CROM SOURCE
A ClinChoice Company

REGULATORY

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Including the latest updates on the 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 Commission

New Multi-Stakeholder Platform (MSP) or Forum to Share and Implement Ideas for Improving Clinical Trials in the EU

The European Commission, European Medicines Agency and Heads of Medicines Agencies have published a concept paper which describes a proposal for the creation of a MSP that aims to promote dialogue and collaboration for improving clinical trials in the EU. The Commission is calling for representatives of sponsors, patients or patient's organisations, Contract Research Organisations (CROs), clinical trials Investigators, regulators and others depending on the topic under discussion. The forum will explore all aspects of clinical trials including trial design, conduct and/or statistical analysis. The virtual meetings will be from two to four times per year plus ad hoc topic group meetings, if needed.

The MSP is going to have its own secretariat. First upcoming meeting where the aims will be to present the MSP governance proposal and agree MSP preliminary workplan based on the feedback received from the initial consultation and start discussion on priority topics is planned during the first quarter and second quarter of 2023.

Clinical Trials Regulation (EU) No 536/2014 (CTR) Questions & Answers (Q&A) Update

In February 2023, the European Commission published version 6.4 of *Questions and Answers Document - Regulation (EU) 536/2014*. Additional Q&A number 2.15 has been added explaining the case where the sponsor of a clinical trial is not the product owner of the Investigational Medicinal Product (IMP) and should not have access to the quality Investigational Medicinal Product Dossier (IMPD).

Moreover, answers 260 and 261 to question 6.5 regarding recommended strategy for the publication of trial documents with proprietary information have been revised. They explain whether it is allowed to redact documents and apply for their deferral at the same time. Revised answers 481 and 498 instruct that it is important to submit additional documentation on top of what is being required as a minimum by CTR in the Clinical Trial Application (CTA) to be transitioned by 31 January 2025.

Annex II of Q&As has also been revised of the requirements for Part I documents for France.

CTIS users are recommended to consult the Q&As while preparing their CTA dossiers to ensure the best possible alignment with CTR requirements

News from the European Medicines Agency (EMA)

Clinical Trial Information System (CTIS) Mandatory

Starting from 31 January 2023, the use of CTIS is mandatory for all initial clinical trial applications in the European Union/European Economic Area (EU/EEA). Creating a new EudraCT number or new CTA through EudraCT under Clinical Trials Directive (CTD) is no longer possible from this date.

For trials authorised under the CTD, sponsors can still continue to submit substantial amendments under the regime of the CTD until the end of the transition period on 30 January 2025. Those clinical trials that were approved under the CTD and are not going to be completed by 31 January 2025 will need to be transitioned to the CTIS under the Clinical Trials Regulation (CTR).

CTIS Data in WHO's International Clinical Trials Registry Platform

The EMA has initiated the process to register the Clinical Trials Information System (CTIS) as a World Health Organisation (WHO) data provider. Once the registration process is completed, all future clinical trial data published in CTIS in addition to all data published in CTIS since the launch of the system on 31 January 2022 will be included in WHO's International Clinical Trials Registry Platform (ICTRP) Search Portal.

CTIS Latest Updates in the Clinical Trials Highlights

In February 2023, the EMA issued the 13th edition of the *Clinical Trials Highlights*. In this edition, the EMA is focusing mostly on the recent improvements in CTIS, training material updates, CTIS User Support Services instructions, events updates and provides description of how personal information may be contained in the document properties. The edition also informs about an initial release of a CTIS Business Intelligence (BI) system for Member State users to enable them to customise and save queries for future use.

Clinical Trials Regulation Rules Practical Guidance

On 30 January 2023, the EMA published the guidance document *Clinical Trials Regulation (EU) No 536/2014 in practice* providing the rules governing medicinal products in the European Union to clinical trials. The document describes the steps which applicants must be aware of and complete before the start of the study, while the clinical trial is being conducted and when the study is ended taking into consideration connection with the CTIS and the CTR requirements. The guidance summarises the transparency rules on protection of commercially confidential information (CCI) and protection of personal data. Annexes of the documents remind about the composition of the clinical trial application in CTIS proposed by Clinical Trials Facilitation Group (CTFG) and present overview of all required notifications under CTR.

Questions & Answers (Q&A) Document to Questions Raised by Representatives of Sponsor Associations

The EMA published the *Questions and Answers document prepared by the Query Management Working Group on CTIS and the CTR*. The Q&A provides answers by the Working Group to questions that were raised by representatives of sponsor associations. The questions are grouped by topics related for example to assessment of the clinical trial, General Data Protection Regulation (GDPR), Safety, Transition period, Training & Support or Transparency, and the answers include references to useful sources for a better understanding of the CTR and the use of CTIS.

Clinical Trials Information System (CTIS) - Sponsor Handbook Updated

The EMA has published version 3.01 of *CTIS Sponsor handbook*. The timelines due dates in CTIS have been updated and document file size upload in CTIS has been changed from 10 MB to 50 MB. Moreover, clarifications on dates for transition from Directive to Clinical Trial Regulation have been added in section 5.1 and 5.2.2.

New Training Material Added to Module 03 of the CTIS Training

In January 2023, the EMA added new training material to Module 03 of the CTIS training material catalogue. It is the *Step-by-Step guide* describing how to search and create organisations in CTIS. There are steps on how to retrieve organisations from Organisation Management Service (OMS) or from CTIS, and insert them in their trials in CTIS, as well as how they can create organisations (i.e., third parties, clinical trial sites, etc.) locally in CTIS.

Multi-Factor Authentication (MFA) in CTIS

The EMA informed that on 1 June 2023 will be launched Multi-factor authentication for user logins to CTIS, for both Sponsor and Member State workspaces. In preparation for the introduction of MFA, it is recommended that each user is equipped with a mobile or an office phone that can be used for second factor authentication. Now all users can already log into the EMA ServiceNow portal to set up their MFA for EMA systems, which will work also for CTIS once activated.

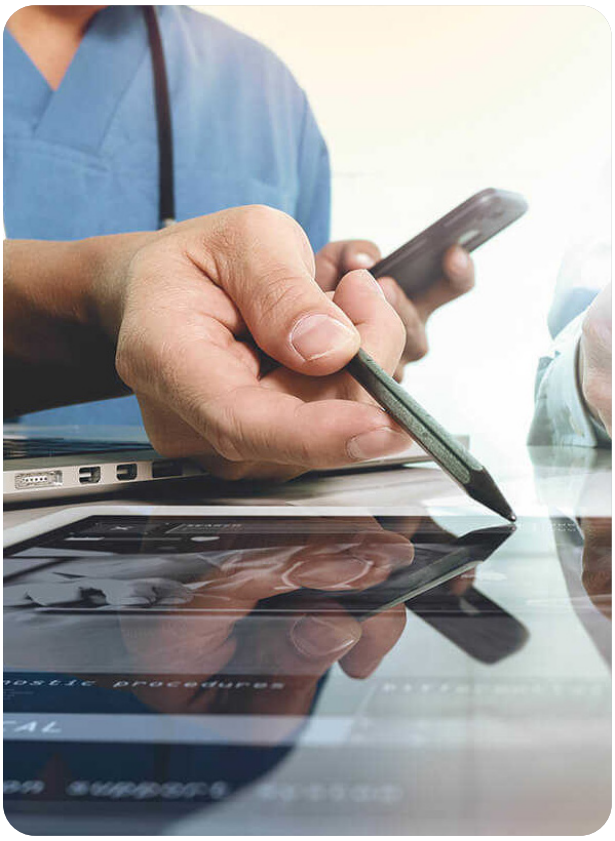
EMA Reports of Clinical Trial Applications Submitted via CTIS Portal

The European Commission, European Medicines Agency and Heads of Medicines Agencies have published in March 2023 Edition 10 of *Key Performance Indicators (KPIs) to monitor the European clinical trials environment*. The metrics presented in the report reflect the status of applications in CTIS and EudraCT as of 31 January 2023 for Clinical Trial Applications (CTAs) submitted between 1-31 January 2023 as well as cumulative figures.

The report presents the number of CTAs, Substantial Modifications (SMs) and addition of a new Member State Concerned (MSC) applications submitted under the CTR in CTIS since the launch on 31 January 2022 and shows that in November 2022 the number of CTA initial submissions under CTR was the highest. See Figure 1 below.

Furthermore, provided are data on the number of mono-national-multinational studies and data on the number of studies for which issued were decisions adopted by phase, therapeutic area; clinical trials with a decision in CTIS per month; National Competent Authority (NCA) decisions and Ethics Committee opinions under CTR or under CTD, Advanced Therapy Medicinal Products (ATMP) decisions under CTR.

The report informs that 793 CTAs have been submitted in CTIS since the launch of the system on 31 January 2022, of which 629 are initial CTAs,



141 are SM applications and 23 are applications for the addition of a new MSC.

From the submitted applications in January 2023, 7 have been re-submitted because they were previously lapsed or withdrawn (3) or were not authorised (2).

CTAs submitted in CTIS per month

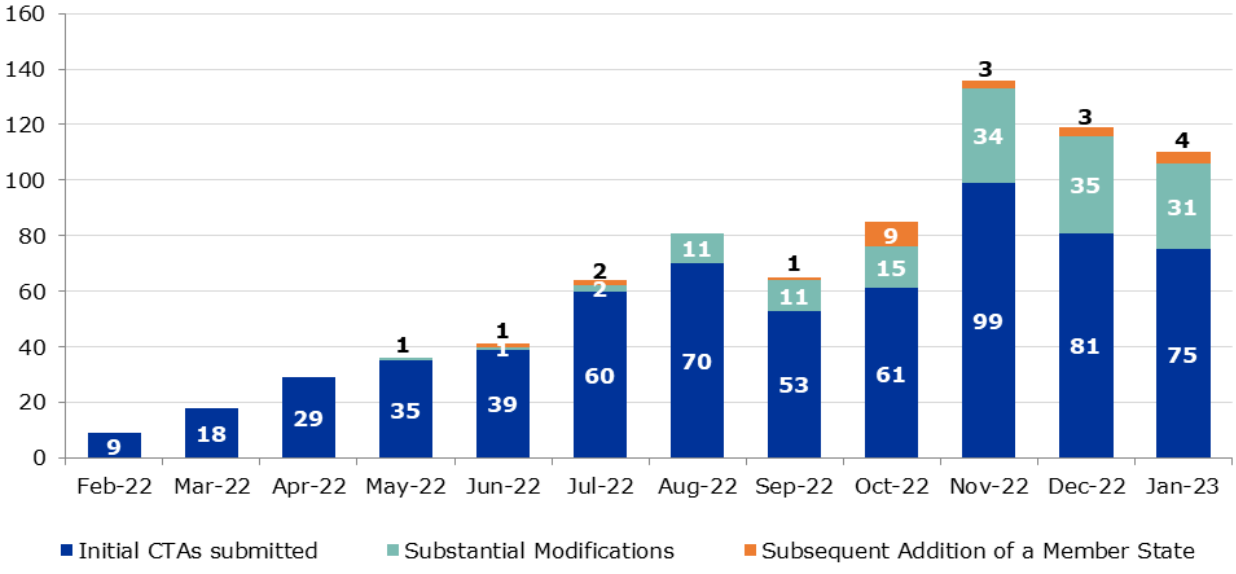


Figure 1

Handling and Shipping of IMPs Guidance Came into Effect

On 1 January 2023 came into effect the *Guideline on the responsibilities of the sponsor with regard to handling and shipping of IMPs for human use in accordance with GCP and GMP*. Draft guidelines were published in 2018 and the final version was released in September 2022.

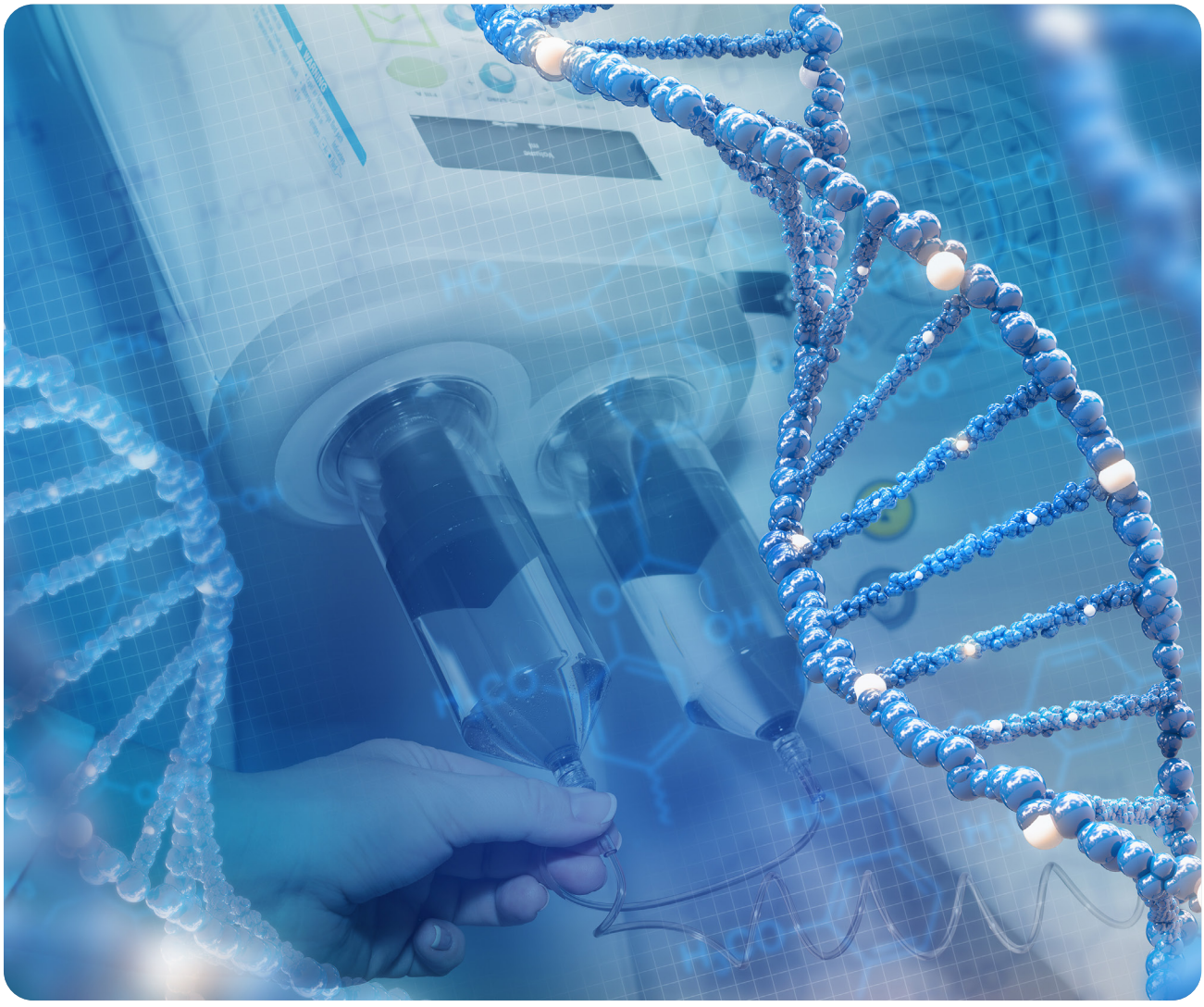
The document states that IMPs should remain under the control of the sponsor until after completion of the two important step procedures.

The first step is the certification of each batch by the Qualified Person (QP) of the manufacturer or importer in line with the Clinical Trials Regulation (EU) No 536/2014 (CTR) and the provisions of the Commission Delegated Regulation (EU) No 1569/2017 have been complied with and documented.

The second step is the regulatory release by the sponsor which is understood by for example the verification of completion of batch certification by the QP and the necessary authorisations in place for the clinical trial, before supply of IMP to the clinical trial site.

Both steps should be recorded and retained in the clinical trial master file (TMF). IMPs should remain under the control of the sponsor until the release process is complete.

The guidelines also point to the Good Distribution Practice (GDP) principles which should be taken into consideration during the IMP shipping for documentation, transportation (including selection of container and packaging, qualification and/or validation activities, monitoring of transport conditions) and outsourced activities.



News from Individual Countries

Italy

A New Registry of Observational Studies Activated

The Italian Medicines Agency (AIFA) restored online services portal for observational studies named Register of Observational Studies (Registro degli Studi Osservazionali), (RSO). The access to the RSO website is similar to OsSC (the National Observatory on Clinical Trials) and was activated on 31 January 2023.

Registration is compulsory only for new applications (paper application/notification) whose letter of transmission to the Ethics Committee was subsequent to 1 January 2023. Registration for all studies is limited to the initial application; Amendments, study start, study end; a summary of the study results. Ethics Committees are required to enter the data that fall within their competence into the RSO within 30 days of the decision.

The AIFA states that: "The new RSO system will allow external users (who have registered to AIFA online services) to search and consult observational studies of their own competence and/or interest (e.g., Regions, citizens/patients)."

New Italian Decrees

On 7 February 2023, The Italian Medicines Agency (AIFA) informed about publication in the Official Gazette, General Series no. 3 of four decrees of the Minister of Health implementing Law no. 31 of 11 January 2018.

Not all of Decrees are going to be entered into force at the same time. Their application is dependent on stabilization of the regulatory framework of clinical trials in Italy, as harmonized at European level by Regulation (EU) no. 536/2014 (CTR).

In particular, the following have been published:

- The Decree of 26 January 2023 on "*Identification of forty territorial ethics committees*", whose entry into force is established as of **7 June 2023** ("DM 40 CET");

- The Decree of 27 January 2023 on "Regulation of the transitional phase pursuant to Article 2, paragraph 15, of Law no. 11 of 2018 January 3, in relation to evaluation activities and methods of interaction between the Coordination Centre, the territorial ethics committees, the ethics committees of national importance and the Italian Medicines Agency", whose entry into force is established as of **22 February 2023** ("*DM FASE" TRANSITORY*");

- The Decree of 30 January 2023 on "*Determination of the single fee for clinical trials*, the attendance fee and reimbursement of expenses for participation in the meetings of the National Coordination Centre of territorial ethics committees for clinical trials on medicinal products for human use and medical devices, of the territorial ethics committees and of the ethics committees of national importance", whose entry into force is established from **22 February 2023**;

- The Decree of 30 January 2023 on "*Definition of the criteria for the composition and functioning of territorial ethics committees*", whose entry into force is established from **8 February 2023**.

Poland

New Act on Clinical Trials of Medical Products for Human Use

New Act on Clinical Trials of Medicinal Products for Human Use dated 9 March 2023 became applicable in Poland. This Act supplements the Clinical Trials Regulation (EU) No 536/2014 (CTR) provisions.

The main change covers the appointment of the National Bioethics Committee (NBC). The ethical evaluation of the study will be carried out by the Chief NBC appointed by the Medical Research Agency (MRA) or by the bioethics committee from the list, appointed by the chairman of the NBC. The NBC will be responsible for sharing the CTA form and Part II documents from CTIS with the applicable EC for ethical review under CTR. The NBC will be supported by the Medical Research Agency (MRA) responsible trainings and administrative tasks for ECs.

New Act also changes the amount and method of payment of fees related to the clinical trial submitted under CTR. The fee will need to be shared between the National Competent Authority (NCA) and the MRA. The MRA will then provide the fees to the NBC and EC issuing a favourable opinion for the clinical study.

The Act also defines the rules of civil liability of the researcher and the sponsor of clinical trials. In addition, the main investigator in a clinical trial of a medicinal product conducted in the territory of Poland may be a licensed physician, dentist, nurse, or midwife with a diploma in nursing or midwifery.

New Act changes the rules of the protection of research participants in terms of the compensation (insurance) system. The most important solutions in this area include establishment of the Clinical Trials Compensation Fund, which will be financed from sponsors' contributions.

Proceedings regarding the compensation benefit will be conducted by the Ombudsman for Patients' Rights.

The amount of the compensation benefit will be:

- from PLN 2,000 to PLN 200,000 – in the case of bodily injury or health disorder.
- from PLN 20,000 to PLN 100,000 in the event of the death of a clinical trial participant.

The limit amounts of compensatory benefits are to be indexed every five years.

Moreover, the new Act will change the rules and procedures for conducting clinical trial inspections.

Spain

CTIS Guidance for Sponsors (Spain)

The Spanish Agency of Medicines and Sanitary Products (AEMPS) published the *CTIS Guidance for Sponsors (Spain)*, version 1.0, dated March 2023.

This guidance is intended for Spain but as it is written in English and most of the topics discussed are also applicable to other EU Member States it can be considered a useful tool as it provides CTIS practical information.

Information Note

On 6 February 2023, the AEMPS published information note announcing that due to the obligation to perform all new clinical trial applications submissions through the Clinical Trial Information System (CTIS) from 31 January 2023 the ECM portal (Spanish portal for submission of clinical trials) has disabled the option for submitting new clinical studies.

Information note also reminds that ongoing clinical trials approved in accordance with obsolete Directive 2001/20/CE must be transferred to CTIS by 31 January 2025. All clinical trials authorized through CTIS will be published both on the EU Database as in the Spanish Registry of Clinical Studies (ReeC) of the AEMPS.

Changes in the Application of Fees for Medicines and Medical Devices

On 19 January 2023, the AEMPS announced that the Law 38/2022 dated on 27 December 2022 introduced changes in the application of fees for **medicines and medical devices** among others.

The modification on the fees will be applicable in **June 2023**:

- Foreseen single national fee for the clinical trial approval/ authorisation (covering EC and CA).
- Exemption of fee for investigations without marketing purposes (According to article 2.2 of Royal Decree 1090/2015)
- Clinical trials approved in accordance with obsolete directive 2001/20/CE transferred to CTIS should do not require additional fees.

Description (see law 38/2022 article 123/Group II)	Fee
Clinical trial evaluation with medicinal product not authorized in the EU	€5.741,27
Clinical trial evaluation with medicinal products authorized in the EU	€3.611,07
Substantial modification of clinical trial with medicinal products	€1.764,71

The United Kingdom

The NHS Digital Merger with NHS England

The Health Research Authority (HRA) informed that in February 2023 the National Health Services (NHS) Digital merged with NHS England. The NHS Digital was responsible for a design, development and operated national IT and data services that supported clinicians at work, helped patients get the best care, and used data to improve treatment. From 1 February 2023 all these responsibilities have been transferred legally to NHS England. The Research Ethics Committee (REC) or Confidentiality Advisory Group (CAG) approvals involving NHS Digital will still apply. The name change from NHS Digital to NHS England will not be considered as an amendment to the study. If participant information for clinical trials mentions NHS Digital, an applicant should change that to NHS England at the next planned update.

Increase the Diversity of People Taking Part in Research in the UK

The Health Research Authority (HRA) and the Medicine and Healthcare products Regulatory Agency (MHRA) informed that they have been starting to work together to help researchers increase the diversity of people taking part in research in the UK and set out their expectations in future guidance.

They want to ensure that the whole UK population can benefit from research. Everyone needs to have an understanding of how interventions work on different groups of people in the UK. The HRA states that "Including a range of people in research provides an understanding of the safety of drugs, devices and information about an illness or condition across different groups. Involving people who the research is for and about in the design stage, will help ensure that the research is more inclusive."

Other Initiatives

ICH E2B(R3) Questions & Answers (Q&As) Updated

In January 2023, the International Council for Harmonisation of Technical Requirements for In January 2023, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use updated the ICH E2B(R3) Questions & Answers (Q&As) for the ICH E2B(R3) Guideline: Electronic Transmission of Individual Case Safety Reports (ICSRs). The updated Q&As version 2.4 has reached Step 4 of the ICH Process, meaning it is ready for regulators to adopt in their jurisdictions.

The updated Q&As document has added a question regarding reporting vaccines given according to a schedule of multiple doses, how should the ICSR message capture which dose (sequence number) in the schedule that was given? Guidance provides three possible scenarios with the relevant data elements provided in the document:

Scenario 1: Patient received two doses of the same or different vaccine(s), the first dose is not suspected, and the second dose is suspected.

Scenario 2: Patient received two doses of the same vaccine and both doses are suspected.

Scenario 3: Patient received two doses of different vaccines and both doses are suspected.

Since 30 June 2022, the ICH E2B (R3) Format for Individual Case Safety Reports (ICSRs) is mandatory to use by all stakeholders (marketing authorisation holders or sponsors of clinical trials) when reporting to the EudraVigilance.

North America

United States of America

FDA Issues Draft Guidance Aimed at Improving Oncology Clinical Trials for Accelerated Approval

On 24 March 2023, the U.S. Food and Drug Administration (FDA) issued draft guidance, *Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics*, regarding clinical trial design considerations to support accelerated approval applications. The accelerated approval pathway is commonly used for approval of oncology drugs in part due to the serious and life-threatening nature of cancer and because of available intermediate clinical endpoints likely to predict clinical benefit.

The draft guidance discusses the design of clinical trials, and ways to improve the data available at the time of accelerated approval and reduce clinical uncertainty for patients by initiating postmarketing confirmatory studies in a timely manner. Specifically, the draft guidance addresses the design, conduct and analysis of data through two randomized clinical trial approaches – conducting two separate randomized controlled clinical trials or using one trial for both accelerated approval and to verify clinical benefit. The draft guidance also provides considerations for sponsors to determine the adequacy of single-arm studies to support an application.

For drugs granted accelerated approval, postmarketing confirmatory trials have been required to verify and describe the anticipated clinical benefit. The draft guidance discusses a potential advantage of randomized clinical trials–compared to single-arm trials–by highlighting that use of the one-trial approach, in appropriate cases, may not require separate clinical trials because longer term follow-up in the same trial could fulfil a postmarketing requirement to verify clinical benefit.

Moreover, confirmatory trials that are in progress at the time of accelerated approval are more likely to result in a timely verification of clinical benefit, therefore minimizing the period of uncertainty for patients.

Canada

Health Canada Moves to Reduce Regulatory Roadblocks and enhance Safety in Health Product Licensing

Health Canada has proposed new targeted provisions and regulatory amendments to the *Food and Drug Regulations* (FDR) and *Medical Devices Regulations* (MDR) in an effort to harmonize regulations and modernize health product practices. Stakeholders can provide feedback until 26 April 2023 on the proposed changes, which are not yet law. Health Canada is seeking feedback on both the proposed regulations and on multiple guidance documents related to the proposal. This regulatory initiative is part of the regulatory innovation agenda and will contribute to the government's biomanufacturing and life sciences strategy.

The proposed changes expand health product safety and reduce certain regulatory barriers. They include:

- earlier market access for drugs eligible for a rolling review;
- modernized requirements for biologic drugs;
- amending requirements for certain drugs that claim a manufacturer's standard;
- expanded use of terms and conditions on approvals;
- expanded use of risk management plans; and
- disaggregated data to evaluate drug safety in diverse populations.

The amendments will propose a requirement for Health Canada to receive disaggregated data about clinical trial participants to support the evaluation of submissions for new drugs or supplements to new drug submissions. Proposed "rolling reviews" will permit a manufacturer to file certain new drug submissions (NDS) and supplementary new drug submissions (SNDS) with Health Canada where only partial information on the safety and effectiveness of a drug is available, provided the missing information is submitted within a reasonable amount of time thereafter.

MEDICAL DEVICES

EUROPE

News from the European Commission

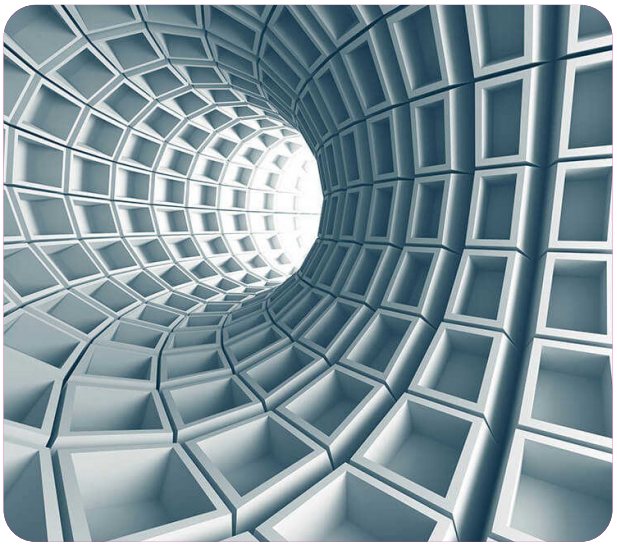
Regulation (EU) 2023/607 to Delay MDR and IVDR Transition

On 20 March 2023, the *Regulation (EU) 2023/607* of the European Parliament and of the Council amending Regulations (EU) 2017/745 (MDR) and 2017/746 (IVDR) as regards the transitional provisions for certain medical devices and in vitro diagnostic medical devices has been published in the Official Journal. The Regulation introduces a longer transition period to adapt to new rules, as foreseen under the MDR and IVDR.

Key elements of the Regulation (EU) 2023/607:

- For medical devices covered by a certificate or a declaration of conformity issued before 26 May 2021, the transition period to the new rules is extended **from 26 May 2024 to 31 December 2027** for higher risk devices (all class III devices, class IIb implantable devices except sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips and connectors) and until **31 December 2028** for medium and lower risk devices.
- A transition period **until 26 May 2026** also for class III implantable custom-made implantable devices, giving their manufacturers more time to obtain certification by a notified body.
- Remove the 'sell-off' date currently established in the MDR and in the In Vitro Diagnostic Medical Devices Regulation (IVDR). This will allow devices placed on the market before or during the transition period to continue to be made available without time limitation.

At the same time *Questions and Answers: Commission proposes an extension of the transitional periods for the application of the Medical Devices Regulation* has been issued together with the *MDR proposal Factsheet*.



Guidance on the Health Institution Exemption under Article 5(5) of MDR and IVDR.

The Medical Device Coordination Group (MDCG) has published the *Guidance on the Health Institution Exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746*. This document is a guide and provides directions on the application of some of the provisions contained in Article 5 (5) of the EU Regulations 2017/745 (Medical Devices Regulation, MDR) and (EU) 2017/746 (In Vitro Diagnostic Medical Devices Regulation, IVDR) which sets out rules for a healthcare institution on the manufacture and use of in-house medical devices, which are exempted from most of the above regulations. The guide addresses medical devices as well as in-vitro diagnostic devices and is intended for healthcare professionals and researchers involved in the design and modification of in-house devices. The guide is also intended to support the application of Article 5(5) by national competent authorities. This document is accompanied by two annexes containing a Public Statement on the manufacture and use of in-house devices by health care institutions, and a Schedule for the application of the various provisions of Article 5(5) of the IVDR.

Questions and Answers (Q&As) on Vigilance Terms and Concepts as Outlined in the MDR

In February 2023, the Medical Device Coordination Group published *Questions and Answers on vigilance terms and concepts as outlined in the Regulation (EU) 2017/745 on medical devices (MDR)*. This document aims to establish a common understanding of terms and concepts so that MDR vigilance requirements can be implemented in an effective and harmonised manner. For this reason, the scope of the document focuses on clarifying the relevant concepts presented in Section 2 of Chapter VII of MDR.

The document covers 20 Q&As and should be read in conjunction with the MDR, the relevant standards and the MDCG guidance documents. Provided are examples of 'incidents' and 'serious incidents' under each categorisation. A document also reminds about timelines of vigilance reporting for manufacturers; the reporting requirements outlined in Article 87 MDR; the reporting timelines defined by Article 87(3) to (5) MDR with examples demonstrating the timelines for the exceptional cases.

In addition, the guidance provides flowchart which illustrates the process to be followed by manufacturers for the management of incidents and serious incidents.

List of Standard Fees for Notified Bodies

The Medical Device Coordination Group (MDCG) published *Lists of Standard Fees* document which is intended to assist notified bodies defining their list of fees for publication in accordance with MDR Article 50 and IVDR Article 46. These articles establish the requirement for notified bodies to make their standard fees publicly available.

Fees can be charged as "flat fees" (i.e., fixed fees that do not depend on the time and resources needed but which should adequately be based on actually incurred costs) and "time-based fees" (i.e., fee items based on the time allocated for the activity). The MDCG clarifies also the meaning of "publicly available" fees, currency to be used and language used for the list of standard fees.

Update of Guidance on Classification Rules for IVDR

Guidance on Classification Rules for In vitro Diagnostic Medical Devices under Regulation (EU) 2017/746 (IVDR) has been revised by the MDCG. The primary purpose of this document is to provide guidance to manufacturers, notified bodies and health institutions on how to classify an IVD prior to placing it on the market, making available on the market or putting into service in the European Union. It is also intended to inform regulators and other stakeholders when assessing the class attributed to an IVD by a manufacturer or a health institution. In second revision Rule 1 and Rule 3 have been updated.

In addition, Annex 2 has been added presenting a flowchart to help determine whether an IVD is a CDx (companion diagnostics).

News from Individual Countries

Germany

MDR and IVDR Initial Submission Workflow

In January 2023, the German Federal Institute for Drugs and Medical Devices (BfArM) published workflow of overview for initial submission to the Ethics Committee (EC) and to the Competent Authorities (CA) in Germany under Medical Device Regulation (MDR) and In Vitro Diagnostic Medical Devices Regulation (IVDR).

The published document shows all possible regulatory pathways steps which should be done to get approval for the clinical investigation with medical device (MD) or in vitro medical device (IVMD) depending on study type. It indicates where the EC assessment, CA assessment (BfArM/PEI- Paul Ehrlich Institute), Competent federal state authority (Local authority) and Local authority for study site assessments are needed.

Spain

New Royal Decree 192/2023

The Spanish Agency of Medicines and Sanitary Products (AEMPS) has informed that the Council of Ministers has approved the new Royal Decree 192/2023 on 21 March 2023 implementing the Medical Devices Regulation (MDR) provisions to the national legislation on medical devices, however during writing the article the final text has not been published yet.

Some of the key points implicated include the manufacture of devices for use in the healthcare institution itself (commonly referred to as "in house"), reprocessing of single-use devices and their use, marketing registration, prescription-only products, authorisation of clinical investigations, and market surveillance and control obligations, amongst others.

The text, at the same time, repeals the previous regulations - i.e., Royal Decree 1591/2009 of 16 October 2009 (the current Royal Decrees on Medical Devices) and Royal Decree 1616/2009 of 26 October 2009 (Active Implantable Medical Devices) - with the exceptions set out in the transitional provisions and in the derogatory provision of the MDR.

The AEMPS will organise an information day for the official presentation of the new Royal Decree. The invitation to attend and the information for the registration to this day will be published on the website of the AEMPS.

Updates in the Instructions for Managing Clinical Investigations with MDs

On 2 February 2023, the AEMPS updated the instructions for managing clinical investigations with Medical Devices (MDs) in Spain to clarify how to proceed in the current complex regulatory scenario:

- Regulation (EU) 2017/745 on Medical Devices (MDR) establishes the general requirements in relation to clinical investigations with medical devices in chapter VI and annexes XIV and XV.
- Electronic system on clinical investigations EUDAMED (MDR art.73) is not yet ready. When available it would be a tool similar to CTIS intended for MDs.
- CTIS and EUDAMED will be interoperable, and this will be quite interesting for combined studies involving medicinal products + medical devices.
- The AEMPS is working on a new royal decree that will repeal current RD 1591/2009 and RD 1616/2009 in order to implement the MDR and develop the aspects to be developed by the national legislations.

Practical considerations will be provided by the AEMPS based on the experience obtained in this dedicated area:

https://www.aemps.gob.es/productos-sanitarios/investigacionclinica-productossanitarios/instrucciones-de-la-aemps-para-la-realizacion-de-investigaciones-clinicas-con-productos-sanitarios-en-espana/?lang=en

Topics covered by the updated instructions:

1. Type of clinical investigations that will lead to different requirements to be able to initiate the clinical investigation.

Aspects under consideration:

- Does the MD bear the CE marking?
- Is the MD used or not within its intended purpose?

- Is the MD used according to its approved Instructions for Use?
- Does the study require procedures additional to those performed under the normal conditions of use of the device that are also invasive or burdensome?

One of the key aspects is that it clarifies the process to be followed with Post-Market Clinical Follow-up (PMCF) studies Defined in MDR art. 74(1). Therefore, if additional and burdensome procedures are required a notification via NEOPS portal is required.

However, if the same MD bearing CE marking is used within the scope of its intended purpose, according to its instruction for use and the clinical investigation is not involving additional and burdensome procedures to the subject the AEMPS notification/ approval is not needed.

2. Procedure of AEMPS authorization explaining:
   - The telematic procedure to be used in Spain till EUDAMED is ready to be used;
   - Timelines for validation and evaluation;
   - Timelines for Substantial modifications;
   - Timelines for Annual report, end of study notification and final report.
3. Some of the key aspects is that it was clarified that:
   - The Instructions for Use and labelling should be in Spanish.
   - Need to have an insurance or damage compensation according the MDR art. 69.
   - Safety notifications should be done according to MDR art. 80 MDCG 2020-10/1 Rev. 1 "Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745" and MDCG 2020-10/2 Rev1 "Guidance safety report form".
4. Additionally related annexes have been updated:
   - Annex A: listing the documentation needed to initiate a clinical investigation *Anexo A – Documentación relativa a la solicitud de investigación clínica*
   - Annex B: listing the documentation needed for substantial modifications *Anexo B – Documentación relativa a la solicitud de enmienda sustancial de investigación clínica*
   - Annex C: Basic data form for the application for authorisation of clinical investigations involving medical devices (Previous form was issued in 2004)
     Anexo C – Formlario de datos básicos de la solicitud de autorización de investigaciones clínicas con productos sanitarios
   - Annex D: Manufacturer's declaration of compliance with the general safety and functional requirements (previous form was still making reference to obsolete directives) *Anexo D – Declaración del fabricante del cumplimiento de los requisitos generales de seguridad y funcionamiento*

Table 1. The regulatory path to be followed for the different kind of clinical investigations with MDs in Spain

Type of clinical investigation	**Study requiring procedures additional to those performed under the normal conditions of use of the device that are also invasive or burdensome**	**Mentioned in MDR:**	**CA (Competent Authority) authorization needed**	**EC (Ethic Committee) approval needed**	**Sites Agreement** (conformidad de la dirección del centro)
MDs **without CE marking** to demonstrate conformity of devices	Not relevant	Defined in MDR Article 62	Yes	Yes, listing all the participating sites	Yes
MDs bearing **CE marking** used **outside the scope of its intended purpose** to demonstrate conformity of devices	Not relevant	Defined in MDR Article 74(2)	Yes	Yes, listing all the participating sites	Yes
MDs bearing the **CE marking** used **within the scope of its intended purpose and according to its instruction for use.**	Yes	'PMCF investigation' Defined in MDR Article 74(1)	Notification of the clinical investigation at least 30 days prior to its commencement through NEOPS*. *NEOPS is a Spanish platform intended for use in these studies. Once EUDAMED will available it is foreseen that NEOPS will no longer be needed.	EC approval. The document should be accepted by all sites and does not need to list all participating sites	Yes
MDs bearing the **CE marking** used **within the scope of its intended purpose and according to its instruction for use.**	No		Not needed	EC approval. The document should be accepted by all sites and does not need to list all participating sites	Yes
MDs **without CE marking** not intended to demonstrate conformity of devices to obtain the CE marking	Not relevant	AEMPS to be consulted about the procedure to follow. It will be evaluated to follow requirements on MDR Article 62	AEMPS to be consulted about the procedure to follow. It will be evaluated to consider the need of AEMPS authorization.	Yes, listing all the participating sites	Yes
MDs bearing **CE marking** used **outside the scope of its intended purpose** not intended to demonstrate conformity of devices to obtain the CE marking.	Not relevant	AEMPS to be consulted about the procedure to follow. It will be evaluated to follow requirements on MDR Article 62	AEMPS to be consulted about the procedure to followed. It will be evaluated to consider the need of AEMPS authorization.	Yes, listing all the participating sites	Yes

North America

United States of America

FDA: FD&C Act is Amended to Include Section 524B "Ensuring Cybersecurity of Devices"

On 29 March 2023, the FDA issued a guidance for immediate implementation: *Cybersecurity in Medical Devices: Refuse to Accept Policy for Cyber Devices Under Section 524B of the FD&C Act*. Beginning on 29 March 2023, manufacturers of cyber devices are now required to include information to demonstrate reasonable assurance that their cyber device and related systems are cybersecure. The new authorities provided in the Omnibus represent a significant step forward in the FDA's role in regulating cybersecurity as part of a medical device's safety and effectiveness. The FDA generally intends not to issue "refuse to accept" decisions for premarket submissions for cyber devices submitted before 1 October 2023, based solely on information required by section 524B of the FD&C Act. Instead, the FDA will work collaboratively with sponsors of such premarket submissions as part of the interactive and/or deficiency review process.

Canada

Health Canada Updates the Forward Regulatory Plan

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 include 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 UNITED STATES

FDA Issues Notice Addressing the Agency's COVID-19 Related Documents: Public Health Emergency Expires in May

On 10 March 2023, the FDA issued a notice addressing the agency's COVID-19-related guidance documents, including which of those guidance documents will no longer be in effect after the expiration of the COVID-19 public health emergency (PHE) declared under the Public Health Service (PHS) Act, and which of those guidance documents the FDA is revising to temporarily continue in effect.

This notice follows an announcement from the U.S. Department of Health and Human Services that, based on current COVID-19 trends, the Department is planning for the COVID-19 PHE declared under the PHS Act to expire on 1 May 2023.

The ending of the PHE declared under the PHS Act will not impact the FDA's ability to authorize devices (including tests), treatments or vaccines for emergency use. Existing emergency use authorizations (EUAs) for products will remain in effect and the agency may continue to issue new EUAs going forward when criteria for issuance are met.

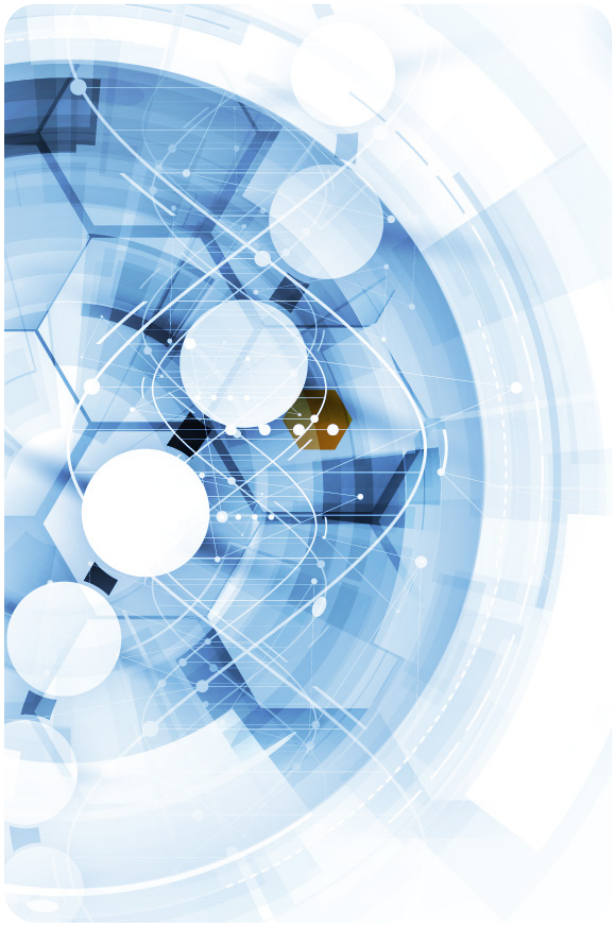
FDA Updated the Breakthrough Devices Program Online Metrics

On 24 February 2023, the FDA updated the Breakthrough Devices Program online metrics to add more device designations and marketing authorizations. As of 31 December 2022, the program's new total for devices granted designations is 760 and for devices authorized for marketing is 62. The Breakthrough Devices Program can help provide patients and health care providers with timely access to certain medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.

The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. The Breakthrough Devices Program replaces the Expedited Access Pathway and Priority Review for medical devices. The FDA considers devices granted designation under the Expedited Access Pathway to be part of the Breakthrough Devices Program.

FDA Continues Important Work to Advance Medical Products for Patients with Rare Diseases

On 23 February 2023, the FDA published the FDA Voices: "FDA Continues Important Work to Advance Medical Products for Patients with Rare Diseases," by Robert M. Califf, M.D., Commissioner of Food and Drugs and Sandy Retzky, D.O., J.D., M.P.H., Director, Office of Orphan Products Development. Rare Disease Week is observed during the last week of February. The agency hosted its virtual Rare Disease Day on 27 February 2023. The goal of this year's Rare Disease Day was to explore ways to engage and collaborate with patients and patient advocates to support the development of medical products for rare diseases.



FDA and Swissmedic Sign MRA

On 12 January 2023, the FDA signed a Mutual Recognition Agreement between the United States and Switzerland, allowing the FDA and Swissmedic to share each other's GMP inspectional findings, which will reduce unnecessary costs and duplicative efforts.

By signing such an agreement, with the Swiss Confederation (Switzerland), the FDA and the Swiss Agency for Therapeutic Products (Swissmedic) will be able to utilize each other's good manufacturing practice inspections of pharmaceutical manufacturing facilities, avoiding the need for duplicate inspections.

FDA Outlines Risk-based Approach to Monitoring Clinical Trials

On 11 April 2023, FDA issued Final guidance meant to assist drug and medical device makers in developing risk-based monitoring strategies for clinical investigations involving drugs, biologics and medical devices.

The question-and-answer format document states that "clinical investigation monitoring is a quality control tool for determining whether investigation activities are being conducted as planned. This guidance contains recommendations on planning a monitoring approach, developing the content of a monitoring plan, and addressing and communicating monitoring results."

The document also expands on FDA's August 2013 guidance for industry entitled "*Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring*" by providing additional information to facilitate sponsors' implementation of risk-based monitoring.

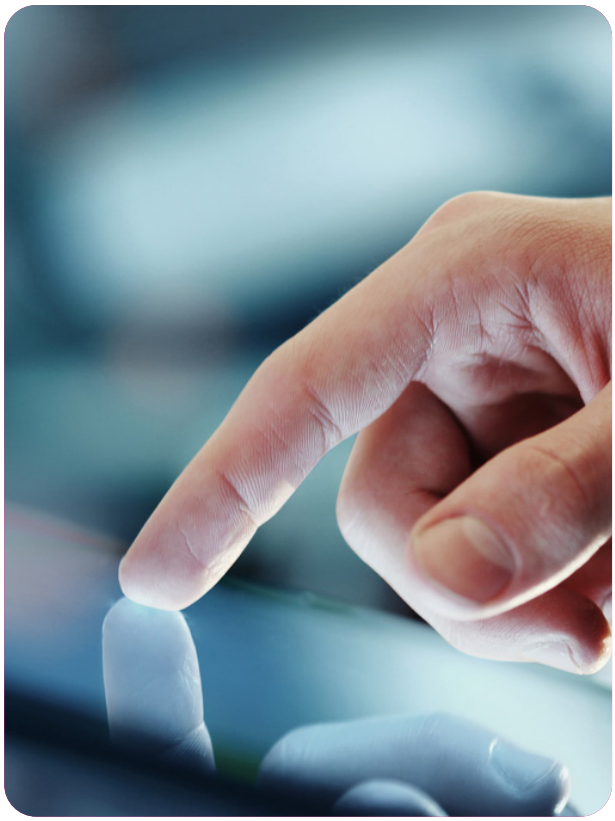
The revision also updates the information to the question: "How can a risk-based approach to monitoring that includes centralized monitoring help minimize missing data or protocol deviations?"

The guidance now states that "centralized monitoring is a systematic analytical evaluation of study conduct across multiple clinical sites, conducted by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians). Centralized monitoring may allow sponsors to (1) review study-wide data for inconsistencies or omissions; (2) perform activities such as data checks, for completeness and consistency; (3) verify source data; (4) ensure that institutional review board and informed consent documents are current; and (5) determine which clinical sites need on-site review."

Congress Pushes for Greater Enforcement of ClinicalTrials.gov

In January 2023, Congress Ranking Member of the House Energy & Commerce Committee Frank Pallone (D-NJ) wrote to FDA Commissioner Robert Califf and Lawrence Tabak, acting director of the National Institutes of Health (NIH), urging greater enforcement of clinical trial results reporting in ClinicalTrials.gov. Pallone cited recent research that found less than one third of registered trials fail to report results, and many that do fail to report them on time.

"Despite these troubling results, the Food and Drug Administration (FDA) and NIH have only carried out limited enforcement activities for failure to comply with ClinicalTrials.gov requirements," Pallone wrote. The congressman noted that FDA did not begin issuing preliminary notices of noncompliance to investigators until 2013, and has sent just four notices of noncompliance since it began sending them out in 2021, none of which have resulted in the agency imposing civil money penalties on delinquent sponsors.



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