[Logo here] State Expert Center of the Ministry of Health of Ukraine

Reference Information on the Clinical Trial Status in Ukraine for the period from 01 January 2024 until 31 March 2024

The State Expert Center of the Ministry of Health of Ukraine (hereinafter referred to as the Center) during the year in question traditionally publishes analytical information on the status of clinical trials (hereinafter referred to as CT) in Ukraine, prepared by the Department for the Expert Review of Nonclinical and Clinical Trial Materials (hereinafter referred to as the Department).

The full-scale military aggression of the Russian Federation in Ukraine is in its third year, but CT potential has been preserved thanks to the joint efforts of all stakeholders. CTs that were initiated in previous years are ongoing, and Approvals by the Central Executive Body prior to the start of new CTs are being granted. Appropriate supervision of the conduct of CTs is carried out by the regulator, through the resuming of clinical audits (from May 2022) and the appropriate supervision of Local Ethics Committees at healthcare facilities where the CT is conducted.

The Center considers it necessary to highlight **on a quarterly** basis dynamic processes in the field of clinical trials in comparison with the corresponding periods in 2022 and 2023, as well as other activities of the Center aimed at supporting CTs in Ukraine, by participating in the development and updating of the legal framework for conducting CTs in accordance with European legislation.

We emphasize that the main and constant priority during the CT life cycle was and remains the observance of international ethical principles and ensuring that the rights, safety, and well-being of subjects is protected. The CT life cycle requires clear, coordinated actions from all participants within the process.

Q1 of 2024

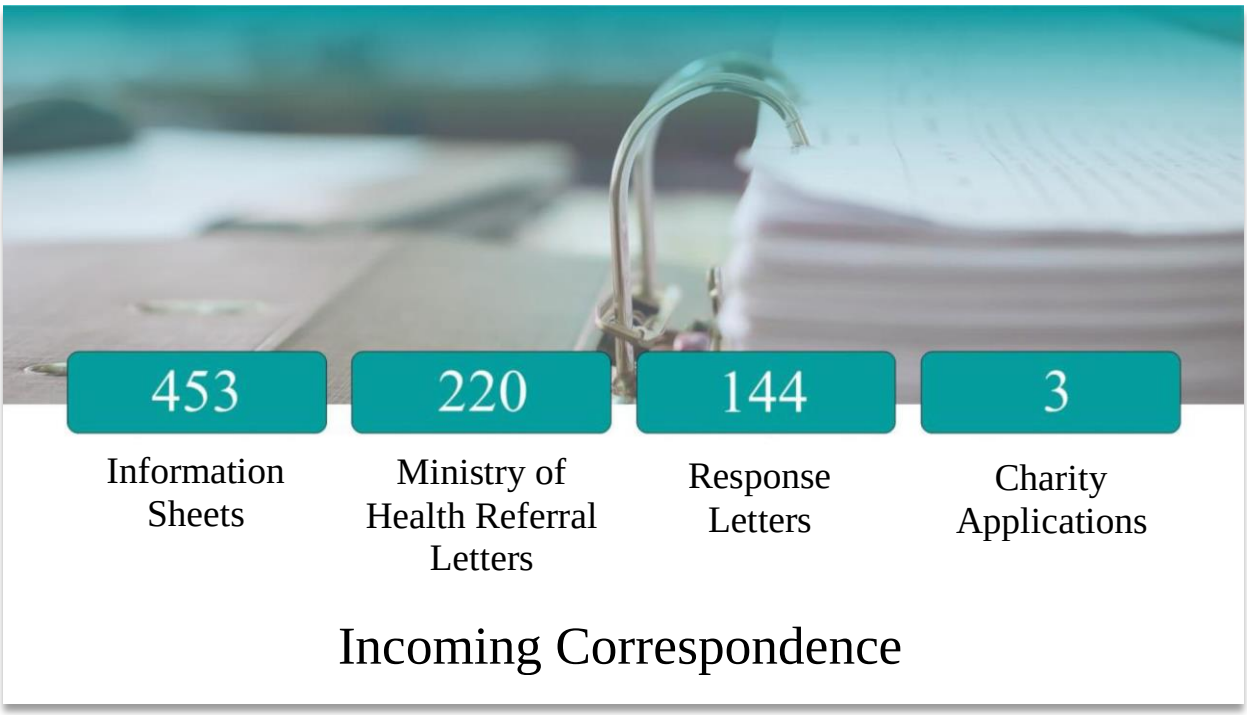
The data below reflect the recorded dynamic changes in CTs in Ukraine for Q1 of 2022–2024.

In Q1 of 2024, the Center recommended that the Ministry of Health of Ukraine (hereinafter referred to as the MoH) approved the conduct of **10 CTs** in total, including **2** CT protocols with domestic manufacturers, as well as **225** substantial amendments (hereinafter referred to as SA) to the protocols of international multicenter CTs.

The priorities of the Center regarding communication with stakeholders did not change in Q1 of 2024, and are supported by all available means, namely: by e-mail, receiving requests through the electronic resource "Online Consultation" on the Center's official website, responding to written requests, reviewing various formats of Information Sheets, offline consultations, holding seminars, etc.

In Q1 of 2024, the Department received and processed 820 incoming correspondences, of which **220** were referral letters from the Ministry of Health to Applications for Conducting a CT and approval of substantial amendments, **3** charity applications; **144 response letters** to letters regarding the completeness of CT materials; **453 Information Sheets:** Applicant Information Sheets according to the passed CT stages; letters of request, consultation letters of request; letters about CT initiation; information on the safety of investigational medicinal products; and other CT-related correspondence, namely:

- **111** CT Periodic Reports
- **33** CT Final Reports
- **45** regarding the end of the CT, including **19** notification letters regarding early completion of the CT in Ukraine,
- **9** notification letters regarding the transfer of 14 patients enrolled in a CT from one approved study site to another study site in Ukraine (**8** patients) or outside Ukraine (**6** patients, to study sites in Poland and Germany).



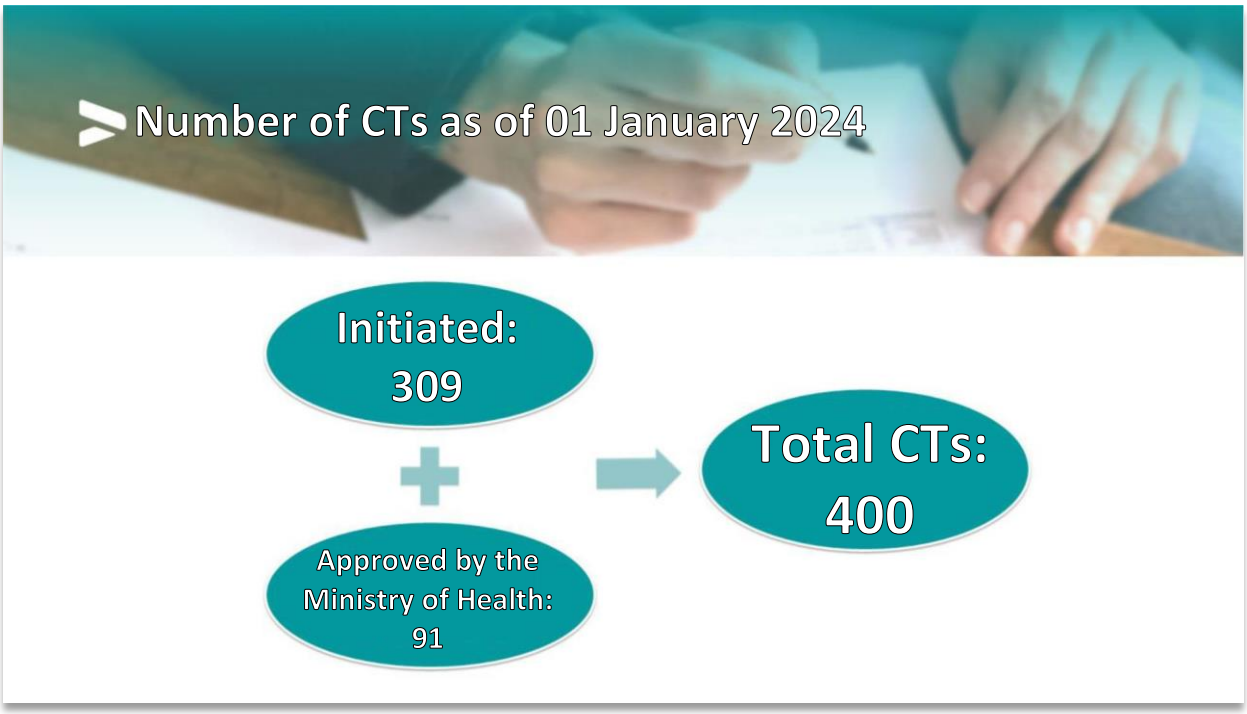
Of the positive trends according to the information received by the Center during the reporting period:

- 14 notifications of the start of a CT
- **3** CT Protocols resuming patient recruitment
- **0** notification letters on the temporary suspension of a CT
- **0** letters regarding the suspension of new patient recruitment and/or screening and/or randomization of subjects.

All incoming documentation was processed by Department staff properly and in a timely manner. Responses were provided by e-mail and/or in paper form through the Center's Service Center.

ANALYSIS OF CT STATUS AT VARIOUS STAGES OF CONDUCT

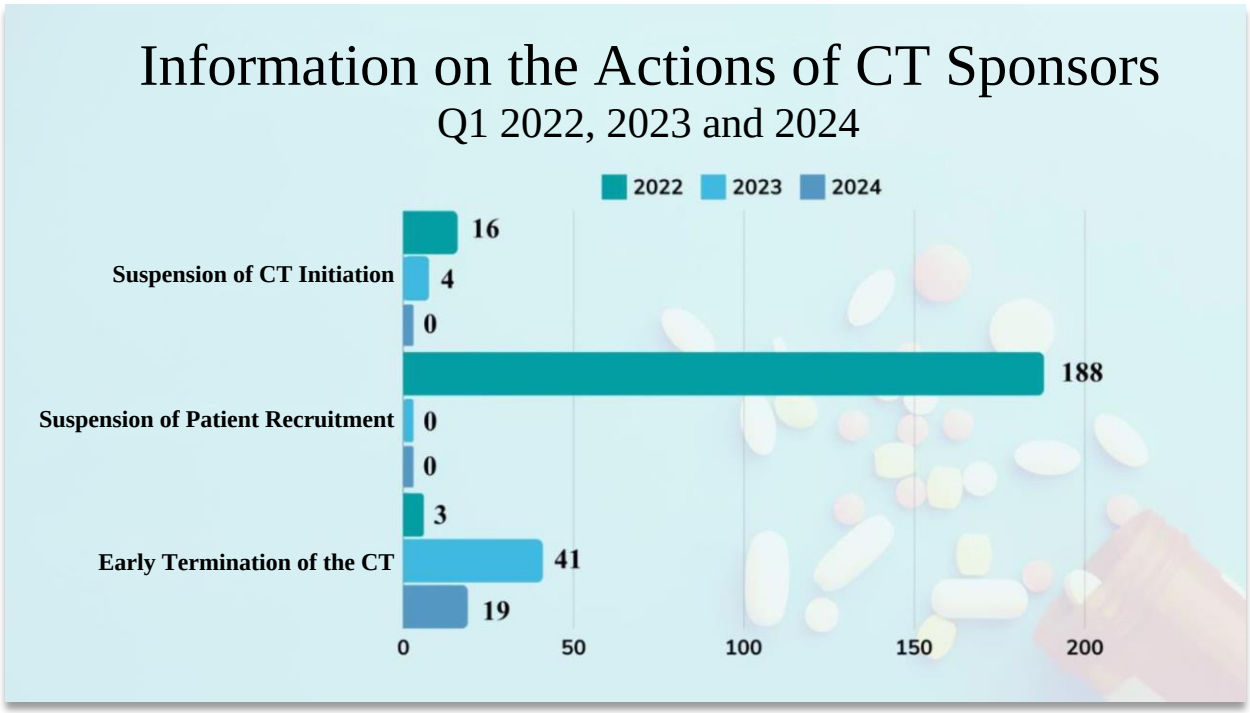
As of 01 January 2024, the following information is current regarding the number of CTs that are being conducted in Ukraine at various stages: **400 CTs** in total, of which **309** CTs have already been initiated, of which **41** were initiated in 2023 and **91 CTs** were approved by the Ministry of Health for conduct.



INFORMATION ON THE ACTIONS OF CT SPONSORS

During the specified period (01 January 2024 – 31 March 2024), the Sponsor took the following actions regarding CTs approved by Orders of the Ministry of Health and initiated CTs:

- **Temporary suspension of CT initiation due to the war in the country:**
  Q1 2024: 0 CTs, Q1 2023: 4 CTs, Q1 2022: 16 CTs.
- **Suspension of patient recruitment** (suspension of patient screening, suspension of patient randomization):
  Q1 2024: 0 CTs; Q1 2023: 0 CTs, Q1 2022: 188 CTs.
- **Early termination of CTs:** Q1 2024: 19 CTs**,** of which 5 were due to the war in Ukraine, and 14 CTs due to low efficacy,
  Q1 2023: 41 CTs, Q1 2022: 3 CTs.



TRANSFER OF SUBJECTS TO OTHER STUDY SITES

In Q1 of 2024, the **Department processed 9 letters** from Sponsors/CROs related to the transfer of study subjects to other study sites (hereinafter referred to as SS) (14 patients in total): in Ukraine (**8 patients: 2 hematology, 1 neurology, 5 hematology**) and abroad: Poland: 5, neurology, and Germany: 1 endocrinology/nephrology (**6 patients: 5 neurology, 1 endocrinology/nephrology**).

Number of study subjects transferred to other CT clinical study sites during 2024:

Country	01	02	03	Total
Ukraine	2	1	5	8
Poland	1	2	2	5
Germany	0	1	0	1
Total	3	4	7	14

The following table provides information regarding the CT therapeutic areas in which patient transfers occurred:

Therapeutic area	Month (abroad/in Ukraine)			
	01	02	03	Total
Neurology	1/0	2/1	2/0	5/1
Hematology	0/2	0/0	0/5	0/7
Endocrinology/Nephrology	0/0	1/0	0/0	1/0
Total	1/2	3/1	2/5	6/8

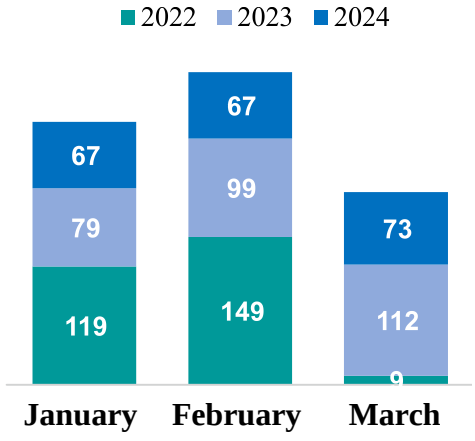
The greatest number of transferred patients was in the therapeutic areas of neurology (6), and hematology (7).

CT LIFE CYCLE

The life cycle of CTs conducted in Ukraine is supported by the incorporation of substantial amendments to CT protocols, information about which is presented on the histogram as dynamics for Q1 of 2022–2024 by the number of applications for substantial amendments received by the Center from the Ministry of Health, and by the number reviewed at the meetings of the Center's Scientific and Technical Councils (STC) and recommended for approval by the Ministry of Health.

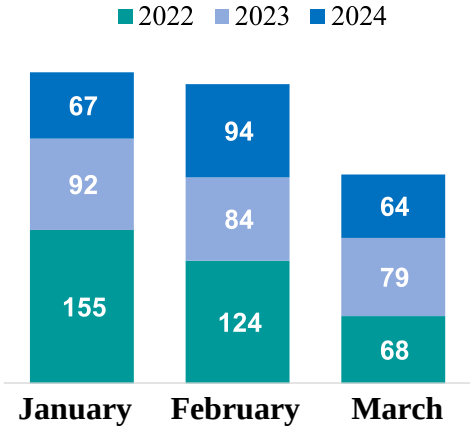
Number of Applications for Substantial Amendments to CT Protocols Received by the Center in Q1 of 2022–2024

Month	2022	2023	2024
January	119	79	67
February	149	99	67
March	9	112	73
Total	277	290	207
% from 2022/2023	**74.5%**	**71.4%**	



Number of Substantial Amendments to CT Protocols Reviewed at STC Meetings in Q1 of 2022–2024

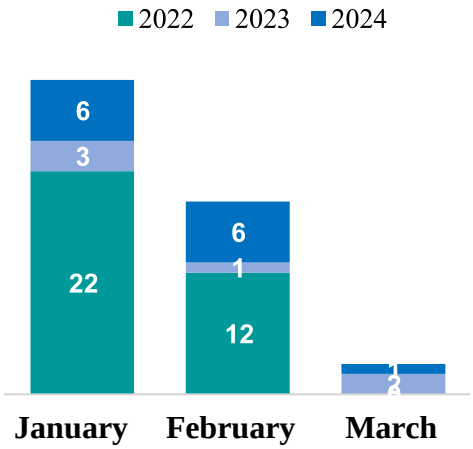
Month	2022	2023	2024
January	155	92	67
February	124	84	94
March	68	79	64
Total	347	255	225
% from 2022/2023	**64.8%**	**88.2%**	



The number of substantial amendments for the specified period compared to the same period in previous years during the military aggression of the Russian Federation indicates the preservation of CT potential and their continuous monitoring during the life cycle and compliance with GCP requirements.

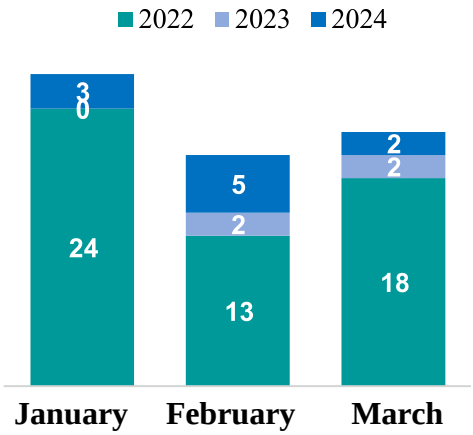
Number of CT Protocol Applications Received by the Center in Q1 of 2022–2024

Month	2022	2023	2024
January	22	3	6
February	12	1	6
March	0	2	1
Total	34	6	13
% from 2022/2023	**38.2%**	**216%**	



Number of CT Protocols Reviewed at Scientific Expert Council Meetings in Q1 for 2022–2024

Month	2022	2023	2024
January	24	0	3
February	13	2	5
March	18	2	2
Total	55	4	10
% from 2022/2023	**18.8%**	**250%**	



During the reporting period, 5 domestic manufacturer CT applications were received.

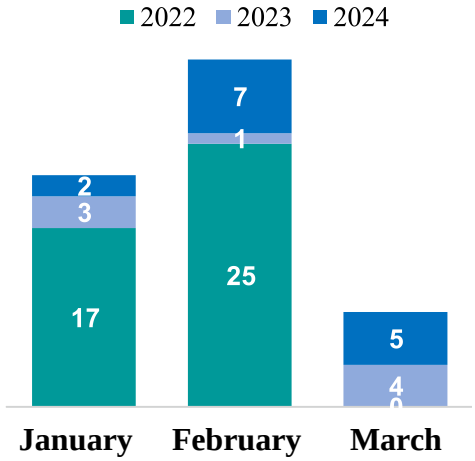
The number of applications for the conduct of a CT increased in Q1 of 2024 compared to the number in Q1 of 2023. Q1 of 2022 contains indicators of received applications for the conduct of a CT for two months prior to the war, therefore they contain significant differences.

POSITIVE TRENDS IN THE RESUMPTION OF CTs IN UKRAINE

In particular, letters began to arrive from Applicants regarding:

- **CT initiation: 14**

Month/Year	2022	2023	2024
January	17	3	2
February	25	1	7
March	0	4	5
Total	42	8	14



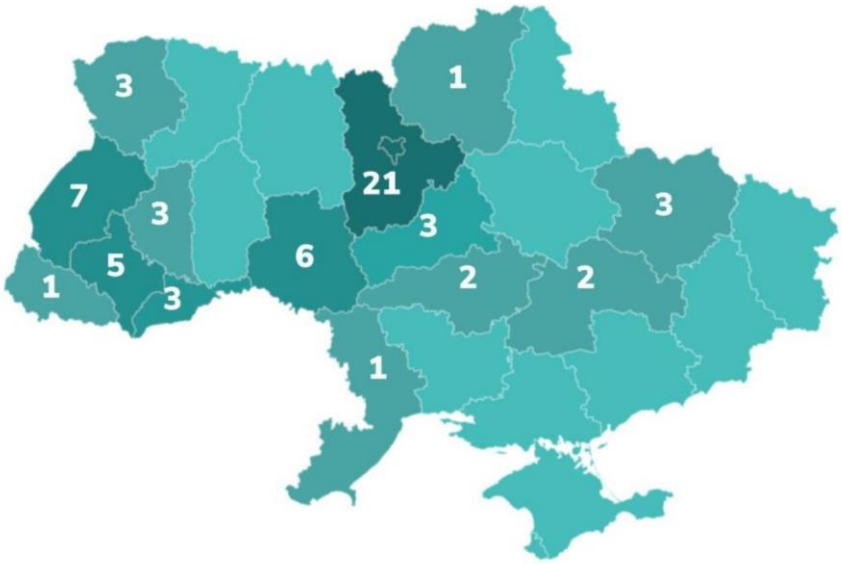
In particular, in Q1 of 2024 CT initiation under the following therapeutic profiles: allergology: **1 CT**, neurology: **2 CTs**, hematological oncology: **2 CTs**, bioequivalence: **1 CT**, gastroenterology/proctology: **3 CTs**, rheumatology: **1 CT**, urological oncology: **1 CT**, pulmonology: **2 CTs**, infections: **1 CT**.

- In Q1 of 2024, **the Sponsor resumed patient recruitment within 3 CTs (2 neurology, 1 psychiatry).**
- In Q1 of 2024, **3 patients within the neurology therapeutic group** returned from abroad to the approved study site in Ukraine.

Department staff are constantly in contact with Applicants in order to properly conduct the CT under martial law in Ukraine.

In Q1 of 2024, **62 study sites for new CT protocols** were recommended for approval **and were incorporated through substantial amendments to already initiated CTs**, in particular: 21 study sites in Kyiv and the Kyiv Region, 7 in Lviv, 6 in Vinnytsia, 5 in Ivano-Frankivsk, 3 study sites each in Lutsk, Ternopil, Kharkiv, Chernivtsi, Cherkasy, 2 study sites in Dnipro and in Kropyvnytskyi, 1 study site in Uzhhorod, Odesa, and Chernihiv.

Study Sites for New CT Protocols in 2024



ON THE INFORMATIONAL AND METHODOLOGICAL WORK CONDUCTED BY THE DEPARTMENT

An important task in the life cycle of the approval procedure for conducting clinical trials in Ukraine is to implement and ensure the continuous functioning of the procedural approach to management, improvement and implementation of legislation governing the organization, the conduct and control of clinical trials.

The participation of the Department in the processing and development of draft proposals or draft development through the following regulatory documents:

- Amendments to Order No. 690 of the Ministry of Health of Ukraine dated 23 September 2009, approved by Order No. 138 of the Ministry of Health of Ukraine dated 26 January 2024, registered with the Ministry of Justice of Ukraine on 13 February 2024 under No. 219/41564, entered into force in March 2024. The changes relate to the conduct of CTs of advanced therapy drugs in accordance with EU legislation.
- The information on Approval No. 480 of the Order of the Ministry of Health of Ukraine dated 20 March 2024, Guideline ST-N of the Ministry of Health of Ukraine 42-9.0:2024 "Medicinal Products. Classification of Advanced Therapy Drugs" has been prepared and uploaded onto the Center's site.
- To implement the Order of the Minister under the Ministry of Health of Ukraine and Order No. 03 of the Center dated 08 January 2024, the following documents were prepared:
- Draft of the Procedure for Conducting Clinical Trials of Medicinal Products and the Expert Review of Clinical Trial Materials and Standard Ethics Committee Regulations and

- Amendments to Order No. 1525 of the Ministry of Health of Ukraine dated 24 August 2022 "On the Approval of the Procedure for the Approval and Conduct of the Extended Patient Access Program to Unapproved Medicinal Products, and the Study Subject (Patient) Access Program to the Investigational Medicinal Product after Completion of the Clinical Trial, and Amendments to the Procedure for the Importation of Unapproved Medicinal Products, Standard Samples, and Reagents into the Territory of Ukraine".

The Department's support for external stakeholder feedback:

Provided by Department staff:

- 3 online and offline consultations for foreign and domestic Applicants/Sponsors
- 51 consultative electronic requests from Applicants were processed and written electronic responses were prepared and provided
- 17 response letters were prepared for Applicants (CT Sponsors) after processing external correspondence (letters related to the conduct of CTs, Periodic Reports, Investigator's Brochures, Final Reports).

Department staff participated in the following:

- In a meeting with representatives of cell and tissue bank associations, organizations, and manufacturers, in order to discuss Amendment No. 138 dated 26 January 2024 to Order No. 690 of the Ministry of Health dated 23 September 2009 on CT advanced therapy drugs.

Under the conditions of martial law, it is extremely important to ensure the proper level of expert review of clinical trials by Local Ethics Committees at healthcare facilities. The Department held an online meeting with Local Ethics Committees in order to properly organize the methodological coordination of their work. The subject of the webinar was "Meeting with Ethics Committee Members: Protecting the Rights of Study Subjects Participating in Trials of Medicinal Products". During the meeting, the following were highlighted: the importance of ethical issues in the context of conducting a CT, familiarized with the main regulatory aspects of the ethical expert review of a CT which prevent possible risks for study subjects; international and national documents regulating the ethical principles of conducting a CT; the features of conducting a CT involving particular (vulnerable) groups of patients were presented in detail.

On the website of the Center in the subsection EXPERT REVIEW OF NONCLINICAL AND CLINICAL TRIAL MATERIALS, under the heading “Methodological Support for Ethics Committees,” there is a notification regarding the requirement and volume of reporting on the work of Local Ethics Committees. Topical ethical issues are published on the official website and on the Center's Facebook page.

The Department reviewed **3** Programs for Extended Access of Study Subjects to Investigational Medicinal Products (IMPs) Following the Completion of a Clinical Trial.

In order to improve the qualifications of experts, the Department held **7** internal webinars and **16** external training events (seminars, webinars), including the pharmaceutical forum "PHARMA@FOCUS ON THE PATIENT 2024. PHARMACOVIGILANCE".

Department staff listened to the 2-day Symposium on Good Clinical Practice and Pharmacovigilance by Health Canada, the Joint Decision of the US Food and Drug Administration (FDA), MHRA-UK. The following subjects were covered at the Symposium:

Session 1: Harmonization of Good Clinical Practice (GCP), ICH E6(R3) Update; Session 2: Technologies in Clinical Trials, Digital Health Technologies (DHT); Session 3: Trials Involving Decentralized Elements or Pragmatic Functions; Session 4: Good Data Management Practices Update.

Department staff joined online and heard the FDA and Health Canada's Regional Consultation on ICH Guidelines. In particular, the following matters were highlighted: ICH Review. Update of Guidelines related to ICH Efficacy; M12, Drug Interaction Studies, Post-Approval Safety Data Management: Definitions and Standards for the Management and Reporting of Individual Case Safety Reports; E6(R3) Principles of Good Clinical Practice and Appendix 1; Update of the ICH M14 Multidisciplinary Guideline, General Principles for the Planning, Development, and Analysis of Pharmacoepidemiological Studies Using Real-World Data to Assess the Safety of Medicinal Products, Update of ICH Quality-Related Guidelines: Q2(R2)/Q14, Review of Q2(R1) of Analytical Validation and Development of Analytical Procedures, Q5A(R2), Evaluation of the Viral Safety of Biotech Products Derived from Human or Animal Cell Lines, Q9(R1), Quality Risk Management; Updates on other important ICH developments.

In Q1 of 2024, Department staff and the Audit Office participated in the preparation and conduct of 2 online training seminars on international requirements for good clinical practice and legal regulations on conducting clinical trials in Ukraine on the subject "Good Clinical Practice (GCP). Legal Regulation of Clinical Trials", which were attended by 130 Investigators, representatives of Local Ethics Committees and experts from advisory and expert groups with the subsequent issuance of certificates.

Under continuous professional development for healthcare workers, Department staff held the first seminar online on the subject "Clinical Trials in Ukraine". The course covered key theoretical and practical aspects in the field of clinical trials of drugs: CT types and phases; information on the latest study designs; CT regulatory framework, taking into account current and new legislation on medicinal products, GCP principles of good clinical practice, EMA, ICH guidelines; the importance of CTs for the country, the health sector, patients; conditions for conducting clinical trials in Ukraine, and other matters.

The Department prepared the following presentation **"Clinical Trials Sector in Ukraine during the War: Expert Analysis"** for the international webinar "Clinical Trials in Ukraine: Current Status and Prospects" (online conference and offline meeting at the ARENSIA EXPLORATORY MEDICINE Medical Center.

The webinar was held by ARENSIA Exploratory Medicine LLC with the aim of attracting new clinical trials to Ukraine).

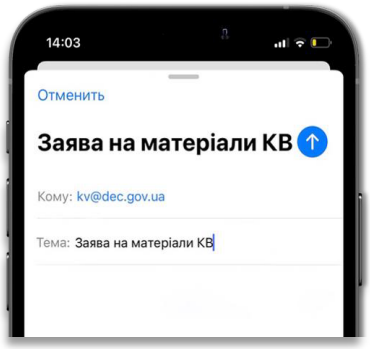
COMMUNICATION CHANNELS WITH THE CENTER

We kindly remind you that in connection with the war in the country, dedicated e-mail addresses have been put in place for the coordination of Sponsor activity, starting from 24 February 2022 and to date, for proper communication between the Sponsor or Sponsor's representative, CRO and Center, namely:

dec@dec.gov.ua: e-mail for all Information Sheets related to the conduct of clinical trials in Ukraine (for example, letters regarding the start and end of a clinical trial, Periodic and Final Reports, etc.)

evikno@dec.gov.ua: e-mail for the submission of Applications for conducting a clinical trial of a medicinal product, substantial amendments, and corresponding cover letters to the Ministry of Health

kv@dec.gov.ua: e-mail for the submission of clinical trial materials and substantial amendment clinical trial materials in accordance with the Procedure for the Conduct of Clinical Trials of Medicinal Products and the Expert Review of Clinical Trial Materials, approved by Order No. 690 of the Ministry of Health of Ukraine dated 23 September 2009; Additional materials, responses to remarks on clinical trial materials and substantial amendments



clinic@dec.gov.ua: e-mail for the submission of Safety Reports (DSURs) and notifications of adverse reactions during the conduct of clinical trials.