ACTO
ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER № 22

Summary of 2020 results

MOSCOW 2021

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SUMMARY

The COVID-19 pandemic that unfolded in 2020 has created a number of challenges for a wide variety of areas of human activity. The clinical trials market in Russia was no exception. This issue of ACTO Newsletter analyzes and describes the crisis-related changes in the industry that can be noted at the beginning of 2021.

Initial concerns that the COVID-19 pandemic would negatively affect the number of approved trial applications in the country have not panned out: in 2020, the Russian Ministry of Health issued 734 approvals, which is only 1.6% less than the previous year. The number of new international multicentre clinical trials (IMCTs) has increased by 2.9%, from 313 in 2019 to 322 in 2020. The number of bioequivalence studies by Russian sponsors has increased from 163 approvals to 199 (+22.1%). Other types of trials have gone down: from 35 to 18 (-48.6%) for local trials by foreign sponsors, from 80 to 56 (-30%) for bioequivalence studies of foreign sponsors, from 155 to 139 (-10.3%) for local trials by Russian sponsors.

In terms of distribution of new IMCTs by therapeutic area the leading position of oncology remains unchanged (95 approvals or 29.5% of all new IMCTs in 2020). Oncology together with oncohaematology (+20 approvals) accounted for more than one third of all new IMCTs (35.7%). Neurology with 32 new protocols and a share of 9.9% ranks second. The third place is taken by the disease, which we singled out from the group of infectious diseases — COVID-19 with 31 approvals and a share of 9.6%.

Territorial distribution of IMCTs across Russia did not bring any surprises. The Central Federal District with 294 new international projects traditionally takes the lead. The North-Western District, where the launch of 287 IMCTs was announced, goes second. Since the gap between the two leading regions is not that big and the North-Western Federal District has already overtaken the Central District in 2019, it is reasonable to expect that the competition for the first place will remain in the future. The Volga Federal District placed third with 210 new international projects, the Siberian Federal District placed fourth with 191, and the Ural Federal District placed fifth with 119 IMCTs. They are followed by the South Federal District and the North Caucasian Federal District with 93 and 51 trials respectively. The Far Eastern Federal District completes the ranking with eight new IMCTs across the region.

Impact of the pandemic is best seen in how the timeframes for issue of approvals have changed. In 2020, the average time period for issue of all documents by the Russian Ministry of Health has increased significantly (with the exception of documents for trials of anti-COVID-19 medications, which were analyzed separately). Thus, as compared to 2019, the average time period for obtaining approvals for conducting a trial has gone up from 87 to 103 days (+18.4%), approvals for amending the protocol — from 48 to 65 days (+35.4%), for import of medicinal products and import/export of bio-samples — from 15 to 17 days (+13.3%) and from 20 to 22 days (+10%), respectively. The time for processing of other requests has increased from 29 to 39 days (+34.5%). The last time the industry faced such long timeframes for issue of approvals was in 2011–2012, when the regulatory system was undergoing reformation. Trials of anti-coronavirus drugs were handled by the regulatory approval system on an expedited basis, on average, it took 25 days for an approval to conduct a clinical trial to be issued, 10 days for import of drugs, and 15 days for import/export of biological materials.

Separate materials in this issue of the newsletter are devoted to describing statistical parameters of clinical trials, where drugs for treatment and prevention of the new coronavirus infection were tested, and “corner cutting” practice in their development.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

The time has come to sum up the results of the year that had almost entirely been spent under the pandemic conditions. Its impact on the field of clinical trials turned out to be multifaceted; it is quite a complicated task to comprehensively reflect on it in the short run. In the spring and early summer, during a period of particularly stringent travel restrictions, the market undoubtedly plummeted. Trials that were not aimed at testing anti-coronavirus drugs suffered, as elsewhere in the world: patient visits were being postponed, the launch of new projects was being delayed, recruitment was being suspended, there have been problems with organization of monitoring visits, etc. But let us start with the data the reader is accustomed to: the number of approved trials.

Contrary to possible expectations, the COVID-19 pandemic had little impact on the total number of trial approvals issued in Russia. Which is quite understandable: the slowdown in some projects was offset by the hyper-acceleration of other projects related to the search for drugs to combat the pandemic. In addition, let's not forget that the fact of obtaining an approval does not mean an immediate start of the trial. In 2020, the Russian Ministry of Health issued 734 approvals, which is only 1.6% less than the previous year (see Table 1). Impact of the pandemic was primarily manifested in the structural change of the issued approvals.

The number of new international multicentre clinical trials (IMCTs) was the least prone to fluctuations, it increased by 2.9%, from 313 in 2019 to 322 in 2020. The most significant growth (+22.1%) was demonstrated by bioequivalence studies of Russian sponsors: from 163 approvals in 2019 to 199 in 2020. All other types of studies have decreased. Local trials by foreign sponsors decreased in numbers the most (-48.6%), the 2019 indicator of 35 approvals changed to 18 in 2020. The number of approved bioequivalence studies by foreign sponsors decreased by 30%: 80 new approvals in 2019 versus 56 in 2020. The minimal reduction (-10.3%) was noted in local trials by Russian sponsors, the number of approvals decreased from 155 in 2019 to 139 in 2020.

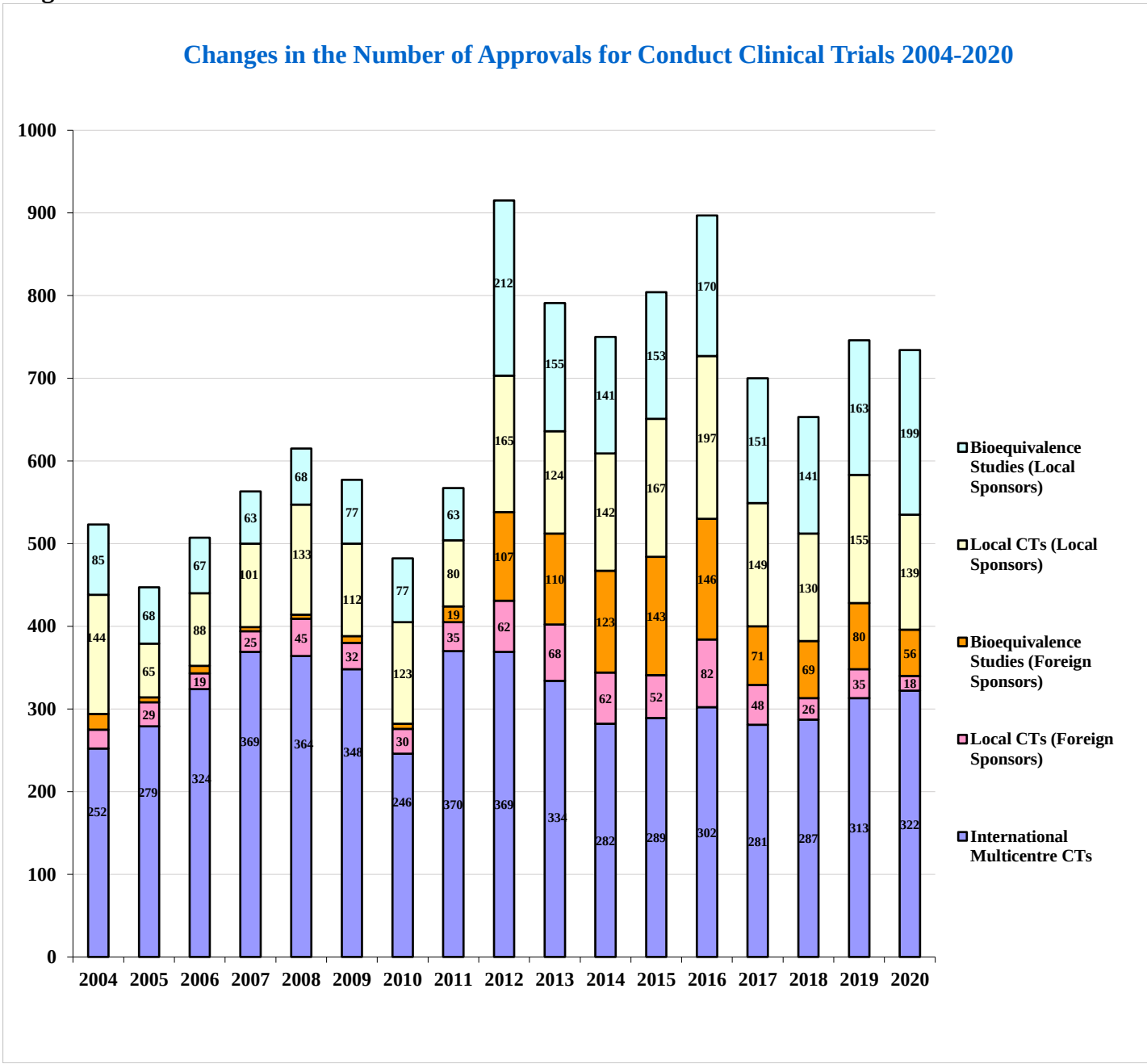
Table 1

Approvals for Conduct Clinical Trials: 2020 vs 2019						
Year	**Total**	**International Multicenter CTs**	**Local CTs (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CTs (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2020	734	322	18	56	139	199
2019	746	313	35	80	155	163
2020 vs 2019, %	-1.6%	2.9%	-48.6%	-30.0%	-10.3%	22.1%

Data from www.grls.rosminzdrav.ru

Diagram 1 shows that the decline in number of local trials by foreign sponsors (and so-called "therapeutic efficacy studies" and bioequivalence studies) in 2020 was the most significant since 2012, when the market re-emerged after the global legislative reform. Other types of trials remained within the fluctuation corridor typical of them in the last eight years.

Diagram 1

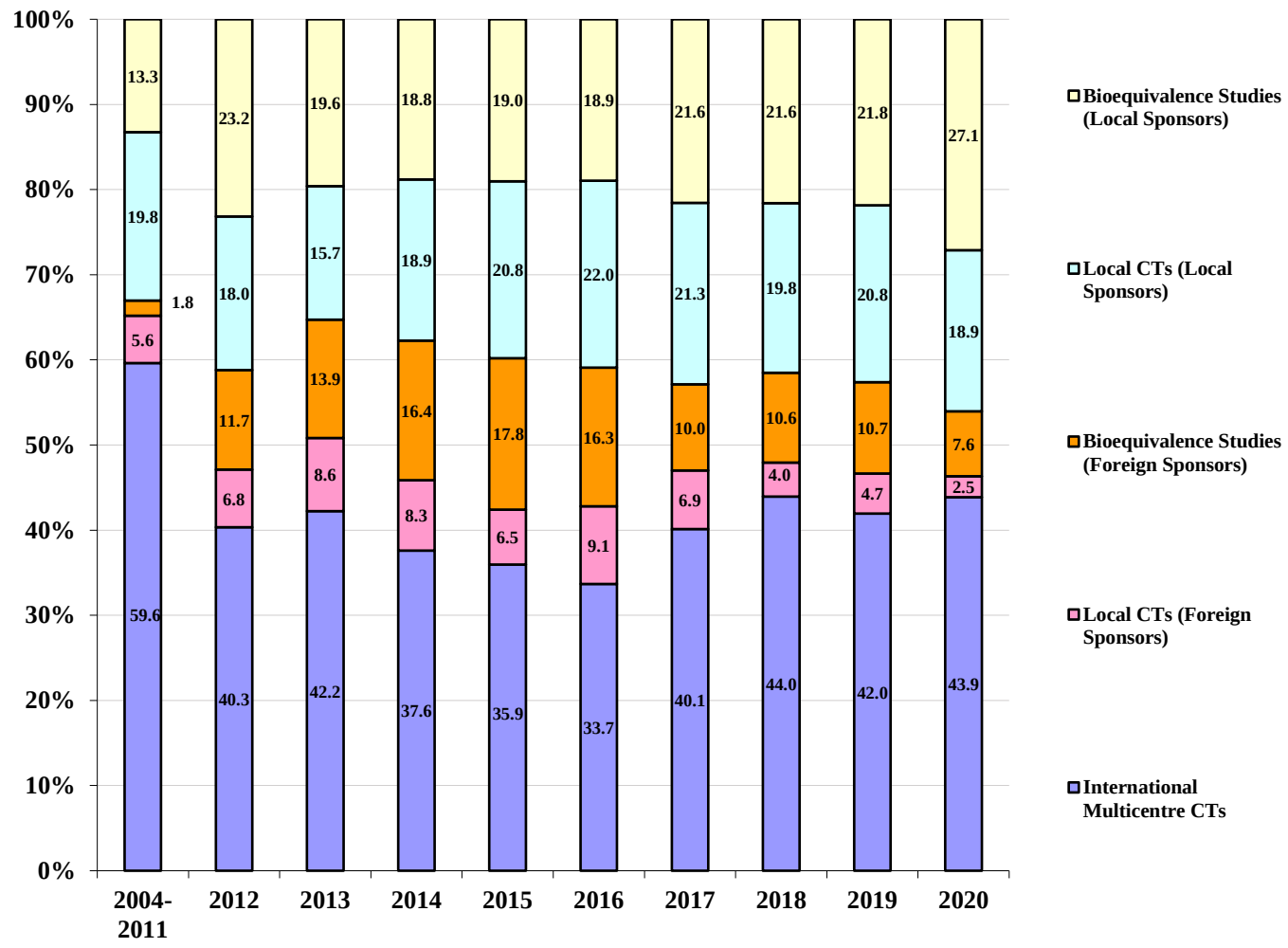


Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

Diagram 2 shows changes in the shares of different types of trials in the overall market structure. The share of bioequivalence studies of Russian generics increased the most: from 21.8% to 27.1%. IMCTs added two percentage points and reached 43.9%, which is almost equal to the 2018 indicator (44%), the best for international projects over the past nine years. Shares of other types of trials decreased: local trials by Russian sponsors went down by two percentage points (from 20.8% to 18.9%), bioequivalence studies by foreign sponsors — by three percentage points (from 10.7% to 7.6%), local trials by foreign sponsors — by two percentage points as well, falling almost by half given the small share size (from 4.7% to 2.5%).

Diagram 2



Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

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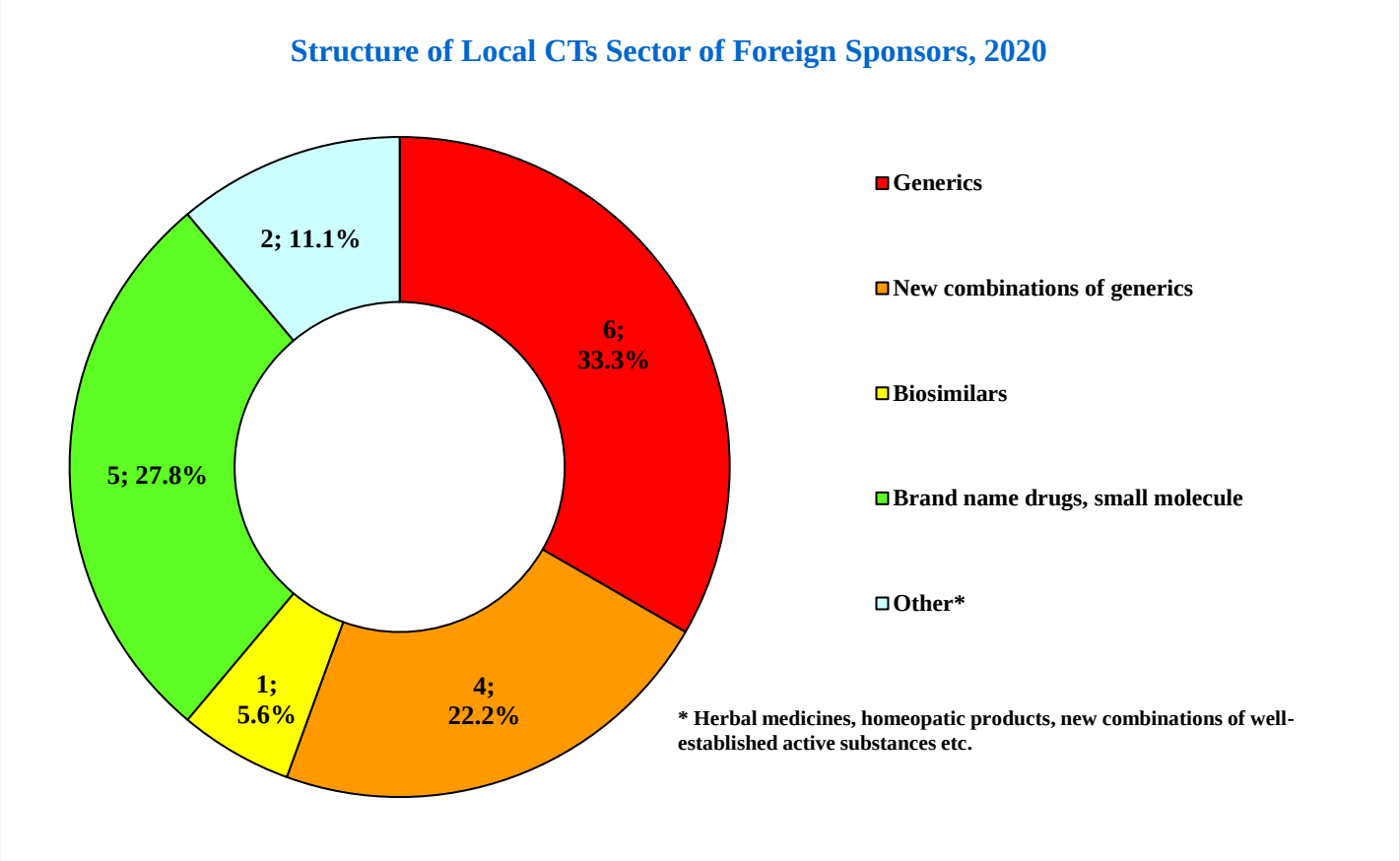
Diagram 3 acquaints us with the groups of drugs, local testing of which by foreign sponsors was approved in 2020 (excluding bioequivalence studies).

Generics traditionally accounted for the largest share of approvals for local trials by foreign sponsors — one third of all protocols (six). The share of trials of new combinations of generics turned out to be significant, as it always has been — 22% (four protocols). Original small molecules, which over the previous five years had never exceeded the 20% bar (a year earlier their share was only 3%, one protocol), made up almost 28% (five). Four of these five trials were dedicated to drugs that were tested as candidates for combating COVID-19: two protocols for American Elsulfavirine, another two for the South Korean developments — Radotinib and Nafabelltan.

One local trial approval (share of 5.6%) was issued for a biosimilar Leuprolerin. Two (11.1%) — for the study of drugs that we classify as “others” (one drug contains lactobacilli, the other one is a “bioactive concentrate made of small sea fish”).

Diagram 3



Data from www.grls.rosminzdrav.ru

Diagram 4 shows the groups of drugs applied for testing in local projects by Russian sponsors.

Here, the ratio of shares of different groups remained almost unchanged compared to the previous year. Generics are in the lead — 28.8%, 40 protocols. Moreover, nine of these 40 were for anti-COVID-19 drugs: five for Favipiravir, two for Remdesivir, and one for each of Hydroxychloroquine and Enisamium Iodide.

Generics are followed by the “others” group — 18.7% or 26 protocols. Of these, four were for drugs that were also studied for COVID-19: immunomodulatory agent Allokin-alpha, Dalargin, Kagocel, and helium-oxygen mixture (heliox).

Vaccines accounted for 10.8% of local trials of domestic sponsors or 15 protocols, of which eight were represented by anti-COVID-19 developments: three trials for each of GamCOVIDVac and EpiVacCorona vaccines, and one for each of GamCOVIDVac Lyo and the whole-virion vaccine developed by the Chumakov Center.

Trials of new combinations of generics (14 protocols) accounted for 10.1% share of the total number of local trials by domestic sponsors. None of these drugs was claimed to fight the new coronavirus infection.

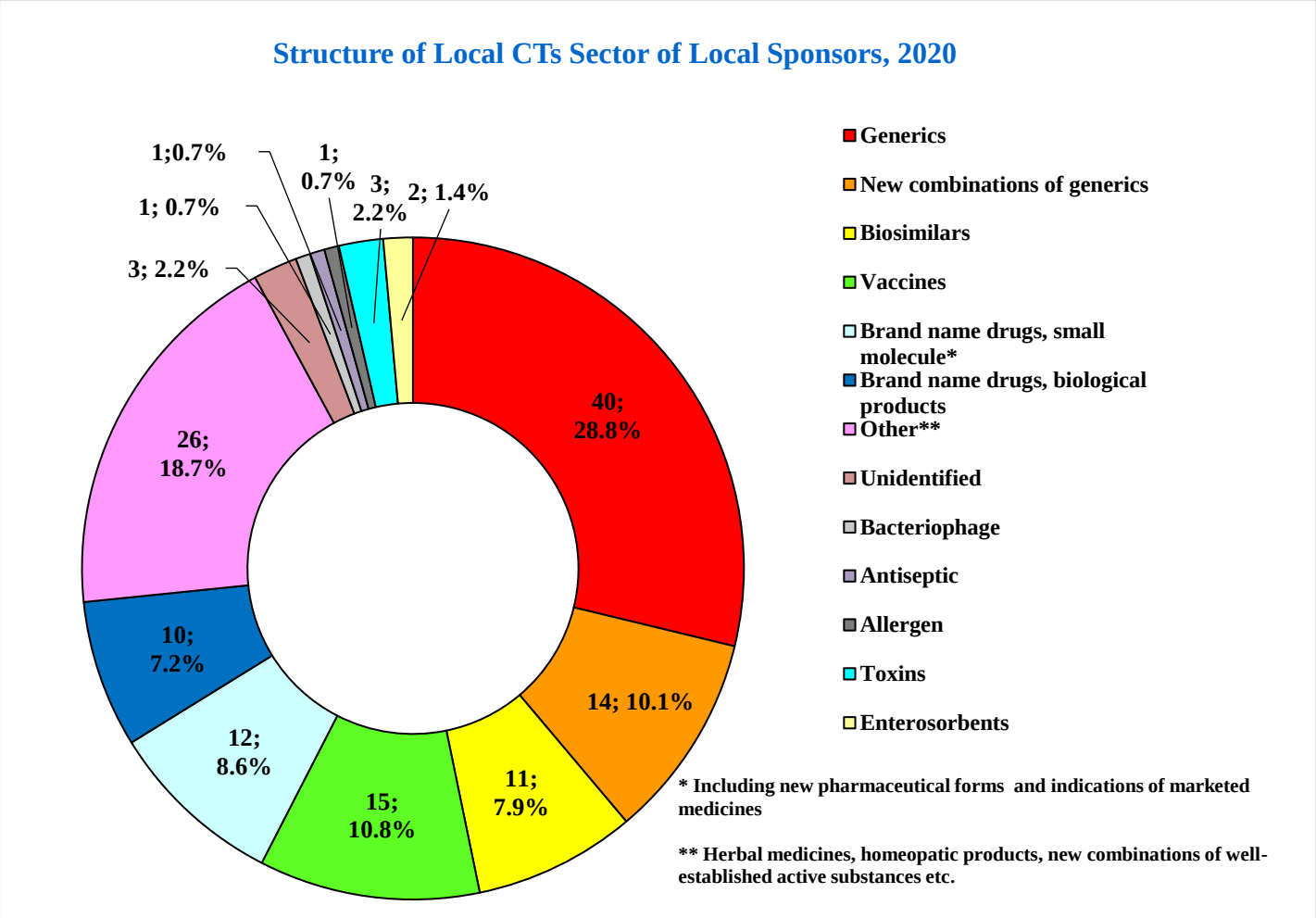
However, such candidates were found in the sector of original small molecules (8.6% share, 12 protocols) and biosimilars (7.9% share, 11 protocols): Generium studied biosimilars Dornase Alfa and Eculizumab for this disease, as well as small molecules codenamed XC7, XC221 and XC268BG and Amidine Hydrochloride.

Another ten protocols (7.2% of the total share) studied original biological products. Of these, three developments belonging to Biocad, R-Pharm and Microgen were intended to combat COVID-19.

Remaining groups of drugs accounted for less than 3% shares: three trials for toxins, two trials for enterosorbents, one for each of bacteriophage, antiseptic and allergen, and two more protocols planned for

studying drugs that could not be classified (one of them was also intended to combat the new coronavirus infection).

Diagram 4



Data from www.grls.rosminzdrav.ru

STRUCTURE OF THE IMCT MARKET BY PHASE

Diagram 5 shows the distribution of IMCTs approved in Russia in 2020 by phase.

The ratio of shares within the distribution varies insignificantly year on year, at the level of error. Thus, in 2019, the share of Phase I protocols was 3% (nine approvals), and in 2020 — 2% (six approvals). Of these six, five were dedicated to studies of drugs for oncological diseases (breast cancer, non-small cell lung cancer and other solid tumors), one — to severe form of the COVID-19 infection.

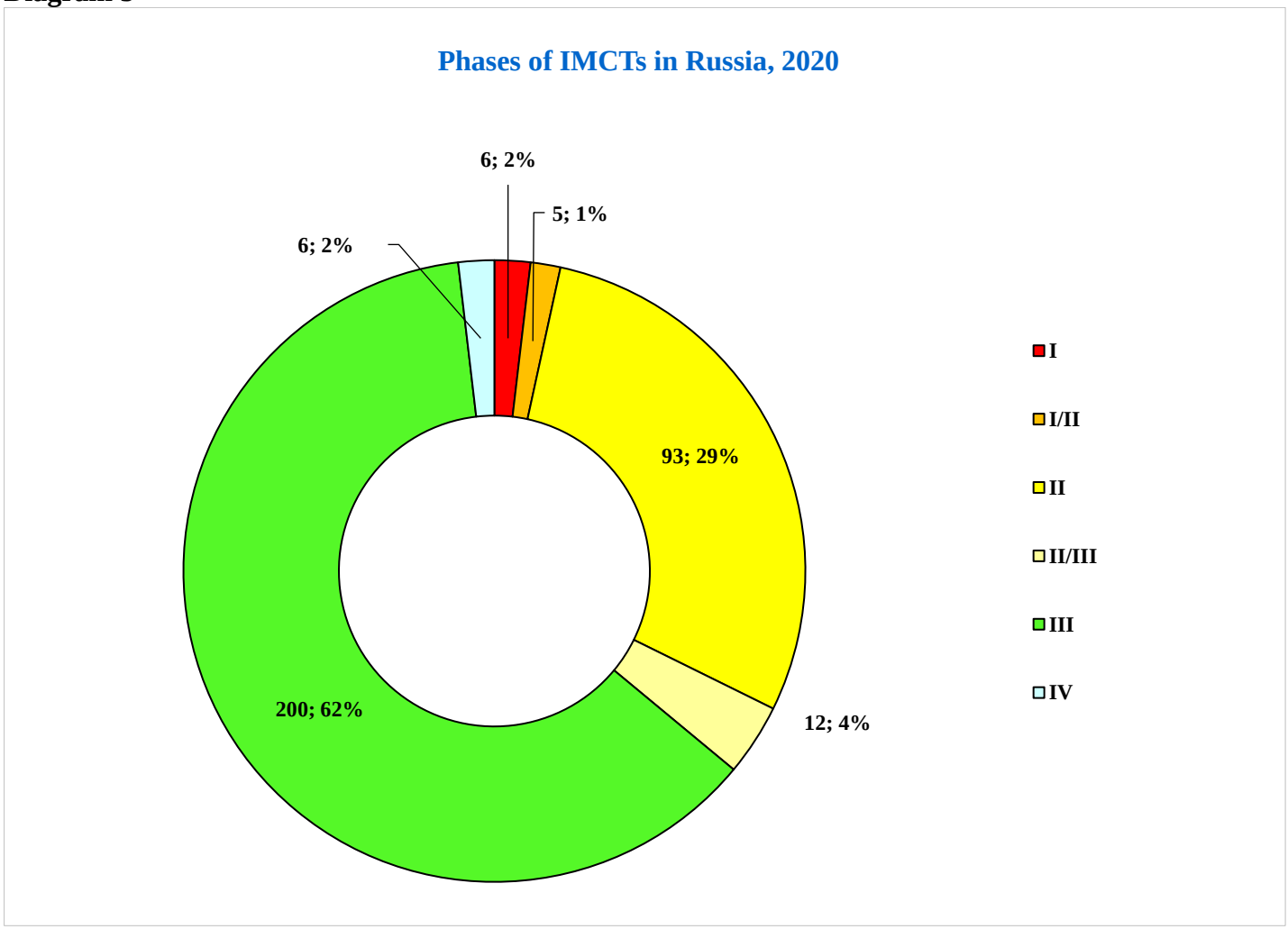
Five protocols were for Phase I–II trials: three in oncology, one in oncohaematology, and one in rheumatology.

The share of Phase II protocols increased slightly from 22% in 2019 (69 protocols) to 29% in 2020 (93 protocols).

The most massive phase, Phase III of trials, accounted for a share of 62% (200 protocols). As a reminder, in 2019 it was 70% (218 IMCTs). Considering how conservative the distribution of approvals issued by phase is, reduction in the share of Phase III protocols caused by the slight increase in the shares of Phases II and II–III, may perhaps be classified as significant.

The share of Phase IV trials remained at 2%, the same as in 2019 (six approvals in both cases).

Diagram 5



Data from www.grls.rosminzdrav.ru, www.clinicaltrials.gov, www.clinicaltrialsregister.eu

STRUCTURE OF THE CLINICAL TRIALS MARKET BY THERAPEUTIC AREAS

Table 2 shows distribution of IMCTs approved in 2020 by therapeutic area.

The last year's leaders occupying the first two spots of the table remained unchanged. Oncology, as usual, retains its number one ranking, this time with 95 approvals and a share of 29.5%. As compared to 2019, the share of approvals issued for trials in this therapeutic area increased by 5 percentage points, in absolute numbers the number of approvals increased by 19. Oncology together with oncohaematology (+20 approvals) in 2020 accounted for more than one third of all IMCT approvals (35.7% versus 29.1% in 2019). Neurology with 32 new protocols and a share of 9.9% ranks second, as a year earlier (33 protocols and a share of 10.5% at the end of 2019).

The most relevant infectious disease in 2020, COVID-19, shot ahead into third place. The Ministry of Health issued 31 approvals for trials of drugs to combat the new coronavirus infection, which amounted to 9.6% of all approvals for IMCTs in 2020[1]. If we look at the number of participants that were expected to take part in the trials (12,710 people), then this area was far ahead of all the others: it alone accounted for 37% of all potential trial subjects over the year.

Table 2

Distribution of International Multicenter CTs by Therapeutic Areas, 2020			
Therapeutic Area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**
Oncology	95	29.5%	6 494
Neurology	32	9.9%	2 573
COVID-19	31	9.6%	12 710
Gastroenterology/Coloproctology	21	6.5%	1 275
Oncohaematology	20	6.2%	900
Cardiology and CVD	14	4.3%	2 178
Rheumatology	13	4.0%	994
Dermatology	12	3.7%	657
Endocrinology	11	3.4%	1 575
Haematology	10	3.1%	168
Ophthalmology	10	3.1%	533
Psychiatry	10	3.1%	1 160
Pulmonology	10	3.1%	1 114
Infectious Diseases (except HIV/HCV/tuberculosis, COVID-19)	8	2.5%	482
HIV	5	1.6%	245
Nephrology	5	1.6%	232
Gynecology	3	0.9%	330
Otorhinolaryngology	3	0.9%	301
Allergology	2	0.6%	70
Immunology/Transplantology	2	0.6%	45
Anesthesiology	1	0.3%	40
Hepatology	1	0.3%	50
Cosmetology	1	0.3%	74
Urology	1	0.3%	30
Surgery/Orthopedics	1	0.3%	100
TOTAL	322	100.0%	34 330

Data from www.grls.rosminzdrav.ru

[1] For more information on anti-COVID-19 drug testing in Russia, see the special text in this issue of the newsletter.

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Table 3 shows the distribution by therapeutic area of bioequivalence studies, as well as local trials of generics and biosimilars by foreign sponsors.

The largest number of approvals relates to trials of drugs used in cardiology and treatment of cardiovascular diseases (CVD): 22 approvals were issued for testing of these medicinal products, which is one third of all approvals of this type. As compared to 2019, when cardiology and CVD ranked second, both the number of protocols (from 19 to 22) and the share in the structure of approvals (from 18.3% to 33.3%) increased. However, it seems that the pandemic contributed to increased interest in studies of certain generics in the area of cardiology. Thus, from Table 5 we learn that foreign sponsors initiated in 2020 as many as nine bioequivalence studies of generic Xarelto (rivaroxaban), which was successfully used in the treatment of complications associated with COVID-19. Endocrinology, which had the largest number of trials in 2019, moved down to the second spot: only 6 studies against 20 or 9.1% against 19.2% in 2019.

The third place was shared by infectious diseases and urology, 5 approvals each with shares of 7.6% of the total volume of such studies. As far as the area of infectious diseases is concerned, it should be clarified that historically we do not include drugs for HIV, hepatitis C and tuberculosis, which are counted separately. Drugs expressly related to the treatment of COVID-19 are also not included in this area (however, there were no such drugs at all among local trials of generics and biosimilars of foreign manufacturers).

Table 3

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars) of Foreign Sponsors, 2020			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD/Vascular surgery	22	32.8%	1 439
Endocrinology	6	9.0%	248
Infectious Diseases (except HIV/HCV/tuberculosis, COVID-19)	5	7.5%	358
Urology	5	7.5%	209
Gastroenterology	4	6.0%	837
Neurology	4	6.0%	408
Pulmonology	4	6.0%	257
HCV	3	4.5%	116
Allergology	2	3.0%	82
Gynecology	2	3.0%	112
Dermatology	2	3.0%	202
Oncology	2	3.0%	111
Rheumatology	2	3.0%	464
Analgesic and NSAIDs	1	1.5%	490
Transplantology	1	1.5%	175
Oncohaematology	1	1.5%	156
Otorhinolaryngology	1	1.5%	412
TOTAL	67	100,0%	6 076

Data from www.grls.rosminzdrav.ru

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Table 4 shows the distribution by therapeutic area of local trials and bioequivalence studies, approvals for which were obtained in 2020 by domestic sponsors.

Neurology retained its first place having slightly improved its indicators as compared to 2019 from 30 to 36 approvals and from 12.8% to 13.6% in the overall structure. The same indicators and, accordingly, the first place as well were demonstrated by cardiology and CVD, which placed only third in 2019 (22 approvals and 9.4%). It should be, however, noted, that as in the case of local trials by foreign sponsors the growth in the number of bioequivalence studies of generics used in cardiology and CVD may have been influenced by the high demand for anticoagulants associated with the COVID-19 pandemic.

Third place in 2020 was taken by endocrinology (25 approvals, share of 9.4%), which is better than the result of the previous year (19 approvals, share of 8.1%, fourth place). This, perhaps, was also influenced by the pandemic to some extent, which contributed to increasing interest in hypoglycemic agents.

The eighth spot in the ranking was taken by a new area — generics and biosimilars of drugs intended for treatment of COVID-19: 11 trials or 4.2% of the total volume.

Table 4

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors, 2020			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Neurology	36	13.6%	2 672
Cardiology and CVD	36	13.6%	1 675
Endocrinology	25	9.5%	1 892
Oncology	23	8.7%	1 359
HIV/HVC/tuberculosis	22	8.3%	1 188
Gastroenterology/Coloproctology	20	7.6%	1 810
Infectious Diseases (except HIV/HCV/tuberculosis, COVID-19)	12	4.5%	375
COVID-19	11	4.2%	2 416
Analgesic and NSAIDs	10	3.8%	706
Haematology	8	3.0%	310
Oncohaematology	8	3.0%	306
Urology	7	2.7%	300
Obstetrics and gynecology	6	2.3%	994
Rheumatology	6	2.3%	380
Surgery/Haematology	6	2.3%	260
Pulmonology	6	2.3%	234
Otorhinolaryngology	3	1.1%	630
Transplantology/Immunology	3	1.1%	166
Hepatology	3	1.1%	113
Psychiatry	3	1.1%	110
Allergology	3	1.1%	76
Ophthalmology	2	0.8%	440
Phlebology	2	0.8%	91
Dermatology	1	0.4%	338
Immunology	1	0.4%	80
Narcology	1	0.4%	34
TOTAL	264	100.0%	18 955

Data from www.grls.rosminzdrav.ru

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Table 5 shows molecules that most frequently appeared in generic and biosimilar study protocols under 2020 approvals.

Table 5

Most Requested INN Used in Clinical Trials of Generics in 2020				
Substance	**Number of CTs of foreign generics**	**Number of CTs of local generics**	**All clinical trials to a given INN**	**Therapeutic Area**
Rivaroxaban	9	5	14	Cardiology and CVD, surgery, COVID-19
Metformin (separately and in fixed combinations)	5	5	10	Endocrinology
Pirindopril (separately and in fixed combinations)	3	4	7	Cardiology and CVD
Ritonavir (separately and in fixed combinations)	–	6	6	HIV
Sitagliptin (separately and in fixed combinations)	2	4	6	Endocrinology
Lenalidomide	1	4	5	Oncohaematology
Rosuvastatin (separately and in fixed combinations)	2	3	5	Cardiology and CVD
Sunitinib	1	4	5	Oncology
Favipiravir	–	5	5	COVID-19
Cinacalcet	–	5	5	Endocrinology
Vildagliptin	–	4	4	Endocrinology
Ibuprofen (separately and in fixed combinations)	–	4	4	Analgesic and NSAIDs, rheumatology
Mebeverine (separately and in fixed combinations)	2	2	4	Gastroenterology
Nadroparin calcium	–	4	4	Surgery, haematology
Sorafinib	–	4	4	Oncology
Tamsulosin (separately and in fixed combinations)	1	3	4	Urology
Ticagrelor	3	1	4	Cardiology and CVD
Amlodipin (in fixed combinations)	1	2	3	Cardiology and CVD
Bosentan	–	3	3	Cardiology and CVD
Dasatinib	–	3	3	Oncohaematology
Diacerein (separately and in fixed combinations)	1	2	3	Rheumatology
Diosmin (separately and in fixed combinations)	–	3	3	Phlebology, obstetrics and gynecology
Lopinavir (in fixed combinations)	–	3	3	HIV
Memantine (separately and in fixed combinations)	1	2	3	Neurology
Sildenafil	1	2	3	Urology
Sofosbuvir (separately and in fixed combinations)	2	1	3	HCV
Tadalafil	1	2	3	Urology
Tenofivir (separately and in fixed combinations)	–	3	3	HIV
Teriflunomide	–	3	3	Neurology
Trimebutine	–	3	3	Gastroenterology
Everolimus	–	3	3	Immunology, transplantology, oncology
Eculizumab	–	3	3	Haematology, COVID-19
Ethylmethylhydroxypyridine succinate (separately and in fixed combinations)	–	3	3	Neurology

Data from www.grls.rosminzdrav.ru

This list was clearly influenced by the COVID-19 pandemic that unfolded in 2020. Thus, as can be noted, the top ten includes drugs that were previously considered or continue to be considered at the beginning of 2021 as potentially effective for symptomatic treatment of COVID-19 and control of complications caused by it. These are anticoagulant Rivaroxaban (14 protocols), sugar lowering agents Metformin (ten protocols) and Sitagliptin (six protocols), anti-viral medications Ritonavir (six protocols) and Favipiravir (five protocols). Moreover, if some medicines (for example, Metformin and, less commonly, Rivaroxaban and Sitagliptin) were in the top ten of the most popular molecules in previous years, others (like Favipiravir, Ritonavir) were of significantly more interest to developers of generic drugs in 2020 than in the previous five years.

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Below is the distribution by therapeutic area of local trials of original medications by foreign (Table 6) and Russian (Table 7) sponsors.

In both cases the top spots are held by drugs intended to combat the new coronavirus infection, as detailed in a separate text of this newsletter. The interest of domestic developers in drugs used to treat other infectious diseases remains high as before. This therapeutic area has been at the top of a similar table in the ACTO newsletters since 2013 with just COVID-19 being able to move it down to second place.

Table 6

Distribution of Local CTs of Brand Name Drugs of Foreign Sponsors, 2020		
Therapeutic Area	**Number of CTs**	**Number of planned participants**
COVID-19	4	408
Gastroenterology	1	1 000
Oncohaematology	1	140
Rheumatology	1	286
TOTAL	7	1 834

Data from www.grls.rosminzdrav.ru

Table 7

Distribution of Local CTs of Brand Name Drugs (Including Biological Products) of Local Sponsors, 2020			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
COVID-19	15	33.3%	45 042
Infectious Diseases (except HIV/HCV/tuberculosis, COVID-19)	10	22.2%	5 306
Gastroenterology/Coloproctology	4	8.9%	2 178
Cardiology and CVD	4	8.9%	406
Urology	2	4.4%	830
Psychiatry	1	2.2%	250
Neurology	1	2.2%	240
Oncohaematology	1	2.2%	212
Rheumatology	1	2.2%	175
Allergology	1	2.2%	125
Dermatology	1	2.2%	125
Immunology	1	2.2%	80
HIV	1	2.2%	44
Antiseptic	1	2.2%	36
Oncology	1	2.2%	30
TOTAL	45	100.0%	55 079

Data from www.grls.rosminzdrav.ru

DISTRIBUTION OF IMCT APPROVALS ACROSS RUSSIA

Table 8 shows the distribution of IMCTs across the territory of the Russian Federation[2].

The Central Federal District with 294 new international projects traditionally takes the lead in terms of "the number of IMCTs per region". It has irremovably been the first since at least 2015 (since the beginning of ACTO's observations) with just the North-Western District being able to push it back to second place in 2019. However, in 2020 the usual way of things was restored with only 287 new IMCTs announced to launch in the North-Western District. Then again, the gap between the two leading regions is vanishingly small being only seven trials, and the competition for first place will obviously continue.

Remaining places were distributed in exactly the same way as in 2019: the Volga Federal District took third place with 210 new projects, the Siberian Federal District became fourth with 191 projects, fifth place was taken by the Ural Federal District with 119 IMCTs, sixth — by the Southern Federal District with 93 trials, and seventh — by the North Caucasian District with 51 projects. The Far Eastern Federal District completes the ranking with eight new IMCTs across the region.

Almost all of the above-mentioned constituent entities of the Russian Federation demonstrate an increase in the number of IMCTs as compared to 2019. The Ural Federal District went up by 14 IMCTs (+13%), the Southern District — by 10 (+12%), the Siberian District — by 13 (+7%), the Central District — by 11 (+4%), the Volga District — by 2 (+1%). For the Far Eastern Federal District an increase in the number of IMCTs per region by only five projects means more than a twofold increase in activity, since only three new international studies were announced in the district in 2019, and by the end of 2020 there were eight of them. Only the North-Western Federal District, where the number of new international projects is equal to the last year's showing zero growth, and the North Caucasus, where four new IMCTs less were announced in 2020 than in 2019 corresponding to a 7% decrease in activity, fall out of the trend towards increase in activity.

In the Central Federal District the following regions showed the most intense growth of indicators: Ryazan Region (36 IMCTs in 2020 against 23 in 2019, +57%), Kaluga Region (an increase from 35 to 43 IMCTs, +23%) and Moscow (274 versus 268 a year earlier, +2%). A decline in activity was noted in Moscow Region (from 30 new projects in 2019 to 25 in 2020, i.e. -17%), Voronezh Region (from ten to seven, -30%) and Smolensk Region (from 42 to 39 IMCTs, -7%).

In the North-Western Federal District an increase in activity was demonstrated by Arkhangelsk Region (47 new IMCTs in 2020 against 31 in 2019, +52%), Murmansk Region (an increase from 6 to 12 IMCTs, i.e. two-fold) and the Komi Republic (from 5 to 10 IMCTs, two-fold growth as well). Activity has decreased in Leningrad Region (from 40 in 2019 to 22 in 2020, -45%), the Republic of Karelia (from 26 to 19, -27%) and Vologda Region (from seven to two new projects, -71%).

In the Volga Federal District an increase in the number of new IMCTs was demonstrated by the Republic of Tatarstan (101 IMCTs in 2020 versus 71 in 2019, +42%), the Republic of Bashkortostan (53 versus 30, +77%) and Kirov Region (25 versus 17, +47%). A decline in activity was noted in Samara Region (57 IMCTs in 2020 against 74 in 2019, -23%), Ulyanovsk Region (reduction from 21 to 9 IMCTs, -57%) and the Udmurt Republic (7 against 18 in 2019, -61%).

The indicator "the number of IMCTs per 1 million of population" is rather conservative, the top three here remains the same: the North-Western District with 20.5 new IMCTs per million of population (the same as in 2019), Siberian District with 11.2 (10.4 a year earlier) and Ural District with 9.6 (8.5 in 2019).

[2] See the calculation methodology in ACTO Newsletter No. 12.

Table 8

Distribution of IMCTs approved in 2020 by regions of the RF									
Region	**Number of IMCTs, per region**	**Number of IMCTs, per million population***	**Number of health care organizations, which approved sites for IMCTs, per region**	**How many times medical organizations of the region were involved in IMCTs (number of open sites)**	**Region**	**Number of IMCTs, per region**	**Number of IMCTs, per million population***	**Number of health care organizations, which approved sites for IMCTs, per region**	**How many times medical organizations of the region were involved in IMCTs (number of open sites)**
Central Federal District	**294**	**7.5**	**162**	**980 (1022)**	**North Caucasian Federal District**	**51**	**5.1**	**13**	**58**
Moscow	274	21.6	103	657(690)	Stavropol Territory	48	17.1	11	54
Yaroslavl Region	77	59.2	14	87 (88)	Kabardino-Balkarian Republic	4	4.4	2	4
Kaluga Region	43	43.0	4	49 (55)					
Smolensk Region	39	43.3	6	39	**Siberian Federal District**	**191**	**11.2**	**72**	**420**
Ryazan Region	36	32.7	4	37 (39)	Novosibirsk Region	96	34.3	30	125
Moscow Region	25	3.2	7	25	Omsk Region	65	34.2	9	68
Kursk Region	20	18.2	3	20	Tomsk Region	63	57.3	8	68
Ivanovo Region	17	17.0	4	17	Krasnoyarsk Territory	50	17.2	7	57
Tver Region	11	8.5	2	11	Altai Territory	46	20.0	7	46
Vladimir Region	10	7.1	5	10	Kemerovo Region	43	15.9	7	47
Tula Region	8	5.3	1	8	Irkutsk Region	9	3.8	4	9
Voronezh Region	7	3.0	2	7	**Ural Federal District**	**119**	**9.6**	**34**	**156**
Lipetsk Region	4	3.6	2	4	Chelyabinsk Region	67	19.1	11	70
Kostroma Region	3	5.0	1	3	Sverdlovsk Region	52	12.1	16	56
Tambov Region	3	3.0	1	3	Tyumen Region	27	7.5	7	30
Belgorod Region	2	1.3	2	2	**Volga Federal District**	**210**	**7.2**	**91**	**457 (464)**
Bryansk Region	1	0.8	1	1	Republic of Tatarstan	101	25.9	16	108 (110)
Southern Federal District	**93**	**5.6**	**24**	**119 (121)**	Nizhny Novgorod Region	66	20.6	17	74
Krasnodar Territory	51	8.9	11	58	Samara Region	57	17.8	11	63
Rostov Region	36	8.6	10	37 (39)	Saratov Region	56	23.3	13	62 (64)
Volgograd Region	24	9.6	3	24	Republic of Bashkortostan	53	13.3	6	55 (57)
Northwestern Federal District	**287**	**20.5**	**141**	**851 (870)**	Kirov Region	25	19.2	5	25 (26)
Saint-Petersburg	280	51.9	119	725 (744)	Republic of Mordovia	17	21.3	2	17
Arkhangelsk Region	47	42.7	5	49	Orenburg Region	14	7.0	5	14
Leningrad Region	22	11.6	6	25	Perm Territory	13	5.0	6	13
Republic of Karelia	19	31.7	1	19	Ulyanovsk Region	9	7.5	2	9
Murmansk Region	12	17.1	3	13	Penza Region	7	5.4	2	7
Republic of Komi	10	12.5	2	10	Udmurtian Republic	7	4.7	5	7
Kaliningrad Region	6	6.0	2	6	Mari El Republic	1	1.4	1	1
Novgorod Region	2	3.3	2	2	**Far Eastern Federal District**	**8**	**1.0**	**5**	**9**
Vologda Region	2	1.7	1	2	Republic of Sakha (Yakutia)	4	4.0	2	4
					Trans-Baikal Territory	3	2.7	1	3
					Primorye Territory	2	1.1	2	2

*We used data of Rosstat on the resident population of the region as of January 1, 2020

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Diagram 6 shows activity of the constituent entities of the Russian Federation in new international projects.

The "over 200 IMCTs" segment is traditionally occupied by two constituent entities: Moscow and St. Petersburg.

Previously there was no "101-200 IMCTs" segment, however, in 2020 the Republic of Tatarstan managed to get into this new weight category (with exactly 101 new IMCTs).

The "51–100 IMCTs" segment is represented by 11 regions, specifically, Krasnodar Territory (returned to the segment after the 2019 decrease in positions), the Republic of Bashkortostan (apparently, made it to the segment for the first time), Nizhny Novgorod Region, Novosibirsk Region, Saratov Region, Samara Region, Sverdlovsk Region, Tomsk Region, Omsk Region, Chelyabinsk Region (returned after having dropped out of the segment in 2018) and Yaroslavl Region. It is pleasant to note the growth of the segment, it included ten regions in 2019 and only eight in 2018. According to the results of 2020 only Stavropol Territory worsened its positions having migrated to a less prestigious weight category with 48 new IMCTs against 52 a year earlier.

As in the previous year, 31 to 50 new IMCTs were planned in Arkhangelsk Region, Kaluga Region, Kemerovo Region, Rostov Region, Smolensk Region, as well as in Altai and Krasnoyarsk Territories. In addition, the segment included the aforementioned Stavropol Territory that moved down there and Ryazan Region that moved up having increased its activity from 23 new IMCTs in 2019 to 36 in 2020.

The "21–30 IMCTs" segment includes, as a year earlier, Volgograd Region, Moscow Region and Tyumen Region. They were joined by Leningrad Region that dropped in rank (22 new IMCTs against 40 IMCTs a year earlier), as well as Kirov Region that announced its participation in 25 new projects against 17 in 2019 and, accordingly, rose to its current position from the "11–20 IMCTs" segment.

As in 2019, 11 to 20 new international trials were announced in Perm Territory, Ivanovo Region, Kursk Region and Orenburg Region. The segment was also joined by the Republic of Karelia that demonstrated decline in its activity (19 new IMCTs against 26 in 2019), as well as by regions that, on the contrary, became more active: Republic of Mordovia (17 new IMCTs against nine), Murmansk Region (12 against six) and Tver Region (11 against seven).

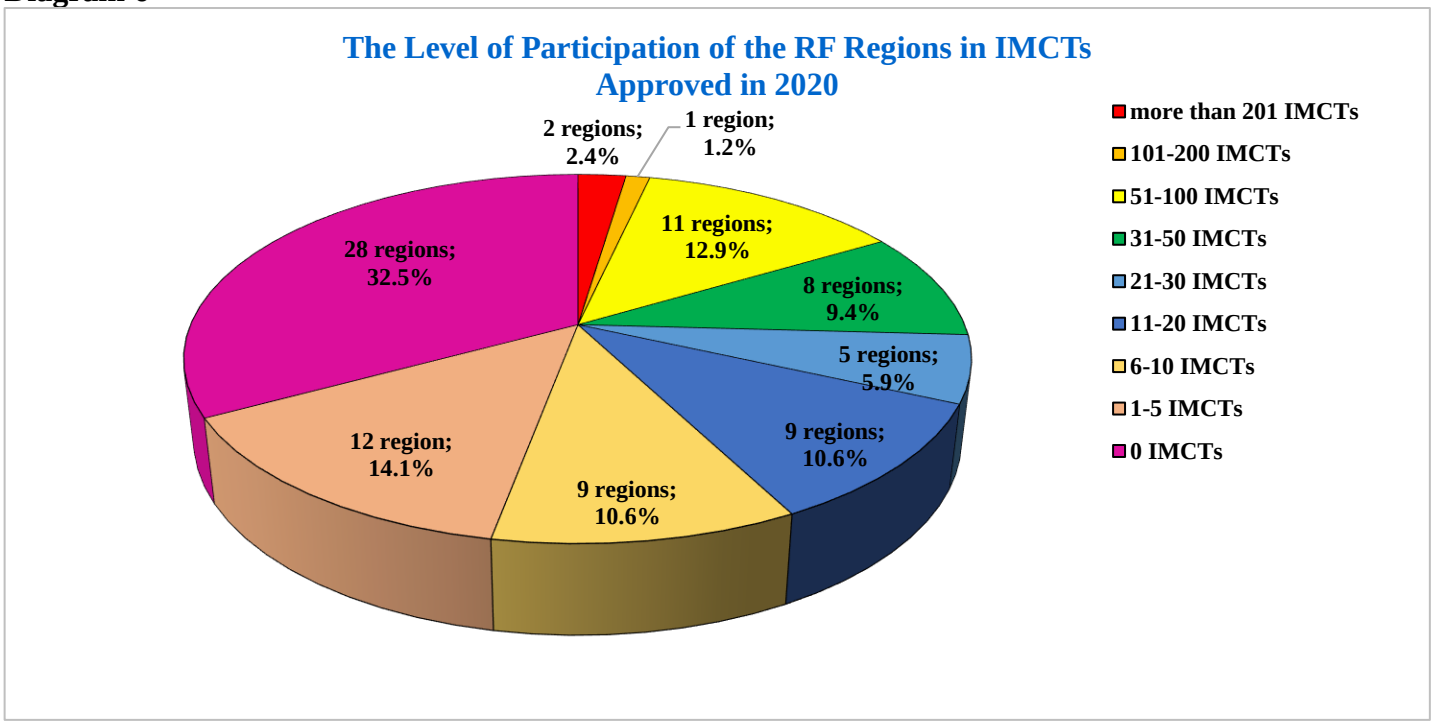
The "6–10 IMCTs" segment is represented, as in the previous year, by Vladimir Region, Voronezh Region, Kaliningrad Region and Tula Region, which were joined by the less active Udmurtian Republic (seven new IMCTs against 18 in 2019,) Penza Region (seven against 16) and Ulyanovsk Region (nine against 21), as well as by regions with increased activity: the Republic of Komi (10 new IMCTs against five in 2019) and Irkutsk Region (nine protocols against three).

The least active regions, with 1 to 5 new IMCTs, are, as before, the Kabardino-Balkarian Republic, the Republic of Mari El, Belgorod Region, Bryansk Region, Kostroma Region, Novgorod Region and Tambov Region, joined by less active Vologda Region (two IMCTs against seven in 2019) and Lipetsk Region (four against six) that moved down from the higher activity segment, as well as by three Far Eastern regions at once that did not participate in any new protocol in 2019: the Republic of Sakha (Yakutia) (four IMCTs), Trans-Baikal Territory (three IMCTs) and Primorye Territory (two IMCTs).

28 regions of Russia did not plan to start any new international clinical trials at all in 2020, which is one region more than a year earlier. Unfortunately, the list was supplemented by Kurgan Region, Khanty-Mansi Autonomous Area, the Republic of North Ossetia-Alania (all three regions had two new IMCTs each in 2019),

as well as Khabarovsk Territory (three IMCTs at the end of 2019). At the same time, the above-mentioned Trans-Baikal Territory, Primorye Territory and the Republic of Sakha (Yakutia) left the segment.

Diagram 6



Data from www.grls.rosminzdrav.ru

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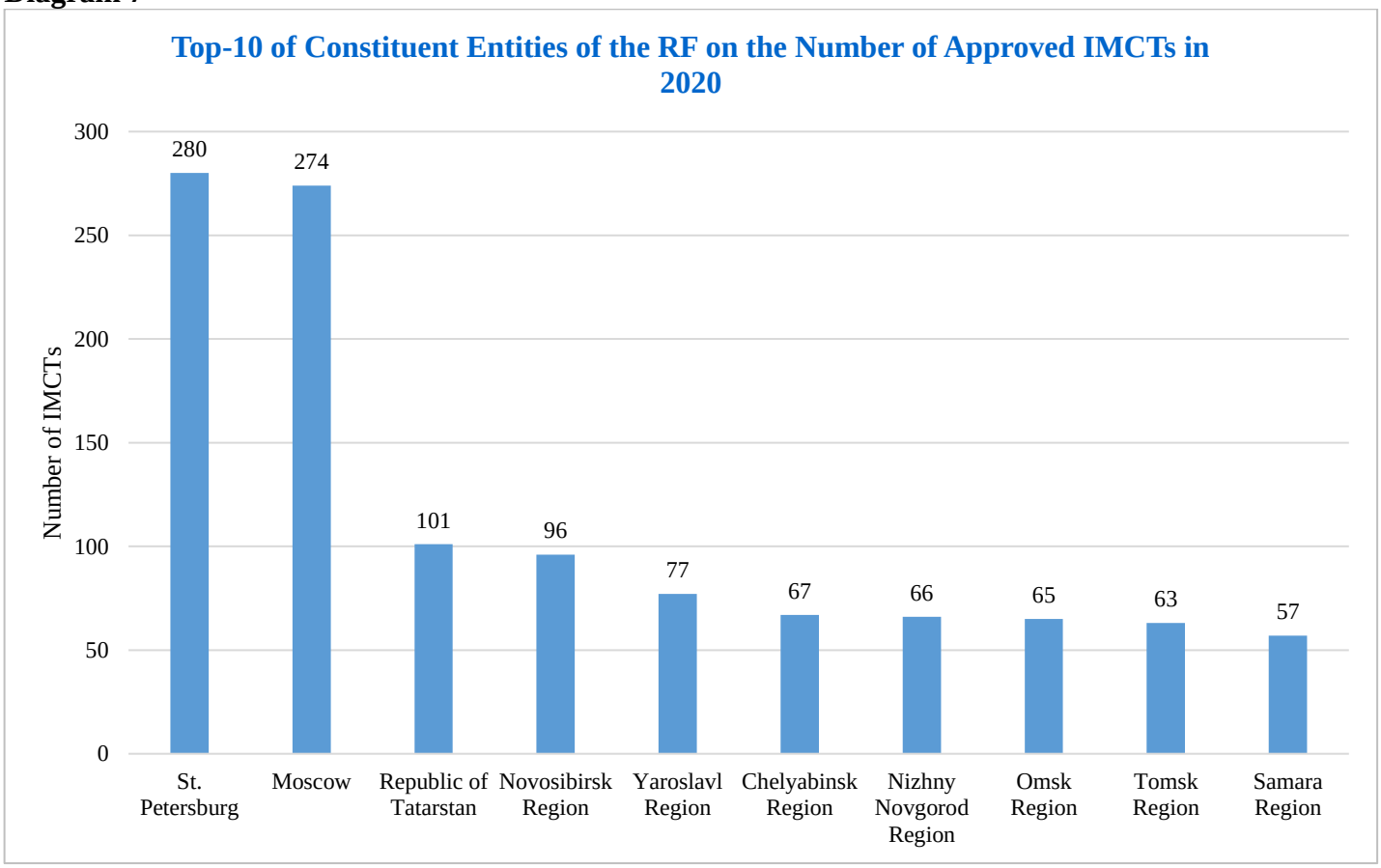
Top 10 constituent entities of the Russian Federation leading by number of IMCTs approved in 2020, in absolute and relative figures, are shown in Diagrams 7 and 8.

As compared to 2019, Saratov Region and Sverdlovsk Region dropped out of the top ten in terms of the number of approved IMCTs (ninth and tenth places a year ago) being replaced by Chelyabinsk Region and Tomsk Region (sixth and ninth places in 2020). Tatarstan rose from sixth to third place (101 IMCTs in 2020 against 71 in 2019). Samara Region dropped from fourth to tenth place (57 against 74 IMCTs). Nizhny Novgorod Region (66 against 65) managed to overtake Omsk Region (65 against 70) due to decreased activity of the latter. Aside from these small rearrangements, top 10 in terms of the number of new IMCTs remained the same. Even the traditional Moscow — St. Petersburg reshuffle did not take place, the northern capital maintained its leading position despite the slightly decreased activity in St. Petersburg and increase in activity in Moscow (280 against 284 IMCT in St. Petersburg and 274 against 268 in Moscow).

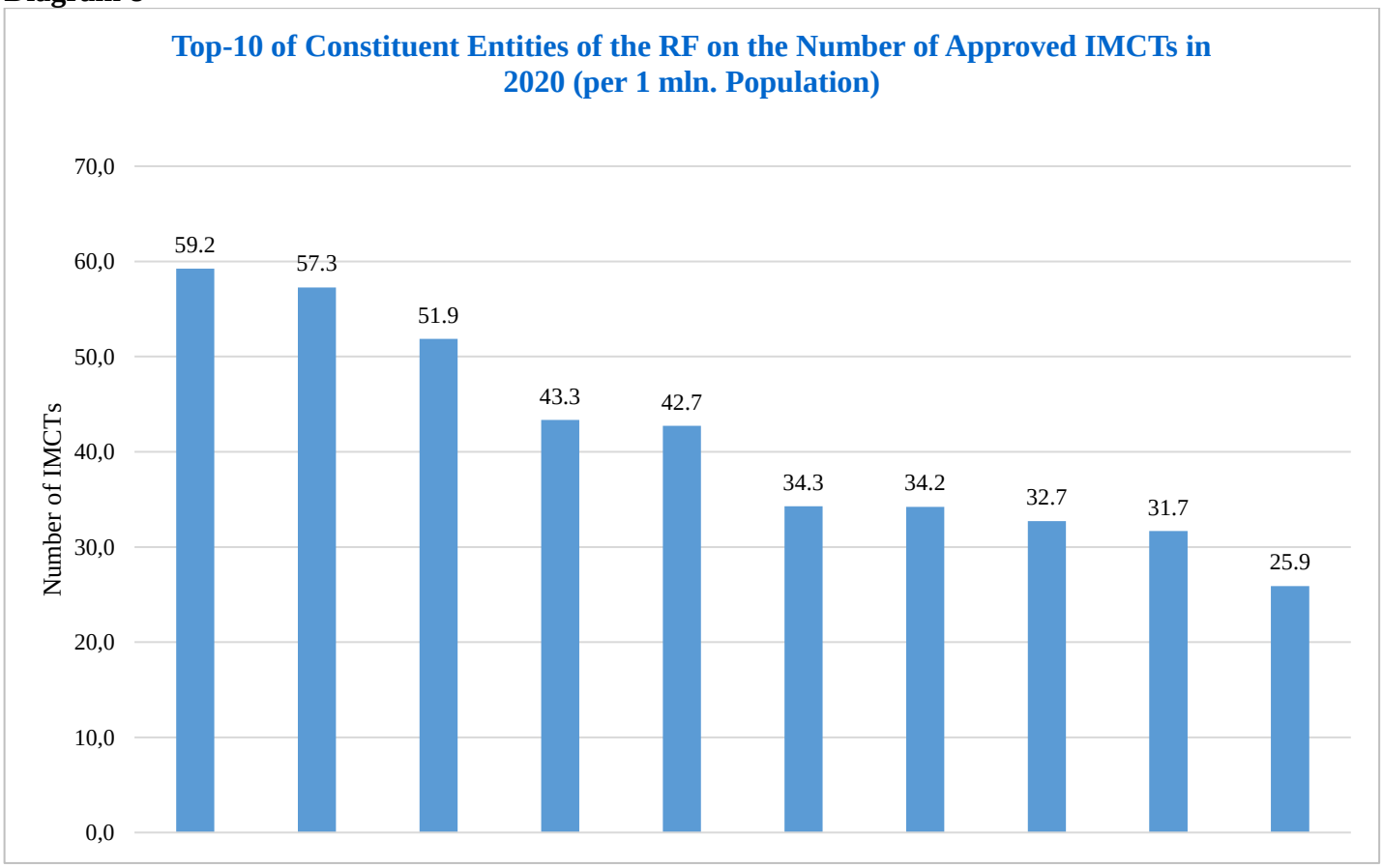
Changes in Diagram 8, as compared to 2019, are also insignificant. The usual leader, Yaroslavl Region, continued to ramp up its activity (59.2 IMCTs per million of population against 55.4 in 2019). Tomsk Region and St. Petersburg switched spots, activity of the former increased from 47.3 IMCTs per million of population to 57.3 (resulting in the second spot of the ranking) and activity of the latter slightly decreased from 52.6 in 2019 to 51.9 in 2020 (third place). Smolensk remained on the fourth spot slightly losing in activity to itself last year (43.3 against 46.7 in 2019). Arkhangelsk Region moved up from ninth to fifth place (42.7 against 28.2 a year earlier), Novosibirsk Region — from eighth to sixth (34.3 against 30.4). The Republic of Karelia dropped from fifth to ninth place (31.7 against last year's 43.3), Omsk Region — from sixth to seventh (34.2 against 35). Kaluga Region and Saratov Region dropped out of the top 10 (seventh and tenth places in 2019) being replaced by Ryazan Region and the Republic of Tatarstan (eighth and tenth places in 2020).

Diagram 7



Data from www.grls.rosminzdrav.ru

Diagram 8



Data from www.grls.rosminzdrav.ru

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The ranking of medical organizations that were most often involved in conducting new IMCTs under approvals in 2020 has undergone the following changes.

Eight organizations retained their top 20 spots from the previous year:

– Pavlov First Saint Petersburg State Medical University ranked first again, activity increased from 63 to 71 new IMCTs;

– N.N. Blokhin Russian Cancer Research Center, Moscow — remained second having increased the number of new IMCTs from 46 to 61;

– N.N. Petrov National Medicine Research Center of Oncology, St. Petersburg — moved up from ninth to third place, the number of IMCTs increased from 27 to 44;

– Sechenov University, Moscow — fourth place and 39 IMCTs in 2020 against the fifth spot in the ranking with 29 IMCTs in 2019;

– St. Petersburg Clinical Scientific and Practical Center for Specialized Types of Medical Care (Oncological) — fifth place with 38 IMCTs in 2020 and 17th place with 21 IMCTs in 2019;

– Omsk Clinical Oncological Dispensary — sixth spot with 37 IMCTs against third place with 44 international trials a year ago;

– Obninsk National Medical Research Radiological Centre — seventh place with 34 IMCTs in 2020 against sixth place with 29 IMCTs in 2019;

– Saratov State Medical University named after V. I. Razumovsky — 12th spot in the ranking with 26 new IMCTs in 2020 and tenth place with 25 IMCTs in 2019.

Six organizations that were included in the top 20 of the previous years and returned to it after a temporary absence:

– Almazov National Medical Research Centre, St. Petersburg — eighth place with 33 IMCTs in 2020, 21st place with only 19 IMCTs in 2019;

– Arkhangelsk Clinical Oncological Dispensary ranked ninth with 33 IMCTs, last time it was included in the top 20 in 2018 (11th place with 28 IMCTs).

– Kazan Republican Clinical Oncological Dispensary — eleventh place with 30 IMCTs at the end of the year, last time it was in the top 20 in 2018 in sixteenth place with 26 IMCTs.

– Rostov State Medical University — 18th place with 22 IMCTs in 2020, last time it was in the top 20 in 2018 in sixth place with 37 IMCTs.

– St. Petersburg Military Medical Academy named after S.M. Kirov shared spots 19–20 in the ranking with Ryazan State Medical University (21 new IMCTs each), last time it was in the top 20 in 2018 in tenth place with 29 IMCTs, ending 2019 with only 61st spot with 11 new projects.

– Ryazan State Medical University named after I.P. Pavlov — ranked 19–20 with 21 of IMCTs, last time it was in the top 20 in 2017 ranking 19–21 with 19 new international projects.

Another six organizations were included in the top 20 by number of new IMCTs for the first time over the course of ACTO's monitoring.

– Regional Clinical Oncology Hospital, Yaroslavl — from 46th spot in the ranking in 2019 straight to tenth place.

– City Clinical Hospital No. 52, Moscow, and City Hospital No. 40, Kurortny District, St. Petersburg — spots 101–115 in 2019 and 13–14 in 2020.

– City Clinical Hospital № 15 named after O.M. Filatov, Moscow — 87th in 2019 and 15th at the end of 2020.

– Medsi Group of Companies, Moscow — the only clinic in the top 20 representing the non-governmental sector of the healthcare system, has increased its activity starting with just three new IMCTs in 2019 (spots 244-295) going up to 23 projects at once (16th place at the end of 2020).

– City Clinical Hospital No. 40, Moscow — 17th spot versus 101-115th in 2019.

Table 9

Top-20 Medical Organizations on the Activity of Participation in IMCTs Approved in 2020				
Place in ranking	**Name of medical organization**	**Number of IMCTs approved in 2020 with participation of this medical organization**	**Number of sites approved in 2020 for conducting IMCTs**	**Number of IMCTs and ranking of the sites (on approvals issued in 2019)**
1	I. P. Pavlov First St. Petersburg State medical University, Russian Ministry of Health, St. Petersburg	71	72	63 (1)
2	N. N. Blokhin Russian Cancer Research Centre, Russian Ministry of Health, Moscow	61	66	46 (2)
3	N.N. Petrov National Medicine Research Center of Oncology, Russian Ministry of Health, St. Petersburg	44	45	27 (9)
4	I. M. Sechenov First Moscow State Medical University, Russian Ministry of Health, Moscow	39	44	29 (5)
5	St. Petersburg Clinical Scientific and Practical Center for Specialized Types of Medical Care (Oncological), St. Petersburg	38	38	21 (17)
6	Clinical Oncological Dispensary, Omsk	37	37	44 (3)
7	National Medical Research Radiological Centre, Obninsk	34	40	29 (6)
8	Almazov National Medical Research Centre, St. Petersburg	33	34	19 (21)
9	Arkhangelsk Clinical Oncological Dispensary, Arkhangelsk	33	33	19 (22-23)
10	Regional Clinical Oncological Hospital, Yaroslavl	32	32	13 (46-47)
11	Republican Clinical Oncological Dispensary, Kazan	30	31	15 (34-39)
12	Saratov State Medical University named after V. I. Razumovsky, Russian Ministry of Health, Saratov	26	27	25 (10)
13-14	City Clinical Hospital No.52, Moscow Department of Healthcare, Moscow	26	26	8 (101-115)
13-14	City Hospital No. 40, Kurortny District, St. Petersburg	26	26	8 (101-115)
15	City Clinical Hospital No.15 named after O. M. Filatov, Moscow Department of Healthcare, Moscow	24	24	9 (87)
16	JSC Group of companies Medsi, Moscow	23	25	3 (244-295)
17	City Clinical Hospital No.40, Moscow Department of Healthcare, Moscow	23	23	8 (101-115)
18	Rostov State Medical University, Rostov-on-Don	22	24	16 (28)
19-20	St. Petersburg Military Medical Academy named after S.M. Kirov, Russian Ministry of Defense, St. Petersburg	21	23	11 (61-69)
19-20	Ryazan State Medical University named after academician I.P. Pavlov, Ryazan	21	23	12 (48-49)

Data from: www.grls.rosminzdrav.ru

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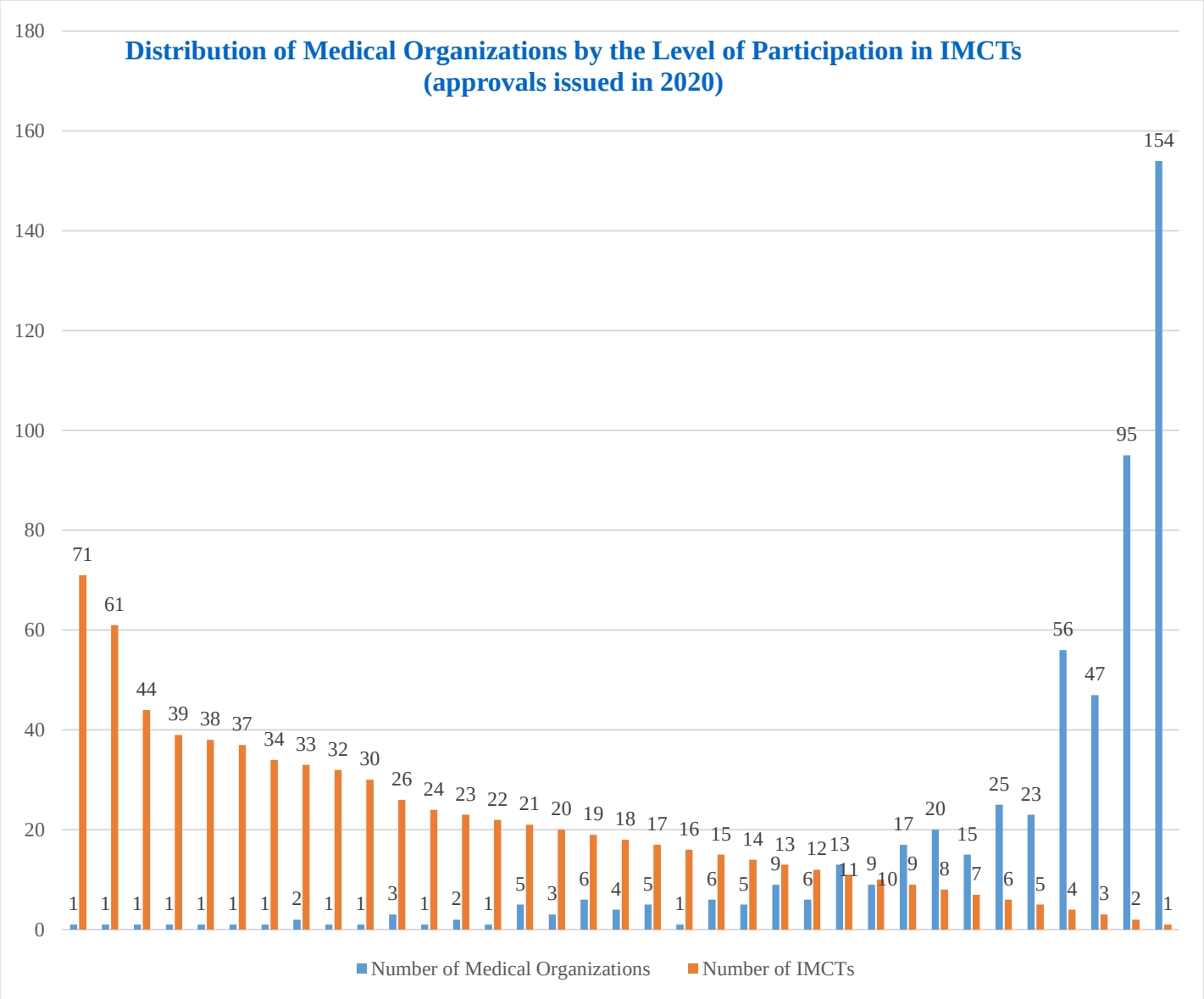
Distribution of IMCTs approved in 2020 by medical organization, where it was planned to conduct the trial, is shown in Diagram 9. Thus, ten clinics were involved in conducting more than 30 new IMCTs, 13 — in conducting 21 to 30 studies, 58 — 11 to 20, 86 — 6 to 10 studies, 126 — three to five, 95 organizations were declared as participants in two IMCTs and 154 — in only one. In total, 542 institutions were involved in new international projects in 2020, which is give less than a year earlier.

Diagram 9



Data from www.grls.rosminzdrav.ru

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Tables 10 and 11 show the distribution of IMCTs by medical organizations of various departmental subordinations in Moscow and St. Petersburg. We consider these regions separately and in a more detailed way as the most active.

In Moscow (Table 10) the total number of medical organizations involved in conducting IMCTs during 2020 was 103, which is six clinics more than in 2019. The number of approved sites increased from 573 to 690 over the year.

Table 10

The level of participation of healthcare organizations in Moscow in IMCTs depending on subordination						
Subordinated to	**The number of medical organizations involved in new IMCTs**		**The number of sites approved for IMCTs**		**Activity Coefficient**	
	2020	**2019**	**2020**	**2019**	**2020**	**2019**
Ministry of Healthcare of the Russian Federation	23	20	270	248	**11.7**	12.4
JSC "Russian Railways"	2	3	16	11	**8.0**	3.7
Ministry of Healthcare of the Moscow region	3	4	19	34	**6.3**	8.5
Moscow Department of Healthcare	33	33	201	139	**6.1**	4.2
Federal authorities (except Ministry of Healthcare of the RF)	17	16	82	86	**4.8**	5.4
Non-governmental health system	25	21	102	55	**4.1**	2.6
TOTAL	103	97	690	573	**6.7**	5.9

Data from www.grls.rosminzdrav.ru

In terms of the number of IMCT sites approved in 2020, clinics of the Ministry of Health of Russia are traditionally in the lead with their number having grown since 2019 by 22 and reached 270. They are traditionally followed by clinics of the Moscow Department of Healthcare, where 201 IMCT sites were announced to open in 2020, which is 62 more than a year earlier. However, as can be seen from the table, the number of medical organizations involved remained the same — 33. Such a noticeable increase in the number of open sites (almost 45%) is due to the active participation of Moscow clinics in international trials aimed at combating COVID-19. One example is City Clinical Hospital No. 52, where 12 out of 26 IMCTs were trials of medicines for the new coronavirus infection, or City Clinical Hospital No. 15 named after O.M. Filatov, where out of 24 new projects 19 IMCTs were dedicated to testing drugs for COVID-19. Shares of such trials also turned out to be significant in City Clinical Hospitals No. 40, No. 24, No. 51 and in N.V. Sklifosovsky Research Institute of Emergency Medicine. All eight IMCTs conducted in Infectious Clinical Hospital No. 1 of the Department of Health of Moscow were dedicated to this disease only.

Third place in Moscow is taken by the non-governmental healthcare system with 102 new sites, which is almost twice as many as last year's 55. The growth in the non-governmental sector has occurred, apparently, due to oncological protocols. Thus, the aforementioned JSC Group of Companies Medsi that made a hit in 2020 with 23 protocols at once against three in 2019 had 17 new IMCTs dealing with oncological diseases and six — with COVID-19. VitaMed LLC ranking second in Moscow among private clinics was declared to participate in 11 IMCT protocols, all of which turned out to be oncological. Among other participants in this sector two oncological protocols were given to Neuro-Clinic LLC (a total of eight new IMCTs in 2021), eight of eight new IMCTs — to a branch of Hadassa Medical LTD, four of four — to ZAO MCK. It is, of course, difficult to assess the rates of recruitment of patients in private clinics, however the trend towards expanding participation of this category of medical organizations in oncological IMCTs should definitely be welcomed.

Fourth place is taken by medical organizations subordinated to federal authorities (except for the Ministry of Health of Russia), where 82 sites were approved, which is four less than in 2019. The lowest rates are demonstrated by clinics of the Russian Railways (16 sites approved, five more than a year before) and Ministry of Health of Moscow Region (19, a significant drop as compared to 34 new sites last year). Among institutions subordinated to the Ministry of Health of Moscow Region, the most active participant of IMCTs is usually M.F. Vladimirsky Moscow Regional Research and Clinical Institute (MONIKI). In 2020, the number of sites there decreased drastically (for comparison, it was planned to open 29 sites in 2019 and only 14 in 2020).

Since several sites can be opened in the same medical organization, a coefficient that expresses the ratio of the number of new sites to the number of organizations is calculated additionally. In clinics of the Ministry of Health of Russia this indicator decreased from 12.4 to 11.7 over the year, which was caused by expansion of the range of medical organizations participating in new IMCTs (it increased from 20 to 23 as compared to 2019). It also decreased in clinics of other federal authorities (from 5.4 to 4.8) and in clinics of the Ministry of Health of Moscow Region (from 8.5 to 6.3). In the first case the number of medical organizations increased by one and the number of new sites turned out to be slightly lower than last year. In the second case the number of medical organizations has not only failed to show growth but has, in fact, decreased by one, while the number of new sites has almost halved. There has been an increase in activity of organizations subordinated to the Russian Railways (from 3.7 to 8.0 due to an increase in the number of sites and a decrease in the number of clinics), the Moscow Department of Healthcare (from 4.2 to 6.1 due to an increase in the number of sites in the same 33 clinics) and clinics of the non-governmental healthcare system (from 2.6 to 4.1 due to both expansion of the number of clinics involved and a significant increase in the number of new sites).

In St. Petersburg (table 11) the total number of medical organizations decreased by six as compared to 2019 and amounted to 125. The number of approved IMCT sites has also decreased, from 765 to 744.

Table 11

The level of participation of healthcare organizations in St. Petersburg in IMCTs depending on subordination

Subordinated to	The number of medical organizations involved in new IMCTs		The number of sites approved for IMCTs		Activity Coefficient	
	2020	2019	2020	2019	2020	2019
Ministry of Healthcare of the Russian Federation	11	11	215	207	**19.5**	18.8
Committee of Health of the Leningrad Region	1	1	18	31	**18.0**	31.0
JSC "Russian Railways"	1	1	9	18	**9.0**	18.0
Federal authorities (except Ministry of Healthcare of the RF)	11	11	68	57	**6.2**	5.2
Health Committee of Saint-Petersburg	46	54	268	279	**5.8**	5.2
Non-governmental health system	49	47	166	173	**3.4**	3.7
TOTAL	119	125	744	765	**6.3**	6.1

Data from www.grls.rosminzdrav.ru

In terms of the number of sites, clinics of the St. Petersburg Healthcare Committee are in the lead, 268 of them were approved in 2020, which is 11 less than a year before. They are followed by clinics of the Russian

Ministry of Health, where the number of sites has gone up from 207 to 215. Third place is taken by the non-governmental healthcare system with 166 new IMCT sites, which is seven less than in 2019. Ranking fourth by the number of new sites are medical organizations subordinated to federal authorities, excluding the Ministry of Health of Russia, 68 sites with their participation were approved, 11 more than the previous year. Least of all new sites were planned to be opened in clinics of the Healthcare Committee of Leningrad Region (18 versus 31 a year earlier) and Russian Railways (9 versus 18 in 2019).

The average activity of medical organizations in 2020 was the highest among clinics of the Russian Ministry of Health (19.5 in 2020). It has gone up as compared to the previous year, since the number of clinics involved in new IMCTs remained unchanged (11) and the number of new sites increased. The average activity of medical organizations subordinated to other federal authorities also increased (from 5.2 in 2019 to 6.2 in 2020 due to an increase in the number of new sites while maintaining the number of active organizations) and the Healthcare Committee of St. Petersburg (from 5.2 to 5.8 due to reduction in the number of organizations involved from 54 to 46). The average activity of clinics of other departmental affiliation decreased from 31.0 to 18.0 for those subordinated to the Healthcare Committee of Leningrad Region (the number of new sites in one clinic decreased by 42%), from 18.0 to 9.0 for those subordinated to the Russian Railways (the number of new sites in the only clinic participating in IMCTs) and from 3.7 to 3.4 for organizations of the non-governmental healthcare system (the number of sites decreased, while the number of clinics, on the contrary, increased, from 47 to 49).

PARTICIPATION OF MEDICAL ORGANIZATIONS IN BIOEQUIVALENCE STUDIES

Table 12 introduces medical organizations that were the most active in bioequivalence studies. Most clinics were included in a similar ranking for the previous year. Probiotech Medical Center, Serpukhov, retained its first place losing somewhat in the number of new studies: 25 against 28 in 2019. Clinical Hospital No. 3, Yaroslavl, moved up from 8th–9th place to second sharing it with the St. Petersburg Eco-Safety Research Center (spots 3–4 in 2019) with 22 new studies each. Moscow Certa Clinic rose sharply in the ranking going up from spots 27–31 (one approval) in 2019 straight to fourth place (20 approvals) in 2020.

Two more organizations indicated in Table 12 were not listed among the approved sites for conducting bioequivalence studies a year earlier — these are Ligand Research, Moscow, and the Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, Odintsovo. According to the results of 2020, the first organization ranked 14–15 with six approvals, and the second one took 11th place with 11 approvals.

Table 12

Top-15 medical organizations on the activity of participation in bioequivalence studies (approvals issued in 2020)					
Place in ranking	**Name of medical organization**	**Total number of bioequivalence studies**	**Number of bioequivalence studies conducted by local sponsors**	**Number of bioequivalence studies conducted by foreign sponsors**	**Number of bioequivalence studies and sites ranking on approvals issued in 2019**
1	Medical Center Probiotech, Serpukhov	25	25	–	28 (1)
2-3	Clinical Hospital № 3, Yaroslavl	22	22	–	12 (8-9)
2-3	Eco-Safety Research Center, St. Petersburg	22	18	4	17 (3-4)
4	Certa Clinic, Moscow	20	20	–	1 (27-31)
5	Clinical Hospital "RZD-Medicine", Yaroslavl	19	7	12	8 (14)
6	Clinical Hospital № 2, Yaroslavl	18	15	3	23 (2)
7	Yaroslavl Regional Clinical Narcological Hospital, Yaroslavl	17	14	3	16 (5)
8-9	Cardiology Dispensary, Ivanovo	13	10	3	10 (10-11)
8-9	X7 Clinical Research, St. Petersburg	13	8	5	12 (8-9)
10	N.P. Bekhtereva Institute of Human Brain of the Russian Academy of Sciences, Saint Petersburg	12	7	5	17 (3-4)
11	Federal Research and Clinical Center of Physical-Chemical Medicine of FMBA, Moscow region, Odintsovo	11	2	9	n/a
12	North-West Public Health Research Center, St. Petersburg	10	10	–	10 (10-11)
13	Bessalar clinic, Moscow	8	7	1	4 (17-21)
14-15	Ligand Research, Moscow	6	1	5	n/a
14-15	Belgorod State National Research University, Belgorod	6	6	–	4 (17-21)

Data from www.grls.rosminzdrav.ru

MAIN PLAYERS ON THE RUSSIAN CLINICAL TRIALS MARKET – 2020

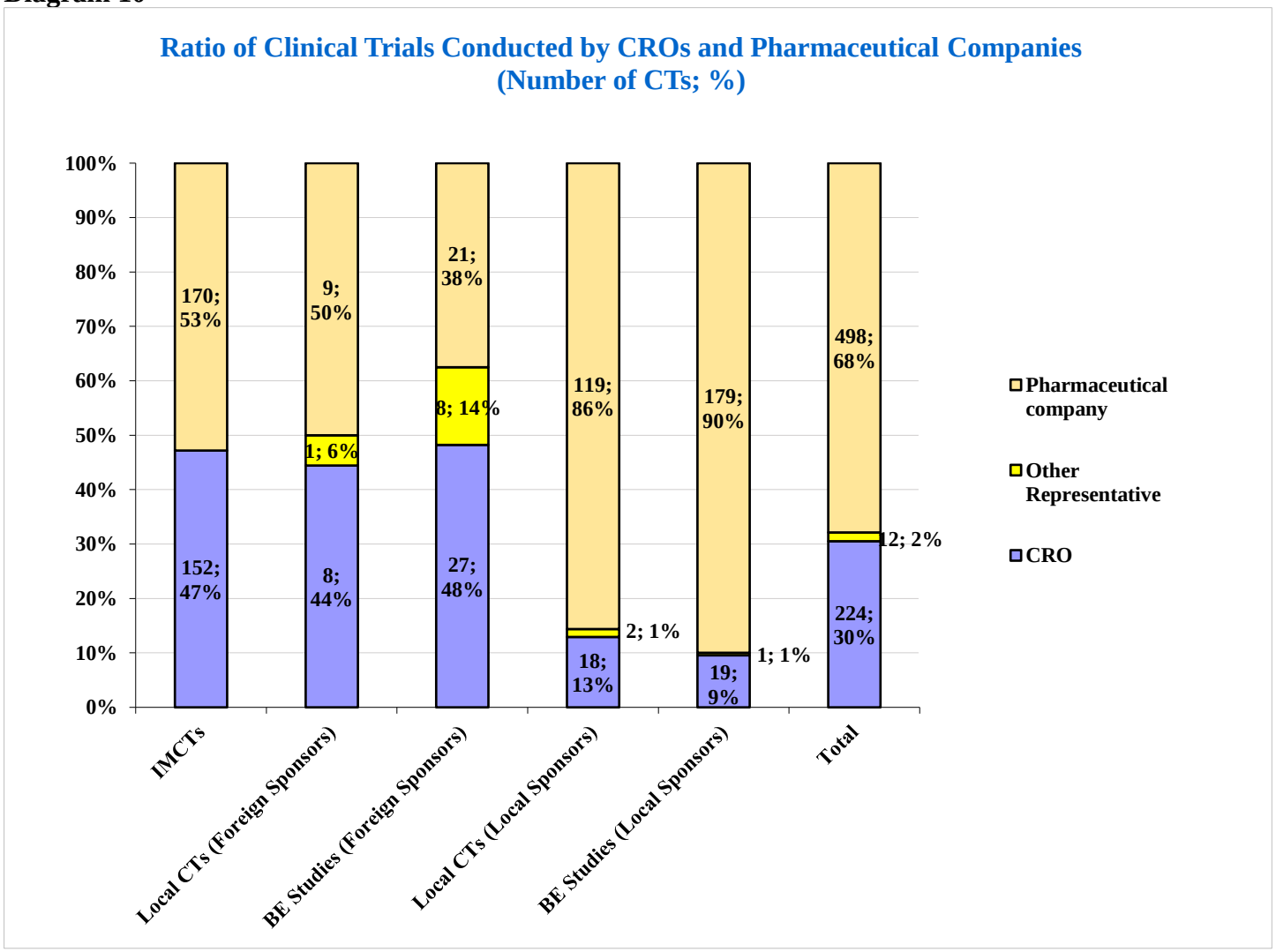
The classification applied in the description of activity of the main market participants presented below is set forth in the corresponding sections of Newsletters No. 14 and No. 12.

Sponsors and CROs, general structural distribution

The register of approvals of the Ministry of Health provides for an option to indicate whether a sponsor engaged other organizations (primarily contract research organizations, CROs) when conducting a trial. Not all sponsors use this option, for which reason the statistics below is not a 100% perfect representation of the actual situation, however it still gives a general idea of the main players and their importance in the market. Diagram 10 shows the ratio between trials that the sponsor planned to conduct by itself and trials involving CROs and other players falling under the "other representative" category (companies that are not engaged in conducting trials as their primary activity, but, generally, provide pharmaceutical manufacturers with services for introduction of products to the market).

In 68% of approvals in 2020 (without division by type of trials) only the sponsor was indicated as the organizer — this indicator returned to its usual values after dropping to 63% in 2019 (in 2016-2018, the value ranged from 66% to 69%). The share of trials involving contract research organizations has also returned from an unusually high 35% in 2019 to the level of 2016–2018 (from 25 to 31%) and amounted to 30%.

Diagram 10



Data from www.grls.rosminzdrav.ru

If we consider the types of trials separately, the following can be noted. In IMCTs the ratio between trials conducted by sponsors themselves and trials involving CRO is traditionally close to 50/50. However, while in 2019 the balance was tilted towards CRO (featured in 54% of approvals), then in 2020 it shifted in the opposite direction (in 53% of cases sponsors declared independent conducting of trials).

In general, they reproduced the usual proportions and studies of Russian sponsors, both local and bioequivalence. In 2020, foreign companies engaged CROs in local trials and bioequivalence studies more often than in recent years: 44% in 2020 versus 11–29% in 2016–2019 in local trials and 48% in 2020 against 12–17% in 2016–2019 in bioequivalence studies. However, since the total number of these two types of trials, which were already few in number, declined even more in 2020, this change had almost no effect on the overall result. These two types of trials, as always, account for almost all cases of involving “other representatives”.

International multicentre clinical trials, sponsors

Table 13 shows sponsors that obtained the most approvals for IMCTs in 2020.

F. Hoffmann-La Roche that was only seventh at the end of 2019 (11 IMCTs) broke into the first spot in the ranking with 26 approvals. Growth was also demonstrated by AstraZeneca, AbbVie and GSK. At the end of 2019, all three companies shared spots 11–13 in the ranking with seven approvals each. In 2020, AstraZeneca climbed straight to second place with 25 new IMCTs, while AbbVie and GSK once again ended up next to each other sharing the eighth and ninth positions with nine approvals each. In contrast, the 2019 top three, Merck, Novartis and Janssen, each moved down two notches and ranked third, fourth, and fifth, respectively. Sanofi and Eli Lilly also slightly dropped changing their shared position in 2019 on the fifth and sixth spots in the ranking to sixth and seventh places, respectively.

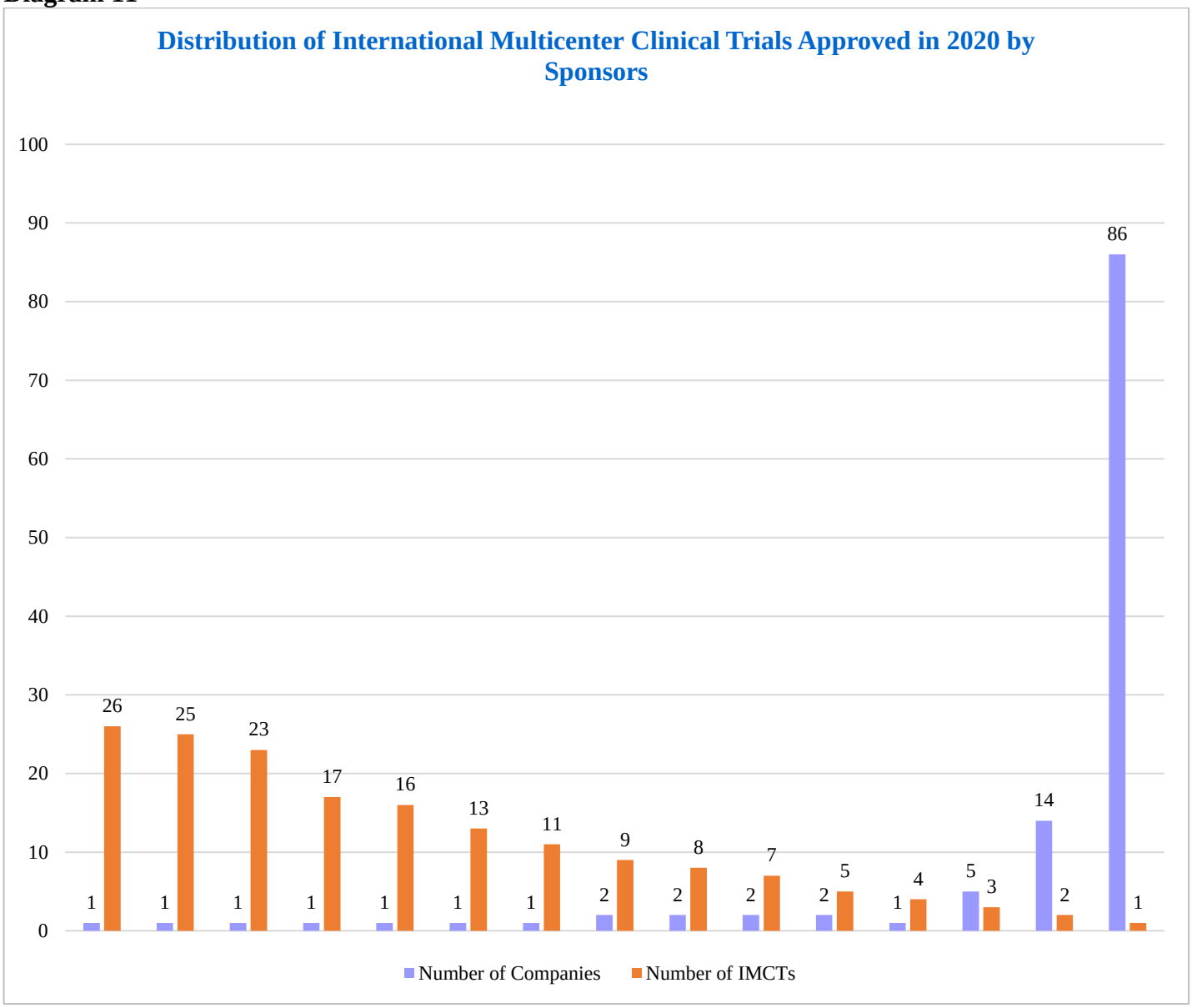
Table 13

Ranking of Leading Pharmaceutical Companies on Approvals for International Multicenter CTs, 2020					
Rating in 2020	**Company (including separate companies, associated in group of companies, as well as independent divisions of the company)**	**Conducted by themselves**	**Conducted by CRO**	**Total**	**Number of IMCTs; Ranking in 2019**
1	F. Hoffmann-La Roche	26	–	26	11 CTs; 7
2	AstraZeneca AB (incl. Acerta Pharma B.V.)	20	5	25	7 CTs; 11–13
3	Merck & Co.	23	–	23	29 CTs; 1
4	Novartis	17	–	17	25 CTs; 2
5	Janssen Pharmaceutica (incl. Actelion Pharmaceuticals)	13	3	16	17 CTs; 3
6	Sanofi (incl. Genzyme Corporation)	13	–	13	13 CTs; 5–6
7	Eli Lilly	10	1	11	13 CTs; 5–6
8–9	AbbVie. (incl. Allergan Limited)	6	3	9	7 CTs; 11–13
8–9	GSK (incl. ViiV Healthcare UK Limited)	7	2	9	7 CTs; 11–13

Data from www.grls.rosminzdrav.ru

Diagram 11 shows the distribution of approvals for IMCTs issued in 2020 among all sponsors. Three companies obtained more than 20 approvals each, four — 11 to 20 approvals, six companies — six to ten approvals. 108 sponsors obtained five or less approvals each, of which 86 companies obtained only one approval each. As compared to 2019, the total number of sponsors that obtained approvals to conduct IMCTs during the year increased from 108 to 121. This can be explained by the fact that quite a few IMCTs in Russia are initiated by small companies representing the so-called Biotech sector.

Diagram 11



Data from www.grls.rosminzdrav.ru

International multicentre clinical trials, CROs

Table 14 shows CROs that were most often engaged by sponsors to conduct IMCTs according to approvals issued in 2020.

This is a very steady ranking, which was topped by IQVIA four times over the past five years, including 2020. Only two companies were not in the top ten in the previous year: Medpace and IPHARMA. And while Medpace, starting from 2016, was seen twice in the bottom spots of the top 10, IPHARMA (more familiar to us from the ranking of CROs specializing in local trials) made it there for the first time over the course of ACTO's monitoring (so far the best recorded result of this company was one IMCT per year).

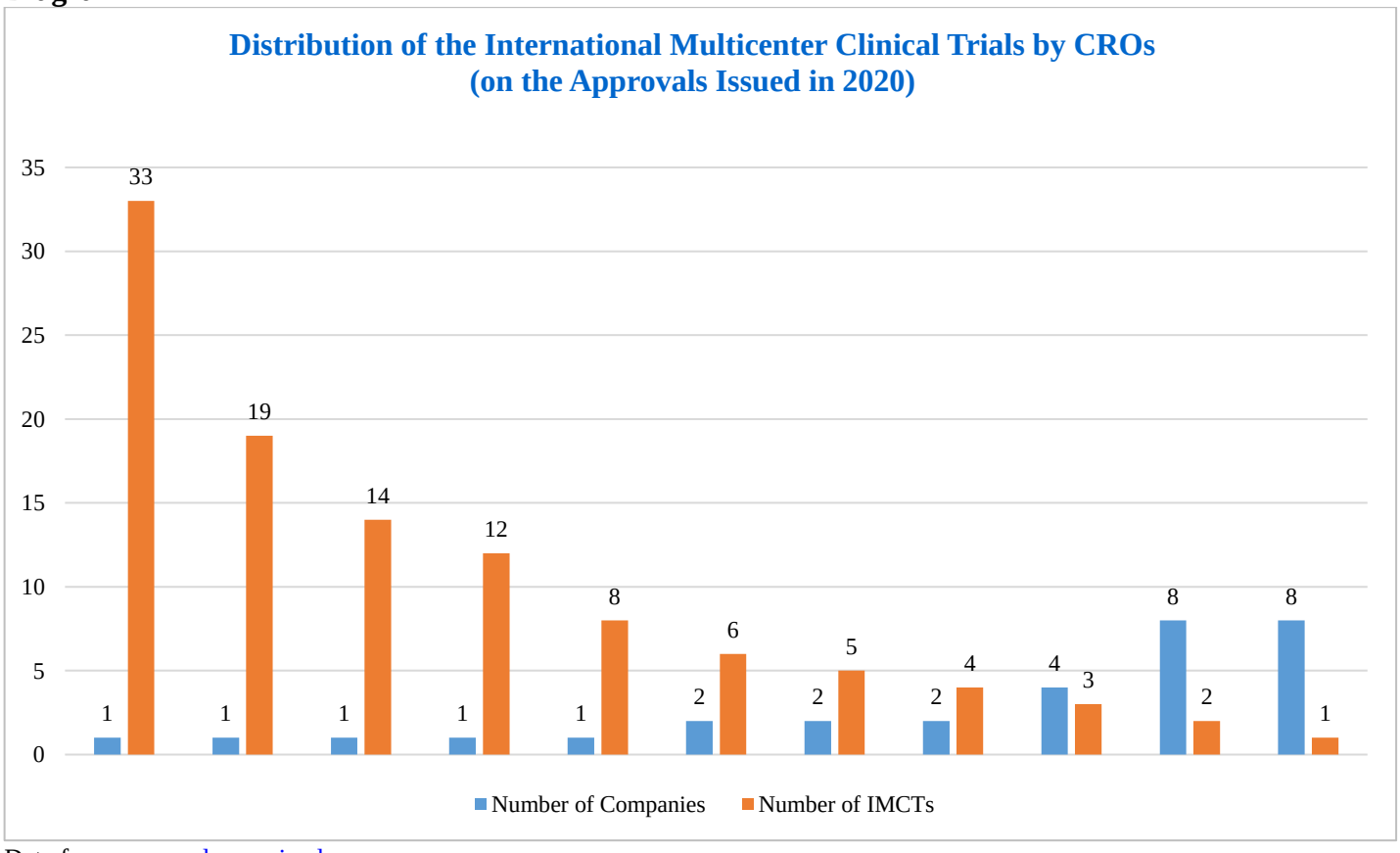
Table 14

Ranking of Leading CROs on Approvals for International Multicenter CTs, 2020				
Ranking in 2020	**Company**	**Number of IMCTs**	**Number of Sponsors**	**Number of IMCTs; Ranking in 2019**
1	IQVIA	33	24	34 CTs; 1
2	Parexel	19	13	12 CTs; 5
3	PPD	14	12	15 CTs; 4
4	Syneos Health	12	11	22 CTs; 2
5	PSI	8	8	8 CTs; 7–8
6–7	Covance	6	4	8 CTs; 7–8
6–7	Medpace	6	6	3 CTs; 12–16
8–9	PRA Health Siences	5	5	16 CTs; 3
8–9	IPHARMA	5	5	1 CT; 19–27

Data from www.grls.rosminzdrav.ru

Diagram 12 shows the distribution of new IMCTs among contract research organizations. Four CROs were engaged to conduct more than ten IMCTs each, three — six to ten studies, and 24 — five or fewer. The total number of CROs named in the 2020 IMCT approvals increased slightly as compared to the previous year, from 27 to 31 organizations.

Diagram 12



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, foreign sponsors

Foreign sponsors that obtained most approvals for local trials and bioequivalence studies in 2020 are shown in Table 15. The leader of 2020, the Belarusian Pharmtechnology LLC with seven new trials, was not present in the last year ranking at all, as was another Belarusian enterprise, AmantisMed LLC (four approvals, place 5–8 in the ranking), and the Moroccan Laboratoires Pharma 5 (three approvals, place 9–10).

The leader of 2019, Hetero Labs, dropped to the very bottom of the top ten, sharing the 9th-10th position with the afore-mentioned Laboratoires Pharma 5. Gedeon Richter and KRKA switched places (second and third places in 2019 and, vice versa, third and second in 2020). The rest of the ranking participants have also slightly changed their positions. In general, the ranking of foreign sponsors turned out to be flexible due to the scarcity of this type of trials.

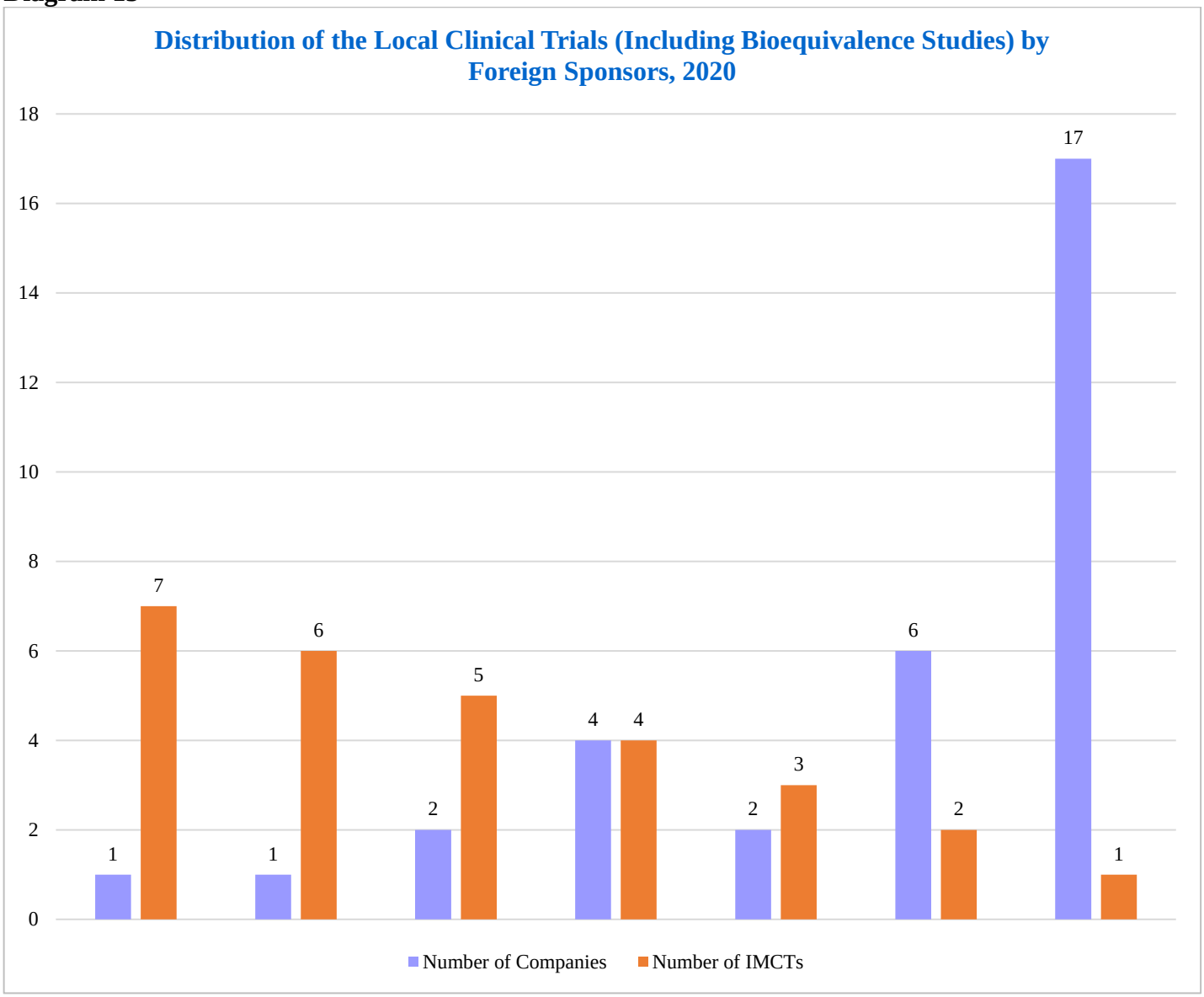
Table 15

Top-10 Foreign Sponsors on Approvals for Local CTs and Bioequivalence Studies, 2020					
Ranking in 2020	**Company**	**Conducted by themselves**	**Conducted by CROs/other representatives**	**Total**	**Number of CTs; Ranking in 2019**
1	Pharmtechnology LLC	–	7	7	n/a
2	KRKA	6	–	6	7 CTs; 3
3–4	Gedeon Richter	–	5	5	8 CTs; 2
3–4	Dr. REDDY's Lab.	5	–	5	6 CTs; 4–5
5–8	AmantisMed LLC	–	4	4	n/a
5–8	Berlin-Chemie	–	4	4	6 CTs; 4–5
5–8	Micro Labs Limited	1	3	4	2 CTs; 18–25
5–8	Sun Pharma	4	–	4	3 CTs; 10–16
9–10	Laboratoires Pharma 5	–	3	3	n/a
9–10	Hetero Labs	3	–	3	9 CTs; 1

Data from www.grls.rosminzdrav.ru

The distribution of new local trials and bioequivalence studies among foreign companies is shown in Diagram 13. The total number of sponsors in this category decreased significantly in 2020 and amounted to only 33 companies. For comparison: there were 48 in 2019, 47 in 2018, 59 in 2017, and as much as 99 in 2016.

Diagram 13



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, domestic sponsors

Table 16 introduces Russian sponsors leading by the number of approvals for local trials and bioequivalence studies in 2020. Atoll, the 2013–2016 leader, that lost its position for three years, has returned to the first place with 22 new protocols, 20 of which were bioequivalence studies. Pharmasyntez dropped from first to fourth position. As for Biocad, which ranked second a year earlier, it dropped out of the top ten and landed on 16th place in the ranking. However, given the portfolio of the latter, this is clearly trading off quantity for quality. There were no first-timers in the top at the end of the year. Almost all companies demonstrated an increase in the number of approvals as compared to 2019. Promomed stood out the most having increased the number of new studies almost fivefold. The rest of the companies mentioned in Table 16 improved their results by 1.5–2 times, with the exception of the afore-mentioned Pharmasyntez, which ended the year with 15 approvals versus 20 a year earlier.

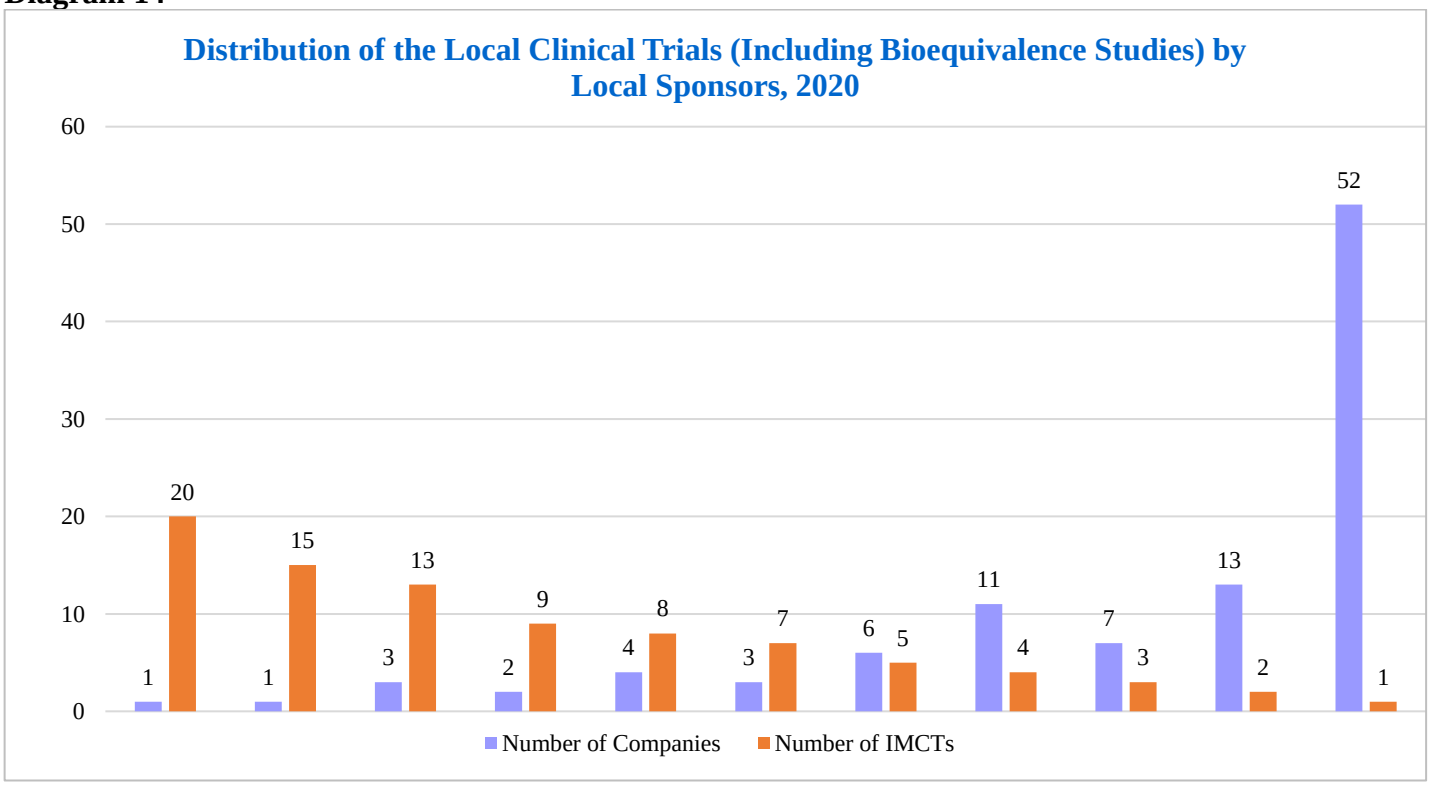
Table 16

Ranking of Leading Local Sponsors on Approvals for Local Clinical Trials and Bioequivalence Studies, 2020					
Ranking in 2020	**Company**	**Conducted by themselves**	**Conducted by CRO**	**Total**	**Number of CTs; Ranking in 2019**
1	Atoll	22	–	22	8 CTs; 8–11
2	Promomed Rus	19	–	19	4 CTs; 21–31
3	Canonpharma Production	16	–	16	13 CTs; 3–5
4	Pharmasyntez (incl.Pharmasyntez-Tyumen)	15	–	15	20 CTs; 1
5	Renewal	12	–	12	5 CTs; 15–20
6–7	Pharmstandard (incl. PharmstandardUfaVita, Phs-Leksredstva, Pharmapark)	11	–	11	7 CTs; 12–14
6–7	PSK Pharma	11	–	11	5 CTs; 15–20
8	Severnaja Zvezda	10	–	10	7 CTs; 12–14

Data from www.grls.rosminzdrav.ru

Diagram 14 shows the distribution of approvals for local trials and bioequivalence studies issued to domestic sponsors in 2020. As in the previous year, the total number of companies was 103.

Diagram 14



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, CROs

Table 17 indicates, which CROs were most sought after in 2020 when organizing local trials and bioequivalence studies. The leader of 2017 and 2018, IPHARMA, after the last year's 4th-5th spots in the ranking, regained its first place. Speaking of which, this is the only company that managed to be among the best in two rankings at once, both among local and international trials.

Besides IPHARMA, OCT Rus, Probiotech, Biomapas, IPHAR, MDA and X7 Research maintained their positions in the top 10. ClinPharmInvest and ClinPharmDevelopment moved up from 12th–24th to second and fifth places. Accellena Research and Development, which was not included in the 2019 ranking, ranked 6–7.

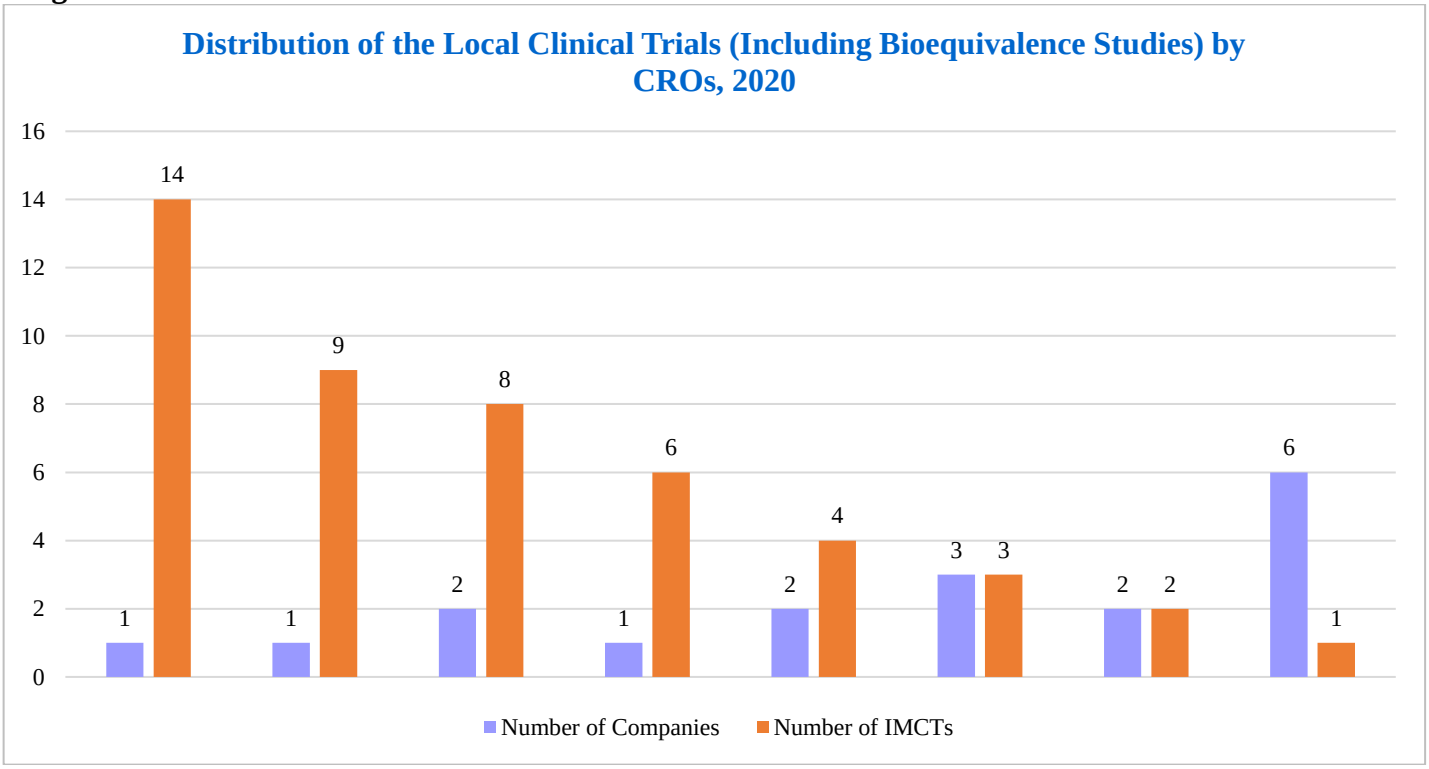
Table 17

Top-10 CROs Involved in the Local CTs and Bioequivalence Studies (on Approvals Issued in 2020)						
Ranking in 2020	**Company**	**Number of CTs of foreign sponsors**	**Number of CTs of local sponsors**	**Total number of local CTs, 2020**	**Number of sponsors**	**Number of CTs; Ranking in 2019**
1	IPHARMA	5	9	14	10	7 CTs; 4–5
2	ClinPharmInvest	8	1	9	3	1 CT; 12–24
3–4	OCT	7	1	8	4	2 CTs; 10–11
3–4	Probiotech	–	8	8	2	23 CTs; 1
5	ClinPharmDevelopment	5	1	6	3	1 CT; 12–24
6–7	Biomapas	4		4	1	5 CTs; 6–7
6–7	Accellena Research and Development	–	4	4	2	n/a
8–10	Innovative Pharmacology Research (IPHAR)	–	3	3	3	3 CTs; 8–9
8–10	Medical Development Agency (MDA)	–	3	3	2	14 CTs; 2
8–10	X7 Research	2	1	3	2	5 CTs; 6–7

Data from www.grls.rosminzdrav.ru

Diagram 15 shows the distribution of local trials and bioequivalence studies by contract research organization. The total number of CROs involved in such projects in 2020 was 18, six less than a year earlier.

Diagram 15



Data from www.grls.rosminzdrav.ru

TIMEFRAMES FOR OBTAINING APPROVALS

To analyze the timeframes for issue of the main types of approvals of the Ministry of Health of Russia, we used the results of a survey of ACTO and AIPM members, 28 pharmaceutical companies and CROs. Data on applications filed in 2020, as well as on applications filed earlier, if decisions on them were made during 2020, were taken into consideration.

This time the analysis was somewhat different from the usual. Since it was necessary to assess the period of operation of the regulatory approval system, which largely fell within the pandemic, the impact of special circumstances had to be taken into account. In particular, although no special regulations regarding the timing for approval of trials of drugs intended for combating COVID-19 were adopted in Russia, it was still clear from the practice of companies that such projects were given priority in consideration. On the contrary, the "regular" applications due to the introduction of restrictions designed to prevent the spread of infection and the increased overall burden on the regulatory authority and expert organizations were clearly processed longer than usual. Therefore, it was decided to differentiate the submissions and calculate on a separate basis the timing for issue of approvals for trials of drugs intended for the treatment and prevention of the new coronavirus infection and for trials of other drugs, the protocols of which did not mention COVID-19.

The increase in the overall timeframes was expected: throughout 2020 ACTO received complaints from companies and CROs that faced a slowdown in the operation of the regulatory authority. The expectations were confirmed after processing the aggregated data. The average timeframe for issue of an approval to conduct a trial (except for trials of anti-coronavirus drugs) increased by 16 days (+18.4%) as compared to the result of 2019, from 87 to 103 (Table 18.1). Over the course of ACTO's monitoring, i.e. since 2005, there have been only two instances where the period for issue of approvals for trials was longer: in 2011 (130 days) and 2012 (116 days), when the entire regulatory approval system was undergoing reformation and the period of adaptation thereto. The minimum and the maximum periods for issue of this type of approvals increased by a week and by almost two weeks, respectively, as compared to 2019.

The average period for issue of approvals for amending the protocol increased by 17 days (+35.4%) as compared to the 2019 survey, from 48 to 65 days. Over the course of ACTO's monitoring, it was longer only once in 2011 (92 days), however, already in 2012 it decreased to 64 and never reached this value again. The minimum period for issue of this type of approvals has increased as compared to the previous year by two days, the maximum — by 36 days.

The average period for approval of other applications (for extension of the trial, for increasing the number of participants, for opening of new sites, etc.) increased by ten days (+34.5%) and reached 39 against 29 in 2019, almost reaching the result of 2012 with an indicator of 41 days.

Less dramatic, although also noticeable, were the changes in the timeframes for issue of approvals for import of medicinal products and for the import/export of biological samples. In both cases, the average time period increased by two days, from 15 to 17 days (+13.3%) for import of medicines and from 20 to 22 days (10%) for import/export of bio-samples. This is the worst result for issue of approvals for import of medicinal products since 2012, when the average period amounted to 18 days; and since 2014 for import/export of bio-samples, when it took an average of 23 days to obtain an approval.

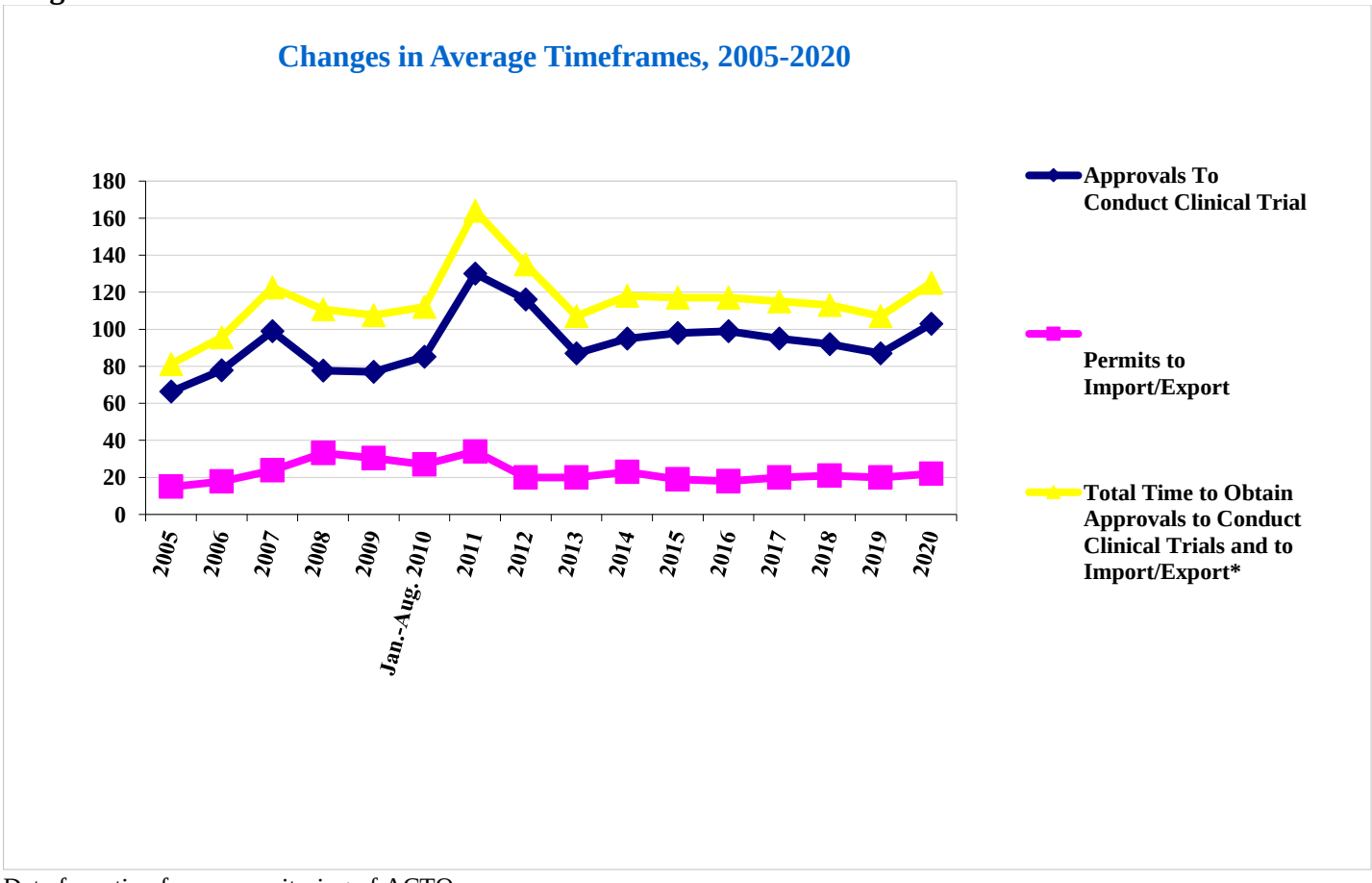
Table 18.1

Timeframes for Issuing Approvals, 2020 (Excluding Clinical Trials on COVID-19)					
Type of approval	**Timeframes according to legislation (workdays/calendar days)**	**Average timeframes (calendar days)**	**Minimum timeframes (calendar days)**	**Maximum timeframes (calendar days)**	**Sampling**
To Conduct Clinical Trials*	41/57**	103	58	286	197
To Import Medicines	8/12	17	6	49	434
To Import/Export Biosamples	13/19	22	6	80	772
To Make Amendments to the Protocol	34/48	65	10	120	517
Other Approvals	25/35	39	7	126	836

Data from timeframes monitoring of ACTO and AIPM
* For all applications, regardless of the availability of requests from expert organizations or the Ministry of Health. If there is a request, the response time is not excluded from the calculation;
** In the absence of requests from expert organizations or the Ministry of Health;

The uniqueness of 2020 as a crisis year after seven stable and relatively trouble-free years can be clearly seen in Diagram 16, where the data on the timeframes since 2005 are shown.

Diagram 16



Data from timeframes monitoring of ACTO

While the timeframes for issue of all types of approvals for trials not related to COVID-19 objectively worsened, the regulatory approval system handled the trials of anti-coronavirus drugs in an expedited manner (Table 18.2). Approvals for trials were issued within 25 days on average (the minimum period we saw in our survey was 10 days), i.e. four times faster than for trials of other drugs.

The average time period for obtaining approvals for import of medicinal products amounted to 10 days (5 to 15 days according to our data) and to 15 days (8 to 33) for approvals for import/export of biological materials. Approvals for amending protocols that mentioned COVID-19 were issued within 22 days on average. Finally, the average time period for obtaining other approvals for anti-coronavirus drugs amounted to 15 days.

It only remains for us to add a few words about what is not shown in the summary tables, but was noticeable when processing the data: while at the beginning of the pandemic the timeframes for issue of approvals for trials of anti-COVID-19 drugs have been actually minimal (the first approval for trial was obtained at the end of March 2020), by the end of the year they, unfortunately, also began to increase.

Table 18.2

Timeframes for Issuing Approvals, 2020 (Only For Clinical Trials on COVID-19)					
Type of approval	**Timeframes according to legislation (workdays/calendar days)**	**Average timeframes (calendar days)**	**Minimum timeframes (calendar days)**	**Maximum timeframes (calendar days)**	**Sampling**
To Conduct Clinical Trials*	41/57**	25	10	65	17
To Import Medicines	8/12	10	5	15	14
To Import/Export Biosamples	13/19	15	8	33	17
To Make Amendments to the Protocol	34/48	22	10	37	16
Other Approvals	25/35	15	2	48	22

Data from timeframes monitoring of ACTO and AIPM

* For all applications, regardless of the availability of requests from expert organizations or the Ministry of Health. If there is a request, the response time is not excluded from the calculation;

** In the absence of requests from expert organizations or the Ministry of Health;

***

Table 19 shows statistics on violations of timeframes for issue of approval documents (with the exception of trials of anti-coronavirus drugs). It clearly shows that, compared to 2019, the shares of all types of approvals issued in due time decreased significantly: from 22.8% to paltry 2.8% for trial approvals, from 34.6% to 15.9% — for approvals for import of medicinal products, from 42.7% to 35.0% — for import/export of biological samples, from 64.8% to 12.4% — for amending the protocol, from 78.9% to 47.1% — for other submissions. As a result, the share of approvals issued in due time in 2020 failed to reach 50% for any type of approvals, which has only been seen in 2011 that was due to reform a challenging year for the industry.

Worsening of statistics on violation of timeframes was mainly caused by the growth in shares of approvals of various types issued in excess of the statutory deadline by 1.5–1.9 times. Thus, for the main approval to conduct a trial, the share of applications approved with such a delay increased from 0.7% to 20.2% of the total volume of applications. For amending the protocol, the share of cases of increase in the processing time grew by 1.5–1.9

times from 3.1% in 2019 to 36.6% in 2020. For approvals for import of medicinal products, the share of cases of violation of timeframes increased by 1.5–1.9 times from 15.7% to 28.6%, and the share of applications, consideration of which exceeded the established deadlines by two or three times, also increased quite significantly, from 6.3% to 12.4%.

Table 19

Violations of Timeframes, 2020 (Excluding Clinical Trials on COVID-19) vs 2019								
Type of Approval		**Approvals Issued on Time**	**Approvals Issued in Violation of Timeframes**					
			Total	**Less than in 1,5 times**	**In 1,5-1,9 times**	**In 2-2,9 times**	**In 3-3,9 times**	**In 4 times and more**
To Conduct Clinical Trials*	**2020**	2.8%	97.3%	71.6%	20.2%	5.5%	0.0%	0.0%
	2019	22.8%	77.2%	76.5%	0.7%	0.0%	0.0%	0.0%
To Import Medicines	**2020**	15.9%	84.1%	42.2%	28.6%	12.4%	0.7%	0.2%
	2019	34.6%	65.4%	43.0%	15.7%	6.3%	0.2%	0.2%
To Import/Export Biosamples	**2020**	35.0%	65.0%	44.8%	16.1%	3.5%	0.5%	0.1%
	2019	42.7%	57.3%	49.1%	7.5%	0.7%	0.0%	0.0%
To Make Amendments to the Protocol	**2020**	12.4%	87.6%	48.5%	36.6%	2.5%	0.0%	0.0%
	2019	64.8%	35.2%	32.1%	3.1%	0.0%	0.0%	0.0%
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	**2020**	47.1%	52.9%	43.7%	7.1%	1.9%	0.2%	0.0%
	2019	78.9%	21.1%	19.5%	1.3%	0.0%	0.1%	0.1%

Data from timeframes monitoring of ACTO and AIPM

* For all applications, regardless of the availability of requests from expert organizations or the Ministry of Health.

We believe that there is no point in going into further details about what is already clearly obvious from the table: worsening of the main parameters affected all types of approvals. We can only hope that such a significant disruption in the operation of the regulatory mechanism that seemed to have stabilized in recent years is solely due to the difficulties caused by the pandemic, and will end together with it.

SITUATION WITH CLINICAL TRIALS OF MEDICINES FOR TREATMENT AND PREVENTION OF COVID-19

Perhaps the most important topic of 2020, and not only for subject matter experts, was the development of drugs for treatment and prevention of the new coronavirus infection. Methods for combating SARS-CoV-2 greatly vary from country to country, and in order to understand the Russian situation with clinical trials of anti-coronavirus drugs it is necessary to take into account the legal framework of their organization, which was formed shortly after the outbreak of the pandemic.

In April 2020, the Government of the Russian Federation adopted Order No. 441 (hereinafter, Order No. 441), which regulates the circulation of medicines in an emergency situation[3]. The regulatory document provides for a simplified procedure for initiating a study of effectiveness of already registered medicinal products for new indications. Simplification suggests, in particular, that testing can be started without the approval from the Russian Ministry of Health. This means that these studies will not be included in the register of issued approvals, the data from which constitute the basis of our statistics. Order No. 441 requires organizers to notify the regulatory authority of the beginning of the study of the medicine, but does not oblige the Ministry of Health to make this information public. Due to this limitation, the outline presented below covers only those clinical trials of anti-coronavirus drugs, which were approved by the Ministry of Health.

In the course of 2020, the Russian Ministry of Health issued 66 approvals for testing of drugs intended for treatment and prevention of COVID-19, which amounts to 8.9% of all approvals issued during this period. For comparison: a search on ClinicalTrials.gov gives 2,322 interventional clinical trials, the start of which, according to the register, was planned for 2020. The Russian share in the global volume of clinical trials of anti-coronavirus drugs is thus equal to 2.8%, which is slightly more than the share of the Russian Federation in the total global volume of clinical trials in 2020 (1.6%). However, this is a broad-brush comparison, given the possibility that some of the actually conducted experiments might not be included in the registers, both in Russia and in other countries of the world.

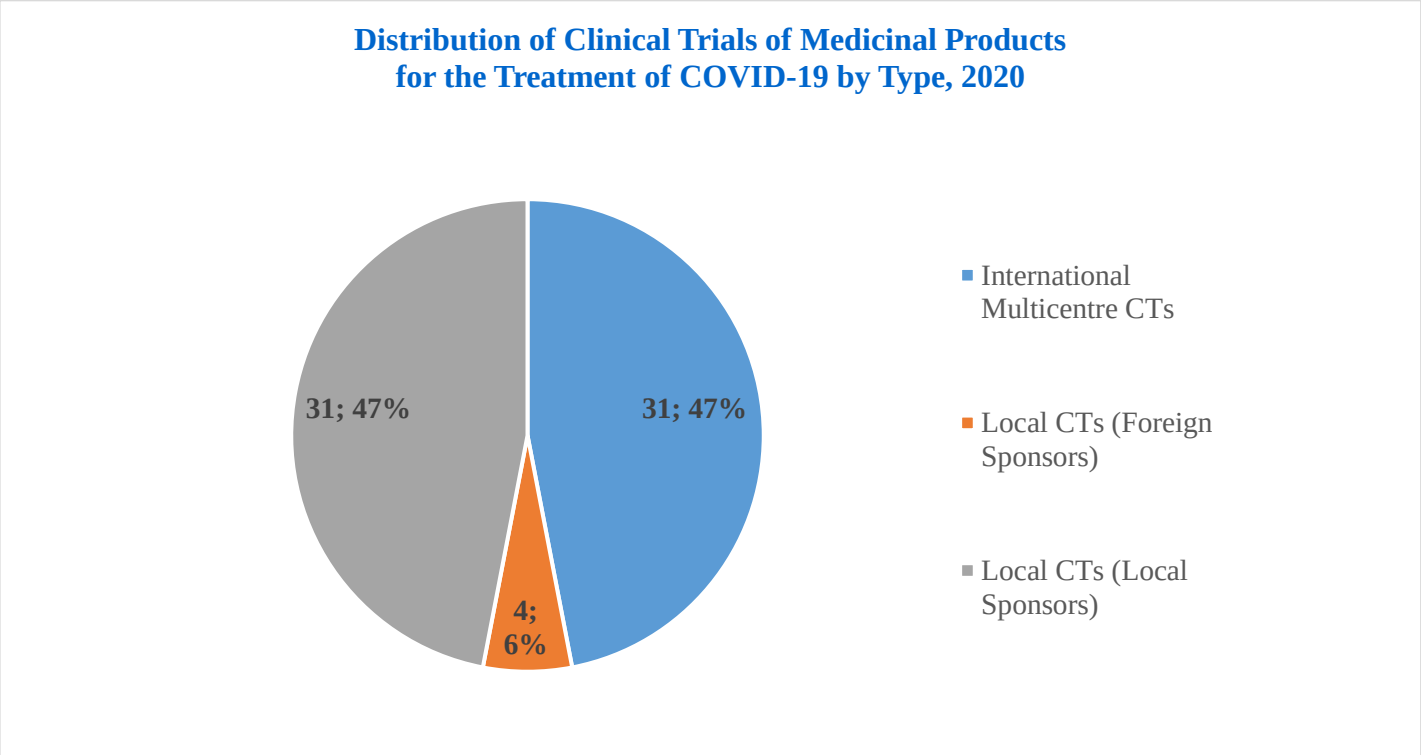
Diagram 17 shows the distribution of trials of anti-coronavirus drugs in Russia by type. As compared to the first half of 2020[4] the share of IMCTs increased from 31% to 47%. The share of local trials by Russian sponsors decreased proportionally: from 65% in the first half of the year to 47% for the entire year. The share of local trials by foreign sponsors remained small: 4% in the first half of the year and 6% at the end of the year.

The planned number of participants in these trials ranged from 11 to 40,000. Most patients were expected to take part in vaccine studies: 40,000 for testing of Gam-COVID-Vac (also known as Sputnik V) of Gamaleya Center, 3,000 for testing of EpiVacCoV of Vector Center, and 8,000 and 783 participants in two trials of Ad5-nCoV of CanSino Biologics. Excluding the four above-named trials the average patient population in the remaining 62 trials was 156.

[3] Full name of the document: "Order of the Government of the Russian Federation No. 441 dated 03 April 2020 On specifics of circulation of medicinal products for medical use intended for use under the threat of occurrence, occurrence of and response to an emergency and for organization of medical aid to people who suffered as a result of emergencies, prevention and treatment of diseases posing a threat to the wider public, diseases and damage caused by exposure to adverse chemical, biological and radiation factors"

[4] See a similar overview in the previous issue of the Newsletter.

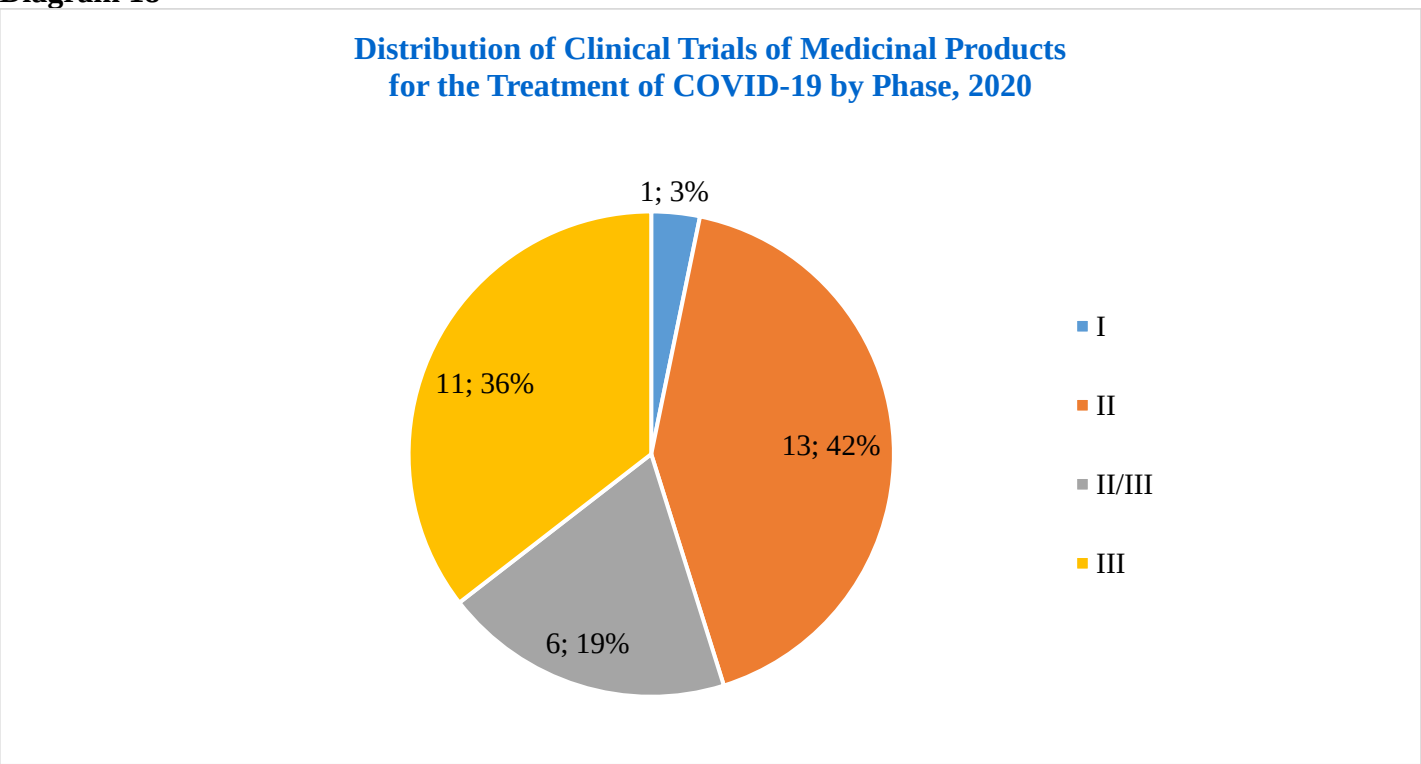
Diagram 17



Data from: www.grls.rosminzdrav.ru

Diagram 18 shows the distribution of IMCTs of anti-coronavirus drugs by phase. The share of Phase I protocols was 3%, Phase II and Phase II–III protocols — 61%, and Phase III protocols — 35%. Protocols of local trials were excluded from consideration, since phases indicated by the developers have not always corresponded to the objectives set for the local trials according to their description.

Diagram 18



Data from: www.grls.rosminzdrav.ru

Table 20 lists the drugs most often tested as agents for treatment and prevention of COVID-19. The top three included two antiviral agents — Favipiravir with five approvals and Remdesivir with three approvals, as

well as Gam-COVID-Vac (Sputnik V) vaccine with four approvals. Favipiravir and Remdesivir have been tested by different sponsors. The vaccine was studied by one developer, first within the Phase I–II study (a solution for intramuscular administration and a lyophilisate for preparation of such solution were tested separately), then within two Phase III–IV protocols. For uncertain reasons, the developer decided to conduct a separate study on "safety, tolerability and immunogenicity" of its vaccine with the participation of 150 volunteers aged 60 and older, although the main study of "efficacy, immunogenicity and safety" with the declared number of participants of 40,000 people did not contain any restrictions on inclusion of subjects over 60 years old.

Table 20

Most Requested INN Used in Clinical Trials of Medicinal Products for the Treatment of COVID-19, Approved in 2020			
Name of medicinal product	**Product type**	**Number of trials**	**Company and number of trials**
Favipiravir	RNA polymerase inhibitor	5	Chromis – 1; Medicine Technology – 1; Promomed Rus – 1; Pharmasyntez – 1; Alium – 1
Gam-COVID-Vac (Sputnik V)	two-vector vaccine based on human adenoviruses Ad26 and Ad5	4	The Gamaleya National Center under the Ministry of Health of the Russian Federation – 4
Remdesivir	RNA polymerase inhibitor	3	Pharmasyntez – 1; R-Pharm – 1; F. Hoffmann-La Roche (in combination with the interleukin-6 inhibitor tocilizumab) – 1
EpiVacCorona	one component vaccine based on peptide antigens	2	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector" – 2
Ad5-nCoV	one-vector vaccine based on human adenoviruse Ad5	2	CanSino Biologics and Petrovax Pharm – 2
Molnupiravir	RNA polymerase inhibitor	2	Merck Sharp & Dohme Corp. – 2
Ruxolitinib	tyrosine kinase inhibitoror JAK1 and JAK2	2	Novartis – 1 ; Insight – 1
Elsulfavirin	non-nucleoside reverse transcriptase inhibitor	2	Viriom Inc. – 2
44 medicines more	***1 CT each***		

Data from: www.grls.rosminzdrav.ru

According to the Global Coronavirus COVID-19 Clinical Trial Tracker[5], worldwide antimalarial drugs were most often tested in trials of medicines for the new coronavirus (about 13% of all protocols recorded by the tracker with the exception of non-drug treatment methods) followed by antiviral drugs (about 11 %) and blood plasma of those who had recovered from this disease (about 6%). Among the approvals for trials issued in the Russian Federation antiviral drugs are in first place (24% of all approvals for testing anti-coronavirus drugs), vaccines are in second place (17%), and immunomodulators are in third place (12%). It is worth repeating here

[5] https://www.covid19-trials.com/

that due to the introduction in Russia at the beginning of 2020 of a simplified procedure for initiating trials of anti-coronavirus drugs, some of the actually conducted trials (including, but not limited to, antimalarial drugs) are not included in the register of the Ministry of Health of Russia and not covered in this comparison.

It is worth noting that certain medicinal products that were actively tested in 2020 as potentially effective in combating COVID-19 and were sometimes even included in official recommendations for the treatment of this disease appeared in the protocols of bioequivalence studies. Thus, in 2020 Russia issued 14 approvals for testing of analogs of Rivaroxaban (anticoagulant), 10 — for Metformin (Biguanide), 6 — for Ritonavir, of which 3 in combination with Lopinavir (antiretroviral drugs), another 6 — for Sitagliptin (Gliptin), 5 approvals to study analogues of Favipiravir (antiviral agent). All of these drugs (among others — see Table 5) in 2020 were considered as medicines that can reduce the risk of complications, alleviate the symptoms of COVID-19, or otherwise help the human body fight the virus.

Table 21 lists sponsors that most actively initiated trials of anti-coronavirus drugs in Russia in 2020. Gamaleya Center is in the lead with four approvals for testing the Gam-COVID-Vac vaccine. The second place was shared by R-Pharm, Novartis and Center Vector with three approvals each. Vector studies the EpiVacCorona vaccine. The R-Pharm group of companies studied Favipiravir (approval issued to Medicine Technology LLC), Remdesivir (approval issued to R-Pharm JSC) and a combination of IL-1 heterodimeric fusion protein under the name of RPH-104 with Olokizumab (approval issued to R-Pharm International LLC). Nominal third place was shared by CanSino Biologics, MSD, Sanofi, Viriom, Generium and Pharmasyntez with two approvals each.

Table 21

Pharmaceutical Companies with Clinical Trials of Medicinal Products for the Treatment of COVID-19 Approved in 2020				
Company	**Conducted by themselves**	**Conducted by CRO**	**Total**	**Type of CT**
The Gamaleya National Center of Epidemiology and Microbiology under the Ministry of Health of the Russian Federation	4	–	4	Local CT (Local Sponsor)
R-Pharm	3	–	3	Local CT (Local Sponsor)
Novartis	3	–	3	IMCT
Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	3	–	3	Local CT (Local Sponsor)
CanSino Biologics	2	–	2	IMCT
Pharmasyntez	2	–	2	Local CT (Local Sponsor)
Generium	2	–	2	Local CT (Local Sponsor)
Viriom	–	2	2	Local CT (Foreign Sponsor)
Merck Sharp & Dohme Corp.	2	–	2	IMCT
Sanofi	2	–	2	IMCT
41 companies more	***1 CT each***			

Data from: www.grls.rosminzdrav.ru

For 24 trials sponsors, as it follows from the register of issued approvals, involved contract research organizations (see Table 22). The most sought-after were IPHARMA (eight trials), IQVIA (four trials), Parexel and Synergy Research Group (two protocols each).

Table 22

CROs Involved in the Clinical Trials of Medicinal Products for the Treatment of COVID-19, 2020			
Company	**Number of CTs of foreign sponsors**	**Number of CTs of local sponsors**	**Total number of CTs**
IPHARMA	5	3	8
IQVIA	4		4
Synergy Research Group	1	1	2
Parexel	2		2
8 companies more	***1 CT each***		

Data from: www.grls.rosminzdrav.ru

In the distribution of trials of anti-coronavirus agents by region, Moscow and St. Petersburg are predictably in the lead having far surpassed other constituent entities of the Russian Federation both in the number of trials launched in their territory and in the number of sites planned to be opened within the framework of these trials.

Table 23

Regions of the Russian Federation, where in 2020 new trials of drugs for the treatment and prevention of Covid-19 were approved		
Constituent Entitiy of the RF	**Number of Clinical Trials for the Treatment of COVID-19**	**Number of sites approved for conducting clinical trials for COVID-19**
Moscow	57	278
St. Petersburg	47	161
Ryazan Region	20	22
Yaroslavl Region	19	25
Republic of Bashkortostan	17	21
Smolensk Region	17	18
Nizhny Novgorod Region	15	20
Altai Territory	15	15
Saratov Region	11	12
Krasnodar Territory	10	14
Tomsk Region	10	11
Republic of Tatarstan	10	10
32 Constituent Entities more	***less than 11 sites and less than 10 CTs in each***	

Data from: www.grls.rosminzdrav.ru

In conclusion of our overview, Table 24 shows ten medical organizations leading by the number of trials approved with their participation.

Table 24

Distribution of Clinical Trials of Medicinal Products for the Treatment of COVID-19 by Medical Organizations, 2020			
Place in ranking	**Name of medical organization**	**Number of approved clinical trials that involved this medical organization**	**Number of sites approved for conducting clinical trials**
1	I. M. Sechenov First Moscow State Medical University, Russian Ministry of Health, Moscow	28	33
2	City Clinical Hospital No.15 named after O. M. Filatov, Moscow	28	28
3	City Hospital No. 40, Kurortny District, St. Petersburg	27	27
4	City Clinical Hospital No. 52, Moscow	23	23
5	Pokrovskaya City Hospital, St. Petersburg	21	21
6	Bashkir State Medical University, Ufa	16	19
7-9	Sklifosovsky Research Institute of Emergency Medicine, Moscow	15	15
7-9	Clinical Hospital No. 1, Smolensk	15	15
7-9	Ryazan State Medical University named after academician I.P. Pavlov, Ryazan	15	15
10	City Hospital No. 5, Barnaul	14	14
	166 medical organizations more	***13 and less new trials and sites***	

Data from: www.grls.rosminzdrav.ru

"CORNER CUTTING" PRACTICE IN THE DEVELOPMENT OF ANTI-CORONAVIRUS DRUGS IN RUSSIA: NON-CONTROLLED TRIALS[6] AND REGISTRATION SIMPLIFICATION

In the previous issue of the ACTO Newsletter we have already published a commentary on the negative impact of the COVID-19 pandemic on the practice of conducting clinical trials in Russia7. It concerned studying of drugs for the new coronavirus infection and covered the period from March to about September 2020. This material summarizes and further elaborates that commentary.

As noted above in the section on drugs for treatment and prevention of COVID-19, the Government of the Russian Federation adopted Order No. 441 in April 2020 that opened the way for testing medicines that have already been registered for new indications without the approval from the Ministry of Health of Russia (that includes an expert evaluation of the protocol quality). Order No. 441 requires to notify the Ministry of Health of the start of the experiment, but does not oblige the regulatory authority to make this information available outside the department, therefore, complete statistics on such experiments is not available to the public.

However, the subject of development of drugs for a new disease has been exciting keen public interest throughout 2020, for which reason journalists paid much attention to the start and progress of experiments that are of interest to us. Media reports remain the only source of information on drug testing under the simplified procedure for ACTO. Although there are only fragmentary data at our disposal, even a fragmentary picture raises certain concerns. A simpler procedure for initiating an experiment and less control over its conduct and results have potentially increased the risks for trial subjects.

Table 25 can provide a general idea of organization of such tests. It contains descriptions of experiments reconstructed from materials available in the media, which have been initiated no on the basis of the approval from the Ministry of Health of Russia, but something different. Sometimes it was Order No. 441, which was expressly declared by the initiators (as in the case of studying mefloquine by FMBA), in other cases the organizers documented intervention trials as observational, which also contributed to the simplified launch of the project (for example, testing of the polio vaccine at the Kirov State Medical University), while the legal basis of still others remains completely unknown to us.

Table 25

Drug	Initiator or location of the experiment	Legal basis
Hydroxychloroquine	**Moscow Healthcare Department**	**Unknown**
The use of hydroxychloroquine as a means of COVID-19 prevention in clinics subordinate to the Moscow Healthcare Department (MHD) was described in detail in the previous issue of the ACTO Newsletter. Below is the summary of events. The so-called "prevention programme" was announced by order of the MHD on 30 March 2020 and provided for taking hydroxychloroquine by employees of clinics subordinate to the Department for the purposes of prevention of the new coronavirus infection. According to ACTO, organization of the programme did not provide adequate protection of its participants against risks (the drug has a number of pronounced adverse reactions) and potential abuse (such as coercion to participate by the higher-ups). In an open letter		

[6] The notion of "controlled clinical trial" in the narrow (professional) sense usually means having a control group and a comparator drug (i.e. "controlled" is a synonym for "comparative trial"). In this case, when speaking of a non-controlled trial we refer to a different, broad sense — as an actual lack of control by the state and society.

[7] Critical Testing of Clinical Trial Standards, ACTO Newsletter No. 21 http://acto-russia.org/files/bulletin_21.pdf#page=23&zoom=100,34,57

addressed to the MHD ACTO noted that the goals of medical practice (prevention of the disease) were mixed with the goals of medical science (obtaining new knowledge about the properties of the drug) in the description of the programme, that participants of the programme were deprived of adequate legal protection, that organization of the programme did not guarantee compliance with the procedure for obtaining a voluntary informed consent.

Late in May the statement was published in media that the MHD's "research" demonstrated inefficacy of hydroxychloroquine for COVID-19 prevention. At the same time, the MHD representatives affirmed that those who took the drug had a milder progression of the disease. According to the information from open sources, the active part of the "prevention programme" ended in June 2020. Results of the experiment were not published. In response to the ACTO's request in the summer of 2020 the Department promised to publish the results in the future, however, as of March 2021 this has still not been done.

Mefloquine	**Federal Medical-Biological Agency of Russia**	**Order No. 441**

More details about the treatment regimen for the new coronavirus infection with mefloquine developed by the FMBA of Russia can be found in the previous issue of the ACTO Newsletter, a summary is set forth below.

In early April 2020 the FMBA announced the start of "comparative clinical trials" of hydroxychloroquine, mefloquine and a combination of lopinavir with ritonavir in COVID-19 patients with different severity of the condition. The FMBA has not obtained an approval from the Ministry of Health justifying it by the fact that the drugs are being tested in accordance with the requirements of Order No. 441. At the same time, in April, mefloquine was included in the Temporary Methodological Recommendations of the Ministry of Health of the Russian Federation as a drug for prevention and treatment of COVID-19.

ACTO voiced its protest to the FMBA that human experimentation with a disputable legal basis is publicly referred to as "clinical trials". Another protest was expressed by ACTO in May 2020 after a press conference with the FMBA head, where — along with the acknowledgment that the recruitment of patients was still in progress — it was announced that mefloquine was effective in comparison with other investigated drugs.

Despite the declared success, no reports on the results of the experiment have been published. Since June 2020 the drug was no longer mentioned in the FMBA press releases. In September 2020 it was excluded from the Temporary Methodological Recommendations of the Ministry of Health of the Russian Federation for prevention, diagnosis and treatment of the new coronavirus infection.

Triazavirin	**Ural State Medical University**	**Order No. 441**

The antiviral drug triazavirin was registered in Russia as a medication for treatment of influenza since 2014 and is produced in the Urals, in Sverdlovsk Oblast. In March 2020 scientists from the Ural Federal University and the Ural Branch of the Russian Academy of Sciences won grants from the Russian Foundation for Basic Research and the National Natural Science Foundation of China for creation of anti-coronavirus drugs based on triazavirin[8].

In April the scientists submitted an application to the Ministry of Health for testing triazavirin as an anti-coronavirus agent[9]. They have never received an approval. "The application was returned to us with

[8] http://www.apiural.ru/news/society/154883/
[9] https://xn--80aesfpebagmfblc0a.xn--p1ai/news/20200430-0657.html

critical comments, we are proceeding in accordance with order 441 so far," the developer's representative told reporters at the beginning of the summer[10].

Even before the start of the trial, at the end of April 2020, the governor of Sverdlovsk Oblast advertised triazavirin on his Instagram and wrote about its effectiveness against the coronavirus infection as a proven fact[11]. In his statements he referred to the experience of doctors in the region, where since the beginning of the pandemic the drug has indeed been used to treat patients with coronavirus, including those with asymptomatic course of the disease. Journalists were unable to find out the legal basis for this practice, all we know is that it was done by order of the governor[12]. The drug was used and advertised so actively that its production has gone up from 3 to 7 thousand packages per day[13].

The launch of the trial in Yekaterinburg was reported by the media in May[14], some publications noted that this was being done under the instruction of the governor[15]. At the same time, the Academic Council of the Ural State Medical University approved the guidelines "On the use of Triazavirin for treatment and post-exposure prophylaxis of the new coronavirus infection"[16].

In mid-July the media reported that doctors had not identified any serious side effects of triazavirin in the treatment of coronavirus[17] — although this could hardly be called news, since it was a registered drug. Nevertheless, the positive tone of publications created a good image for the drug and could contribute to further sales growth.

In September the press service of the Ural Federal University reported that triazavirin was tested in China in patients infected with coronavirus with mild to medium severity. The preliminary, unofficial conclusion was that the drug shortens the duration of the course of the disease from 12 to 7 days and alleviates the symptoms[18]. The developers promised to complete the testing in Russia in October 2020 and report the results by the end of the year[19].

In December the results were reported to the governor ("the drug demonstrated high prophylactic activity, efficacy and safety") and reports were prepared for sending to the Ministry of Health[20]. In early February the results of the experiment were presented at a press conference[21], however, the fragmentary descriptions of the design cited by journalists gave the impression that the test had not provided for blinding or a control group. It is known from the materials available in the media that only patients aged 30 to 50 were selected for the trial. And the actual results ("after three days of taking the drug the symptoms of the disease subsided in 25% of patients, by the 12th day the PCR analysis showed a negative result in 97.5% of patients") were not compared with the standard course of the disease in the same age group. Nevertheless, the developers were expressing the hope that triazavirin would will be included in the next version of the Temporary Methodological Recommendations of the Ministry of Health of the Russian Federation for prevention, diagnosis and treatment of the new coronavirus infection[22]. As of March 2021, their hopes have not been fulfilled.

[10] https://newdaynews.ru/ekaterinburg/693832.html
[11] https://serovglobus.ru/istorii/gubernator-proreklamiroval-lekarstvo-dlya-profilaktiki-covid-kto-na-etom-zarabotaet-i-pri-chem-tut-e/
[12] https://www.znak.com/2020-04-28/kuyvashev_poruchil_zakupit_triazavirin_dlya_profilaktiki_koronavirusa_u_vrachey
[13] https://urfu.ru/ru/news/31837/
[14] https://otr-online.ru/news/na-urale-nachinayut-klinicheskie-ispytaniya-preparata-protiv-koronavirusa-154685.html
[15] https://ura.news/news/1052431911
[16] http://www.triazavirin.ru/novosti/69-triazavirin-rekomendovan-dlya-profilaktiki-i-lecheniya-covid-19
[17] https://ria.ru/20200713/1574280171.html
[18] https://iz.ru/1059384/2020-09-10/v-kitae-podtverdili-effektivnost-rossiiskogo-preparata-protiv-covid-19
[19] https://tass.ru/ural-news/9492257
[20] https://www.uralweb.ru/news/medicine/521682-kuyvashemu-dolojili-o-rezultatah-klinicheskih-issledovaniy-triazavirina.html
[21] https://www.kommersant.ru/doc/4672331
[22] https://www.interfax.ru/russia/749018

At the end of March 2021 the Ural University has once again received a grant from the Russian Foundation for Basic Research and the National Natural Science Foundation of China for development of an anti-coronavirus agent based on triazavirin[23]. This means that the story will be continued in 2021.

Methylene Blue Dye	Sechenov University and Prokhorov General Physics Institute of the Russian Academy of Sciences	Presumably, Order No. 441

Employees of Sechenov University tested methylene blue from 25 April to 25 May at the University Clinical Hospital No. 1. Participants were 49 patients infected with COVID-19 and 39 volunteers, mainly from doctors working in the red zone. The media reported that "the authors of the experiment themselves were the first to take the drug, even before the start of the trial"[24]. Scientists said that methylene blue can destroy coronavirus in the human body and that the results of the experiment were sent to Nature Medicine[25]. However, no publications on the results (as of March 2021) could be found. It seems that the only people who saw the study protocol besides its organizers were members of the ethics committee of Sechenov University[26].

Although methylene blue does not seem to be a drug, use of which involves severe risks, moreover, according to some publications, it can really be beneficial[27], the lack of external independent control (risk assessment, scientific expertise of the protocol, etc.) is alarming, since this way the very practice of non-controlled human experiments is normalized. In addition, in this particular case it is unclear how the experiment is justified in principle, since it does not give an increment of knowledge in the form of a published scientific article.

Surfactant-BL	LLC Biosurf	Presumably, Order No. 441

"Russian drug reduced COVID-19 deaths five-fold. Domestic development has shown revolutionary results in serious patients"[28] — this is just one of the numerous flashy headlines in September 2020. This was about Surfactant-BL, registered in 2000-2008 in Russia (and nowhere else), a medicinal product for treatment of respiratory distress syndrome and tuberculosis, which is a mixture of surface-active agents derived from alveoli of bovine lungs.

At the very least from May to August, in several medical organizations, patients with a severe form of COVID-19 received inhalations of Surfactant-BL, which was said to have reduced mortality in this category of patients to 14.3% instead of 80%. In total, about 120 people, including pregnant women, became participants in the experiment, and another 90 patients were soon to become participants in another trial of the same drug, this time with a control group and randomization.

Sergei Avdeev, Chief Consulting Pulmonologist of the Ministry of Health and one of the investigators of Surfactant, told reporters that the medicine has no side effects and is safe for children[29]. The tone of publications in the media was sometimes indistinguishable from the tone of advertisements, even despite the obviously incomplete data (""Patients who are treated with Surfactant are statistically less likely to be put into intensive care unit on mechanical ventilation, and the mortality rate among them is 3-5 times lower," said Rosenberg (representative of the developer) explaining that the summarized data on all cases of drug use are

[23] https://www.obltv.ru/news/science/uralskie-uchyenye-vyigrali-grant-na-razrabotku-preparatov-ot-covid-19/
[24] https://www.sechenov.ru/pressroom/news/uchenye-sechenovskogo-universiteta-vyyavili-effektivnost-metilenovogo-sinego-pri-lechenii-koronaviru/
[25] https://nauka.tass.ru/nauka/8816933
[26] https://trends.rbc.ru/trends/innovation/5f1a9dd39a79474cf7f7bb35
[27] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7728423/
[28] https://iz.ru/1057781/nataliia-mikhalchenko/legche-legkomu-rossiiskii-preparat-v-piat-raz-snizil-smertnost-ot-covid-19
[29] https://www.sechenov.ru/pressroom/news/sergey-avdeev-otsenil-effektivnost-preparata-surfaktant-bl-dlya-lecheniya-koronavirusa-/

still being collected"[30]). The story of the miraculous healing of one severe patient, who was given Surfactant, among other means, became popular with journalists.[31]

The media reported that the Russian pharmaceutical company Nativa undertook to promote Surfactant-BL, and that it was with its money that a randomized trial of the drug[32] was launched in the summer. Results of this randomized trial were published in the Russian journal "Tuberculosis and Lung Diseases" (Vol. 98, No. 9, 2020)[33], investigators concluded that "inhalation therapy with Surfactant reduces the incidence of putting patients on mechanical ventilation and statistically significantly reduces mortality" in cases of severe pneumonia caused by coronavirus. A separate article was published on the experience of using Surfactant in obstetric patients infected with COVID-19[34]. There were also other publications and announcements[35, 36, 37].

It seems that the drug was tested by several sponsors at once. FMBA of Russia published the results of its own randomized trial of Surfactant in 39 patients in the Russian journal "Medical Council"[38] and presented it at the conference "COVID-19: today's situation and unresolved challenges"[39] in the autumn of 2020. Some interviews with medical professionals about the treatment of severe patients with COVID-19 included statements "experience of colleagues who used Surfactant in such situations has not been confirmed"[40], which also implies its use. It still remains unclear, who controlled the quality of the performed experiments and how it was done.

In February 2021, in the tenth version of the Temporary Methodological Recommendations of the Ministry of Health of the Russian Federation for prevention, diagnosis and treatment of COVID-19 the use of Surfactant was announced as a promising treatment option for ARDS associated with the new coronavirus infection.

Polio vaccine	**Kirov State Medical University**	**Unknown**

In May 2020 the media reported that the Kirov State Medical University plans to test BiVac Polio poliovirus vaccine as a means of COVID-19 prevention[41]. At the end of July it became known that vaccination of subjects was already taking place[42]. In publications drug testing has been referred to as an "observational programme".

ACTO addressed the KSMU with a question, what gives reason to call an apparently interventional clinical trial, during which people who would not have been vaccinated outside the trial are vaccinated, an observational programme (and not ask for approval from the Ministry of Health). The university insisted that their study does not imply further changes in the instructions for use of the medicinal product, and, in the organizer's opinion, cannot be considered a clinical trial on this basis. Testing of drugs with human participation "for scientific and marketing purposes", according to the letter addressed to ACTO, can be considered scientific work and be carried out without standard regulatory oversight.

[30] https://www.gazeta.ru/social/2020/09/08/13241378.shtml
[31] https://riavrn.ru/news/voronezhskie-vrachi-spasli-patsienta-kotoryy-3-mesyatsa-provel-v-kovidnoy-reanimatsii/
[32] https://stimul.online/articles/innovatsii/kak-raspravit-alveoly/
[33] https://biosurf.ru/upload/iblock/aa6/aa6b0b4bc652cb8f6e61cbf04cd28ce4.pdf
[34] https://www.elibrary.ru/item.asp?id=44512773
[35] https://transmed.almazovcentre.ru/jour/article/view/588/412
[36] https://umedp.ru/articles/opyt_primeneniya_surfaktantabl_pri_pnevmonii_assotsiirovannoy_s_covid19_v_akusherstve_forum_anestezi.html
[37] https://www.youtube.com/watch?v=-692M2qKsmo
[38] https://www.med-sovet.pro/jour/article/view/5879/5364
[39] https://rusfond.ru/news/884
[40] https://medvestnik.ru/content/news/Sergei-Carenko-obosnoval-primenenie-citostatikov-pri-tyajelom-techenii-COVID-19.html
[41] https://gxpnews.net/2020/05/v-rossii-provedut-issledovaniya-poliomielitnoj-vakciny-v-otnoshenii-covid-19/
[42] https://m.progorod43.ru/news/73461

In August 2020 promises were made in the media to get the final results by the end of the year and publish them[43]. As of March 2021 no such publications could be found.

Betukladin	Institute for Biological Problems of Cryolithozone, Siberian Branch of Russian Academy of Sciences	Approval of the Ministry of Health for the study of dietary supplements is not required

Biologically active dietary supplement Betukladin is produced from birch bark and reindeer lichen. Its developers from the Institute for Biological Problems of Cryolithozone used it as a hepatoprotector in the complex therapy of viral hepatitis[44] and tuberculosis[45].

In the summer of 2020 they announced that the supplement would help those infected with coronavirus to avoid complications[46]. In August-September an experiment was conducted with the participation of 33 doctors working in the red zone and at least 12[47] patients of the Republican Hospital No. 2 in Yakutsk. The experiment was considered successful enough to start another test in November, expanding, with the approval of the Ministry of Health of Yakutia, the number of medical organizations involved[48]. The media wrote that "work on these projects is being carried out with the organizational and informational support of the Academy of Sciences of the Republic of Sakha (Yakutia)[49]".

In December 2020 the media reported that it is planned to launch the production of Betukladin in 2021 mentioning its anti-coronavirus activity, since "effectiveness of the drug has already been proven practically"[50]. In mid-January 2021 the developers told reporters about the results of the second testing stage and assured that Betukladin reduces the duration and severity of the acute phase, accelerates remission, has prophylactic efficacy and does not have any side effects[51]. However, details of the design were not described in the media.

As of the end of January the drug was not on sale and, as it turned out from an interview with the developer, its testing was still in progress[52]. Based on this interview, testing in outpatients was carried out as follows: a participating patient was given a certain number of doses of the drug together with a questionnaire, which later, after answering all questions about the general condition, should be sent back to the developers. No other descriptions of the test design or its results could be found as of the end of March 2021. At the same time, the developers hoped to launch small scale production by the summer.

Longidaza	Petrovax	Presumably, Order No. 441

The enzyme product Longidaza by Petrovax was registered in Russia in 2007 for the treatment of connective tissue hyperplasia in a number of diseases. In this capacity it is prescribed in Russia for rehabilitation after pneumonia caused by coronavirus[53].

[43] https://remedium.ru/news/otsenka-effektivnosti-poliomie/
[44] http://science-education.ru/ru/article/view?id=30521
[45] https://federalcity.ru/index.php?newsid=9825
[46] https://rusvrach.ru/node/4438
[47] See the statement on slide 8 of the presentation https://tiir.tech/wp-content/uploads/2020/10/betukladin.pdf
[48] https://tass.ru/obschestvo/9969433
[49] http://www.xn--m1acy.xn--p1ai/news/noc-sever-territoriya-ustoichivogo-razvitiya-biotehnologii-na-borbe-s-covid-191601982174
[50] https://www.minobrnauki.gov.ru/press-center/news/?ELEMENT_ID=26327
[51] https://www.sakha.gov.ru/news/front/view/id/3256068
[52] https://exo-ykt.ru/articles/betukladin-protiv-kovid-19
[53] https://anews.com/novosti/131987160-fibroz-legkih-chem-opasen-pnevmofibroz-grozjawij-posle-koronavirusa.html

In November 2020 the launch of the Longidaza trial was announced with the participation of 200 volunteers on 14 clinical sites in the Russian Federation and Kazakhstan organized by Petrovax together with Intellogic. One half of the patients received 15 injections of Longidaza, one every 5 days, the second half was the control group[54]. A distinctive feature of the project was the use of artificial intelligence for analysis of CT images[55].

The trial was published on ClinicalTrials.gov under ID NCT04645368[56]. The estimated end date for the trial on ClinicalTrials.gov is July 2021, and the results are promised to be disclosed by mid-2021.

Interferon gamma	**Trial site — City Clinical Hospital named after M.E. Zhadkevich**	**Presumably, Order No. 441**

Interferon gamma came to the attention of the media in the autumn of 2020 after the famous doctor, head of the City Clinical Hospital named after M.E. Zhadkevich, as well as TV and radio host Aleksandr Miasnikov who has almost a million followers on Instagram, told about the drug on his social media[57, 58]. He stated that testing of Interferon gamma was carried out at his hospital, which showed efficacy of the drug for prevention of COVID-19. He also stated that results of the trial have already been published. This information was widely distributed in the media, the doctor himself continued to publicly recommend the drug[59].

Although the very fact of publication is good news, it is somewhat concerning that the International Journal of Biomedicine, where the publication with the results of the experiment was made[60], is not exactly a reliable source. It was founded in 2010 by a US-registered legal entity, its partners include Russian and Uzbek universities and research centers[61]. The journal publishes almost exclusively authors from Russia and neighboring countries.

Finally, it is rather unsettling that according to information from the social media of Dr. Miasnikov[62] testing of interferon gamma in his hospital, this time as a means of prevention of severe course of the disease in those already infected with COVID-19, was in active phase at the end of December 2020. The article with the results of apparently this very experiment in the first issue of the journal "Problems of Virology" of 2021[63] does not shed light on the question, who was controlling the trial besides the local ethics committee.

Aprotinin	**ChemRar**	**Presumably, Order No. 441**

At the end of October 2020 the media reported that ChemRar investigators discovered anti-coronavirus properties of the drug Aprotinin, which is registered in Russia as a means of prevention of hemorrhage and in aerosol form as a remedy for influenza.

It was reported that 32 medical workers of the Sechenov University Covid Hospital from among medical and nursing staff used the drug in the form of a nasal spray, while "not a single person participating in this trial got sick, despite daily work with infected patients in the red zone"[64, 65]. Journalists wrote that the results of the trial had already been published, however the link led to a web-site with preprints, where the text

[54] https://360tv.ru/news/mosobl/testy-v-podmoskove/
[55] https://petrovax.ru/press_centre/news/2020/2010/
[56] https://clinicaltrials.gov/ct2/show/NCT04645368?spons=Petrovax&draw=2&rank=1
[57] https://www.instagram.com/p/CFyhCG-Bf6B/?utm_source=ig_embed
[58] https://t.me/drmyasnikov/672
[59] https://rg.ru/2020/11/05/miasnikov-rasskazal-kak-ne-stat-legkoj-dobychej-koronavirusa.html
[60] http://ijbm.org/vol/ijbm_10(3)_el.pdf — see page 14 of the file
[61] http://imrdcorp.org/
[62] https://www.instagram.com/p/CJNecC3hzLt/?utm_source=ig_web_copy_link
[63] https://virusjour.elpub.ru/jour/article/view/477
[64] https://360tv.ru/news/mosobl/podmoskovnye-farmatsevty-obnaruzhili-v-preparatah-ot-grippa-protivokoronavirusnye-svojstva/
[65] https://gxpnews.net/2020/10/gk-ximrar-obnaruzhila-vysokoeffektivnyj-profilakticheskij-preparat-protiv-sars-cov-2/

of the article was preceded by the comment "Results presented in the preprints should not be reported in the media as verified information"[66]. The preprint is dated 03 October 2020, and as of March 2021 no article based on this preprint was found.

The developers promised reporters to bring the drug to the market by the spring of 2021 as an anti-coronavirus agent, and before that conduct another trial on a larger scale. The fate of the second experiment is unknown. ClinicalTrials.gov announced a trial of Aprotinin at Clinical Hospital No. 1 in Smolensk sponsored by Aviron LLC[67] — the same name is given to one of the startups of ChemRar[68] — with participants already infected with COVID-19, however, with an active period from June to August 2020. In other words, this trial doesn't match the experiment described in the media by the profile of participants, and the one promised in the future — by the timeframes. It is also known that the Russian regulatory authority is considering an application for testing Aprotinin in aerosol form, which was approved by the Ethics Council under the Ministry of Health on 29 December 2020. However, the applicant is not ChemRar, but Binnopharm, which already has a registered Aprotinin in aerosol form in its portfolio. Binnopharm has not yet received approval for this trial as of the end of April 2021.

Interestingly enough, proteolysis inhibitors, and specifically Aprotinin, appeared in the first version of the Temporary Methodological Recommendations of the Ministry of Health of the Russian Federation for prevention, diagnosis and treatment of the coronavirus infection (dated 29 January 2020) as a means of pathogenetic therapy. However, they were excluded from the second version of the Temporary Methodological Recommendations released a few days later (dated 03 February 2020), since it became known that those infected with SARS-CoV-2 are at risk of thrombus formation, and this group of drugs increases blood coagulability.

Molixan	**Pharma Vam** **Trial site — North-Western State Medical University named after I.I. Mechnikov**	**Order No. 441**

The immunomodulatory drug Molixan has been registered in Russia since 2011 as a remedy for viral hepatitis B and C.

From 01 June to 10 July 2020 Molixan in aerosol form was tested in a specialized hospital for treatment of patients with COVID-19 at Mechnikov University as a means of prevention of the coronavirus infection. One hundred health professionals who worked in the red zone of the inpatient facility became participants of the "low-intervention, open, single-centre study of efficacy and safety". Based on the results of the experiment a preprint[69] was prepared (with its translation into Russian[70]), the organizers of the study told journalists about it in detail[71]. The organizers cited Government Order No. 441 as a legal basis for the experiment. It was reported that the ratio of cases of infection in the Molixan group and in the control group was 2% versus 9%. No published article on the results of the study was found.

[66] https://covid19-preprints.microbe.ru/article/125
[67] https://clinicaltrials.gov/ct2/show/NCT04527133?intr=Aprotinin&cntry=RU&strd_s=01%2F01%2F2020&draw=2&rank=1
[68] https://chemrar.ru/aviron/
[69] https://www.medrxiv.org/content/10.1101/2020.09.25.20199562v1
[70] https://molixan.ru/wp-content/uploads/2020/10/Dubina-et-al-2020-medRxiv-%D0%BF%D0%B5%D1%80%D0%B5%D0%B2%D0%BE%D0%B4-%D0%BD%D0%B0-%D1%80%D1%83%D1%81%D1%81%D0%BA%D0%B8%D0%B8%CC%86-%D1%8F%D0%B7..pdf
[71] https://www.fontanka.ru/2020/12/07/69600471/

However, these results were considered sufficient enough by the developers to place a number of advertising materials on the Internet, where it was claimed that the drug "freely sold in local pharmacies" effectively prevents infection with the SARS-CoV-2 virus, which is confirmed by the studies[72, 73, 74, 75, 76].

In early February 2021 the developers of Molixan obtained an approval from the Ministry of Health for its testing in severe cases of the coronavirus infection. The trial should include 22 sites, 350 patients and last until the end of 2021.

Blood plasma from vaccine recipients	**Armed Forces of the Russian Federation**	**Unknown**

At the end of April 2020 the clinical use of blood plasma was mentioned in the Temporary Methodological Recommendations of the Ministry of Health for treatment of the new coronavirus infection in the status of an experimental method. Since at least June 2020 Russia began to use COVID-19 convalescent plasma to help those infected with coronavirus with moderate and severe forms of the disease[77, 78]. In October the Clinical Committee on COVID-19 of the Moscow Healthcare Department approved the use of donor plasma with antibodies to coronavirus as one of the treatment methods[79]. By that time the first Russian vaccine was not only registered, but actually began to enter the civilian circulation, thus another category of potential plasma donors started to form — vaccinees with sufficient immune response.

At the end of November 2020 Russian Defense Minister Sergei Shoigu said that the military was testing blood plasma from vaccinated servicemen as a treatment for the new coronavirus infection. "Use of this method has already demonstrated its effectiveness in severe forms of the disease. Currently, more than 500 vaccinated service members are involved in the study," said the Minister[80]. The Minister did not specify, by whom and where the study was conducted. It remains unknown whether the rights of the test subjects were properly protected, given that violations of rights of servicemen in the Russian military sometimes occur. For example, the media reported on the involuntary nature of vaccination in the armed forces and on the case, when a sailor was admitted to intensive care with Quincke's edema after the doctors in charge of vaccination ignored his warning about contraindications[81].

In January 2021 the media reported, with reference to the study conducted by doctors of the Military Medical Academy named after S.M. Kirov, that treatment of patients with coronavirus with plasma from donors vaccinated against COVID-19 is more effective than treatment with convalescent plasma[82]. It was also reported that about a thousand service members acted as donors. Beside mentioning in the media no other traces of the conducted test were found so far.

7272 http://www.press-release.ru/branches/medicine/rossiyskiy_akademik_predlozhil_lekarstvo_ot_kovida_31_12_2020_12_13/
73 https://www.medicinform.net/stat/molixan.htm
74 https://www.youtube.com/watch?v=ScU2P0O7o-k
75 https://drvedov.ru/stati/primenenie-preparata-moliksan-pri-covid-19
76 https://jenjur.ru/zdorove/uchenye-predlozhili-unikalnyj-sposob-borby-s-kovidom/
77 https://4s-info.ru/2020/06/16/v-novosibirske-nachali-perelivat-plazmu-s-antitelami-k-koronavirusu/
78 https://www.rbc.ru/society/29/01/2021/60139b4f9a79471c4a9e4354
79 https://www.kommersant.ru/doc/4519622
80 https://tvzvezda.ru/news/20201127125-rjcs5.html
81 https://www.svoboda.org/a/31049470.html
82 https://tass.ru/obschestvo/10585547

Chaga mushroom aqueous extract	**Head of the Mycology Laboratory of Center Vector Tamara Tepliakova**	**Approval of the Ministry of Health for the study of dietary supplements is not required**

In November 2020 many Russian media wrote about the anti-coronavirus efficacy of the chaga (*Inonotus obliquus*) extract[83, 84, 85] that is freely sold in Russia. The reason was the story of Tamara Tepliakova, the head of the Mycology Laboratory at the Center Vector, about the results of an experiment conducted by the researcher on herself, her relatives, friends and colleagues. At the same time Rospotrebnadzor also wrote about the benefits of chaga in coronavirus on Instagram[86].

An article about Tepliakova's laboratory was published back in April, where it was stated that employees had revealed the ability of fungi to suppress the viruses of encephalitis, influenza A, herpes, West Nile fever, smallpox and HIV[87]. Among them chaga mushroom was noted as particularly effective, and the authors of the article advised to brew it as tea.

The media noted that the Russians took up the call and started to actively buy this traditional medicine[88]. However, there were no publications about clinical or preclinical trials and even about applications for trials.

Immunomodulatory agent based on formic aldehyde with addition of isotonic sodium chloride solution	**Federation Council member Sergei Riabukhin**	**Unknown**

In July 2020 the State Duma Committee on Health Protection held a meeting, where a member of the Federation Council Sergei Riabukhin said that he "himself, his friends and relatives, about 50 persons already, had tried out" an immunomodulatory agent developed by a group of Saratov scientists under the leadership of Dr. Vladislav Laskavyi[89]. Sergei Riabukhin made no secret of the fact that the drug that is not registered in Russia was used outside the studies on a private initiative and, apparently, did not see any problem with it. Earlier, in May, he had already told about the drug in the Federation Council and, together with a group of other deputies, addressed Deputy Prime Minister Tatiana Golikova offering to help with its promotion[90].

The start of this development was triggered by the epidemic of coronavirus infection of pigs that happened in the USSR in the 1970s, but at that time simple slaughter of animals turned out to be the fastest solution. However, the scientists from the Saratov Research Institute of Veterinary Medicine continued to look for a cure. In 1998 one of them, Vladislav Laskavyi, defended his doctorate in veterinary medicine, where he substantiated the use of formaldehyde in saline for the treatment of viral infections of pigs (the abstract is available on the Internet[91]). A year earlier he obtained a patent for this invention together with Vladimir Rybin[92]. In 1996 the Saratov Oblast Prosecutor's Office initiated and in 1999 ceased criminal proceedings against Vladimir Rybin, who was accused of treating seriously ill patients with a variety of diagnoses, including

[83] https://scfh.ru/news/koronavirus-novyy-lekarstvo-staroe-spetsialisty-novosibirskogo-vektora-pokazali-effektivnost-ekstrak/
[84] https://medportal.ru/mednovosti/rossiyskie-uchenye-hotyat-sozdat-lekarstvo-protiv-covid/
[85] https://www.vedomosti.ru/society/news/2020/11/11/846496-tsentr-vektor-nashel-novoe-sredstvo-ot-koronavirusa?fbclid=IwAR1h3Qx5Q1_2KFXXw9bxZmzjHDIXt_y5zmsz8WWt-aWVslrwMP0dHEpiWHU
[86] https://www.instagram.com/p/CHcbT0kputU/
[87] https://scfh.ru/news/prirodnaya-farmakologiya-griby-protiv-virusov/
[88] https://sibkray.ru/news/1/940122/
[89] https://www.pnp.ru/social/ryabukhin-oproboval-na-sebe-novyy-preparat-protiv-koronavirusa.html
[90] https://www.pnp.ru/politics/v-rossii-otyskali-preparat-ot-koronavirusa-tridcatiletney-davnosti.html
[91] http://medical-diss.com/veterinariya/profilaktika-virusnogo-transmissivnogo-gastroenterita-sviney-v-promyshlennyh-kompleksah
[92] https://patents.google.com/patent/RU2077882C1/ru

cancer, with formaldehyde solution. The drug was used without conducting clinical trials, without the approval of the Ministry of Health and before obtaining a patent. The media wrote that Rybin charged large sums of money for the treatment[93]. Since some of Rybin's clients assured that the treatment helped them, and in connection with the issue of a patent for the drug, the investigation was stopped and the case never made it to court. This historical insight is only important in light of the fact that in 2020 the media wrote about the drug of Saratov scientists as if it had already been tested on humans and demonstrated its effectiveness "in the treatment of diseases such as tuberculosis, leukemia, hepatitis B, hepatitis C and even AIDS"[94]. At the same time it was stated that no clinical trials were conducted in Russia.

According to Laskavyi, in the early 2000s the drug was tested in Belarus and even received a certificate in 2005, which fits the description of the GMP certificate[95]. However, the drug apparently did not gain widespread use in Belarus. The statements that the drug was "recognized" in Kazakhstan are also not clarified in any way. No independent confirmations of the use of the drug in Belarus and Kazakhstan, as well as its use in veterinary medicine outside the experiments, were found. Thus, it turns out that the support of Senator Riabukhin became the first ever chance for Saratov scientists to legalize their development in the status of a medicinal product.

In October 2020 Vladislav Laskavyi told reporters that the head of the FMBA of Russia, Veronika Skvortsova, took an interest in his development and offered to help with clinical trials[96]. This is where the trail of the Saratov drug ends.

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Table 25 describes the trials of drugs against COVID-19 conducted on an alternative legal basis, without going through the standard procedures in the Ministry of Health. Although in some cases the trials with the approval of the regulatory authority were not quite usual either. The afore-mentioned Order No. 441 opened the way for registering drugs in Russia on the basis of incomplete data. As a result, the path to the market for some anti-coronavirus agents has been greatly shortened. First and foremost, this applies to the Russian vaccines against COVID-19.

Considerable part of the twists and turns in the development of **Gam-Covid-Vac** vaccine (trade name Sputnik V) of the Gamaleya Center was described in the previous issue of the ACTO Newsletter. Here we will recap certain points. First talks about the drug started in May 2020 after it became known that it was being tested on employees of the development center without a clear legal basis. Later, director of the Gamaleya Center, Aleksandr Gunzburg, even named the exact date of vaccination of his subordinates — 30 March 2020[97] (although approval to conduct the trial was issued only on 16 June 2020). The developers were also accused of inoculating the Russian elite with Sputnik V since the spring of 2020.

The most heated battles erupted after the registration of the drug on 11 August based on the data of monitoring of 76 healthy volunteers aged 18 to 60 from among the military personnel for 42 days. Formally, these were the results of a Phase I–II trial. The debate has been (and is) revolving around the issue of whether the pandemic justifies such a radical "corner cutting" and whether the data collected was enough to assess the safety of the vaccine.

[93] https://www.kommersant.ru/doc/218643
[94] https://mirnov.ru/nauka-i-tekhnika/spasti-lyudei-ot-koronavirusa-mozhet-saratovskii-uchenyi.html
[95] https://www.business-vector.info/saratovskij-uchenyj-izobrel-preparat-kotoryj-pomogaet-pobedit-koronavirus-i-drugie-tyazhelye-bolezni/#comments
[96] https://lgz.ru/article/-42-6757-21-10-2020/speshka-v-nauke-nedopustima/
[97] https://rg.ru/2021/02/12/privivshiesia-sputnikom-v-mogut-stat-donorami-plazmy.html

After registration of Sputnik V in Russia a phase III–IV trial started in parallel with vaccination of representatives of risk groups. However, in fact, not only representatives of risk groups had the opportunity to get vaccinated. This leak in the distribution system affected the study of the drug. After the vaccination study participants often privately tested their blood for antibodies, and some of them concluded that they were in the placebo group. Learning of this, they looked for a way to get vaccinated within the framework of civilian circulation, many of them succeeded and withdrew from the study, which, naturally, made it difficult to collect and analyze data. As a result, recruitment of new study participants was simply stopped[98].

Despite all the controversial points in the development of Sputnik V, an important advantage of this vaccine over other Russian vaccine products is that its creators published two articles in the international journal The Lancet, one based on the results of the phase I–II study[99] and the second on the preliminary results of phase III–IV[100]. Due to these publications Sputnik V became not only the first, but also the most transparent Russian vaccine. However, publication on the results of preclinical trials and the final results of phase III are still lacking for full transparency.

Unfortunately, the confirmed information about the vaccine is drowning in the sea of unsubstantiated statements of the developers (about its effectiveness against new strains[101], about equal effectiveness in all age groups[102], about the hope for indefinite immunity[103], about effectiveness in vaccination of animals — "however we still need to vaccinate people first" [104 and many others]). There is an opinion that these constant bald statements about the high quality and superiority of Sputnik V over competitors diminish public confidence in it resulting in slowing down the pace of vaccination in Russia, since even in April 2021 Sputnik V still remains the only relatively freely available vaccine in the country.

Not only Sputnik V, but other Russian vaccines were registered after the completion of early development phases. Moreover, the registration deadlines were discussed even before the start of phase I clinical trials. Thus, plans to register **EpiVacCorona** of Center Vector in the autumn of 2020 were announced in May of the same year[105], and the registration was announced on 14 October 14[106]. The decision was made on the basis of data of monitoring of 100 healthy volunteers aged 18 to 60 for 42 days after the first injection in the period from July to September 2020 (phase I–II study, as approved by the Ministry of Health). No official statements about introduction into civilian circulation followed immediately after the registration, the first of them were made only two months later, on 11 December 2020[107].

An interesting episode in the development of EpiVacCorona was the so-called "popular study" of the vaccine organized by the participants of the Phase III–IV trial, which started on 16 November 2020. Those who received the vaccine created a community on one of the social media, where they exchanged the results of testing their blood for antibodies. A large percentage of participants that ordered analysis in an independent laboratory did not find neutralizing antibodies in their blood, after which they addressed to the Ministry of Health with an

[98] https://www.bbc.com/russian/news-55436957
[99] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31866-3/fulltext
[100] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00234-8/fulltext?fbclid=IwAR2fv3C_tAIy14BLDqx-DesBjybp1sjJvQ8zfeExHP8hISqQwzVmB0qF0o0
[101] https://www.interfax.ru/russia/760369
[102] https://tass.ru/obschestvo/10898285
[103] https://www.interfax.ru/russia/760529
[104] https://ria.ru/20210416/sputnik-v-1728510697.html
[105] https://rg.ru/2020/05/14/reg-sibfo/novosibirskij-vektor-zaregistriruet-vakcinu-ot-covid-19-v-sentiabre.html
[106] https://ria.ru/20201014/vaktsina-1579781530.html
[107] https://www.interfax.ru/russia/740922

open letter[108] urging to organize a study of the drug independent of Rospotrebnadzor, to which the Center Vector is subordinated.

It was only after this public criticism, five months after the vaccine was registered, in March 2021, that an article was published with the results of Phase I–II trial[109]. Unfortunately, despite the promises of the developers[110], it was published not in an international, but in a Russian journal, which is even not that well-known. According to this article, it is only possible to detect neutralizing antibodies after inoculation with EpiVacCorona and confirm its immunogenicity by means of a special test, which was developed at the Center Vector and is not available to independent laboratories. However, the test is not described in the article, it only states the fact of its existence, which has caused criticism from subject matter experts[111].

While discussions are being held around EpiVacCorona and disputes revolving around Sputnik V, too little is currently known about the third Russian vaccine, **CoviVac** from the Chumakov Center, for a thoughtful discussion. It was registered on 19 February 2021 after a Phase I–II trial, which started on 21 September 2020. Developers told journalists about 300 healthy volunteers aged 18 to 60[112]. It was reported that small doses of CoviVac have been released into civilian circulation since April 2021[113], however, no articles have been published on the results of the Phase I–II trial at the end of April. The immunological efficacy of 90% by the 21st day after introduction of the second dose is still based solely on the statements of the staff of the Chumakov Center[114]. The Phase III trial, within which it was promised to vaccinate 3,000 people, has not yet started at the time of publication of this newsletter.

Registration before Phase III is an exception made not only for vaccines. On 31 March 2021 the Russian Ministry of Health registered the drug Covid Globulin based on the COVID-19 convalescent blood plasma, which was studied only in Phase I. Its benefits for patients are also known only from press releases.

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All of the above examples illustrate one general observation: in Russia the pandemic of the new coronavirus infection has pushed regulatory authorities to loosen control and oversight of clinical trials. On the one hand, the motivation of the Ministry of Health is clear: such policy can be expected to speed up development of medicines that can stop the pandemic. On the other hand, this practice is alarming considering the fact that the culture of clinical trials in Russia is, unfortunately, developed unevenly. While some research organizations adhere to international research standards in the most rigorous manner, employees of others tell journalists that they consider it common practice for developers to test new drugs on themselves, friends and family without waiting for clinical trials[115].

The media in the Russian Federation also tend to be lenient to violations of rules by the developers. Thus, in Germany, the reason for initiation of criminal proceedings was a case when a doctor injected himself, his family members and about a hundred volunteers with a homemade COVID-19 vaccine[116]. Russian outlets, when talking about him, focused on the benefits of the vaccine and were surprised that the incident attracted the

[108] https://epivakorona.com/openletter2.html
[109] https://www.iimmun.ru/iimm/article/view/1699
[110] https://rg.ru/2021/02/10/itogi-ispytanij-vakciny-centra-vektor-napravleny-v-zarubezhnye-zhurnaly.html
[111] https://meduza.io/feature/2021/03/26/sozdateli-epivakkorony-opublikovali-pervuyu-nauchnuyu-statyu-ne-v-lancet-a-v-maloizvestnom-rossiyskom-zhurnale-hotya-obeschali-zarubezhnyy?fbclid=IwAR2l6z75lIfN46CfrF7Hv0GbtuNiHYd86FftJ_fjZHOPsKtwKq8uqNYE2c0
[112] https://ria.ru/20201026/vaktsina-1581605154.html
[113] https://www.interfax.ru/russia/757751
[114] https://polit.ru/news/2021/01/21/chumakov/
[115] https://www.bbc.com/russian/news-52772808
[116] https://www.dw.com/ru/v-frg-zaveli-delo-na-vracha-iz-za-sozdannoj-im-vakciny-ot-covid-19/a-56510421

attention of the prosecutor's office[117, 118]. The text above describes several episodes, when the drugs were tested by the developers on themselves and family members, but none of them became the reason for initiation of formal proceedings.

In the spring of 2021 BMC Medical Ethics published an article[119] by a group of Russian scientists who checked how strict the requirement to get an approval for the start of a trial from the Ministry of Health was adhered to in Russia before the start of the pandemic, when Order No. 441 had not yet been adopted and simplified procedures were not in place. The database of the Russian-language scientific articles used by them included 26 studies that fitted the requirements of the scientists. Of these, 22 were carried out without the approval of the Ministry of Health. Although 21 out of these 22 were dedicated to testing drugs registered in Russia, in nine cases indications, dose or method of administration used in the study were inconsistent with the registered specifications.

The article in BMC Medical Ethics demonstrates that the practice of testing medicinal products without the approval of the Ministry of Health and the required expert examinations existed in Russia even before the pandemic. The crisis only shed light on what had previously remained in the shadows. However, such developments of 2020 as simplification of procedures for launching a trial and registration of a drug (and specifically Order No. 441) legitimized these shadow practices at the same time. In other words, the Ministry of Health played along with that part of the industry community, for which the standards for conducting clinical trials had not yet become sacred.

For another part of the community, and for ACTO as well, this means that normalization after the end of the pandemic will not happen by itself, but will certainly require efforts, the more significant the longer the protracted emergency lasts and the more routine it becomes.

[117] https://og.ru/ru/news/117582
[118] https://www.fontanka.ru/2021/02/09/69758351/
[119] https://link.springer.com/epdf/10.1186/s12910-021-00617-3?sharing_token=Y7BRP87QyFWGZwBOYyIrfm_BpE1tBhCbnbw3BuzI2RN582kNg9N2DA-FAII9_I7QzmpX26hCBPyFrj7Y1dbfXKAEcZHYAKBsi4kx_yxqvbMrTxfJ86pZOO_kil7ewdhIgihgZqp7YI7quHO2KWBDY1o_q8nY2Iwxjis_hZSETpQ%3D