CROMSOURCE
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REGULATORY

NEWSLETTER N.42
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Including the latest updates on the EU CTR

CROMSOURCE, a ClinChoice company, is an international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialised in clinical development and staffing solutions.

Contents

MEDICINAL PRODUCTS/DRUGS

Europe

News from the European Medicines Agency (EMA)

EMA Annual Report for 2022 - Regulatory Highlights

The European Medicines Agency (EMA) has published its Annual Report for 2022, detailing the EMA key achievements and key figures in 2022. The report includes two chapters. Chapter 1 is highlighting the EMA evaluation and monitoring of medicines, involving the environment for clinical research in the EU and EMA Regulatory Network's response to public health emergencies. Chapter 2 provides figures for the EMA's human and veterinary medicines programs, for medical devices, inspections and compliance activities and others related to clinical trials and the EMA's various involved committees.

"Although we saw some return to more routine activities, largely thanks to the speed of scientific progress and the roll-out of effective vaccination campaigns across the EU, the COVID-19 virus continued to force us to pivot, innovate and adapt," said EMA's Executive Director Emer Cooke.

How to Approach the Protection of Personal Data and Commercially Confidential Information (CCI) while using the Clinical Trials Information System (CTIS) - Guidance Update

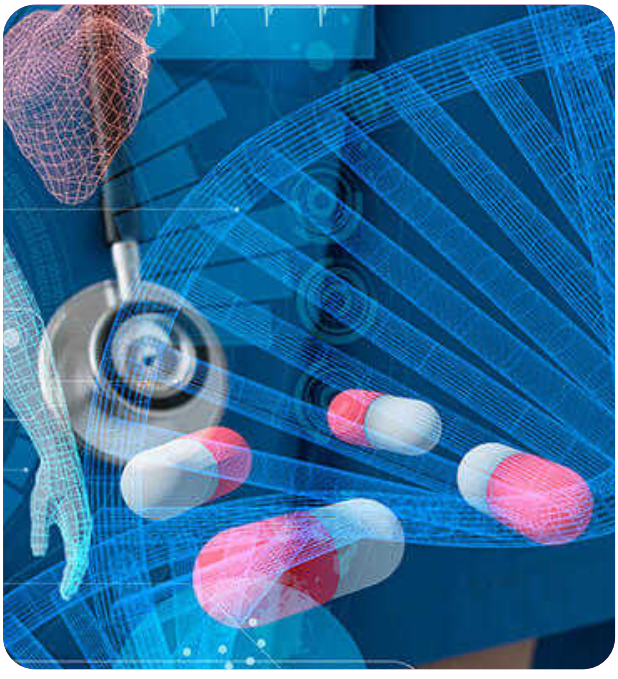
The EMA has updated Guidance document on how to approach the protection of personal data and CCI while using the CTIS, Version 1.1, 11 July 2023 and Annex I to this guidance. This Guidance document aims to help CTIS users to navigate through the system functionalities and understand the main principles to be followed to enable protection of personal data and commercially confidential information (CCI) while using CTIS and publishing clinical trials data and documents.

The following chapters provide information on:

- Description of the functionalities and publication rules for clinical trials information submitted to CTIS, consideration of deferrals, the steps if deferrals are not accepted (chapter 2).
- Principles to be followed on anonymisation of personal data in the document version 'for publication'; principles of pseudonymisation applicable in the version of documents 'not for publication' (chapter 3).
- Principles to be followed enabling protection of CCI as part of the clinical trial information submitted to CTIS, examples of what may be considered as CCI or would not qualify as CCI (chapter 4).
- The protection of personal data and CCI in inspection reports (chapter 5).

Transparency Rules for the EU Clinical Trials Information System (CTIS) – Under EMA Review

In May 2023, the EMA opened a public consultation to review the transparency rules for the publication of information on clinical trials submitted through the Clinical Trials Information System (CTIS) in the EU/EEA. Comments were collected from stakeholders via an online form by 28 June 2023. Finalisation of this guidance based on the current transparency rules is expected in the third quarter of 2023.



Questions and Answers (Q&As) on Data Protection

The European Commission, the EMA and the Heads of Medicines Agency (HMA) prepared a questions and answers document on the protection of Commercially Confidential Information (CCI) and Personal Data while using CTIS. Q&As guidance includes three main chapters related to Deferrals, Personal Data and CCI. It addresses several questions related to the transparency aspects of the CTIS which were communicated by sponsors.

In May 2023, the EMA published an update of these Q&A documents providing a clarification on deferrals in section 1, that clinical trials with a decision issued after mid-August 2022, for which sponsors have requested any type of deferrals in the application form are currently not published in CTIS. This is a temporary measure until EMA completes its public consultation on the functionalities of the public portal and implements its decisions accordingly. Moreover, new Q&A 3.3 has been added: How can details be protected from disclosure from CTIS for certain trials falling within category 2? In addition, Q&A 1.8 and Q&A 2.2 have been revised.

Guideline on Computerised Systems and Electronic Data in Clinical Trials

The EMA has published new Guideline on computerised systems and electronic data in clinical trials which will become applicable six months after publication on 9 September 2023.

This guideline is focusing on computerised systems used in the creation/capture of electronic clinical data and to the control of other processes with the potential to affect participant protection and reliability of trial data, in the conduct of a clinical trial of investigational medicinal products (IMPs). These include, but may not be limited, to the following:

- Electronic medical records;
- Tools supplied to investigators/trial participants for recording clinical data via data entry (e.g., electronic clinical outcome assessments [eCOAs], electronic trial participant data capture devices used to collect ePRO data, e.g., mobile devices supplied to trial participants or applications for use by the trial participant on their own device i.e., bring your own device (BYOD));
- eCRFs (e.g., desktop or mobile device-based programs or access to web-based applications), which may contain source data directly entered, transcribed data, or data transferred from other sources, or any combination of these;
- Tools that automatically capture data related to the transit and storage temperatures for investigational medicinal product (IMP) or clinical samples;
- Tools to capture, generate, handle, or store data in a clinical environment where analysis, tests, scans, imaging, evaluations, etc., involving trial participants or samples from trial participants are performed in support of clinical trials (e.g., LC-MS/MS systems, medical imaging, and related software);
- eTMFs, which are used to maintain and archive the clinical trial essential documentation;
- Electronic informed consent;
- Interactive Response Technologies (IRT);
- Systems/tools used to conduct remote activities such as monitoring or auditing;
- Computerised systems implemented by the sponsor holding/managing and/or analysing or reporting data relevant to the clinical trial e.g., clinical trial management systems (CTMS), pharmacovigilance databases, statistical software, document management systems, test management systems and central monitoring software;
- Artificial Intelligence used in clinical trials.

European Union Member State Public Holidays Recorded in CTIS for 2023

EMA has published a document with all official EU/EEA Member State public holidays for the year 2023 as recorded in CTIS. The timelines of each phase - validation, assessment, and decision - are set in calendar days and are visible in CTIS. The system takes into consideration weekends and a national holiday for the calculation of due dates in the system. A Request for Information (RFI) will not be issued by Member State Concerned (MSC) during weekends and when MS has national holiday. Timers are calculated starting from the next day following the creation of the task. All activities with a due date shall be due at 23:59:59 on that day in Central European Time (CET).

Clinical Trials Information System (CTIS) - Sponsor Handbook Updated

In April 2023, the EMA published version 3.02 of CTIS Sponsor handbook. Section 2.2.2. Organisation registration locally in CTIS for use in CTIS has been added explaining that sponsor organisations can be retrieved only from Organisation Management Service (OMS), but others such as third-party organisations, trial sites, details of the site where the serious breach occurred, third country inspection site can be registered locally in CTIS. Organisations that are created locally in CTIS are not validated by EMA. Section includes the link to the step-by-step instruction on how to register organisations locally in CTIS.

Moreover, the information about the multi-factor authentication (MFA) in CTIS has been added to section 2.1.1. MFA for user logins to CTIS, for both Sponsor and Member State workspaces have been launched on 1 June 2023. It is recommended that each user is equipped with a mobile or an office phone that can be used for second factor authentication. Instructions on setting up the MFA for EMA systems are available here.

CTIS Becomes a Data Provider for World Health Organization (WHO)

CTIS is now a registered data provider for the WHO. List of all data providers for the WHO is available here.

Data from authorised trials published on the CTIS website - excluding those with category 1 deferrals (Bioequivalence and Bioavailability trials and Bio-similarity trials) - is now included in the search portal of WHO's International Clinical Trials Registry Platform (ICTRP). This applies to relevant clinical trial data, as required by WHO, which has been published on CTIS since the launch of the system on 31 January 2022.

Note: Clinical trials with a decision issued after mid-August 2022 that have deferrals of any type in the application form are currently not published on CTIS. This is a temporary measure until the functionalities of the public portal are fully restored.

CTIS Latest Updates in the Clinical Trials Highlights

In April 2023, the EMA issued the 14th edition of the Clinical Trials Highlights. In this edition, the EMA explains commercial sponsors' perspective submitting clinical trials under EU CTR and using CTIS.

The document is focusing also on the recent improvements in CTIS, training material updates and CTIS upcoming events.

The edition presents four Accelerating Clinical Trials in the EU (ACT-EU) Priority Actions (PAs): Multi-stakeholder platform kick-off meeting date; GCP modernisation - ICH E6 R3 Public consultation workshop; Open consultation on single-arm trials reflection paper and ICH E19 Training of CT assessors.

It is also highlighted that the Clinical Trials Highlights Newsletter is moving to a new platform, a Newsroom, used by European institutions and agencies to create and disseminate information online. Resubscription is needed for those who already subscribed to the Newsletter.

EMA's Q&As of Good Clinical Practice (GCP) Updated

In June 2023, the EMA updated Q&As of Good clinical practice (GCP). New Q&As 11 has been added explaining whether it is allowed that sponsors could contract service providers to conduct trial-related tasks, procedures, duties, and functions that are under the responsibility of Investigator according to the applicable EU CTR and ICH E6. Another Q&A refers to the expectations for productivity applications used in clinical trials. The EMA also explains what are the considerations when direct remote access of identifiable personal and health data is required in a clinical trial.

Reflection Paper that Discusses Key Concepts for Single-Arm Clinical Trials for New Therapies

The EMA has opened a public consultation on Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation. Stakeholders are invited to send their comments until 30 September 2023.

A reflection paper discusses key concepts for single-arm clinical trials that are submitted as key evidence to demonstrate efficacy in a marketing authorization application for medicines in the European Union (EU). It outlines practical considerations for single-arm clinical trials.

A single-arm clinical trials are those where there is no randomised comparator, all patients in the trial receive the experimental treatment and only the outcomes under the experimental treatment can be observed. Such clinical trials are dedicated for new therapies, in certain areas such as rare diseases, including rare cancers, where target populations of new medicines are often very small. This reflection paper is the first guidance document by an international medicine regulator articulating the considerations and challenges associated with this type of clinical trials.

News from Individual Countries

Belgium

Clinical Trial Application (CTA) Part II Documents Update

The Federal Agency for Medicines and Health Products (FAMHP), the Belgian Regulatory Agency published a new template for Site Suitability to be used for Belgian sites and submitted in Part II of the Clinical Trial Application under EU CTR. A new version dated 6 June 2023 has only to be signed by the Chief Executive Officer (CEO) of the hospital. However, until the end of September 2023, the old Belgian template, which had to be signed both by Principal Investigator and CEO, still can be used for submissions.

Moreover, from October 2023 onwards, the new template should be used. The FAMHP strongly recommends using them, but they are not mandatory:

- Informed consent template for interventional clinical trials of drugs in adult patients (under revision);
- Template for informed consent for clinical trials of vaccines in healthy adult volunteers;
- Curriculum vitae of the principal investigator (developed by the European Commission with BE addendum on specific technical expertise).

Italy

New and Updated Guidance under the EU Clinical Trial Regulation (EU CTR)

The Italian Medicines Agency (AIFA) published important guidelines presenting the new requirements under the EU CTR.

- AIFA makes available a question and answer (Q&As) document on the operational indications for the census of Territorial Ethics Committee (CET)/ National Ethics Committee (CEN) in OsSC (the National Observatory on Clinical Trials) and management of the transfer of competences from Coordinating Ethics Committees (CECs), published in the communication of 7 June 2023 OSSC Operational Guidance FAQ (aifa.gov.it).
- List of the Territorial Ethics Committee, with their status if they are available in CTIS and/or in OsSC EU Regulation on Clinical trials | Italian Medicines Agency (aifa.gov.it).
- Operative Instruction for CET and CEN EU Regulation on Clinical trials | Italian Medicines Agency (aifa.gov.it).
- AIFA Q&A, version 1.0, May 2023 in which there are all indication for OsSC management in this period until full transition in CTIS of all studies.

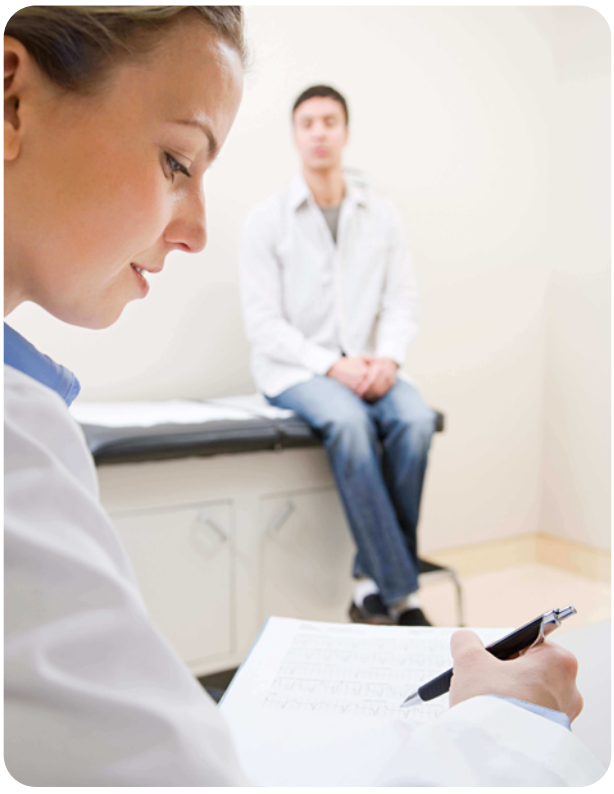
Poland

Safety Reporting in Clinical Trials of Medicinal Products Announcement

The Polish Competent Authority, the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products informed on their website that in connection with the entry into force of the New Act on Clinical Trials of Medical Products for Human Use of 9 March 2023 (Journal of Laws, item 605), i.e., as of 14 April 2023, the rules for reporting information on safety in clinical trials of medicinal products to the President of the Office are changing.

For studies submitted under EU CTR via CTIS, Annual Safety Reports (ASRs) should be submitted to the ASR EudraVigilance Module in the CTIS Portal. All Suspected Unexpected Serious Adverse Reaction (SUSARs) reports must be reported directly to EudraVigilance database (EVCTM). It is not required anymore to submit safety reports directly to the President of the Office.

For active substances not yet present in CTIS, ASRs should be submitted to the President of the Office electronically via ePUAP or by sending a message containing EudraLink to the address urpl@urpl.gov.pl.



Spain

CTIS Guidance for Sponsors (Spain)

On 27 June 2023, the Spanish Agency of Medicines and Sanitary Products (AEMPS) updated the Instructions for conducting clinical trials with a new document (version 18). The AEMPS have maintained the questions and answers format but have re-organized it into 14 sections and a list of annexes.

In addition, the AEMPS has issued the second version CTIS Guidance for Sponsors to update section 4 of request for further information (RFI) and section 6 regarding Authorisation. Some sections have been revised and typographical errors have been corrected. Guidance provides practical information for applicants.

Switzerland

Changes to the Guidance Document GMP Compliance by Foreign Manufacturers

The Swiss Agency for Therapeutic Products (Swissmedic) has updated its Guidance document on good manufacturing practice (GMP) compliance by foreign manufacturers with an explanation about the use of audit reports as proof of the GMP compliance of foreign manufacturers from countries whose GMP control systems are not deemed to be equivalent to that in Switzerland.

The guidance is intended for authorisation holders or applicants for the authorisation of ready-to-use medicines that are manufactured abroad and/or those manufactured in Switzerland, and that contain active pharmaceutical ingredients produced by foreign manufacturers.

Swissmedic requires foreign manufacturers to provide proof that they operate in compliance with Swiss GMP requirements. Swissmedic will also accept GMP certificates issued by foreign regulators in countries with equivalent GMP control systems, or alternatively official documents confirming that the manufacturer satisfies the Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP requirements.

Swissmedic also published Declaration by the Responsible Person for foreign manufacturers.

Guidance for CTA Dossier

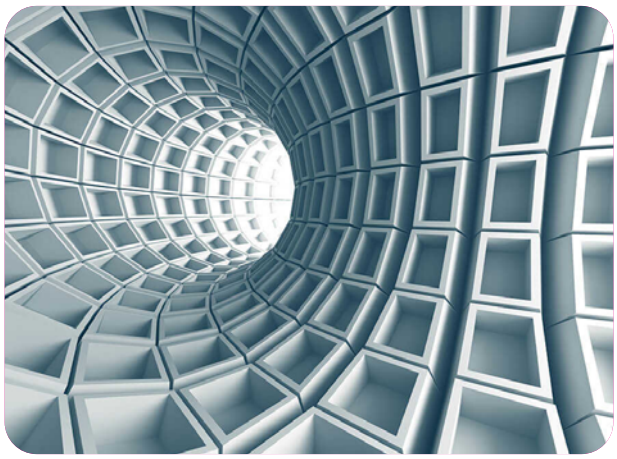
In May 2023, Swissmedic updated Working Instruction (WI) of the clinical trial application (CTA) dossiers to be submitted to the Agency. The guideline clarifies the requirements for CTA dossiers concerning clinical trials with medicinal products.

Clarified within the guidance:

- The FO Submission Form (Application Form) must be saved in PDF and only signatures can be scanned, no acceptable electronic signature.
- If any of the documents submitted - such as Investigator's Brochure (IB) or Pharmaceutical Quality Dossier (PQD) - which were previously approved by Swissmedic for another clinical trial, cross reference to the other clinical trial should be made in the CTA.
- The documents must be submitted with a new submission form.
- Possibility to perform a parallel submission if for confidentiality reasons documents must be submitted by different providers. e.g., in investigator-initiated trials, the PQD is submitted by the Drug master File holder and the rest of the dossier is submitted by the Sponsor.

WI provides practical information which must be completed by sponsors to receive Swissmedic approval for the clinical trial.

Moreover, Swissmedic published List of countries with which Switzerland has a mutual recognition agreement covering – among other areas – Good Manufacturing Practice (GMP) inspections and batch certification.



The United Kingdom

Public Consultation on New Clinical Trials Legislation

The UK Medicines and Healthcare products Regulatory Agency (MHRA) has launched a public consultation on proposals for legislative changes for clinical trials (CTs). Because the EU CTR was implemented after Brexit the EU Regulation was not implemented by the UK.

Many organisations which took part in the consultation agreed that change in the UK legislation is needed to make it easier to do clinical trials that everyone can trust.

The MHRA and Health Research Authority (HRA) will work with patients and the public, researchers, commercial and non-commercial research funders to inform legislative change and develop guidance that is proportionate, flexible and reflects the scale and nature of different clinical trials.

The main points to be considered in a new legislation are:

- make research more transparent;
- increase public involvement and diversity in research;
- help make research happen faster.

"Under the new framework, clinical trials application processes in the UK will be more proportionate, streamlined, and flexible without compromising on safety, helping to cement the UK as an attractive destination for trials, including global "multi-site" trials.", MHRA states.

For more information please see the press release MHRA to streamline clinical trial approvals in biggest overhaul of trial regulation in 20 years - GOV.UK (www.gov.uk)

Update of Template Agreements

- The new April 2023 versions of the bi-partite and tri-partite Primary Care model Clinical Trial Agreements (PC-mCTAs) have been published. The January 2021 versions will continue to be accepted in IRAS applications until the end of October 2023 as part of a grace period. These template model agreements are applicable to the health services in England, Northern Ireland, Scotland, and Wales.

- The new April 2023 versions of the model Non-Interventional Study Agreements mNISA and CRO-mNISA are published. The major changes from the previous versions are:
  - corrections of typographical errors in CRO-mNISA;
  - clarifications in clauses that the agreements are suitable for use with primary care organisations;
  - making clauses about recruitment or enrolment of participants optional so that the agreements can be used for studies where there is no recruitment of participants, for example studies only using anonymised data.

The January 2022 versions will continue to be accepted in IRAS applications until October 2023 as part of a grace period.

Other Initiatives

Draft ICH E6(R3) Guideline on Good Clinical Practice (GCP) Available for Public Consultation

In May 2023, a draft ICH E6(R3) Guideline on Good Clinical Practice (GCP) reached step 2b and is available for public consultation. The deadline for EU comments is 26 September 2023. Anticipating finalisation as a Step 4 document is planned in August/September 2024.

"What is new about E6(R3) structure and content?

- New structure to provide clarity and better readability.
  - Annexes and appendices
- Provide additional clarity on the scope.
- Language to facilitate innovations in clinical trial design, technology, and operational approaches.
  - Facilitate innovative clinical trial designs, for example, clinical trials utilising Decentralised Clinical Trial (DCT) elements and pragmatic elements, reflecting trials that closely resemble routine clinical practice.
- Set a foundation for practical/feasible expectations around the responsibilities of sponsor and investigator in a digital ecosystem.
- Encourage fit-for-purpose approaches.
- Incorporate learning from innovative clinical trial designs and lessons from public health emergencies/pandemics.
- Encourage transparency by clinical trial registration and result reporting.
- Provide additional language to enhance the informed consent process."

For more information, please see ICH Official website : ICH

ICH Adopts M7(R2) Guideline on Mutagenic Impurities to Limit Carcinogenic Risk

On 3 April 2023, the International Council for Harmonisation (ICH) announced the adoption of its M7(R2) guideline that aims to harmonize the framework for assessing and controlling DNA mutagenic impurities in pharmaceuticals as well as an addendum listing impurities that are considered to be mutagens and carcinogens.

This guideline emphasizes considerations of both safety and quality risk management in establishing levels of mutagenic impurities that are expected to pose negligible carcinogenic risk. It outlines recommendations for assessment and control of mutagenic impurities that reside or are reasonably expected to reside in the final drug substance or product, taking into consideration the intended conditions of human use.

M7(R2) guideline does not apply to drug substances and drug products such as biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation products, herbal products, crude products of animal or plant origin, and intended for advanced cancer indications as defined in the scope of ICH S9.

North America

United States of America

FDA Takes Additional Steps to Advance Decentralized Clinical Trials

On 2 May 2023, the U.S. Food and Drug Administration (FDA) is taking additional steps to support the use of decentralized clinical trials (DCTs) for drugs, biologics, and devices, where some or all the trial-related activities occur at locations other than traditional clinical trial sites. The Agency released a new draft guidance that provides recommendations for sponsors, investigators, and other stakeholders regarding the implementation of DCTs to advance medical product development and research. Examples of decentralized elements include obtaining laboratory tests at a local facility rather than a research medical center or conducting a clinical follow-up visit in the trial participant's home using telemedicine.

Decentralizing clinical trials will allow some or all trial-related activities to take place at trial participants' homes or other convenient locations, instead of having them visit research sites. By reducing barriers to participation, FDA expects that DCTs will increase the breadth and diversity of participants in clinical trials and improve accessibility for those with rare diseases or mobility challenges. FDA anticipates that this approach will facilitate the development of drugs including in areas of medical need, resulting in more treatment options and improved patient outcomes.

This new draft guidance covers recommendations on topics such as:

- design considerations for a DCT;
- conduct of remote clinical trial visits and clinical trial-related activities in a DCT;
- use of digital health technologies to remotely acquire data in a DCT;
- roles and responsibilities of the sponsor and investigators in a DCT;
- obtaining informed consent (IC) and institutional review board oversight of the IC process in a DCT;
- determination of the appropriateness of investigational products for use in a DCT;
- packaging and shipping of investigational products in a DCT;
- safety monitoring of trial participants in a DCT

This draft guidance builds on agency recommendations issued in 2020, which provided clarity for investigators to facilitate trial decentralization in response to the COVID-19 public health emergency and associated disruptions such as quarantines, site closures and travel limitations.

Canada

Health Canada's Position on the CADTH Guidance for Reporting RWE to Support Decision-Making

Canada's Drug and Health Technology Agency (CADTH) collaborated with Health Canada and other stakeholders to develop the Guidance for Reporting RWE to Support Decision-making on 18 May 2023. This guidance promotes the use of high-quality real-world data (RWD) and real-world evidence (RWE) in drug development and regulatory decision-making. It also emphasizes the importance of transparent and comprehensive reporting of RWE studies to assess reliability and reproducibility.

While traditional clinical trials are still the main source of evidence for regulatory decision-making, Health Canada recognizes there is value in using RWD/RWE. Health Canada is open to receiving submissions that rely on high-quality RWD/RWE in certain situations, such as:

- expanding evidence-based indications for populations often excluded from clinical trials, e.g., children, older adults and expectant mothers;
- addressing diseases where clinical trials are not feasible, e.g., rare diseases;
- responding to emergencies where clinical trials are unethical.

To support the use of RWD/RWE in regulatory decision-making, Health Canada has produced several documents, including Optimizing the use of real world evidence to inform regulatory decision-making and Elements of real world data/evidence quality throughout the prescription drug product life cycle.

The CADTH guidance aligns with the principles outlined in these documents.

MEDICAL DEVICES

EUROPE

News from the European Commission

The European Commission Implementing Regulation (EU) 2023/1194

On 21 June 2023, the Official Journal of the European Union published the Implementing Regulation (EU) 2023/1194 amending the transitional provisions laid down in Implementing Regulation (EU) 2022/2346 for certain products without an intended medical purpose listed in Annex XVI to Regulation (EU) 2017/745 (MDR).

Products covered by a certificate issued by a notified body in accordance with Directive 93/42/EEC benefit from a specific transitional provision laid down in Implementing Regulation (EU) 2022/2346. The provision, defined in Article 120 of MDR, allows those products to be placed on the market or put into service subject to certain conditions, even if the certificate has expired or if no Competent Authority has issued a Derogation under Article 59 or a communication under Article 97 of the MDR.

The transitional provisions in Implementing Regulation (EU) 2022/2346 for products for which clinical investigations are performed or for which a notified body must be involved in the conformity assessment procedure apply from 22 June 2023. The transitional provisions for products listed in Annex XVI for which a notified body must be involved in the conformity assessment procedure are extended until 31 December 2028 or 31 December 2029, depending on if a clinical investigation is performed or not and under certain conditions.

Guidance on Significant Changes Regarding the Transitional Provision under Article 120 of the MDR with Regarding Devices Covered by Certificates According to MDD or AIMDD

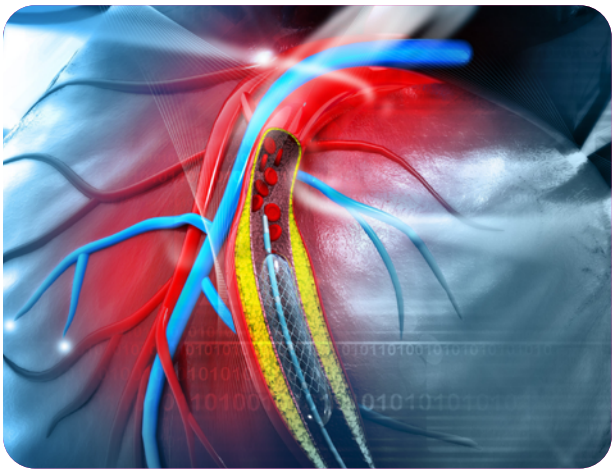
The Medical Device Coordination Group (MDCG) has updated the Guidance on significant changes regarding the transitional provision under Article 120 of the MDR, Revision 1. The MDCG made adjustments throughout the document to align it to Regulation (EU) 2023/607 of 15 March 2023 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the transitional provisions for certain medical devices and in vitro diagnostic medical devices and guidance MDCG 2022-2- Guidance on general principles of clinical evidence for In Vitro Diagnostic medical devices (IVDs) from January 2022.

The guidance refers to 'legacy devices' and according to the last amendment by Regulation (EU) 2023/607 allows them to continue to comply with the Active Implantable Medical Devices Directive (AIMDD) or Medical Devices Directive (MDD). Those devices may be placed on the market or put into service until 31 December 2027 or 31 December 2028, as applicable, provided the conditions set out in Article 120(3c) MDR are fulfilled.

Addendum to the MDCG 2022-18 Position Paper

In June 2023, the MDCG published Addendum to the MDCG Position Paper on the application of Article 97 MDR to legacy devices for which the MDD or AIMDD certificate expires before the issuance of a MDR certificate from December 2022.

With the entry into force of Regulation (EU) 2023/607 on 20 March 2023, the MDR transitional period and the validity of MDD/AIMDD certificates have been extended, provided that the conditions in the amended Article 120 MDR are met. In the Addendum the MDCG recommends that National Competent Authorities (CAs) limit the application of Article 97 MDR as set out in MDCG 2022-18 to very exceptional situations, e.g., where the national CA has received information justifying the application of Article 97 MDR prior to 20 March 2023.



Guidance on the Content and Structure of the Summary of the CIR

In May 2023, the Official Journal of the European Union published the European Commission Guidance on the content and structure of the summary of the clinical investigation report.

The Medical Devices Regulation (MDR) requires for the sponsor of an investigation to report the results of the clinical investigation within one year of the end of the investigation, regardless of its results. In case of an early termination or temporary halt of the clinical investigation, within three months.

A report with detailed results must be submitted to the Member States where the investigation was conducted, and the report summary must be made public to all in EUDAMED before a device is placed on the market. As EUDAMED is not ready for use yet, sponsors must submit their reports and summaries to the Competent Authorities (CAs).

According to guidance, the summary of the report must include information on the planning, process, analysis, and results of the investigation with concepts and format that are easy to understand for the intended users of the medical device. A significant part of the results is safety information, including potential adverse events.

News from Individual Countries

The United Kingdom

Validation Checklist

The Medicines and Healthcare products Regulatory Agency (MHRA) published Clinical Investigations Application Check list to be considered by the applicants planning to submit a clinical investigation of a medical device to the UK Agency. The list includes a description of requirements for each document depending on the type of medical device or the UK nation where the investigation is going to be performed. The key role of publication of the Checklist is to support all applicants in submitting a valid application.

New MHRA / HRA Coordinated Assessment Pathway for Clinical Investigations

The Medicines & Healthcare products Regulatory Agency (MHRA) and the Health Research Authority (HRA) informed about the setting up a new coordinated assessment pathway which will streamline the review of clinical investigations involving medical devices. From 22 May 2023 applicants may submit the clinical investigation dossier first to the MHRA Devices. The application to Research Ethics Committee (REC) can only be submitted once MHRA has confirmed that the device's application is valid, therefore both applications should be ready to be submitted at the time of submitting the MHRA application. It will not be possible for the applicant to request review by a specific REC.

If the sponsor decides go through a new coordinated assessment pathway, the applicant must inform MHRA in advance of submitting any applications by emailing CI-applications@mhra.gov.uk, and confirm whether the REC application has not yet been made, the study does not involve adults lacking capacity, the study is not a CTIMP, the estimated application date and provide with the Integrated Research Application System (IRAS) Project ID number (if available).

Placing CE Marked Medical Devices and IVDs on the Great Britain Market-Implementation of the Future Regulations

The government has put in place legislation that amends the Medical Device Regulations 2002 (SI 2002 No 618, as amended) (UK MDR) to extend the acceptance of CE marked medical devices on the Great Britain market (England, Scotland, and Wales). This will support the ongoing safe supply of medical devices to Great Britain and ease the transition to the future regulatory framework for medical devices.

It has introduced legislation which provides that CE marked medical devices may be placed on the Great Britain market to the following timelines:

- general medical devices compliant with the EU medical devices directive (EU MDD) or EU active implantable medical devices directive (EU AIMDD) with a valid declaration and CE marking can be placed on the Great Britain market up until the sooner of expiry of certificate or 30 June 2028;
- in vitro diagnostic medical devices (IVDs) compliant with the EU in vitro diagnostic medical devices directive (EU IVDD) can be placed on the Great Britain market up until the sooner of expiry of certificate or 30 June 2030; and
- general medical devices, including custom-made devices, compliant with the EU medical devices regulation (EU MDR) and IVDs compliant with the EU in vitro diagnostic medical devices regulation (EU IVDR) can be placed on the Great Britain market up until 30 June 2030.

For more information please see Implementation of the Future Regulations - GOV.UK (www.gov.uk)

Infographic of the timelines for placement of CE marked medical devices in the GB market under the Medical Devices (Amendment) (Great Britain) Regulations 2023 can be downloaded here.

Update of Template Agreements

The model Clinical Investigation Agreement (mCIA) and Clinical Research Organisation model Clinical Investigation Agreement (CRO-mCIA) have been updated. The April 2023 templates are UK wide, replacing the 2021 templates. The September 2021 versions of these templates will still be accepted in Integrated Research Application System (IRAS) submissions, but applicants are encouraged to adopt the April 2023 versions at their earliest opportunity.

Spain

Instruction for Combined Studies involving Medicinal Product (MP) and Medical Devices (MDs)

On 19 June 2023, the Spanish Agency of Medicines and Sanitary Products (AEMPS) published detailed instructions how to submit Clinical Trials (CTs) for combined studies, involving Medicinal Product (MP) and Medical Devices (MDs).

The guidance is applicable for new clinical trials conducted through the Clinical Trials Information System (CTIS), as well as substantial modifications of CT approved under Clinical Trials Directive (CTD) which have not been transitioned yet. It provides clear instructions taking into consideration the current regulatory situation in the EU. It states that:

- Electronic system on clinical investigations EUDAMED (MDR art.73) is not ready yet. When available it would be a tool similar to CTIS.
- CTIS and EUDAMED will be interoperable, and this will be used for combined studies involving MPs and MDs.

The guidance provides two different scenarios to be followed by applicants currently if in combination studies:

1. Clinical trials with Investigational Medicinal Product (IMP) and MD without CE marking/ bearing CE marking but used outside the scope of its intended purpose.

- This scenario should follow the regulatory process for Clinical Trial with IMP + Clinical Investigations with MDs.
- Both applications must be submitted simultaneously for evaluation, which will be carried out in parallel following the deadlines according to the legislation applicable to each of them.
- The leading Ethics Committee must be the same for both the clinical trial with drugs and for clinical investigation with MDs.
- Applicable fees for evaluation of new/substantial modification of clinical trials AND evaluation of clinical studies with MDs should be paid.
- Two authorizations will be issued: one for clinical trial with IMP and one clinical study with MDs.
- Two authorizations are needed to initiate the study or implement the substantial modification.

How to submit:

➜ **Clinical Trial (IMP)** should be submitted through CTIS or through the Spanish portal for Clinical Trials (for substantial amendments of studies approved under the former CTD).

➜ **Clinical investigation (MD) or performance studies involving in vitro diagnostic medical devices (2017/746 art. 58)** should be submitted through the general Registry of the AEMPS a dressed to the Medical Devices Department (See: Registro Electrónico General de la Administración General del Estado).

This will be used until the European Eudamed database is operational. Same process also applies to substantial modifications including extension of the investigational sites.

Note: Substantial modifications of combined studies that obtained approval under the former CTD.

Even if the clinical trial involving the MD was jointly authorized through the Spanish portal, from now on the request of substantial modification must be sent separately to the Medical Devices Department of the AEMPs.

In the same way, if a substantial modification of a trial under former CTD processed and authorized by the Spanish Portal consists of the inclusion of a new MD without CE marking, in addition to what is required in terms of the modification of the clinical trial, the application for authorization from the performance study or clinical investigation must be performed separately to the Medical Device Department of the AEMPS.

2. Clinical trial with an integrated product.

Clinical trials involving an integrated product with components that are used separately, could be considered a MD or MP. The applicable legislation depends on the qualification of the investigational product as a MP or MD according to its mechanism of action.

Different situations:

- When the main action is the drug, the study falls under the umbrella of Clinical Trials. The clinical trial application must be submitted through CTIS (or Spanish Portal in case of substantial modification authorized under former CTD) and only the fee corresponding to clinical trials should be paid.

  In this case, it will not be necessary to submit any application to the Medical Devices Department. The part of the product that could be considered a MD separately must meet the safety and operating requirements that are included in Annex I of Medical Device Regulation (MDR).

- When the main action is the MD, the study falls under the umbrella of clinical investigations with MDs. The clinical investigation application must be submitted through the general registry of the AEMPS and only the fee corresponding to the clinical investigation of MDs should be paid.

Other Initiatives

TEAM-NB Practical Guidance on Technical Documentation

In April 2023, the European Association of Medical devices Notified Bodies (TEAM-NB) published as version 2, position paper Best Practice Guidance for the Submission of Technical Documentation under Annex II and III of Medical Device Regulation (EU) 2017/745 (MDR). The position paper provides a coordinated approach to the expectations of Notified Bodies regarding technical documentation. It refers to Annex II of the Medical Devices Regulation 2017/745 and Annex III which describes the requirements for a technical Documentation for post-market surveillance. Reference to the Medical Device Coordination Group (MDCG) guidance documents should be considered as suggested guidance for the purposes of Team-NB guidance.

The position paper has been prepared and provides practical tips on how to communicate with the Notified Body before a submission, contents of the technical documentation for a submission and how to facilitate the use of evidence still coming from the old medical device directives.

North America

United States of America

FDA Made Updates to the Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program Final Guidance

On 2 June 2023, the FDA is making minor updates to the Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program final guidance. The Medical Device User Fee Amendments of 2022 (MDUFA V) includes refined performance goals related to FDA feedback for Pre-Submissions or "Pre-Subs," which are part of the Q-Submission Program. To address a MDUFA V commitment, the FDA intends to issue a revised draft guidance including information on when informal communication is appropriate instead of a Pre-Sub, among other updates. While this new draft guidance is being developed, the FDA is making minor procedural updates and clarifications on the mechanisms that stakeholders can use to request feedback.

This final guidance provides minor clarifications on:

- Examples of common review topics and questions for a Pre-Sub;
- Timing considerations for multiple submissions;
- Administrative content to include in Q-Subs to facilitate FDA review;
- Q-Sub meeting minutes format and submission process;
- Existing mechanisms to obtain FDA feedback outside of the Q-Sub Program.

Canada

Health Canada Updates Forward Regulatory Plan with New Initiatives

Health Canada has updated its Forward Regulatory Plan: 2022-2024, providing information on regulatory initiatives Health Canada aims to propose or finalize over the next two years. Some of the new and updated initiatives pertaining to the Food and Drugs Act are highlighted in the Forward Regulatory Plan. However, one new initiative is focused on the Advanced Therapeutic Products Pathway for Adaptive Machine Learning-enabled Medical Devices.

Health Canada is proposing to add a description of Adaptive Machine Learning-enabled Medical Devices to Schedule G, allowing these devices to be regulated as Advanced Therapeutic Products. These devices would be the first Advanced Therapeutic Products to be listed in Schedule G, a schedule added when new authorities were added to the *Food and Drugs Act* in 2019. These new authorities are intended to enable the use of customized regulatory requirements to allow for the agility and flexibility necessary to determine the appropriate oversight of innovative health products.

OTHER "HOT" TOPICS FROM THE EUROPEAN UNION

The New European Data Act

On 28 June 2023, The European Commission informed in its press release that the European Parliament and the Council of the EU reached an agreement on the European Data Act, proposed by the Commission in February 2022.

"The Data Act aims to boost the EU's data economy by unlocking industrial data, optimising its accessibility and use, and fostering a competitive and reliable European cloud market. It seeks to ensure that the benefits of the digital revolution are shared by everyone."

The main points included in the Data Act:

- Measures that enable users of connected devices to access the data generated by these devices and by services related to these devices.
- Measures to provide protection from unfair contractual terms that are unilaterally imposed.
- Mechanisms for public sector bodies to access and use data held by the private sector in cases of public emergencies such as floods and wildfires, or when implementing a legal mandate where the required data is not readily available through other means.
- New rules that grant customers the freedom to switch between various cloud data-processing service providers.
- Measures to promote the development of interoperability standards for data-sharing and data processing, in line with the EU Standardisation Strategy.

Once the European Data Act is adopted, it will enter into force on the 20th day following its publication in the Official Journal and will become applicable 20 months after the entry into force.

The European Data Act is ready for downloading here.

OTHER "HOT" TOPICS FROM THE UNITED STATES

FDA Issued the Final Guidance for Content of Premarket Submissions for Device Software Functions

On 13 June 2023, the FDA issued the final guidance: Content of Premarket Submissions for Device Software Functions. The final guidance provides information regarding the recommended documentation sponsors should include in premarket submissions for the FDA's evaluation of the safety and effectiveness of device software functions. The guidance replaces FDA's Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices issued on 11 May 2005, and updates FDA's thinking related to the risk-based approach to the documentation FDA recommends sponsors include for the review of device software functions in premarket submissions.

The final guidance takes a simplified risk-based approach to help determine the device's Documentation Level, which is either Basic or Enhanced. The Documentation Level helps to identify the minimum amount of information that would support a premarket submission that includes device software functions.

FDA Announces Additional Steps to Modernize Clinical Trials

On 6 June 2023, the U.S. Food and Drug Administration is announcing the availability of a draft guidance with updated recommendations for good clinical practices (GCPs) aimed at modernizing the design and conduct of clinical trials, making them more agile without compromising data integrity or participant protections. The updates are intended to help pave the way for more efficient clinical trials to facilitate the development of medical products. The draft guidance is adopted from the International Council for Harmonisation's (ICH) recently updated E6(R3) draft guideline that was developed to enable the incorporation of rapidly developing technological and methodological innovations into the clinical trial enterprise.

This draft guidance, once finalized, would update the existing guidance titled, E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) (March 2018). The revised draft recommendations are designed to be applicable to a broad range of clinical trials including those with innovative design elements. These elements have the potential to make trials more efficient and less burdensome. Additionally, the modernized GCP recommendations encourage the use of fit-for-purpose innovative digital health technologies (DHTs). DHTs, such as wearable sensors could potentially facilitate more agile data collection and assist with patient recruitment.

In addition to the recommendations supporting the modernization of trials, the principles outlined in the draft recommendations aim to make trials more efficient and potentially accelerate evidence generation for medical products by emphasizing the use of risk-based and proportionate approaches across the lifecycle of a clinical trial (e.g., data collection, monitoring, quality management).

With this approach, investigators are encouraged to determine which data and clinical trial processes are most important to participant safety and data integrity and focus efforts accordingly. This helps ensure investigators are allocating resources and efforts toward collecting and analyzing key data for the trial.

FDA Issues Final Guidance on Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products

On 26 May 2023, the FDA issued the Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products Final Guidance for Industry. This final guidance describes the agency's current recommendations regarding adjusting for covariates in the statistical analysis of randomized clinical trials in drug and biological product development programs.

FDA Sees Rapid Increase in Drug and Biologic Submissions with AI/ML Components

On 27 June 2023, at the DIA Global Annual Meeting, Hao Zhu, director of the Division of Pharmacometrics in the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) said the number of drug applications incorporating artificial intelligence (AI) and machine learning (ML) elements have "increased drastically in the past five years." In 2022, he said the agency received 170 submissions containing these elements. In 2018, Zhu said that only three submissions contained AI/ML components.

These tools are used to support enriching the design of the study, identifying patients for the study, identifying patient risk, selecting, and optimizing dosing, assessing endpoints and biomarkers, predicting drug toxicity, or for drug discovery or repurposing.

Artificial intelligence (AI) and machine learning (ML) are no longer futuristic concepts; they are now part of how we live and work. The U.S. Food and Drug Administration uses the term AI to describe a branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions, and making predictions. ML is a subset of AI that uses data and algorithms, without being explicitly programmed, to imitate how humans learn. As with other evolving fields of science and technology, there are challenges associated with AI/ML in drug development, such as ethical and security considerations like improper data sharing or cybersecurity risks. There are also concerns with using algorithms that have a degree of opacity, or algorithms that may have internal operations that are not visible to users or other interested parties. This can lead to amplification of errors or pre-existing biases in the data. FDA aims to prevent and remedy discrimination – including algorithmic discrimination, which occurs when automated systems favour one category of people over other(s) – to advance equity when using AI/ML techniques.

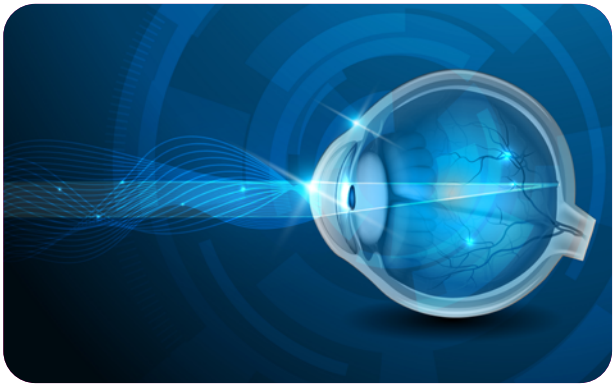
To address these concerns, the FDA has released a discussion paper, "Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products." To further address the use of AI in drug manufacturing, CDER issued another discussion paper, Artificial Intelligence in Drug Manufacturing, as part of the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) Initiative.

Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making

On 1 April 2023, FDA released its draft guidance entitled Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making. This guidance addresses methodologies, standards, and technologies that may be used for the collection, capture, storage, and analysis of clinical outcome assessment (COA) data.

The guidance also addresses methods to better incorporate COAs into endpoints that are considered significantly robust for regulatory decision-making. This includes methods to define meaningful change in a COA-based endpoint and interpretation of results. The guidance includes information on the format and content required for regulatory submissions incorporating patient experience, in particular COA data.

Section II of this guidance discusses considerations for COA-based endpoints to align the study design, endpoint, and analysis with the clinical study objective to improve study planning and the interpretation of analyses. In addition, Section III of this guidance describes methods to aid in the interpretation of treatment effects on COA-based endpoints in terms of patients' views on the effect of a medical product. This information is important because statistical significance does not, by itself, indicate whether the detected effect corresponds to a clinically meaningful treatment effect.



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