Information Report Regarding the Status of Clinical Trials in Ukraine in the Period from July 01, 2023 to September 30, 2023

The State Expert Center of the Ministry of Health of Ukraine (hereinafter referred to as the Center) traditionally publishes analytical information on the status of clinical trials (hereinafter referred to as the CTs) in Ukraine prepared by the Department of Expert Evaluation of Preclinical and Clinical Trials Materials (hereinafter referred to as the Department) and the Office for Laboratory and Clinical Practice (GLP, GCP) Audit.

As the full-scale military aggression of the russia continues and since the current situation has a significant impact on the processes of planning and conducting clinical trials in Ukraine, the Center considers it necessary to highlight the dynamic processes in the field of clinical trials on a quarterly basis. We would like to emphasize that the main and constant priority throughout the life cycle of the clinical trial has been and remains compliance with international ethical principles to ensure the protection of the rights, safety, and well-being of study subjects. The lifecycle of a CTs require clear, coordinated actions from all stakeholders in the process.

The Center's priorities in communication with applicants in the third quarter of 2023 remained unchanged and focused on interaction with stakeholders through available means to support and resume the CTs in Ukraine, namely: e-mail, receiving requests through the electronic resource "online consultation" on the official website of the Center, written requests, consideration of information letters, offline consultations, etc.

The following data reflects the dynamic changes in the field of CTs in Ukraine for the first, second and third quarters of 2023.

In the third quarter of 2023, the Center recommended to the Ministry of Health for approval the following:

- a total of 8 Protocols of CTs, 3 CTs of which are protocols from domestic manufacturers.
- 197 substantial amendments to the protocols of CTs MP section 4 of SAs to the protocols of CTs of domestic manufacturers.

In the third quarter of 2023, the Department received and processed incoming letters in the amount of 672, of which

192 were referrals of the Ministry of Health to applications for conducting CTs and approving Sas (substantial amendments);

480 were responses to letters regarding the completeness of the CT materials and responses to comments of the specialized expert review, information letters from applicants in accordance with the stages of the clinical trial, letters of inquiry, advisory letters, letters of notification of patient transfer, letters of commencement of the clinical trial, letters of completion of the clinical trial (including early completion of the clinical trial), periodic reports, final reports, information on the safety of the investigational medicinal products, other letters related to the clinical trial, among others:

- 103 periodic reports on the status of the CTs in Ukraine were submitted by the Sponsors;
- 34 reports on the premature termination of CTs were received;
- 2 letters of notification regarding the suspension of new patient enrollment and/or screening and/or randomization of subjects;
- temporary suspension of the CTs - 0 notification letters;
- termination of the CTs - 69, including early termination of the CTs in Ukraine - 29 notification letters;
- 13 letters of notification regarding the transfer of patients involved in the CTs from one approved clinical trial site (CTS) to other CTs in Ukraine or outside of Ukraine – 18 patients (to trial sites in Poland, Germany, Bulgaria, Canada, Lithuania, France, and the russia).

Among the positive trends:

- beginning of the CTs - 15 protocols of the CTs;
- recovery of recruitment - 1 protocol of CTs;
- 8 patients returned to the CTSs approved in Ukraine (5 letters).

The Department duly processed the incoming documentation and provided responses by e-mail and/or in hard copy via the Center's Service Center.

An analysis of the status of clinical trials that were at various stages as of the beginning of January 01, 2023 is provided below, namely: 662 clinical trials were approved and were being conducted at various stages in Ukraine, of which 487 were launched and 175 were approved by the Ministry of Health for implementation in Ukraine.

This information will be updated in the 2023 information note which will indicate the number of CTs in these states and the dynamics during the life cycle of CTs in Ukraine

Number of CTs as of January 01, 2023

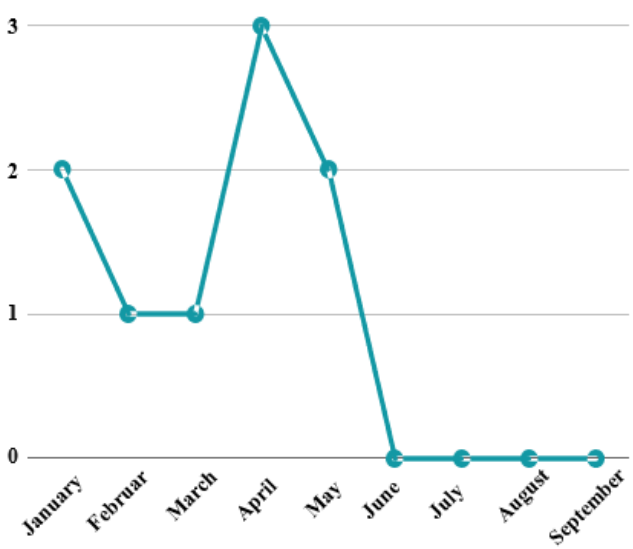
Number of CTs as of January 01, 2023
Started CTs 487
+ – Total CTs 662
Approved by MOH 175

Information on sponsor actions presented in a dynamic sequence on a monthly basis to analyze trends in clinical trials in Ukraine.

During the specified period (01.01.2023 - 30.09.2023), the sponsor took the following actions regarding the approved orders of the Ministry of Health and initiated clinical trials:

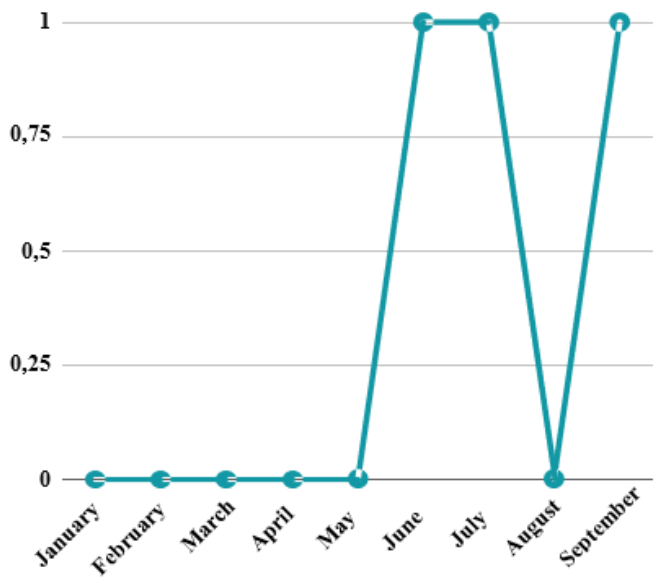
- ✓ **Temporary suspension of the start of the CT due to the introduction of martial law in the country:**

Month	**Total**
January	2
February	1
March	1
April	3
May	2
June	0
July	0
August	0
September	0
Total	**9**



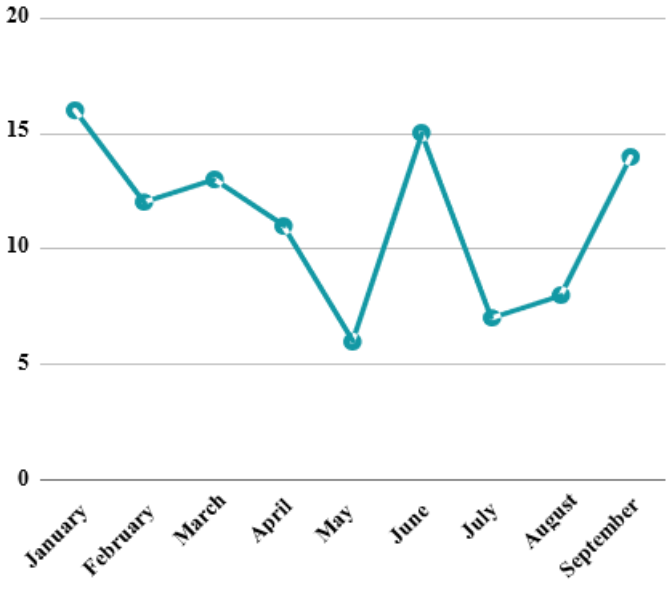
✓ **Suspension of patient recruitment (incl. patient screening and randomization):**

Month	**Total**
January	0
February	0
March	0
April	0
May	0
June	1
July	1
August	0
September	1
Total	**3**



✓ **Premature CT termination for the period 01.07.2023 - 30.09.2023 amounted to 29, of which 19 CTs were due to the introduction of martial law, 10 - for other reasons (economic - 5, efficiency - 5)**:

Month	**Total**
January	16
February	12
March	13
April	11
May	6
June	15
July	7
August	8
September	14
Total	**102**



The geography of the study subjects transfer includes 7 countries of the world.

Patient transfer
Jul 01, 2023 – Sep 30, 2023

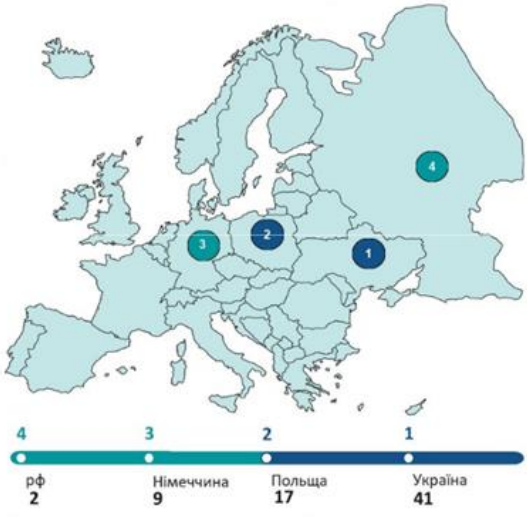
13 letters from Sponsors/CROs regarding the transfer of study subjects (29 patients in total) to other trial sites, namely:

- In Ukraine – 11 patients
- Abroad – 18 patients

The geography of the study subjects transfer includes 8 countries, with Poland being the nearest one and Canada being the most distant one.

The Department has processed 13 letters from sponsors/CROs regarding the transfer of subjects to other clinical trial sites (hereinafter referred to as the "CTS") (29 patients in total): in Ukraine (11 patients) and abroad (18 patients).

Number of study subjects transferred in 2023



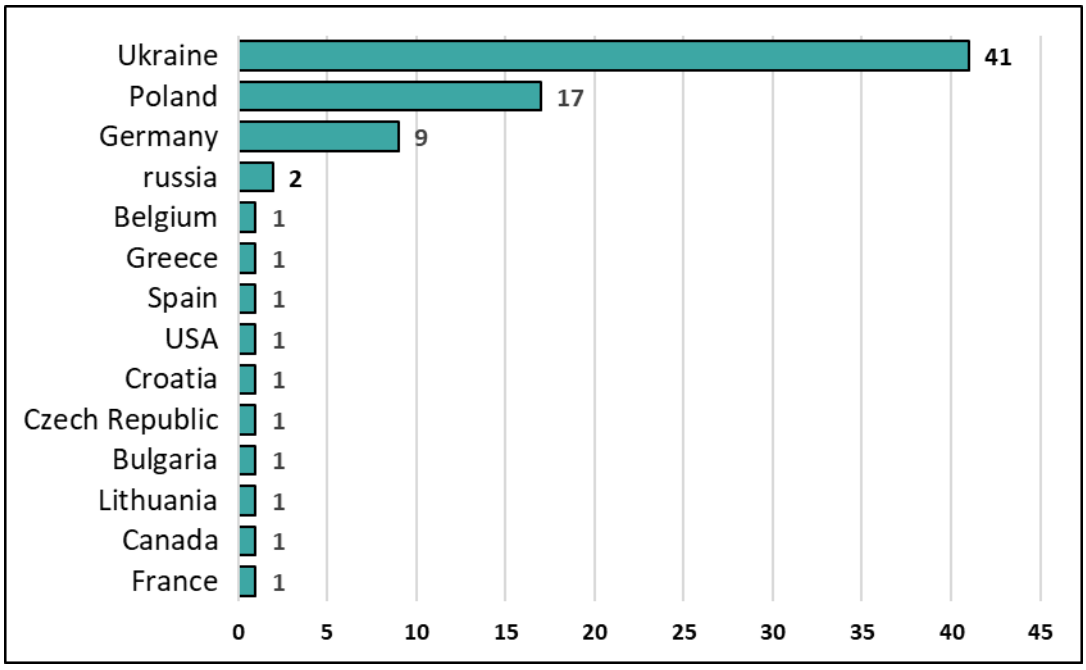
Other:

1 Belgium	1 Czech
1 Greece	1 Bulgaria
1 Spain	1 Lithuania
1 USA	1 Canada
1 Croatia	1 France

2 russia 9 Germany 17 Poland 41 Ukraine

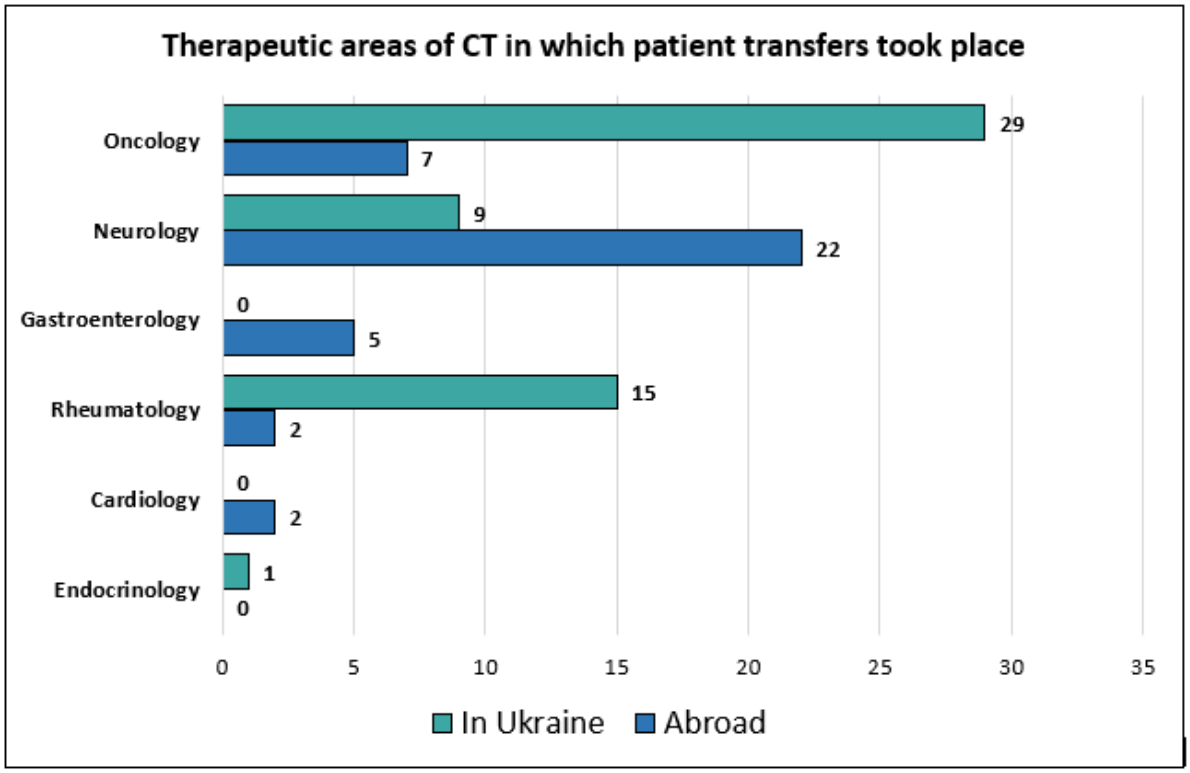
Number of subjects transferred to other Clinical Trial Sites in the CTs during the first, second and third quarters of 2023 (as table and histogram)

	01	02	03	04	05	06	07	08	09	Total
Ukraine	0	9	1	2	2	16	0	10	1	**41**
Poland	0	3	0	2	1	3	1	6	1	**17**
Germany	1	1	0	1	0	1	0	4	1	**9**
Belgium	0	1	0	0	0	0	0	0	0	**1**
Greece	0	1	0	0	0	0	0	0	0	**1**
Spain	1	0	0	0	0	0	0	0	0	**1**
USA	0	1	0	0	0	0	0	0	0	**1**
Croatia	1	0	0	0	0	0	0	0	0	**1**
Czech Republic	0	0	0	0	1	0	0	0	0	**1**
russia	0	1	0	0	0	0	0	1	0	**2**
Bulgaria	0	0	0	0	0	0	1	0	0	**1**
Lithuania	0	0	0	0	0	0	1	0	0	**1**
Canada	0	0	0	0	0	0	0	1	0	**1**
France	0	0	0	0	0	0	0	1	0	**1**
Total:	**3**	**17**	**1**	**5**	**4**	**20**	**3**	**23**	**3**	**79**



The following table provides information regarding the therapeutic area of the CTs in which patients were transferred:

Therapeutic area	Month (abroad/in Ukraine)									
	01	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**Total**
Oncology	0/0	0/3	0/0	1/2	0/1	0/15	0/0	5/8	1/0	7/29
Gastroenterology	1/0	0/0	0/0	0/0	1/0	0/0	1/0	2/0	0/0	5/0
Rheumatology	0/0	0/0	0/1	0/0	0/0	0/0	1/0	1/0	0/1	2/2
Neurology	2/0	8/6	0/0	0/0	1/0	4/1	1/0	5/2	1/0	22/9
Cardiology	0/0	0/0	0/0	2/0	0/0	0/0	0/0	0/0	0/0	2/0
Endocrinology	0/0	0/0	0/0	0/0	0/1	4	0/0	0/0	0/0	0/1
Total	**3/0**	**8/9**	**0/1**	**2/3**	**2/2**	**4/16**	**3/0**	**13/10**	**2/1**	**38/41**



Most of the displaced patients were in the therapeutic area

Oncology - 36,

Neurology - 31,

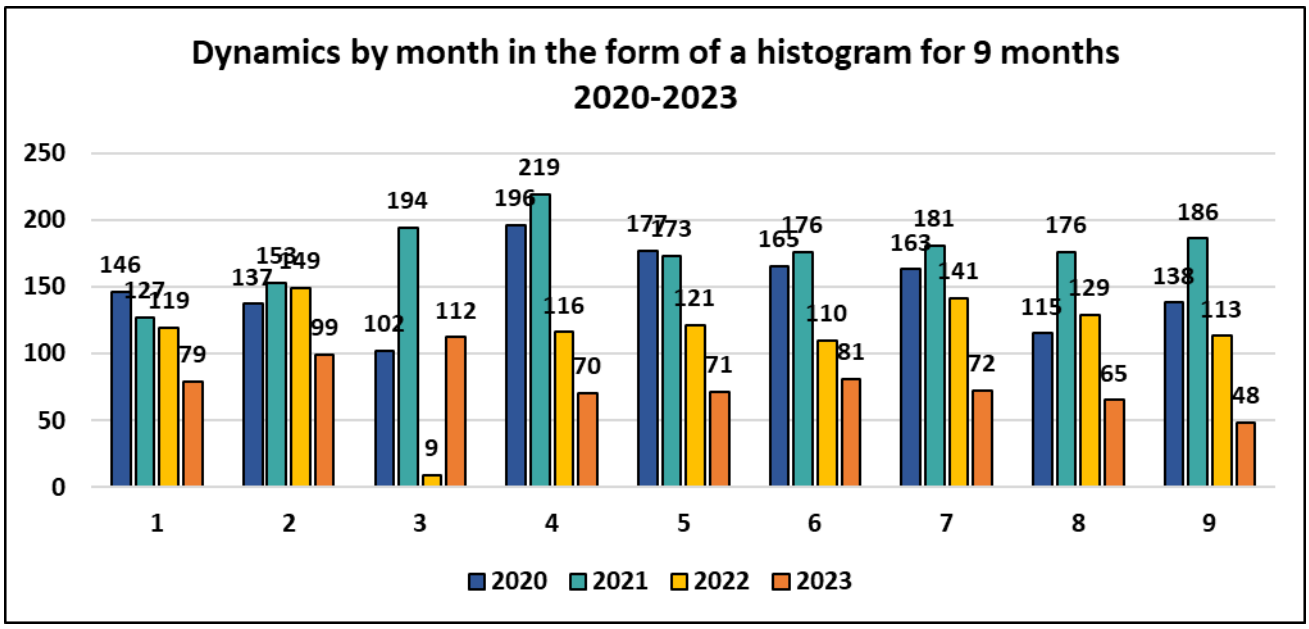
Gastroenterology - 5,

Rheumatology - 4.

The lifecycle of CTs conducted in Ukraine is supported by substantial amendments to the CT protocols, information of which is presented as a histogram showing the number of applications for SAs received by the Center from the MoH and the number of applications reviewed at the meetings of Scientific and Technical Councils (STC) of the Center and recommended for approval by the MoH for each month of 2020-2023.

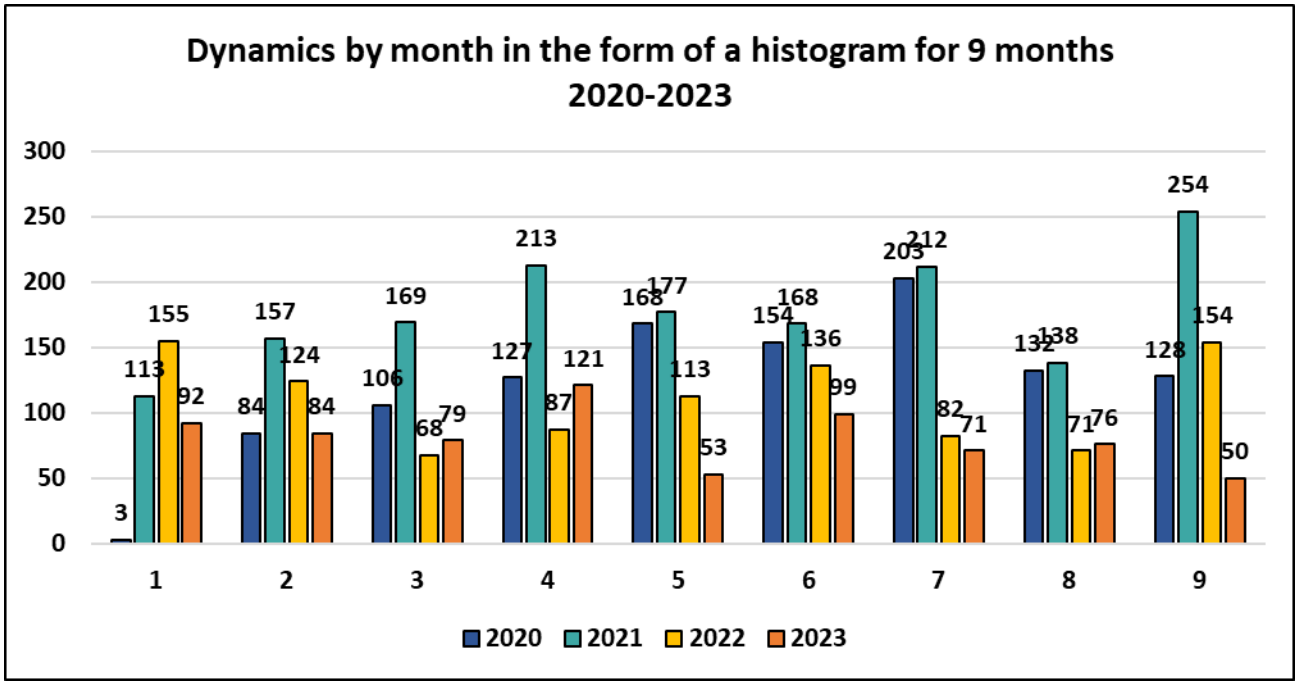
Number of applications for SAs to CT protocols received by the Center (as table and histogram)

Month	2020	2021	2022	2023
1- January	146	127	119	79
2- February	137	153	149	99
3- March	102	194	9	112
4- April	196	219	116	70
5- May	177	173	121	71
6- June	165	176	110	81
7- July	163	181	141	72
8- August	115	176	129	65
9- September	138	186	113	48
Total	**1339**	**1585**	**1007**	**697**
% from 2020/2021/2022	**52%**	**43,9%**	**69,2%**	



Number of SAs to CT protocols reviewed at the STC meetings (as table and histogram)

Month	2020	2021	2022	2023
1- January	3	113	155	92
2- February	84	157	124	84
3- March	106	169	68	79
4- April	127	213	87	121
5- May	168	177	113	53
6- June	154	168	136	99
7- July	203	212	82	71
8- August	132	138	71	76
9- September	128	254	154	50
Total	**1105**	**1601**	**990**	**725**
% from 2020/2021/2022	**65,6%**	**45,2%**	**73,2%**	



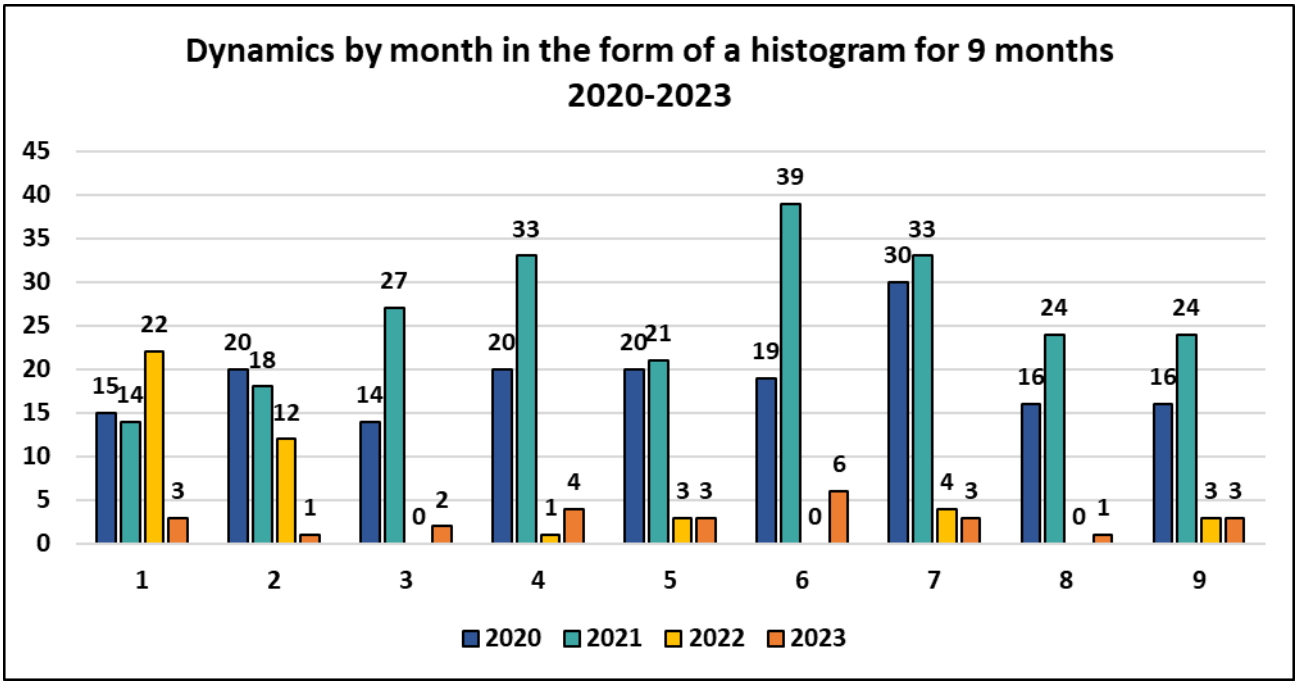
The acceptable level of number in the number of SAs for the third quarter of 20223 compared to the same period in previous years shows the continuous monitoring of CT during its life cycle and CT compliance with GCP requirements. As to the number of applications for CTs is decreasing due to a decrease in the number of applications for clinical trials and the process of completing CTs in accordance with the protocol or their early completion due to the introduction of martial law in Ukraine.

The following tables and histograms provide comparative data on the number of applications for CTs in Ukraine and the number of CT protocols reviewed at the

meetings of the Center's Scientific Expert Councils (SEC) with recommendations for the MoH to approve the conduct of CTs in Ukraine in the dynamics by month for 9 months of 2020-2023.

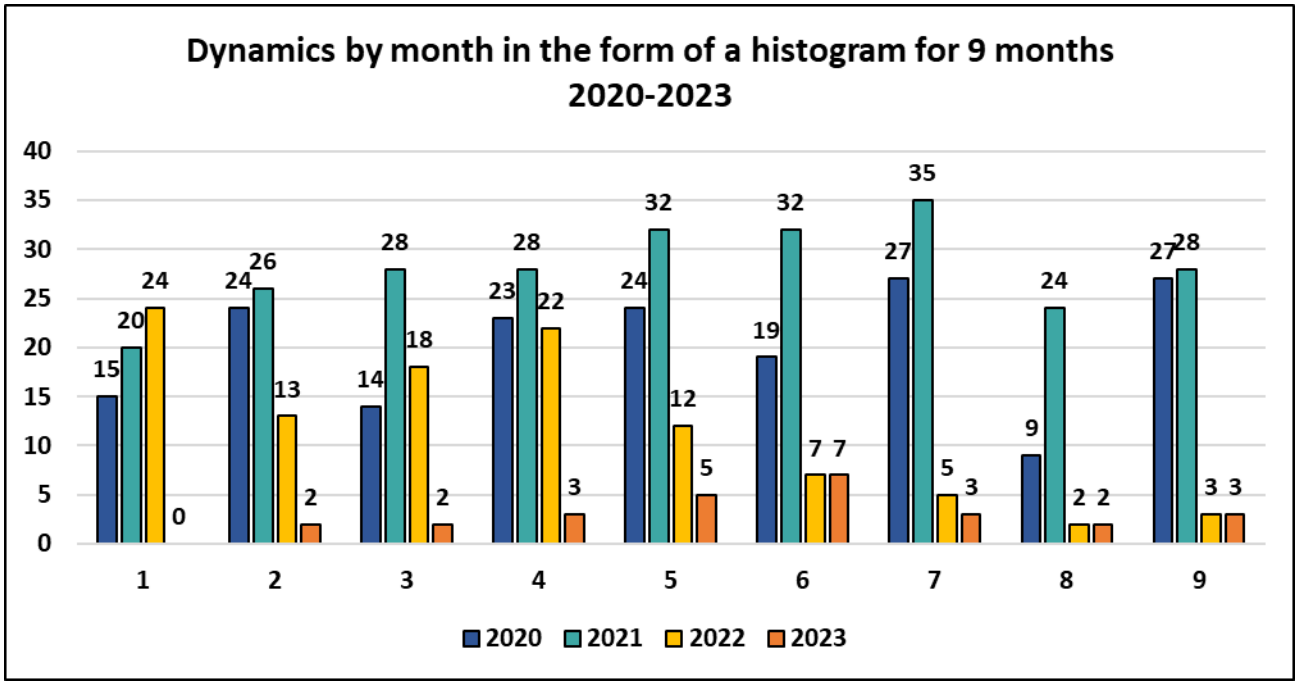
Number of applications for CT received by the Center (as table and histogram)

Month	2020	2021	2022	2023
1- January	15	14	22	3
2- February	20	18	12	1
3- March	14	27	0	2
4- April	20	33	1	4
5- May	20	21	3	3
6- June	19	39	0	6
7- July	30	33	4	3
8- August	16	24	0	1
9- September	16	24	3	3
Total	**170**	**233**	**45**	**26**
% from 2020/2021/2022	**15,3%**	**11,2%**	**57,7%**	



Number of CT protocols reviewed at the SEC meetings (as table and histogram)

Month	2020	2021	2022	2023
1- January	15	20	24	0
2- February	24	26	13	2
3- March	14	28	18	2
4- April	23	28	22	3
5- May	24	32	12	5
6- June	19	32	7	7
7- July	27	35	5	3
8- August	9	24	2	2
9- September	27	28	3	3
Total	**182**	**253**	**106**	**27**
% from 2020/2021/2022	**14,8%**	**10,6%**	**25,4%**	



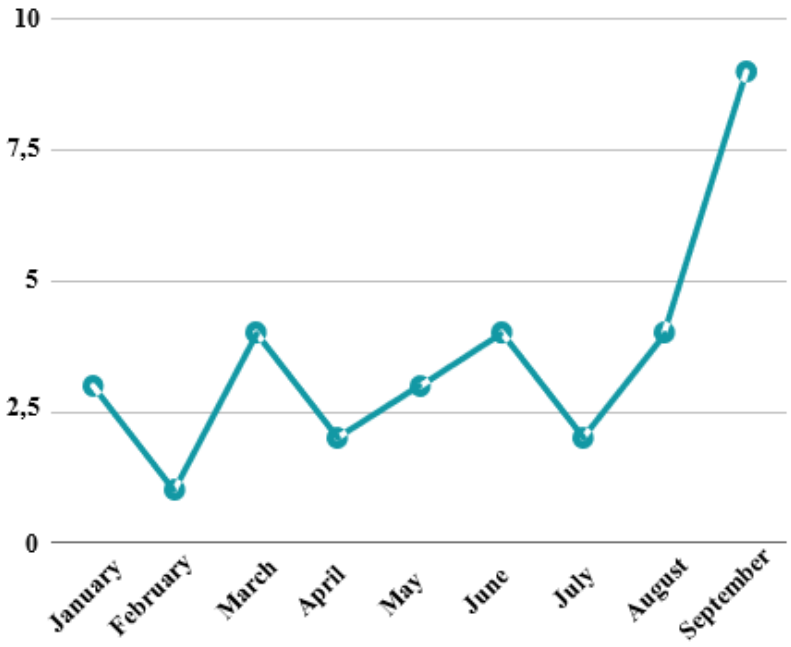
In the reporting period, 1 application for conducting a CT was received from a domestic manufacturer; 1 application for a CT and 1 SAs to CT materials for the treatment and/or prevention of acute respiratory infection COVID-19 was received; 1 SA to the CT protocols for the specific treatment and prevention profile were reviewed at the STC meetings.

As of January 01, 2023, the number of CTs (approved by MoH orders is 175 and started 487) are 662 (https://clinicaltrials.dec.gov.ua/).

Current positive trends in CTs in Ukraine

✓ **Start of CT – 32**

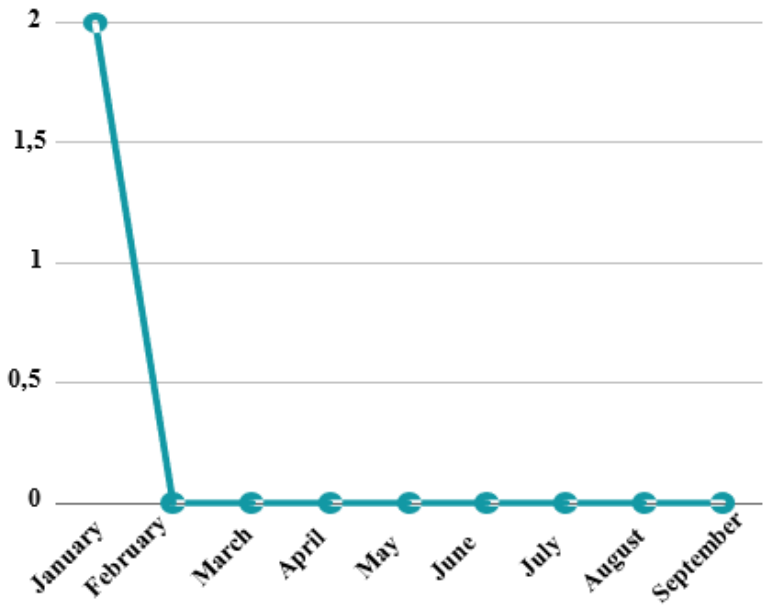
Month	Total
January	3
February	1
March	4
April	2
May	3
June	4
July	2
August	4
September	9
Total	**32**



In particular, allergology - 5 CTs, neurology - 1 CT, oncology - 4 CTs, infectious diseases - 1 CT, rheumatology - 1 CT, dermatology - 1 CT, Bronchiectasis - 1 CT, infectious diseases - 1 CT, cardiology - 1 CT.

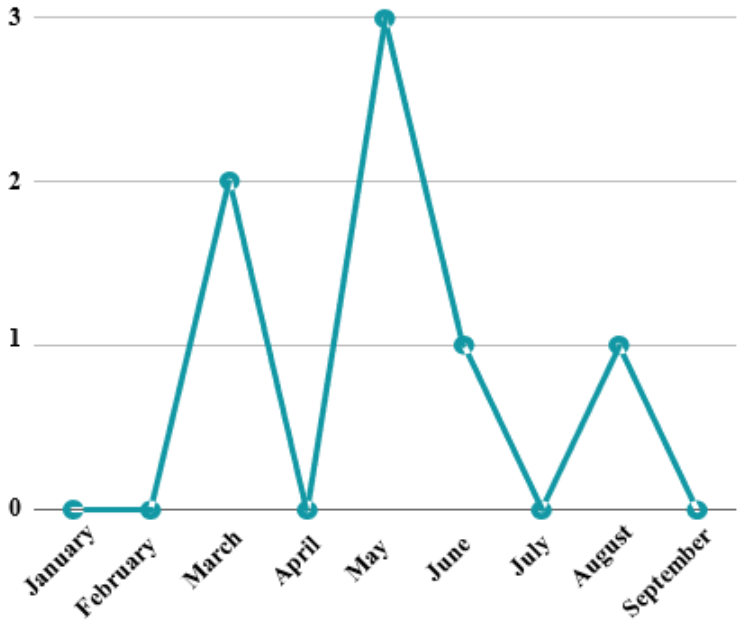
✓ **Resumption of CT - 2, of which 1 CT is pulmonology and 1 CT is COPD:**

Month	Total
January	2
February	0
March	0
April	0
May	0
June	0
July	0
August	0
September	0
Total	**2**



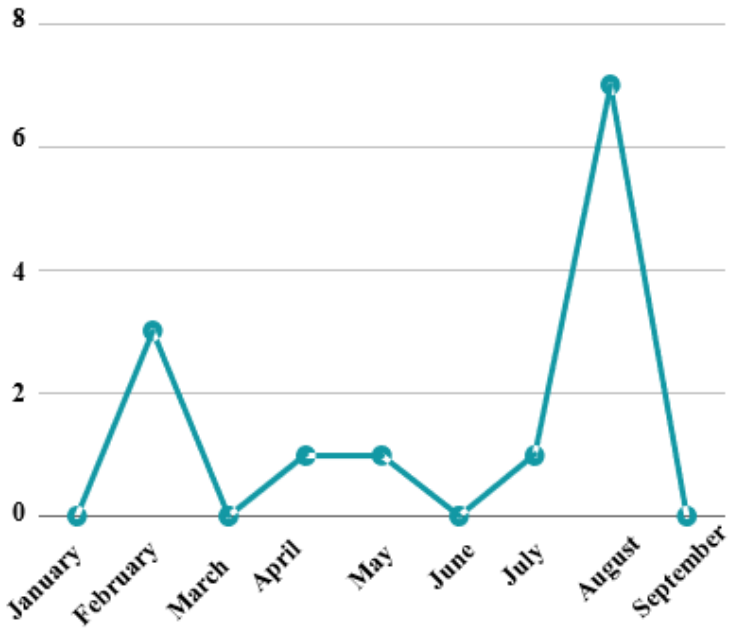
✓ **Resumption of patient enrollment - 7, of which 2 CTs are gastroenterology, 2 CTs are hematology, 1 CT is cardiology, and 2 CTs are pulmonology:**

Month	Total
January	0
February	0
March	2
April	0
May	3
June	1
July	0
August	1
September	0
Total	7



✓ **Returning of patients from abroad to the approved clinical trials sites in Ukraine - 5 patients, of which 1 patient is in cardiology, 7 patients are in neurology, 5 are in oncology**

Month	Total
January	0
February	3
March	0
April	1
May	1
June	0
July	1
August	7
September	0
Total	**13**



The Department constantly maintains contact with applicants in order to properly conduct the CTs under the conditions of martial law in Ukraine.

In the third quarter of 2023, no new clinical trial sites (CTSs) and, accordingly, no new Ethics Commissions at Treatment and Prevention Institutions were announced.

Regarding the activities of the Department:

An important task is to ensure the functioning of the quality management system and the implementation of a process approach to comply with the regulatory framework in the system of conducting and monitoring clinical trials. Based on the results of the WHO pre-benchmarking as part of the assessment of the current national regulatory system in the field of medicines circulation by applying the WHO Global Benchmarking Tool (GBT), the Department continued to work to update the processes that have taken place in accordance with the changes made to the regulatory framework and internal processes.

Employees of the Department participated in the preparation and conduct of 2 online training seminars "Good Clinical Practice (GCP). Regulatory and Legal Regulation of Clinical Trials" which were attended by 131 researchers and members of ethics committees.

Participation of the Department in the development of the Center's proposals for amendments to legislative and regulatory acts:

- amendment to the Order of the Ministry of Health of Ukraine No. 690 dated 23.09.2009 were developed, approved by the Order of the Ministry of Health No. 1034 dated 07.06.2023 and registered with the Ministry of Justice of Ukraine on July 21, 2023 under No. 1235/40291, which came into force in September 2023. The amendments reflect the harmonization of the provisions of the Procedure with EU Regulation 536/2014 of the European Parliament and of the Council dated 16 April 2014 on clinical trials of medicinal products for human use repealing Directive 2001/20/EC, in particular with regard to the stages of the examination, submission of a report on the clinical trial for laypersons for public access, storage of the clinical trial file, and reporting by the participants of the clinical trial on the safety of the investigational medicinal product.

- amendment to the Order of the Ministry of Health of Ukraine No. 690 dated 23.09.2009 on conducting clinical trials of progressive therapy medicines were developed.

In order to harmonize legislative and regulatory acts on clinical trials, 7 EU directives and regulations were reviewed. The degree of harmonization of 2 EU documents was discussed with representatives of the European Business Association (20.09.2023 and 26.09.2023).

Updated documentation was prepared and posted on the Center's official website: "GENERAL PROCEDURE FOR AUTHORIZATION OF CLINICAL TRIALS (CT) OF MEDICINAL PRODUCTS (MP) IN UKRAINE (ORDER OF THE MOH DATED 23.09.2009 690 AMENDED) and "GENERAL PROCEDURE FOR AUTHORIZATION OF SUBSTANTIAL AMENDMENTS (SAs) TO THE CLINICAL TRIAL MATERIALS (CT) OF MEDICINAL PRODUCTS IN UKRAINE (ORDER OF THE MOH DATED 23.09.2009 No. 690 AMENDED)".

The Department reviewed 2 applications for the Program of Extended Access of Investigational Medicinal Product (IMP) after the completion of the clinical trial in July 2023 and 4 applications for amendments to the approved Programs of Extended Access of research subjects after the completion of the clinical trial to IMP Ponesimod (3 amendments), Entyvio (Vedolszumab) and 1 letter was prepared regarding the complete premature termination of the Extended Access Program for Investigational Subjects after the completion of the clinical trial of Tysrelizumab. The relevant information is available on the official website of the Center in the section "Expertise of preclinical and clinical trial materials" at https://www.dec.gov.ua/applicant/nakazy-moz-shhodo-programy-dostupu-subyektiv-doslidzhennya-pacziyentiv-do-doslidzhuvanogo-likarskogo-zasobu-pislya-zavershennya-klinichnogo-vyprobuvannya/?role=applicant

The Department's employees held 3 offline consultations; 65 electronic consultation requests were processed. All inquiries were answered in written form.

Employees of the Department regularly participate in the meetings of the SEC, STC and other events organized by the Center.

The Department held training events for employees:

8 internal webinars/seminars and 3 external training events (seminars/webinars).

Clinical audit of clinical trials during the war in Ukraine

Clinical audit (CA) of a clinical trial (CT) of a medicinal product (MP) is an important aspect of quality assurance of CT of MPs and protection of the rights, safety and well-being of study subjects.

In order to verify compliance with regulatory requirements, Good Clinical Practice in the CTs and patient rights, the Center conducted scheduled CTs in accordance with the CTs Plan of the CA of MP for the third quarter of 2023, approved by the head of Center and unscheduled CA.

Totally 11 CAs were conducted, namely: 6 CAs of CTs at the clinical trial sites (hereinafter referred to as the clinical trial sites (CTSs), including 3 unscheduled CAs of CTs and 5 CAs aimed at checking the organization of CTs of MP at the CTSs

Based on the results of 11 CAs:

- 1 CA - no comments.
- 6 CAs - minor comments (the identified deficiencies did not affect the rights, safety, and well-being of study subjects and the integrity of the study data);
- 4 CAs - critical comments (identified deficiencies that adversely affect the rights, safety, or health of study subjects and/or affect the quality and integrity of clinical trial data).

Based on the results of the analysis of comments on the CTs in the third quarter of 2023, it was found that most of the identified comments are related to:

- organization of the CTs in the CTSs - 4 comments;
- forming the researcher's file - 4 comments;
- maintaining primary medical records - 8 comments;
- the procedure for obtaining informed consent - 3 comments;
- circulation of investigational drugs - 3 comments;
- the activities of ethics commissions - 6 comments.

Based on the results of the CA, the CA Reports of the CTs were drawn up and sent to the responsible researchers / applicants of the CTs.