrospective chart review for new submission and to support digital health tech and pediatric patients.

September 2021



Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document or the RealWorld Evidence Program, please email CDRHMedicalPolicy-RealWorldEvidence@fda.hhs.gov

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

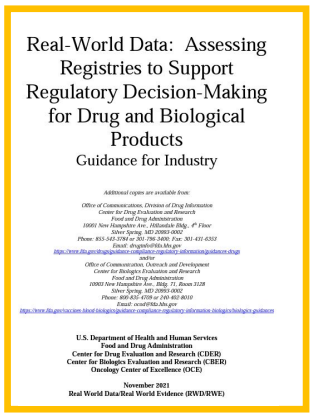
September 2021
Real World Data/Real World Evidence (RWD/RWE)

FDA Assess EHR and Claims data for Reg

These data are widely used in safety studies and increasingly being proposed for use in effectiveness studies.

Topic covered: Selection of data source; development and validation for study design elements; data provenance and quality during accrual, curation in into final dataset

November 2021



Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communications, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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

November 2021
Real World Data/Real World Evidence (RWD/RWE)

FDA RWD Guidance Drug and Biologics

FDA RWE Guidance for medical devices

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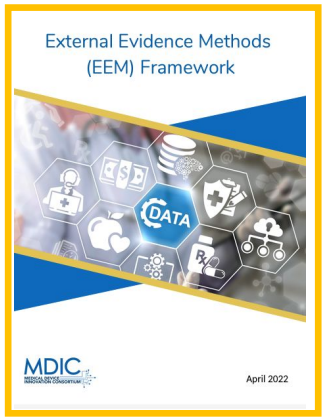
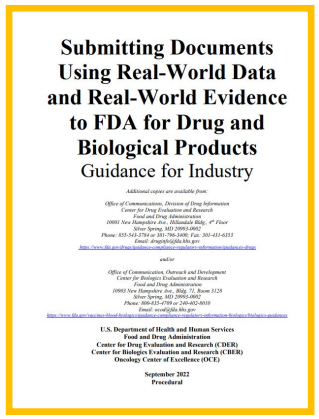
United States Regulatory Activity for Real World Evidence Assessment

April 2022



EEM Framework

September 2022



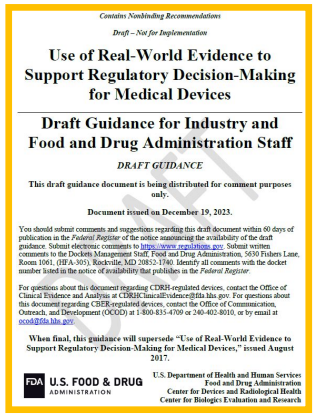
Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products
Guidance for Industry

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

September 2022
Procedural

FDA Drug and Biologics: Submitting Documents Using RWD and RWE

December 2023



Contains Nonbinding Recommendations
Draft – Not for Implementation

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on December 19, 2023.

When final, this guidance will supersede "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," issued August 2017.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

FDA RWE Guidance For Medical Devices

…

…

…

XXX

…

XXX

FDA will track: -RCTs using RWD clinical outcomes for safety or effectiveness, -single arm trials with RWD external control arms, -Observational studies with RWE that support an efficacy supplement, RWD or RWE study that fulfill a post market requirement or commitment.

For full list: FDA Guidance Documents Online, *https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch*

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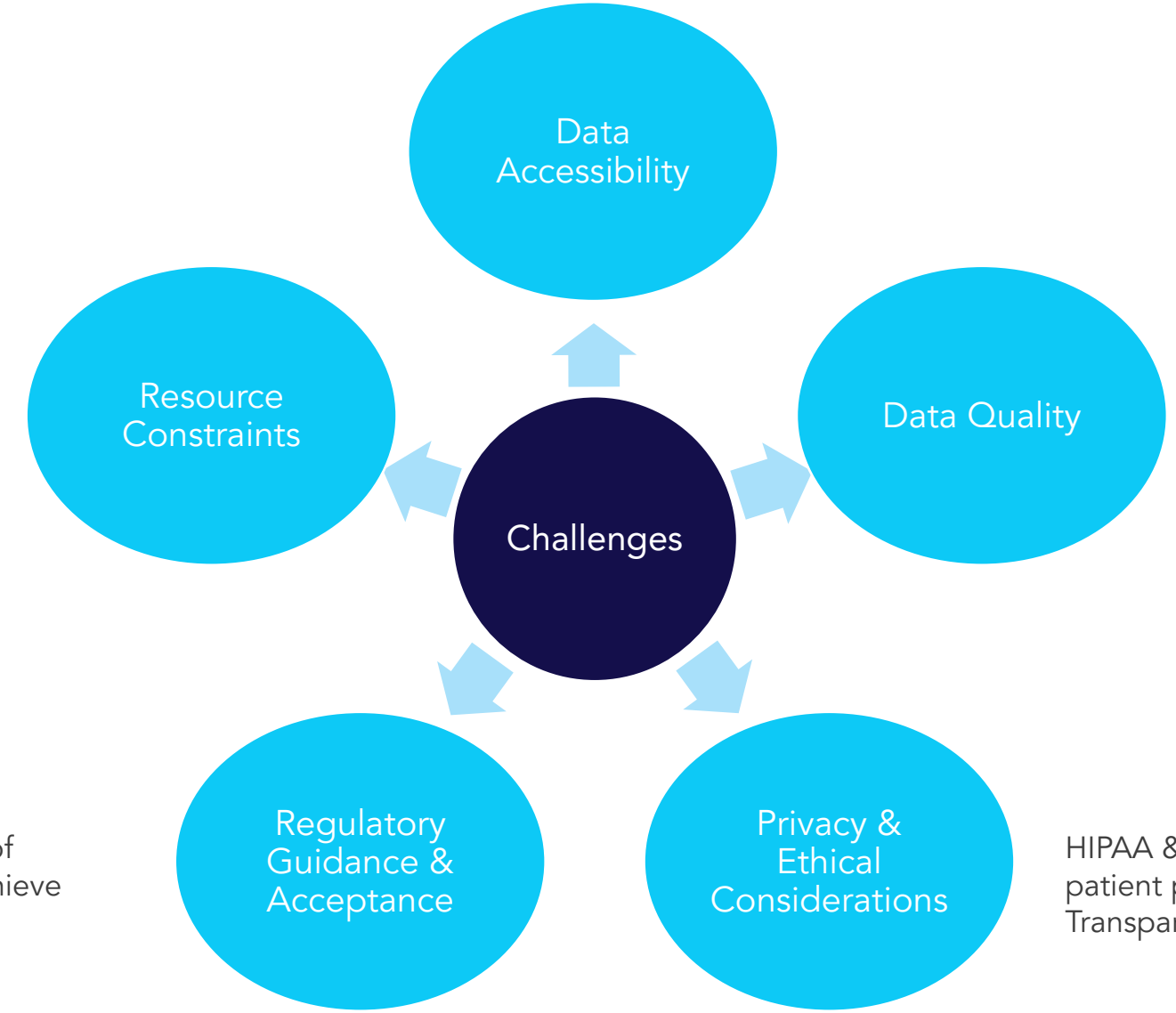
Challenges of RWD

What is your data source?



Funding, expertise, networks

Disparate sources with different formats, terminology, completeness, standard of care. Difficult for analysis.

Evolving understanding of requirements that will achieve acceptance

HIPAA & GDPR safeguards to protect patient privacy & maintain security. Transparency of data use and rights.

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Best Practice for Sourcing RWD

Strategic Considerations of Sourcing RWD

Scope

Purpose of data, Data elements of interest, Dissemination

Quality

Is data fit- for-purpose? Relevance and Reliability checks

Operations

Resources availability

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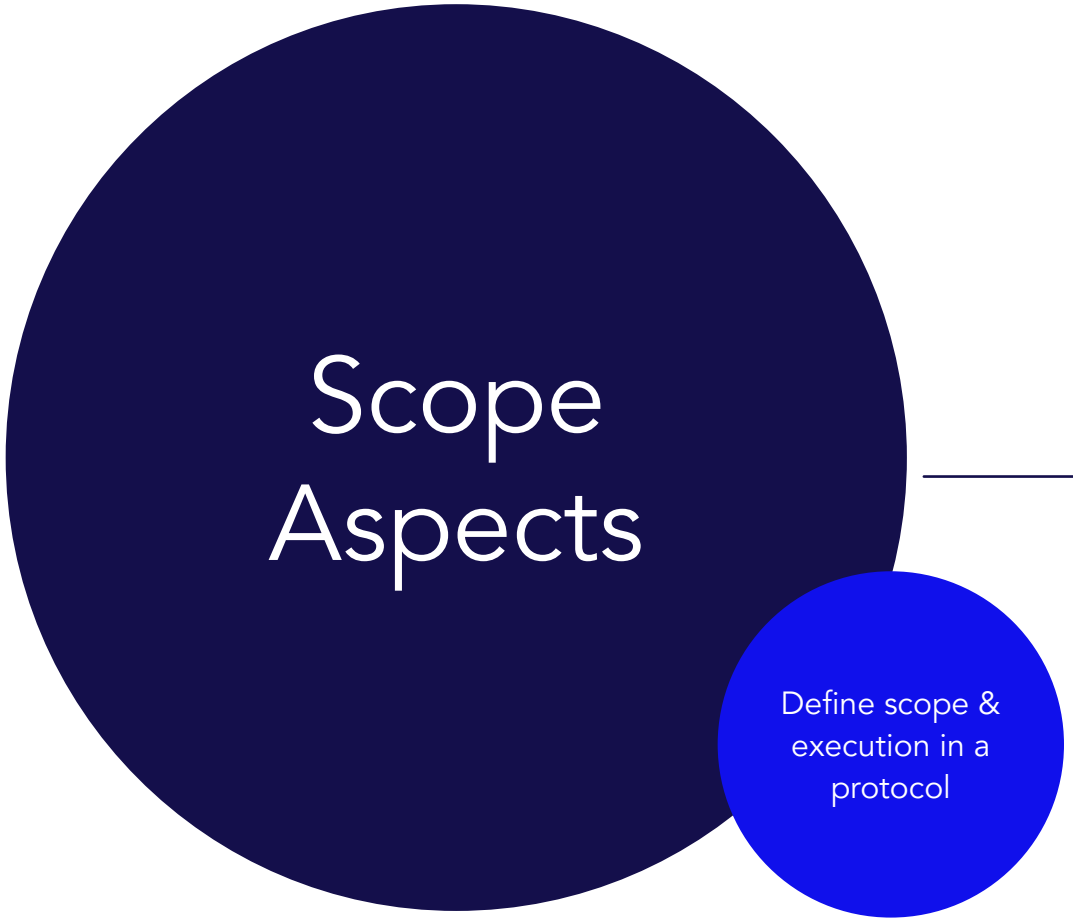
DistillerSR AKRA TEAM 3Aware

Strategic Considerations of Sourcing RWD



Purpose of data

- Define what you intend to use the data for

Data Elements of Interest

- Outline data elements needed to answer the research question
- Determine which elements are mandatory vs optional

Dissemination Plan

- State how data reports will be used

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Strategic Considerations of Sourcing RWD

Relevance

- Availability of data elements to answer the research question in the clinical context of interest
- Transferability

Reliability

- Patient-level data
- Quality Control & Assurance – Representative of intended underlying medical concepts and considered credible & trustworthy

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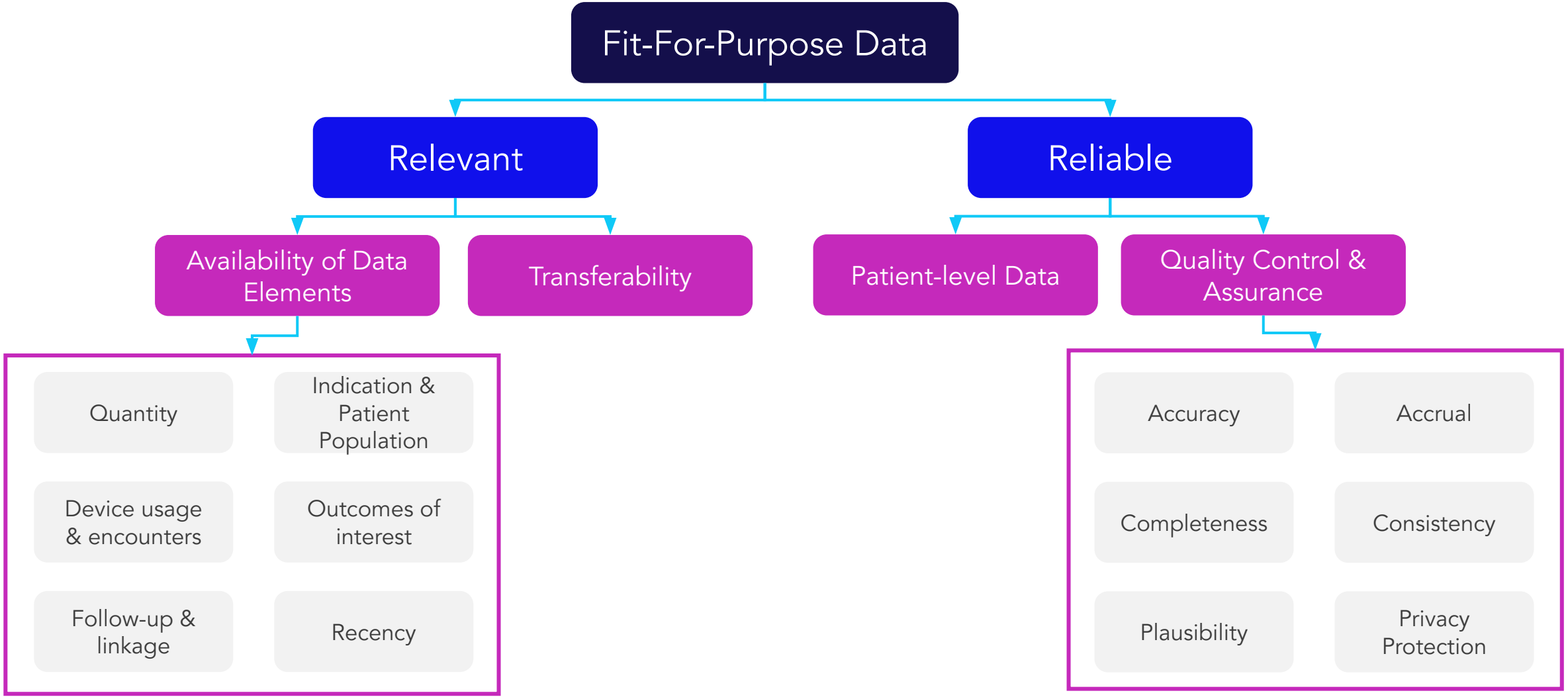
Assessing RWD Quality



FDA Guidance, *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*, August 2017, 2023
Duke-Margolis, *Determining Real-World Data's Fitness for Use and the Role of Reliability*, September 2019
Gatto, *The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework*, June 2021

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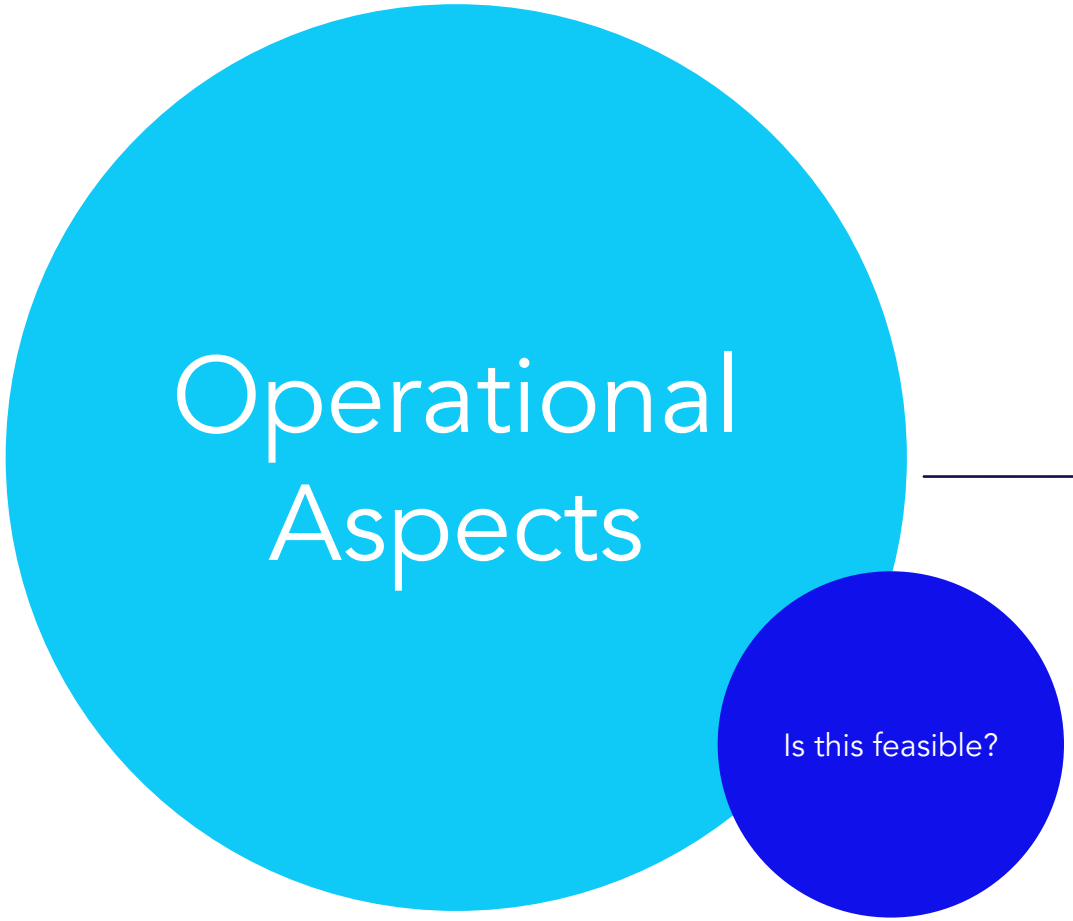
Strategic Considerations of Sourcing RWD



The right source

- Data access and availability
- Data Privacy & Security considerations – protection of patient data, infrastructure
- Institutional assessments and qualification
- Contracting logistics

Timeline

- On time access & delivery
- Sustainability especially for long-term outcomes

Cost

- On budget delivery
- In-house resources

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Best Practice for Sourcing RWD

Strategic Considerations of Sourcing RWD

Scope

Purpose of data, data elements of interest, dissemination

Quality

Is data fit- for-purpose? Relevance and Reliability checklist

Operations

Resource availability

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74M+

Patients served whose lives have been improved by Medtronic therapies in the past year

That's **two people every second** of every hour of every day – and counting.

We aim to sustain quality products on the market to allow patients to live fuller lives.

Thank you

DistillerSR AKRA TEAM 3Aware

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A Breakthrough Approach to Real-World Data

The Future of Electronic Health Record Data in Clinical Research

Amelia Hufford, PhD

Senior Vice President, Clinical and Regulatory Science

3Aware, Indianapolis, Indiana

3Aware

Case study - direct access to RWD in an analytic platform successfully met PMCF needs

- Cohort of interest, including rare indications, was quickly identified
- Depth and longitudinal access of data met each of the study owner’s required data elements and follow-up
- Safety and performance rates were in line with the state of the art
- Study executed within 6 months

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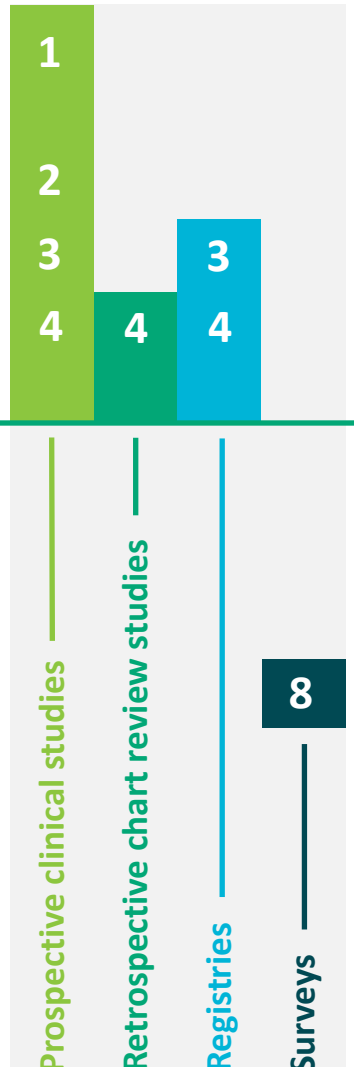
MDCG 2020-6 outlines a hierarchy of clinical evidence



Rank	Type of clinical data
1	Results of high-quality clinical studies covering all device variants, indications, patient populations duration of treatment effect, etc.
2	Results of high-quality clinical investigations with some gaps
3	Outcomes from high quality clinical data collection systems such as registries
4	Outcomes from studies with potential methodological flaws but where data can be quantified, and acceptability justified
5	Equivalence data (reliable / quantifiable)
6	Evaluation of the SOTA, including evaluation of clinical data from similar devices
7	Complaints and vigilance data
8	Proactive PMS data (e.g. surveys)
9	Individual case reports on the subject device
10	Compliance to non-clinical elements of common specifications considered relevant to device safety and performance
11	Simulated use / animal / cadaveric testing involving end users
12	Pre-clinical and bench / compliance to standards

Truncated from MDCG 2020-6 Appendix III

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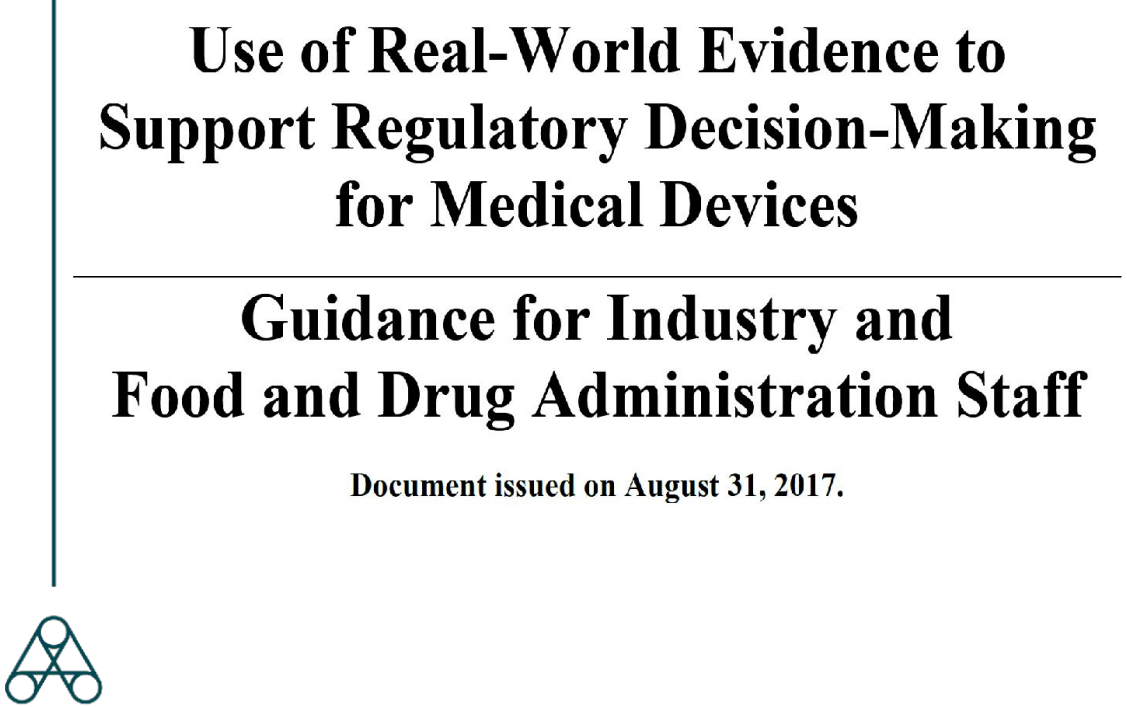
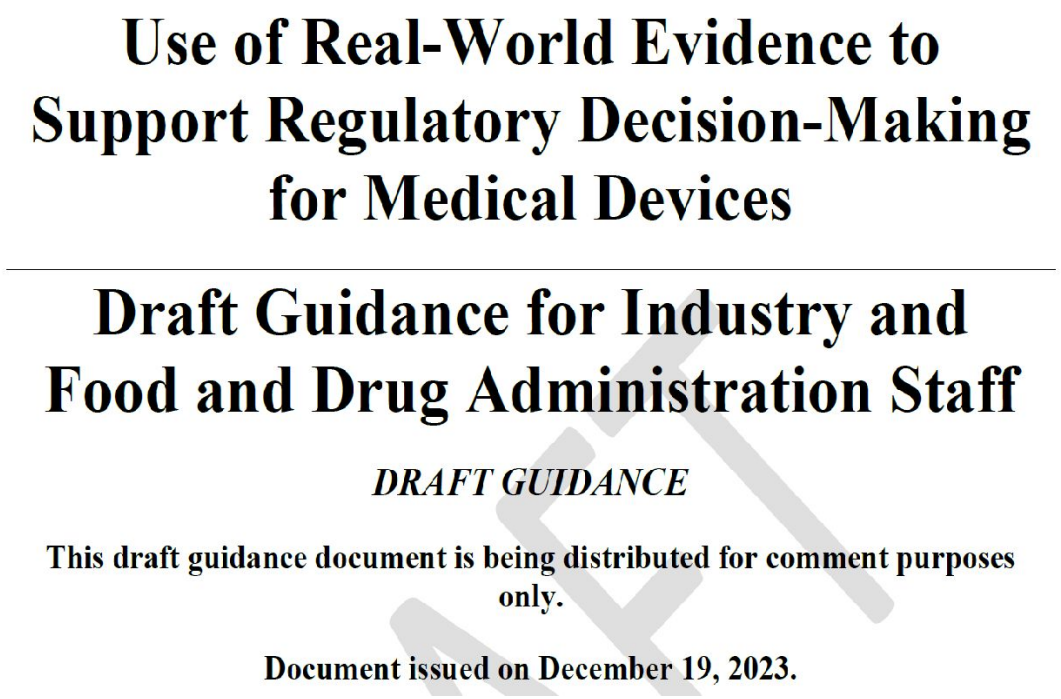
US FDA guidance is the most comprehensive resource currently available



Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.



Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on December 19, 2023.

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Refer to US FDA's current recommendations for data relevance, reliability and methodology

- FDA has greatly expanded their recommendations for how to assess **data relevance, reliability, and methodologies for collection and analysis of RWE**
  - Fourteen pages on just these topics
  - Plus additional information on fit-for-purpose assessment, RWD study protocol, and study report
  - Appendix A is a checklist for recommended elements to include in regulatory documentation
  - Appendix B are examples of how RWE has been successfully used

- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-use-real-world-evidence-support-regulatory-decision-making-medical-devices

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Europe is a little different

- The EU MDR does not explicitly reference RWD or RWE, and MDCG guidance rarely refers to them
- **HOWEVER,** EU MDR allows for the use of multiple clinical data sources if **scientifically valid** methodologies used to generate clinical data are **reliable and robust**
- MDCG 2020-6 *Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC* states that "indirect clinical benefits may be demonstrable by other evidence such as **real-world data**"
- **AND** MDCG 2020-7 *Post-market clinical follow-up (PMCF) Plan Template A guide for manufacturers and notified bodies* references **RWE analyses as a type PMCF strategy**, and the RWD "from which these analyses are based on **should be of sufficient quality and come from reliable data sources**"

3Aware

Utilization of RWE for regulatory decision making for medical devices is a world-wide movement following pharma's lead

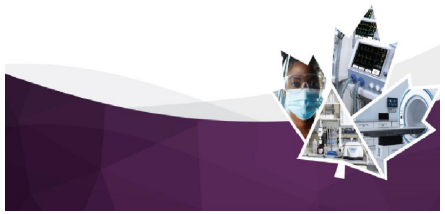
FDA

NEST Coordinating Center
An initiative of MDIC

National Evaluation System for health Technology Coordinating Center (NESTcc) Data Quality Framework

Health Canada Santé Canada

Guidance on clinical evidence requirements for medical devices



Government of Canada Gouvernement du Canada

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Elements of Real World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle

Updated: March 5 2019

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

DARWIN EU

CORE-MD
Coordinating Research and Evidence for Medical Devices

国家药品监督管理局
National Medical Products Administration

pmda 独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

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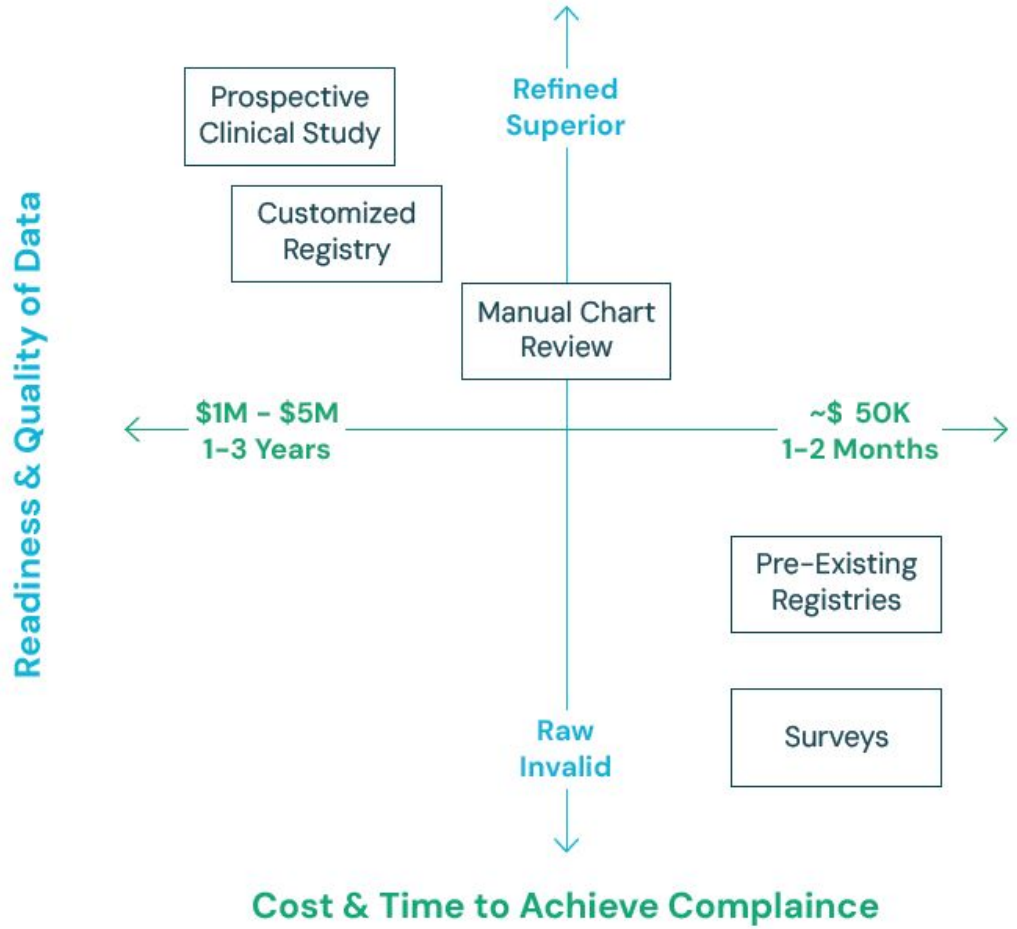
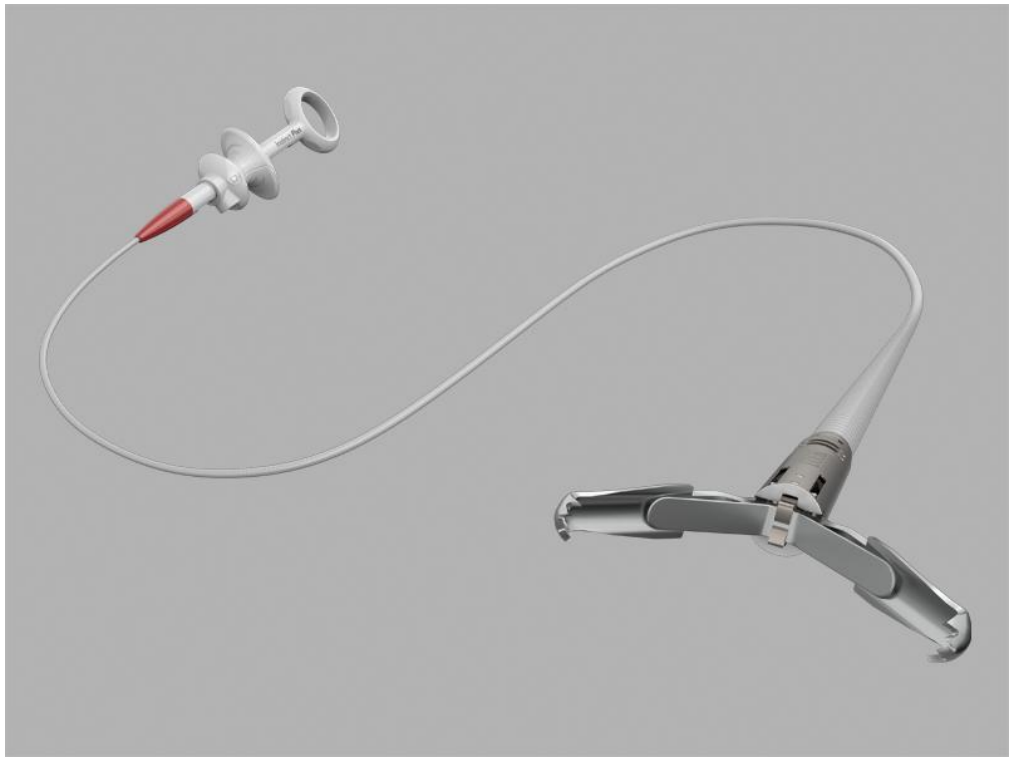
Long term evidence strategy requires refined, high-quality data at a fraction of the cost and time of traditional methods



3Aware

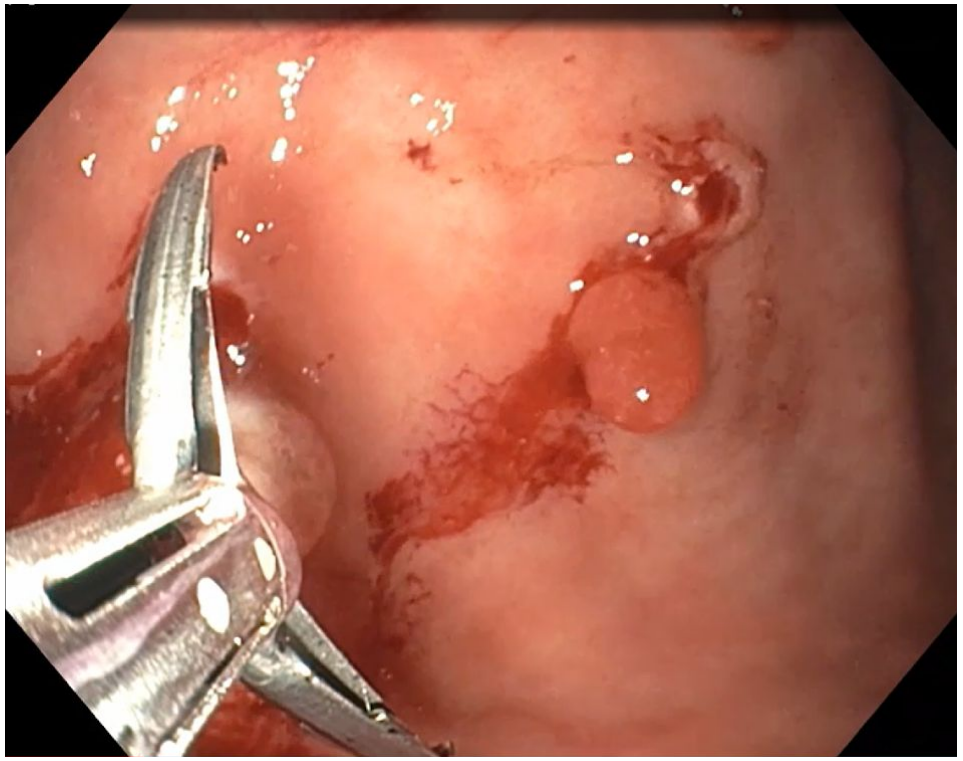
Case study – direct access to complete EHR data in executing a PMCF study

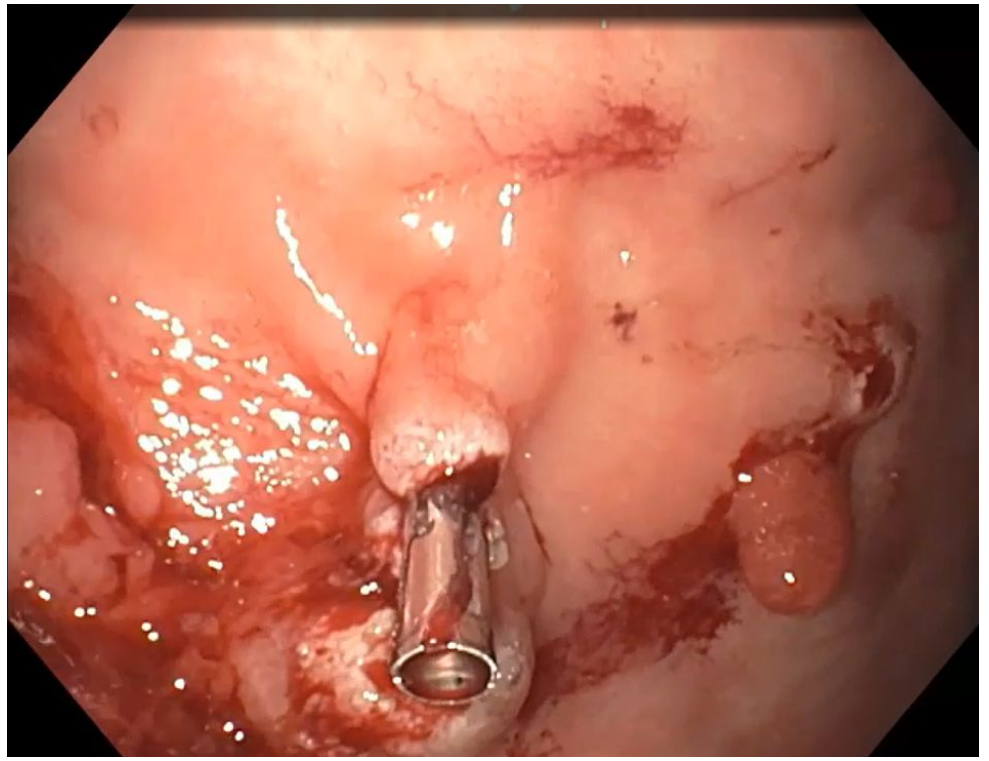
- Class IIb implant
- This device is used for endoscopic clip placement within the gastrointestinal tract for the purpose of:
  - Endoscopic marking,
  - Hemostasis,
  - Prophylactic clipping,
  - Anchoring to affix jejunal feeding tubes to the wall of the small bowel,
  - As a supplementary method for closure of GI tract luminal perforation less than 20mm that can be treated conservatively,
  - Anchoring to affix fully covered esophageal self-expanding metal stents to the wall of the esophagus in patients with fistulas, leaks, perforations, or disunion.



3Aware

Endoscopic hemoclips are commonly used to prophylactically clip a post-polypectomy wound





Images courtesy of Dr. Shou Jiang Tang, The University of Mississippi Medical Center, Jackson, MS

3Aware

Case study – direct access to complete EHR data in executing a PMCF study

- Must collect data across all clinical uses
- Longitudinally follow patients through 30 days post-index procedure
- Required data elements
  - Demographics and relevant medical history
  - Anatomic location of clip deployment
  - Successful delivery and deployment of the endoscopic clip (yes/no)
  - Number of clips used in procedure
  - Use of adjunctive/combination treatments (yes/no)
  - Device malfunction or use error (yes/no)
  - Clinical success (yes/no) by indication
  - Procedural complications
  - Post-procedural complications through 30-days and mortality

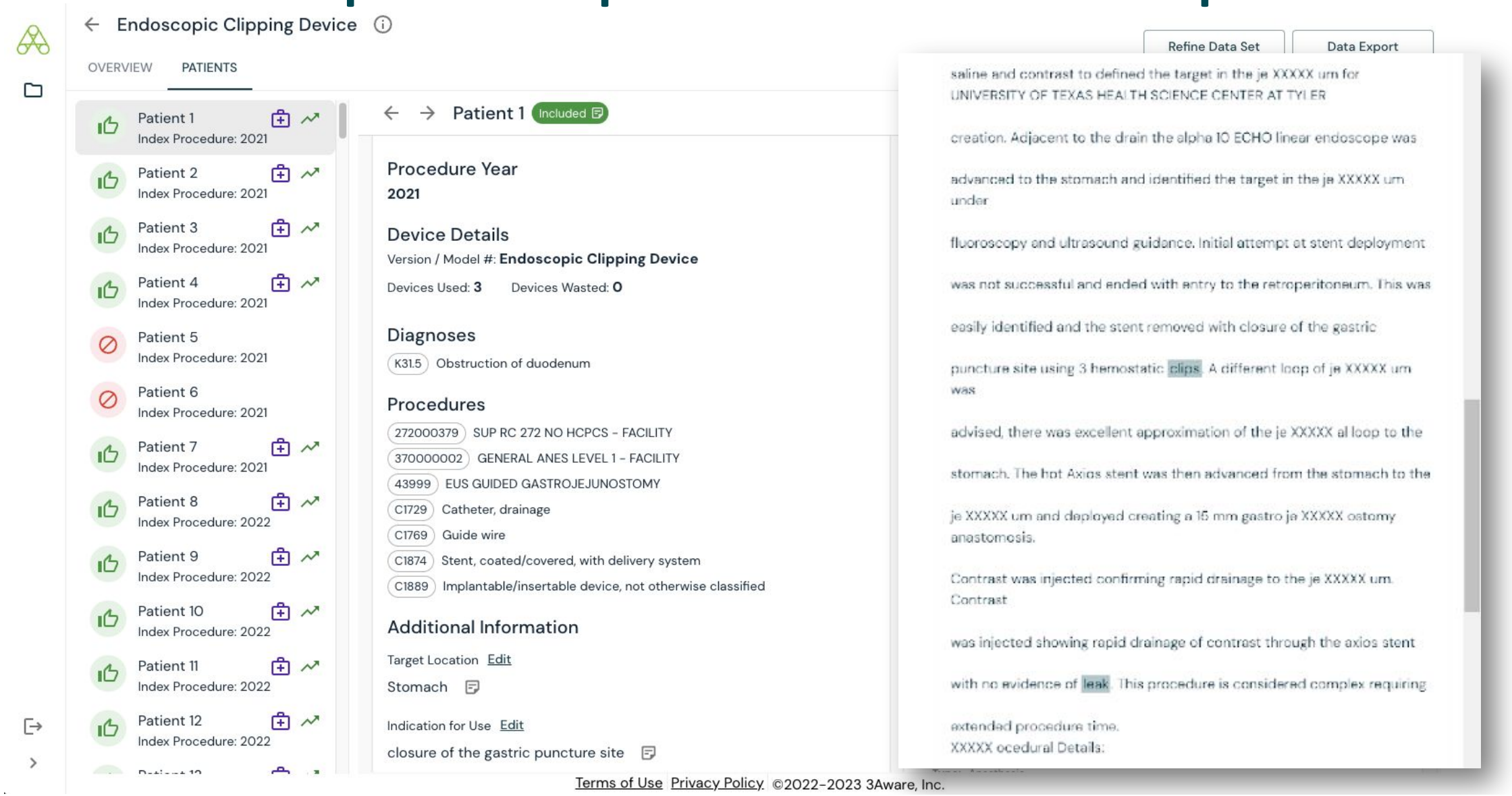
3Aware

Each indication consisted of separate clinical and safety definitions

Indication	Clinical success	Safety
Endoscopic marking	Identify lesion; Clip retained at target	Adverse events associated with clip placement (injury/perforation/bleeding)
Hemostasis	Initial hemostasis	Rebleeding
Prophylactic clipping	Delayed bleeding	Adverse events associated with clip placement (injury/perforation/bleeding)
Anchoring feeding tube	Migration of feeding tube	Bleeding Tube stuck at removal Aspiration pneumonia at removal Bleeding PEG Perforation PEG
Supplementary method for luminal perforations	Closure of perforation; Placement of clips	Small leaks due to inadequate sealing Premature dislodgement Mucosal injury Deployment malfunction
Anchoring metal stents	Stent migration rate	Bleeding Perforation Recurrence of initial disease Intolerance of food intake

3Aware

Access to complete data prevents incorrect assumptions



3Aware

DistillerSR AKRA TEAM 3Aware

Direct access and analysis of comprehensive EHR data delivered relevant, high-quality RWE for PMCF

- Required samples of patients across all indications were quickly identified and included
  - Access to only structure data would have resulted in miss-identification of indications
- Complications, adverse device effects and performance failures were easily uncovered within the unstructured data
  - Rates aligned with SOTA
- Export of patient-level data in CSV format allowed for analysis via SAS
- PMCF study was completed in 6 months

3Aware

Relevant, high-quality RWE in less than half the time and effort

- Study Duration:

Study Execution Type	Study Duration (months)
Chart Review	15
3Aware	6

- Level of Effort:

Study Function	Chart Review (FTE hours)	3Aware (FTE hours)
Clinical Project Management	172.55	42
Clinical Safety	110.75	85.5
Clinical Science	107	153
Data Management and Statistics	260.75	114.5
Legal	49.25	0
Reimbursement	1.75	0
Quality Assurance	13	3.5
Total	**715.05**	**398.5**

3Aware

The 3Aware process ensures success

- 3Aware Clinical Scientists work with device/study owner to learn about device, study objectives, desired data elements, and minimum sample size
- 3Aware Data and Clinical Scientists then execute a feasibility study to evaluate the presence and depth of data within patient records treated with a study owner's device of interest
- 3Aware will present the results of the feasibility study, and if all criteria are met, the full project can be immediately initiated
- Total time required from start to device-specific patient data ready in the platform is less than 1 month
- Once project commences, the 3Aware clinical team supports the study owner per their requirements, for the duration of analysis, and through any regulatory feedback

3Aware

Summary

- MedTech requires an operationally sustainable approach to long-term clinical data collection
- Depending on the source, RWE may constitute valid scientific evidence that is sustainable
- A combined data science/ clinical science approach was used to execute a PMCF study on a class IIb implant device
- Access to unstructured notes is crucial in assessing the safety and performance of medical devices
- Compared to traditional chart review studies, 3Aware provided more data on rarer indications, uncovered complications and performance failures more in line with SOTA, and reduced the overall time and effort by over 50%

3Aware