ACTO

Association of Clinical Trials Organizations

ACTO NEWSLETTER № 18

Summary of 2018 results

MOSCOW 2019

CONTENTS

SUMMARY

ACTO Newsletter №18 opens with an overview of key market indicators for clinical trials in Russia in 2018. The number of clinical trial approvals saw a year-on-year decrease of 7%, from 700 to 653. The decrease was observed across all types of clinical trials except for international multicentre clinical trials (IMCT), which bucked the trend, increasing by 2.1% from 281 to 287. The share of IMCTs reached 44% of the overall number of clinical trial approvals issued, the highest figure since 2012. Foreign-sponsored local trials decreased by more than any other sector, down to 26 from 48 approvals in 2017, representing a 45.8% reduction. The share of this type of trials decreased to 4% of the overall volume of approvals issued, the lowest figure since 2012. 130 approvals for domestic-sponsored local trials were issued compared with 149 in 2017, a 12.8% decrease. Approvals for trials of this type saw a reduction in their overall market share, from 21.3% to 19.8%. Bioequivalence studies for Russian generics saw a 6.6% drop in approvals issued (141 compared with 151 in 2017, with the overall share remaining unchanged at 21.6%), with a 2.8% drop for foreign generics (69 compared with 71, the overall market share growing by 0.6 percentage points to 10.6%).

Breaking IMCTs down by therapeutic areas, oncology held onto its long-established leading position, with 77 approvals issued, representing just over a quarter of all new IMCTs. Together with oncohematology, which is traditionally counted separately, oncological trials account for 97 IMCTs, representing a third of all new approvals (33.8%). Gastroenterology takes second place, with 37 approvals. In third place is cardiology and cardiovascular diseases (CVD), with 21 approvals. Breaking local trials of generics/biosimilars and bioequivalence studies of foreign sponsors down by therapeutic areas, cardiology CVD leads with 18 new trials, followed by endocrinology with 9, and neurology and infectious diseases each with 8 approvals. Breaking local trials of generics/biosimilars and bioequivalence studies of Russian sponsors down by therapeutic areas, neurology led the way with 25 new trials. This was followed by oncology with 20, and both endocrinology and cardiology and CVD with 18 approvals for each therapeutic area.

The next section deals with the regional distribution of IMCTs across Russia. The four federal districts with the highest indicator “Number of IMCTs per region” in 2018 have remained unchanged throughout ACTO’s entire monitoring period. The Central Federal District takes first place with 272 IMCTs in 2018, the Northwestern Federal District is second with 250, the Volga Federal District takes third place with 181, and the Siberian Federal District is fourth with 166. The Southern Federal District overtook the Ural Federal District to take fifth place in 2018, showing year-on-year growth of 50% with 105 new IMCTs compared to 70 in 2017. Moscow and St. Petersburg remain the most active federal subjects of the Russian Federation, with over 200 new IMCTs launches planned each year. The latter is also ranked first in the top 10 list of federal subjects by number of new IMCTs per million population, whereas Moscow does not feature.

Changes to the average time period for issuing approvals of various types in 2018 compared with 2017 proved to be negligible. The figure decreased by 3.2% (from 95 to 92 days) for clinical trial approvals, grew by 12% for protocol amendment approvals (from 42 to 47 days), grew by 5% for approvals to import/export of biosamples (from 20 to 21 days) and did not change for approvals to import medicines (14 days) or other approvals (to prolong clinical trials, to include new sites, to enroll additional patients, etc. – 26 days).

In addition to the abovementioned topics, the newsletter analyses the activity of individual market players and provides statistics on imports into the Russian Federation of medicines for clinical trials, while also looking at other issues.

An article by Maria Nassonova, Executive Director at ALMEDIS, closes out the newsletter. In her piece she addresses the topic of investigator initiated trials.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In 2018 the Ministry of Health of the Russian Federation issued 653 clinical trial approvals, almost 7% fewer than in 2017 (table 1). The decrease was observed across all types of clinical trial, except for international multicentre clinical trials (IMCTs). The number of recent even slightly increased, from 281 in 2017 to 287, representing a 2.1% rise.

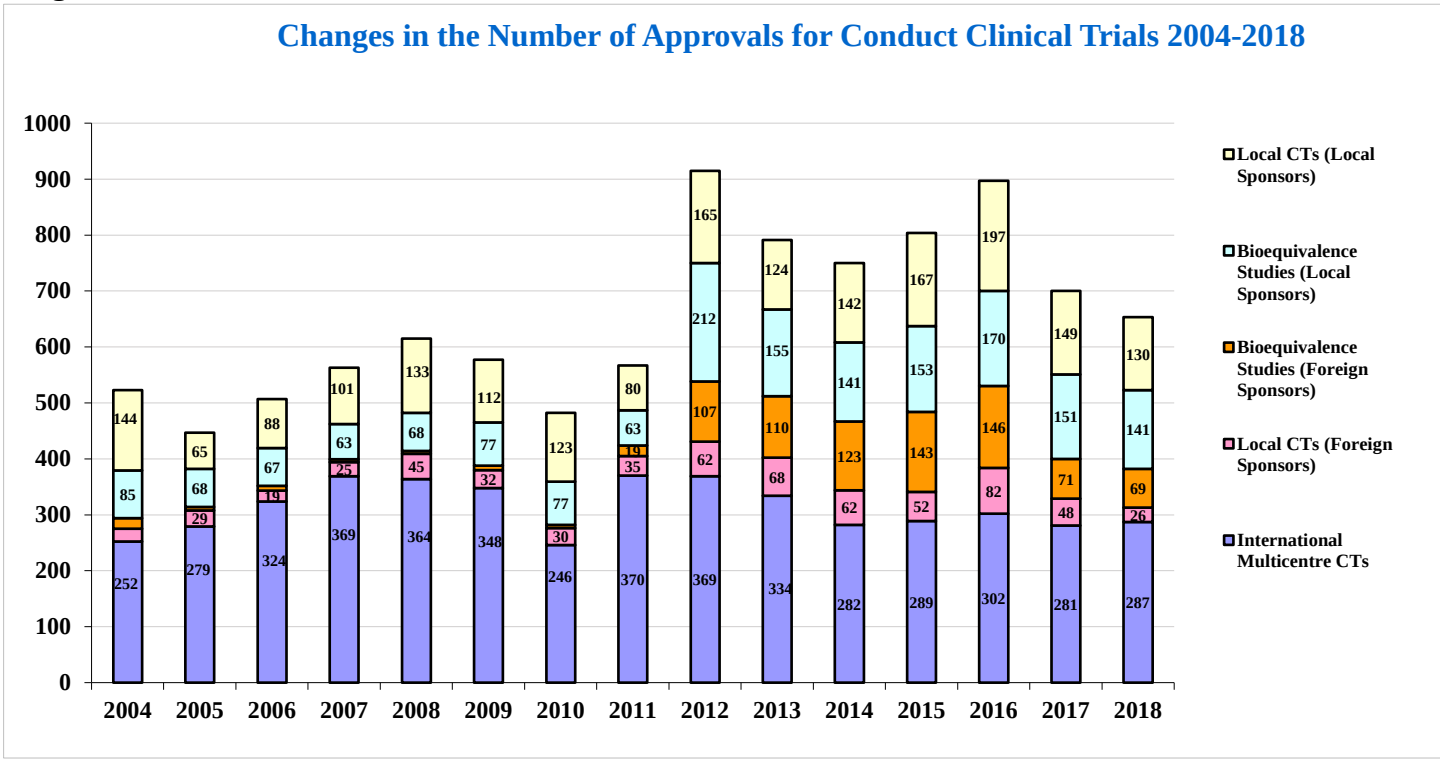
Table 1

Approvals for Conduct Clinical Trials: 2018 vs 2017						
Year	**Total**	**International Multicenter CTs**	**Local CTs (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CTs (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2018	653	287	26	69	130	141
2017	700	281	48	71	149	151
2018 vs 2017, %	-6.7%	2.1%	-45.8%	-2.8%	-12.8%	-6.6%

Data from www.grls.rosminzdrav.ru

The largest reduction in the number of approvals issued (45.8%) was observed in the foreign-sponsored local trials sector, with 26 approvals compared with 48 in 2017. The number of approvals issued for domestically sponsored local trials experienced a decrease which, while not as significant as for foreign-sponsored trials, was nonetheless sizeable at 12.8%, having falling from 149 to 130. The sector for bioequivalence studies also shrunk a little. The number of approvals issued during the year for bioequivalence studies for Russian generics fell by 6.6% (from 151 in 2017 to 141), with the figure for foreign generics falling by 2.8% (from 71 to 69).

Diagram 1



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

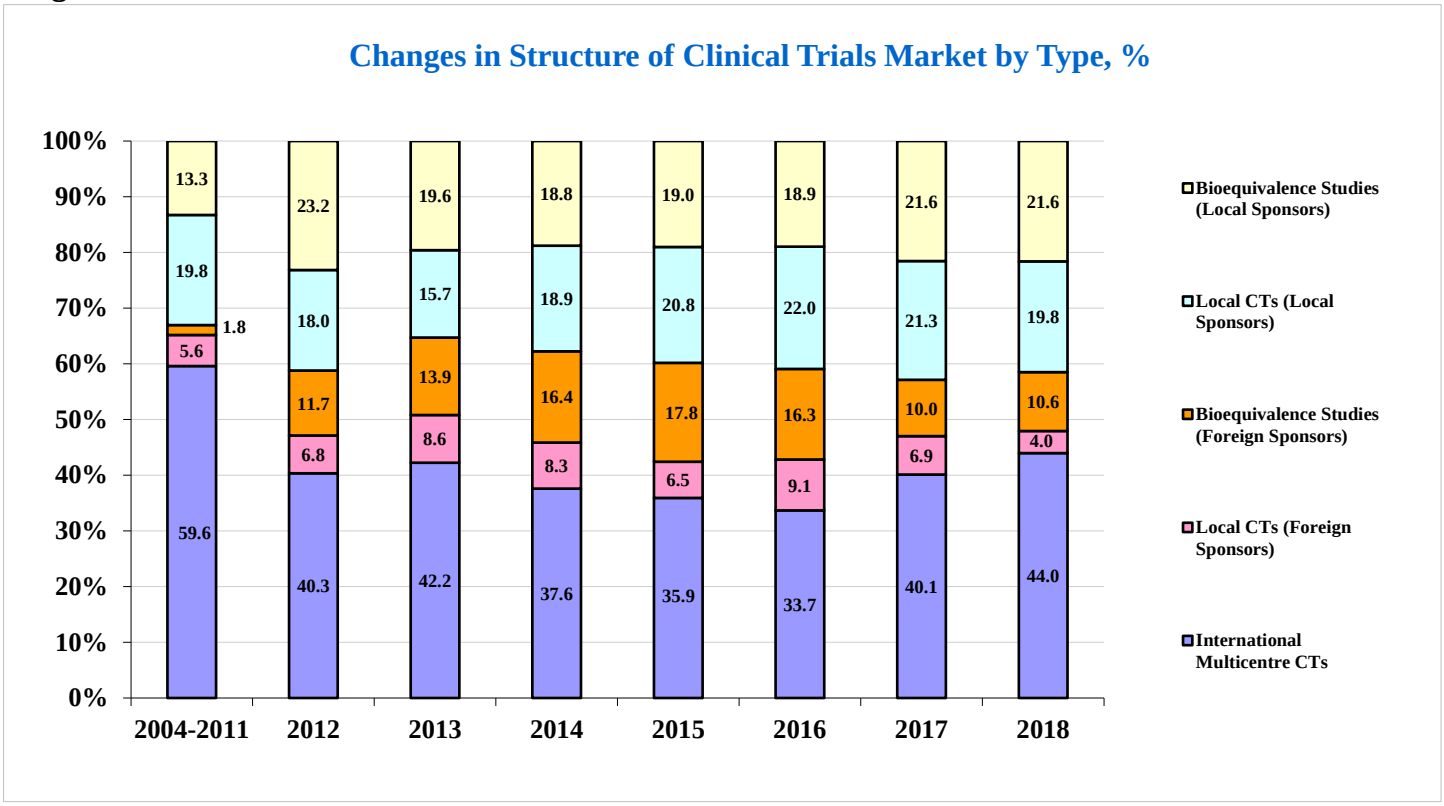
Yearly growth trends for approvals issued across various trial types, beginning in 2004, can be observed in diagram 1. It is notable how over the last five years the highest level of stability has been observed in the IMCT and Russian-sponsored bioequivalence study sectors. A slight drop can be observed with regard to domestically sponsored local trials. The sectors for foreign-sponsored local trials and foreign-sponsored bioequivalence studies have experienced a significant drop. The number of approvals issued for carrying out local trials of foreign medicines has dropped as far as 'pre-reform' (i.e. before the Russian Federal Law "On Circulation of Medicines" came into force) levels, at around 30 approvals.

We gave an explanation for the downward trend in the market share for local trials, primarily of foreign medicines, a year ago (*see ACTO Newsletter № 16*). We can now assert that this trend has only intensified in 2018.

STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

Structural market changes by trial type are shown in diagram 2. The data shows that the share of IMCTs relative to the total number of approvals issued has grown by 4 percentage points over the past year, reaching 44%. This is the highest figure since 2012, though it remains, of course, a considerable distance from 'pre-reform' levels.

Diagram 2



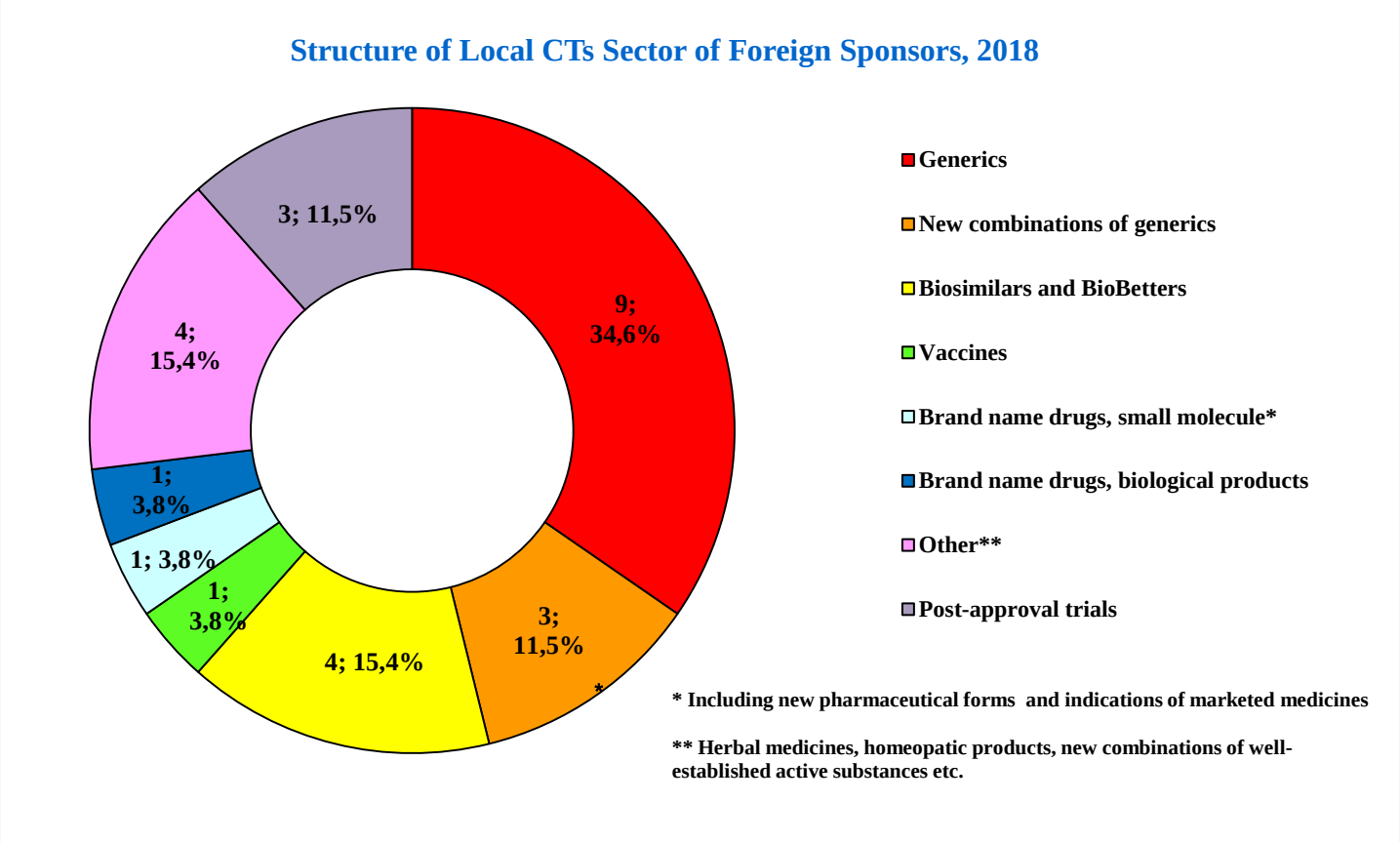
Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

The increase in the share of IMCTs over the last year has come about at the cost of a reduction in the share of local trials, both foreign (which decreased from 6.9% to 4%, the lowest figure since 2012) and domestically sponsored (which saw a reduction from 21.3% to 19.8%). The share of bioequivalence studies for Russian generics remained at its 2017 level of 21.6%, while foreign generics even increased slightly, from 10% to 10.6%.

***

Diagram 3 shows the breakdown of foreign-sponsored local trials by investigational product type. It should be pointed out that the overall number of these trials in 2018 was itself low, with 26 in total, and so the ratio between the respective shares is subject to significant random fluctuations and may be atypical. We can nonetheless evaluate the results obtained. The share of generics trials is, as usual, the largest (9 trials in 2018), though it has fallen quite noticeably compared with the previous year, from 54.2% to 34.6%. Biosimilars and biobetters had 15.4% of the overall share with 4 trials each, as did the other trials category, which traditionally includes plant and animal-derived drugs, homeopathy and other similar remedies. Three approvals (11.5%) were issued both for trials of new combinations of generics and for post-approval trials. The figures for other medicine types are so low as not to merit separate consideration.

Diagram 3



Data from www.grls.rosminzdrav.ru

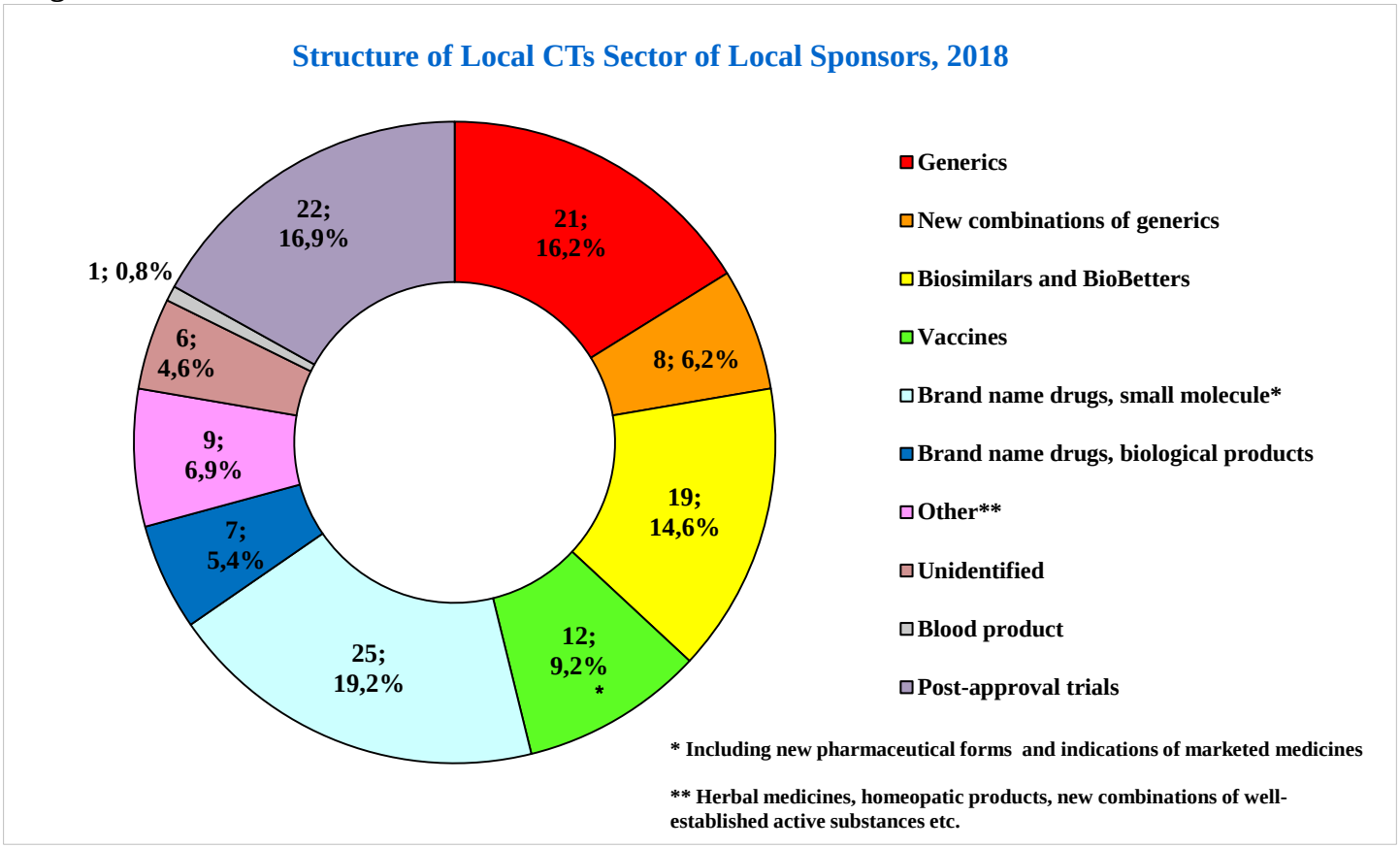
Diagram 4 shows the distribution of Russian local trials by investigational product type.

The largest share – 19.2% – was held by trials for brand-name drugs, small molecules, with 25 trials.(small molecules in all cases). Of these, five trials were accounted for by NPO Petrovax Pharm, and we are talking about the further development of already marketed medicines (Longidase in three protocols, and Polyoxidonium in two). Four were conducted by ChemRar, and two by POLYSAN. Each of the remaining manufacturers represented in this sector carried out one trial each.

Generics accounted for 21 trials or a 16.2% share (compared with 28.2% the previous year). Biosimilars and biobetters had a 14.6% share, with 19 trials. Eight of these trials studied biosimilars of monoclonal antibodies: three eculizumab trials, and one each for adalimumab, omalizumab, bevacizumab, cetuximab and trastuzumab. A further five trials looked at insulins, two each at erythropoietins and botulinum toxin, and one each at glucagon and human hepatitis B immunoglobulin.

A noticeable segment of 12 trials or 9.2% were vaccines (4% in 2017). Of which, seven were for the prevention of influenza, two for polio and one each for hepatitis B, whooping cough and tuberculosis. The most active players here were the N.F. Gamaleya Scientific Research Center of Epidemiology and Microbiology with three trials, and Microgen, FORT and the Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products of Russian Academy of Sciences (two trials each).

Diagram 4



Data from www.grls.rosminzdrav.ru

We would also like to draw our readers' attention to post-approval trials. In the past, few trials of this type were conducted. Therefore, despite the fact that this may not appear to be a very well-defined classification, we included them in the overall local trials category alongside various types of medicinal product, marking it out as its own separate group. In 2017, just five approvals were issued for post-approval trials of Russian-sponsored medicines. By 2018, however, this figure had risen to 22, accounting for a 16.9% share.

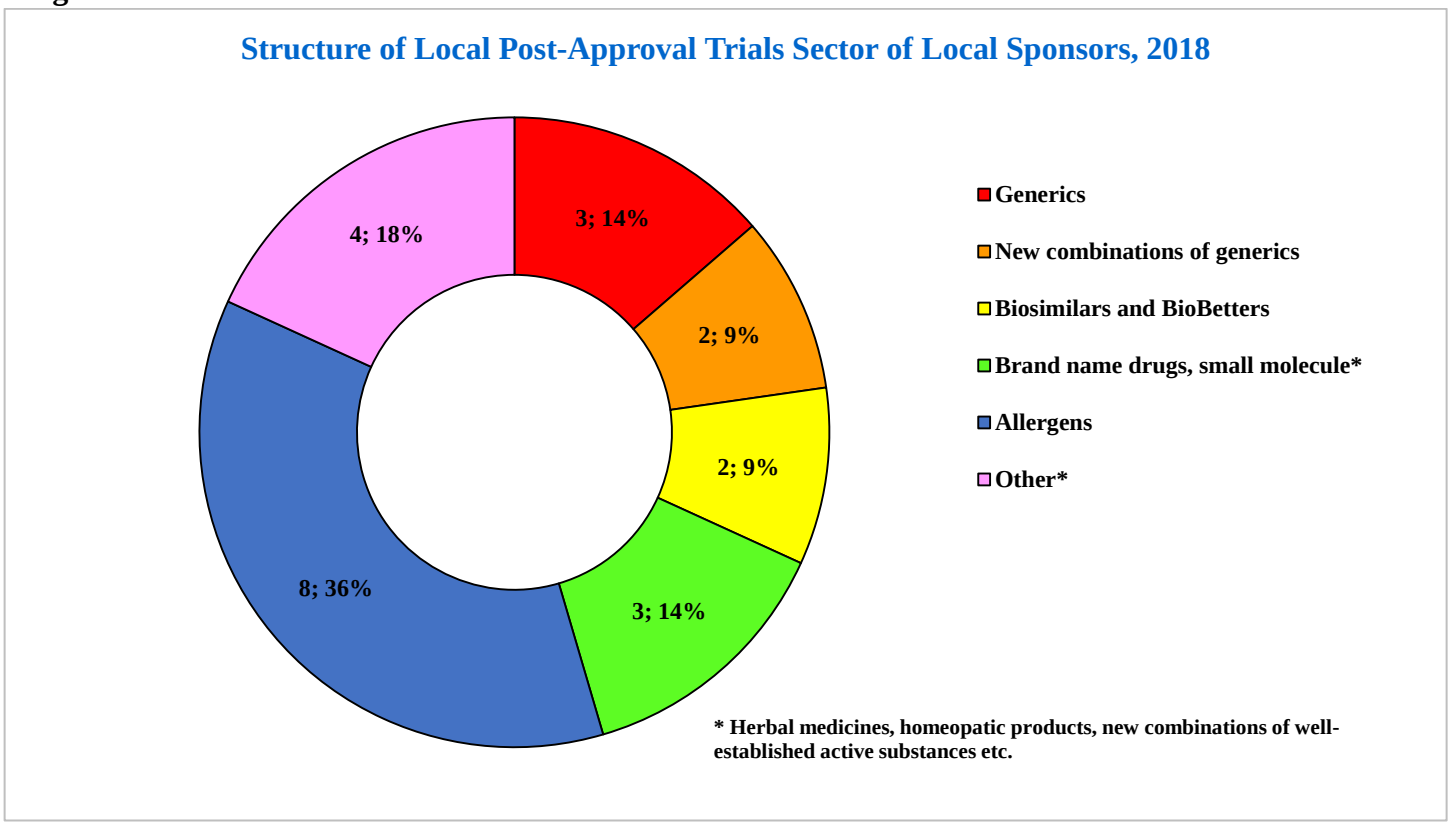
Such a strong growth trend clearly merits separate consideration, and we approached several experts for their views. They offered the following account. As known, EAEU rules state that by 31 December 2025 manufacturers of medicines that are already available on EAEU markets must bring their paperwork into compliance with EAEU regulations. This presupposes, among other things, documented evidence of the effectiveness of the medicines. By all accounts, the prospect of this requirement coming into force has caused some concern among certain manufacturers, who are doubtful of the credibility of the data which they presented at the time of registration. In any case, contract research organizations (CROs) have received such requests for study. It is possible that this accounts in part for the growth in post-approval trials. It is especially credible when considering that the Ministry of Health register of approved trials includes an entry for a phase IV clinical trial purporting to be a "open-label trial of safety and tolerability of the medicine N in healthy volunteers".

Furthermore, a large share of post-approval trials (eight trials, or 36%) dealt with allergens. We have already written about this peculiar grouping of trials conducted, as specified in the registry, with the aim of "studying the specific activity *of allergen X* in keeping with the requirements of the general pharmacopoeia

monograph (GPM) on Allergens for certification as the in-house reference standard" (*see ACTO Newsletter № 16)*. All allergen trials, as in 2017, were initiated by Microgen.

Other medicine groups studied in addition to allergens in post-approval trials in 2018 can be seen in diagram 5.

Diagram 5



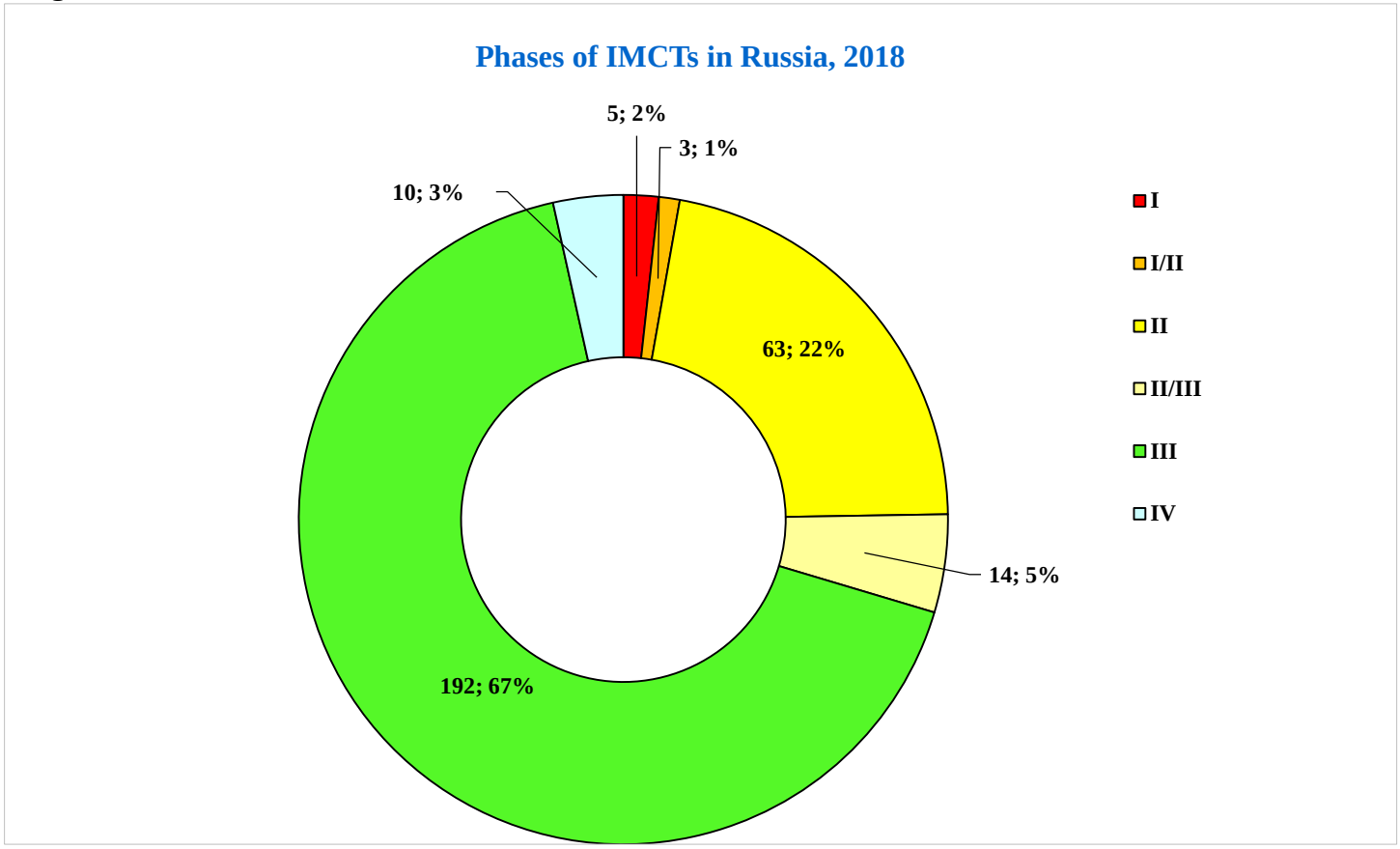
Data from www.grls.rosminzdrav.ru

STRUCTURE OF THE IMCT MARKET BY PHASE

The distribution of approvals for IMCTs issued in 2018 by phase is shown in diagram 6. The general breakdown remains broadly the same as in 2017. The majority of categories remain within 2 percentage points of last year's figures, except for phase II/III trials, which increased their share by 4 percentage points – from three to 14 IMCTs.

Oncological medicines were studied in all five phase I trials and one phase I/II trial. Two more phase I/II trials dealt with child neurology.

Diagram 6



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

STRUCTURE OF THE CLINICAL TRIALS MARKET BY THERAPEUTIC AREAS

Table 2 shows the distribution of IMCT approvals in 2018 by therapeutic areas. As usual, the highest figure is for oncology. The number of approvals for trials in this area grew from 68 to 77 in the space of a year, and now accounts for just over a quarter of all new IMCTs (26.8% compared with 24.2% in 2017). Together with oncohematology, which took fourth place in the 2018 rankings with 20 IMCTs, oncological trials accounted for a third of all new approvals (33.8%). Gastroenterology was placed just seventh in 2017 with 16 trials, but rose to second place in 2018 with 37 IMCTs (12.9%). Cardiology and cardiovascular diseases (CVD) placed third with 21 approvals. This area has also shown an increase compared with 2017, when it was ranked ninth with 15 IMCTs.

The growth leaders in absolute terms when comparing last year's figures with 2017 are gastroenterology (growth of 21 IMCTs, from 16 to 37), dermatology (13 IMCTs, from 4 to 17) and oncology (9 IMCTs, from 68 to 77). The biggest reductions in the number of approvals were observed in the areas of rheumatology (15 fewer new trials, 13 compared with 28 a year earlier) dropping from second to seventh place, endocrinology (12 IMCTs fewer, from 19 down to 7), which placed sixth in 2017 and only 11th in 2018, and hematology (10 fewer approvals, falling from 20 to 10), dropping from fifth the previous year to tenth place in 2018.

Table 2

Distribution of International Multicenter CTs by Therapeutic Areas, 2018			
Therapeutic Area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**
Oncology	77	26.8%	6 681
Gastroenterology	37	12.9%	2 346
Cardiology and CVD	21	7.3%	5 161
Oncohaematology	20	7.0%	964
Neurology	18	6.3%	1 288
Dermatology	17	5.9%	996
Rheumatology	13	4.5%	922
Pulmonology	13	4.5%	894
Infectious Diseases (except HIV/HCV/tuberculosis)	11	3.8%	1 644
Haematology	10	3.5%	262
Endocrinology	7	2.4%	584
Nephrology	6	2.1%	525
Ophthalmology	6	2.1%	616
Psychiatry	5	1.7%	576
Obstetrics and Gynecology	5	1.7%	295
Urology	4	1.4%	647
Allergology	4	1.4%	314
Ophthalmology	3	1.0%	62
Immunology	3	1.0%	31
Hepatology	2	0.7%	155
Phlebology	2	0.7%	448
Tuberculosis	1	0.3%	64
Narcology	1	0.3%	80
Others	1	0.3%	6
TOTAL	287	100.0%	25 561

Data from www.grls.rosminzdrav.ru

***

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

Cardiology and CVD leads the way for the third year running, this time with 18 new trials. Both infectious diseases (excluding HIV/HCV/TB[1]) and analgesics remain from the top five in 2017, with eight new approvals compared with seven the previous year, and down to seven from 14 respectively. The rest of the top five has been filled with new entries. In 2018 endocrinology received seven more approvals than the year before, allowing this therapeutic area to climb from 15th place to second. The approval count for neurology increased by six IMCTs, taking it to third place (compared with 13th in 2017).

Table 3

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars) of Foreign Sponsors, 2018			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD	18	20.9%	1873
Endocrinology	9	10.5%	4247
Neurology	8	9.3%	550
Infectious Diseases (except HIV/HCV/tuberculosis)	8	9.3%	469
Analgesic and NSAIDs	7	8.1%	1013
Allergology	5	5.8%	440
HIV	5	5.8%	284
Gastroenterology	4	4.7%	792
Oncology	3	3.5%	217
Urology	3	3.5%	136
Ophthalmology	2	2.3%	348
Dermatology	2	2.3%	306
Surgery	2	2.3%	170
Oncohaematology	2	2.3%	80
Rheumatology	2	2.3%	75
Gynecology	2	2.3%	70
Psychiatry	1	1.2%	70
Phlebology	1	1.2%	70
Pulmonology	1	1.2%	60
Others	1	1.2%	40
TOTAL	86	100.0%	11310

Data from www.grls.rosminzdrav.ru

***

Table 4 shows the distribution by therapeutic areas of local trials and bioequivalence studies conducted by local sponsors.

In 2018 the leading therapeutic area was neurology with 25 new trials, followed by oncology with 20, endocrinology with 18, and cardiology and CVD, also with 18. Together, these four therapeutic areas accounted for 40% of approvals for domestically sponsored trials in generics and biosimilars. Infectious diseases (first place in 2017 with 28 approvals) and HIV/HCV/TB (second place in 2017 with 22 new trials), which we consider separately, placed just sixth and eighth in 2018 with 17 and 12 approvals respectively.

[1] HIV, Hepatitis C, tuberculosis.

Table 4

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors, 2018			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Neurology	25	12.7%	1819
Oncology	20	10.2%	1689
Endocrinology	18	9.1%	1498
Cardiology and CVD	18	9.1%	879
Infectious Diseases (except HIV/HCV/tuberculosis)	17	8.6%	733
Rheumatology	12	6.1%	1210
HIV/HCV/tuberculosis	12	6.1%	828
Gynecology	11	5.6%	544
Analgesic and NSAIDs	8	4.1%	852
Gastroenterology	8	4.1%	279
Psychiatry	6	3.0%	631
Immunology	6	3.0%	247
Oncohaematology	5	2.5%	286
Urology	5	2.5%	192
Dermatology	4	2.0%	454
Haematology	4	2.0%	210
Otorhinolaryngology	3	1.5%	430
Pulmonology	3	1.5%	256
Surgery	3	1.5%	206
Phlebology	2	1.0%	344
Others	2	1.0%	145
Hepatology	2	1.0%	70
Ophthalmology	1	0.5%	156
Transplantology/Immunology	1	0.5%	80
Allergology	1	0.5%	20
TOTAL	197	100.0%	14058

Data from www.grls.rosminzdrav.ru

***

Table 5 shows the molecules which featured most commonly in protocols for trials of generic medicines in 2018.

The first and second places were taken by rosuvastatin (tested in nine trials, both separately and in combination) and hydrochlorothiazide (tested in seven trials as part of combination medications), used in cardiology and CVD. Ethinylestradiol, which is used in gynecology, took third place (seven trials in combination, the majority of which were for domestic generics), with the antibiotic amoxicillin placing fourth (used separately and in combination across six trials). Gefitinib, which is used in oncology, placed fifth (six trials, predominantly domestic generics).

The majority of generic and biosimilar molecules studied are accounted for by cardiology and CVD with 28, neurology with 22 and infectious diseases with 20 approvals.

Table 5

Most Requested INN Used in Clinical Trials of Generics in 2018				
Substance	**Number of CTs of foreign generics**	**Number of CTs of local generics**	**All clinical trials to a given INN**	**Therapeutic Area**
Rosuvastatin (separately and in fixed combinations)	5	4	9	Cardiology and CVD
Hydrochlorothiazide (in fixed combinations)	4	3	7	Cardiology and CVD
Ethinylestradiol (in fixed combinations)	1	6	7	Gynecology
Amoxicillin (separately and in fixed combinations)	4	2	6	Infectious Diseases
Gefitinib	1	5	6	Oncology
Metformin (separately and in fixed combinations)	2	4	6	Endocrinology
Teriflunomide	3	3	6	Neurology
Amlodipine (separately and in fixed combinations)	3	1	4	Cardiology and CVD
Atazanavir (separately and in fixed combinations)	2	2	4	HIV
Dienogest (separately and in fixed combinations)	1	3	4	Gynecology
Dutasteride (separately and in fixed combinations)	4	–	4	Urology
Ibuprofen (separately and in fixed combinations)	3	1	4	Analgesic and NSAIDs
Rivaroxaban	2	2	4	Cardiology and CVD, Phlebology, Surgery
Tadalafil	1	3	4	Urology
Tolperisone (separately and in fixed combinations)	–	4	4	Neurology
Etoricoxib	–	4	4	Rheumatology
Acidum acetylsalicylicum (in fixed combinations)	3	–	3	Cardiology and CVD
Bosentan	–	3	3	Cardiology and CVD
Botulinum toxin type A (separately and in fixed combinations)	1	2	3	Neurology, Dermatology
Glucosamine	–	3	3	Rheumatology
Glucosaminylmuramyldipeptide	–	3	3	Immunology
Desogestrel (separately and in fixed combinations)	–	3	3	Gynecology
Levonorgestrel (separately and in fixed combinations)	–	3	3	Gynecology
Levofloxacin (separately and in fixed combinations)	1	2	3	Infectious Diseases
Montelukast	3	–	3	Allergology
Oseltamivir	1	2	3	Infectious Diseases
Pazopanib	–	3	3	Oncology
Paracetamol (in fixed combinations)	2	1	3	Analgesic and NSAIDs
Ritonavir (separately and in fixed combinations)	2	1	3	HIV
Tilorone	–	3	3	Infectious Diseases
Febuxostat	–	3	3	Rheumatology
Cinacalcet	1	2	3	Endocrinology
Eculizumab	–	3	3	Haematology

Data from www.grls.rosminzdrav.ru

***

Tables 6 and 7 show the distribution of local trials of brand-named medicines (including biological products) by foreign and domestic sponsors respectively.

Over ACTO's entire monitoring period, which began in 2013, infectious diseases have attracted the highest level of interest among Russian manufacturers. The number of trials of brand-named medicines in this therapeutic area grew by seven compared with 2017, accounting for half of the growth in domestically sponsored local trials of such medicines as a whole.

Table 6

Distribution of Local CTs of Brand Name Drugs (including biological products) of Foreign Sponsors, 2018		
Therapeutic Area	**Number of CTs**	**Number of planned participants**
Endocrinology	2	470
Dermatology	1	65
Infectious Diseases (except HIV/HCV/tuberculosis)	1	50
TOTAL	4	585

Data from www.grls.rosminzdrav.ru

Table 7

Distribution of Local CTs of Brand Name Drugs (including biological products) of Local Sponsors, 2018		
Therapeutic Area	**Number of CTs**	**Number of planned participants**
Infectious Diseases (except HIV/HCV/tuberculosis)	17	1 968
Allergology	9	430
HIV/HCV/tuberculosis	7	922
Oncology	5	683
Urology	3	987
Psychiatry	2	290
Surgery	2	275
Rheumatology	2	247
Cardiology and CVD	2	236
Neurology	2	160
Phlebology	1	450
Dermatology	1	150
Detoxification agent	1	112
Gynecology	1	76
Gastroenterology	1	30
TOTAL	56	7016

Data from www.grls.rosminzdrav.ru

DISTRIBUTION OF IMCT APPROVALS ACROSS RUSSIA

Detailed information about the distribution of IMCT approvals in 2018 by subjects of the Russian Federation is given in table 8 (*for information about the criteria used and calculation method, see ACTO Newsletter № 12*).

The four federal districts with the highest indicator «Number of IMCTs per region» in 2018 have remained unchanged since at least 2015, the year ACTO began collecting data. The Central Federal District takes first place (272 IMCTs in 2018), the Northwestern Federal District second (250), the Volga Federal District third (181), and the Siberian Federal District fourth (166). The Ural Federal District was placed fifth from 2015–2017, but in 2018 the Southern Federal District broke the 100 IMCT milestone, pushing the Ural Federal District into sixth place. The distribution for the three leaders by IMCTs count is as follows.

The number of new IMCTs in the Central Federal District decreased by 12 since 2017, from 284 to 272. The losses were mainly felt in Yaroslavl Region, where just 51 new IMCTs were announced in 2018 compared with 75 in 2017, and Ryazan Region, where the number of new IMCTs fell from 39 to 30. Even such a marked drop did not affect Yaroslavl Region's ranking within the district – the region held onto second place, while Ryazan Region slipped from third place to fifth. These losses were compensated by an increase in IMCTs in Moscow (from 231 in 2017 to 249 in 2018) and Kaluga Region (from 33 to 39). The top five federal subjects within the Central Federal District were Moscow, Yaroslavl Region, Kaluga Region, and Smolensk Region, with Moscow Region and Ryazan Region tied in fifth place. It is also worth noting the significant growth of participation in IMCTs observed in Ivanovo Region, where the number of international projects grew by more than 50% since 2017.

The number of new international trials planned in 2018 in the Northwestern Federal District was eight higher than in 2017, rising from 242 to 250. The most noticeable changes in the ranking of five leading regions in the district affected Kaliningrad, Murmansk and Leningrad regions. Kaliningrad Region unexpectedly took fifth place with 12 IMCTs, even though in 2016 and 2017 there wasn't a single new international project in the region, and there was just one in 2015. Murmansk Region saw its activity level almost triple compared to 2017, increasing from five to 14 IMCTs. Eight new projects were scheduled to launch in Leningrad Region (compared with 10 in 2017), meaning that the region slipped from fourth place to sixth on account of the activity in Kaliningrad and Murmansk regions. St. Petersburg placed first traditionally with 246 IMCTs in 2018, Arkhangelsk Region was second with 36 and the Republic of Karelia was ranked third with 23, followed by Murmansk and Kaliningrad regions.

Volga Federal District saw a drop in activity from 193 to 181 new IMCTs, a fall of 12 compared with 2017. Notable changes within the district included growing participation in international trials in the Republic of Tatarstan (88 IMCTs in 2018 compared with 69 in 2017), with the reverse happening in Nizhny Novgorod Region (73 IMCTs in 2017 but just 47 in 2018). The five regional leaders in the Volga Federal District are as follows: the Republic of Tatarstan, Samara Region (64 IMCTs in 2018), Nizhny Novgorod Region (47), Saratov Region (46) and the Republic of Bashkortostan (36). Both Ulyanovsk Region and the Republic of Mordovia saw a growth in the number of IMCTs of more than 50%.

In addition to the absolute figures, the number of IMCTs per million population are shown in table 8. The Northwestern, Siberian and Ural federal districts lead by this measure, with 17.9, 8.6 and 7.2 IMCTs per million population respectively. These three districts have occupied the top three positions each year and in the same order, with the exception of 2017 when the Ural and Siberian federal districts switched places. The two leading regions saw marginal increases in their numbers compared with the previous year, with only the Ural Federal District experiencing a drop: the figure for the Northwestern Federal District was 17.4 per million population in 2017, with 8.5 and 8.7 for the Siberian and Ural federal districts respectively.

Table 8

Distribution of IMCTs approved in 2018 by regions of the RF									
Region	**Number of IMCTs, per region**	**Number of IMCTs, per million population***	**Number of health care organizations, which approved centers for IMCTs, per region**	**How many times medical organizations of the region were involved in IMCTs (number of open centers)**	**Region**	**Number of IMCTs, per region**	**Number of IMCTs, per million population***	**Number of health care organizations, which approved centers for IMCTs, per region**	**How many times medical organizations of the region were involved in IMCTs (number of open centers)**
Central Federal District	**272**	**6.9**	**155**	**816 (847)**	**North Caucasian Federal District**	**62**	**6.3**	**14**	**75**
Moscow	249	19.9	90	522 (546)	Stavropol Territory	59	21.1	12	70
Yaroslavl Region	51	39.2	14	61	Kabardino-Balkarian Republic	5	5.6	2	5
Kaluga Region	39	39.0	4	41 (46)					
Smolensk Region	34	34.0	6	34 (36)	**Siberian Federal District**	**166**	**8.6**	**60**	**372 (383)**
Ryazan Region	30	27.3	4	31	Novosibirsk Region	90	32.1	20	117
Moscow Region	30	4.0	13	33	Omsk Region	61	30.5	9	63 (70)
Kursk Region	25	22.7	3	25	Kemerovo Region	44	16.3	7	47 (48)
Ivanovo Region	24	24.0	5	24	Krasnoyarsk Territory	44	15.2	6	48 (49)
Tver Region	14	10.8	3	14	Tomsk Region	42	38.2	7	47 (49)
Voronezh Region	10	4.2	4	10	Altai Territory	30	12.5	6	37
Belgorod Region	7	4.4	2	7	Irkutsk Region	12	5.0	4	12
Vladimir Region	5	3.6	2	5	Trans-Baikal Territory	1	0.9	1	1
Tula Region	4	2.7	1	4					
Lipetsk Region	2	1.7	2	2	**Ural Federal District**	**89**	**7.2**	**28**	**118**
Bryansk Region	2	1.7	1	2	Chelyabinsk Region	46	13.1	9	53
Tambov Region	1	1.0	1	1	Sverdlovsk Region	45	10.5	14	48
					Tyumen Region	16	10.7	5	17
Southern Federal District	**105**	**6.4**	**25**	**144 (155)**					
Rostov Region	58	13.8	9	59 (69)	**Volga Federal District**	**181**	**6.1**	**83**	**432 (438)**
Krasnodar Territory	57	10.2	12	63 (64)	Republic of Tatarstan	88	22.6	12	94
Volgograd Region	22	8.8	4	22	Samara Region	64	20.0	14	78
					Nizhny Novgorod Region	47	14.7	13	53
Northwestern Federal District	**250**	**17.9**	**136**	**820 (834)**	Saratov Region	46	18.4	9	53 (56)
Saint-Petersburg	246	45.6	111	706 (720)	Republic of Bashkortostan	36	8.8	7	42
Arkhangelsk Region	36	32.7	5	37	Orenburg Region	19	9.5	6	19
Republic of Karelia	23	38.3	3	23	Perm Territory	18	6.9	7	22 (25)
Murmansk Region	14	17.5	4	15	Ulyanovsk Region	17	13.1	1	17
Kaliningrad Region	12	12.0	1	12	Republic of Mordovia	16	20.0	3	16
Leningrad Region	8	4.4	6	8	Udmurtian Republic	15	10.0	5	15
Vologda Region	7	5.8	3	7	Penza Region	13	10.0	3	13
Novgorod Region	6	10.0	2	6	Kirov Region	10	7.7	3	10
Republic of Komi	4	4.4	1	4					
Far Eastern Federal District	**4**	**0.6**	**2**	**4**					
Primorye Territory	3	1.6	1	3					
Amur Region	1	1.3	1	1					

*We used data of Rosstat on the resident population of the region as of January 1, 2018

Evaluating the subjects of the Russian Federation by absolute growth in the number of IMCTs per region compared with 2017, the top performers are Rostov Region (58 new IMCTs compared with 32 in 2017, growth of 26 IMCTs or 81%), Stavropol Territory (59 IMCTs compared with 34, growth of 74%), Krasnodar Territory (57 IMCTs compared with 33 in 2017, growth of 73%), the Republic of Tatarstan and Novosibirsk Region (both with 19 more IMCTs, representing respective growth rates of 28% and 27%). By this measure the best performing district was the Southern Federal District (an increase of 50%, with 105 IMCTs compared with 70 in 2017).

The highest growth by number of IMCTs per million population in 2018 was observed in the Republic of Karelia (38.3 compared with 17.5, a 119% increase), Kaliningrad Region (12, compared with 0 the previous year), Murmansk Region (17.5 compared with 6.6, a 165% increase), Ivanovo Region (24 compared with 14.7, a 63% increase) and Stavropol Territory (21.1 compared with 12.1, a 74% increase). Out of all the districts, the highest growth was seen in the North Caucasian Federal District (6.3 compared with 3.8, a 66% increase), the result of increased activity in Stavropol Territory.

The biggest losses for the year in absolute terms were seen in Nizhny Novgorod Region (a drop of 26 IMCTs, or 36%), Yaroslavl Region (24 fewer IMCTs, representing a 32% fall), Kemerovo Region (a fall of 21 IMCTs, or 32%), Sverdlovsk Region (17 IMCTs, or 27%) and Altai Territory (14 IMCTs, 32%). The fall in the number of IMCTs in the administrative divisions of the Siberian Federal District (Kemerovo Region and Altai Territory) merely indicates that there has been redistribution within the district, given that the overall number of IMCTs in the Siberian Federal District remained at its 2017 level of 166. Among the districts, the largest reduction in the number of IMCTs over the year was in the Ural Federal District (18 new IMCTs fewer, 17% lower than the previous year).

In terms of the per million population indicator, there was a significant drop in activity in Yaroslavl Region (39.2 new IMCTs per million population compared with 59 in 2017, a 34% drop), Tomsk Region (38.2 compared with 47.3, 19% lower), Nizhny Novgorod region (14.7 compared with 22.5, 35% lower), Kemerovo Region (16.3 compared with 24, 32% lower) and Ryazan Region (27.2 compared with 34.6, 21% lower). Among the districts the maximum fall of this indicator is in the same Ural Federal District (7.2 compared with 8.7, 17% lower).

***

A distribution of Russia's federal subjects by number of new IMCTs announced for the year can be seen in diagram 7.

The "over 200 new IMCTs" category is traditionally represented by Moscow and St. Petersburg. No federal subjects other than the two capitals have appeared in the "over 200 IMCTs" category during ACTO's monitoring period.

The "51–100 IMCTs" category lost two federal subjects after all the changes since 2017, dropping from ten to eight federal subjects. The loss of Nizhny Novgorod, Kemerovo, Sverdlovsk, Saratov, Chelyabinsk and Tomsk regions in this category was partially offset by an increase in the number of IMCTs planned for launch in Omsk Region, Stavropol Territory, Rostov Region and Krasnodar Territory. Yaroslavl, Novosibirsk and Samara regions and the Republic of Tatarstan retained their positions in this category.

The "31–50 IMCTs" maintained its 2017 size of 11 federal subjects, though half of its composition changed. It lost Omsk and Rostov regions as well as Stavropol and Krasnodar territories, which all climbed into the "51–100" category. Two subjects fell into the "21–30" category – Altai Territory and Ryazan Region. They were replaced by the federal subjects which lost their position in the "51–100" category: Nizhny Novgorod, Kemerovo, Sverdlovsk, Saratov, Chelyabinsk and Tomsk regions. Krasnoyarsk Territory, the Republic of Bashkortostan and Kaluga, Arkhangelsk and Smolensk regions remained in the category as before.

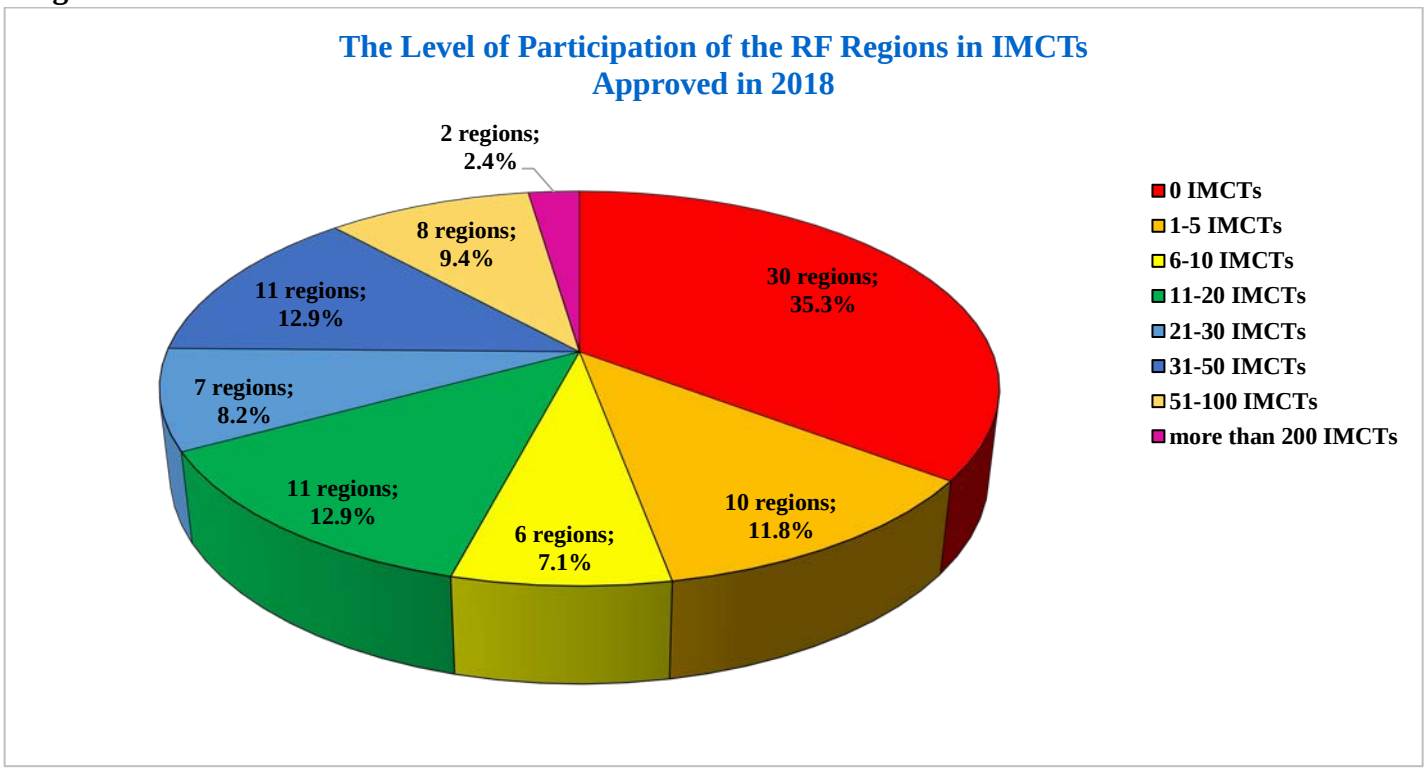
The “21–30” category grew, with a complete changeover of federal subjects. In 2017 the category included just Voronezh Region, which in 2018 dropped into the “6–10” category. In its place, the “21–30” category was filled out by Altai Territory and Ryazan Region, both of which experienced a drop in activity, as well as Moscow, Kursk, Ivanovo and Volgograd regions and the Republic of Karelia, all of which belonged to the “11–20” category the previous year.

The “11–20” category also saw considerable changes, though it remained the same size as in 2017 with 11 federal subjects. The abovementioned Moscow, Kursk, Ivanovo and Volgograd regions and the Republic of Karelia moved out of the category with an increased number of applications for IMCTs. Kirov Region experienced reduced activity and dropped out of the category. At the same time, Ulyanovsk, Tyumen and Murmansk regions and the Republic of Mordovia were added to the category along with Kaliningrad Region, which belonged to the category of federal subjects with no new IMCT launches planned in 2017. Orenburg, Penza and Irkutsk regions, Perm Territory and the Udmurtian Republic retained their positions in the “11–20” category.

The “6–10” category shrunk by three federal subjects, from nine to six. As well as Tver, Tyumen and Ulyanovsk regions and the Republic of Mordovia, which moved out of the category with an increased number of trials, the category also lost Vladimir, Lipetsk and Tula regions to reduced activity in international projects. Voronezh and Kirov regions joined the category after a fall in the number of planned IMCTs, while Vologda and Novgorod regions moved into the category following an increase. Only two federal subjects remain in the category from 2017, Belgorod and Leningrad regions.

The “1–5” category also shrunk, losing Murmansk, Novgorod and Vologda regions, Khabarovsk Territory, the Republic of Crimea, the Chuvash Republic, the Republic of North Ossetia–Alania, and Orel and Kurgan regions to inactivity, with no new IMCTs planned in these federal subjects in 2018. New additions to the category included Vladimir, Tula and Lipetsk regions, which were in the “6–10” category a year earlier, and Tambov Region, where no new IMCTs were recorded in 2017.

Diagram 7



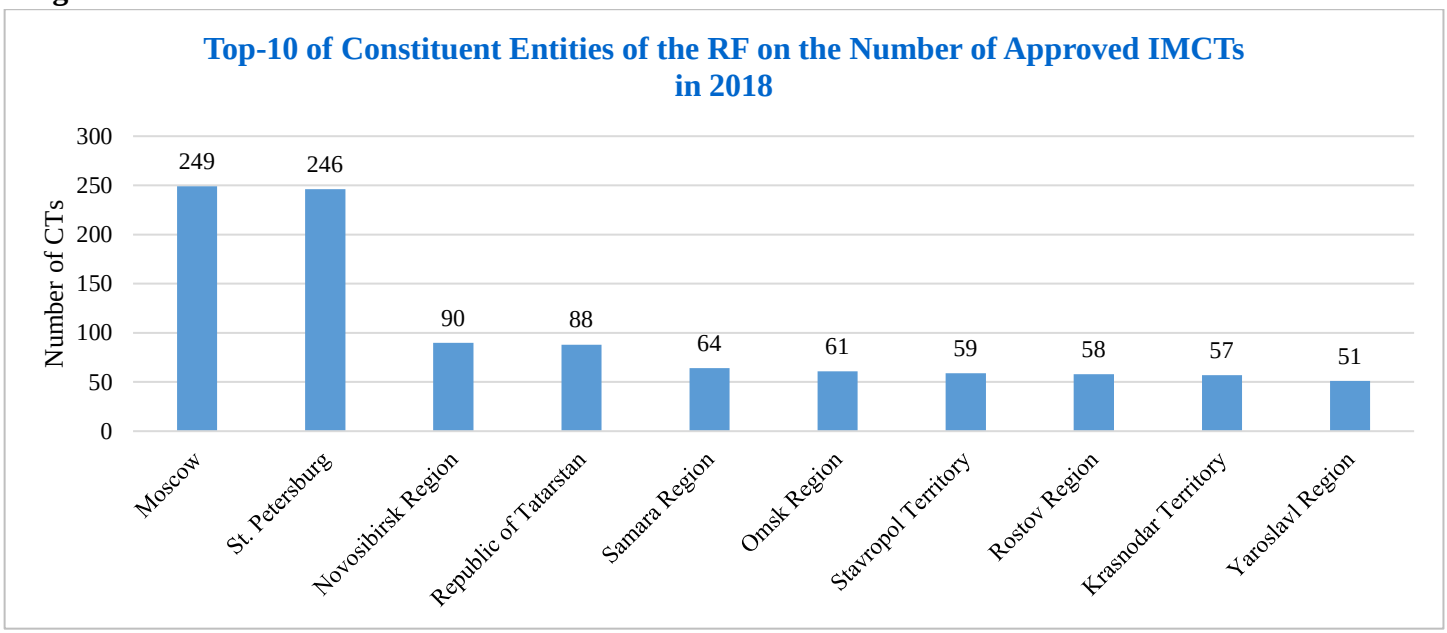
Data from www.grls.rosminzdrav.ru

The group of federal subjects in which no new international project launches were planned in 2018, being the largest, increased in size by four regions compared with 2017. The category lost Kaliningrad and Tambov regions, but gained Orel and Kurgan regions, Khabarovsk Territory, the Republic of Crimea, the Chuvash Republic, and the Republic of North Ossetia–Alania.

***

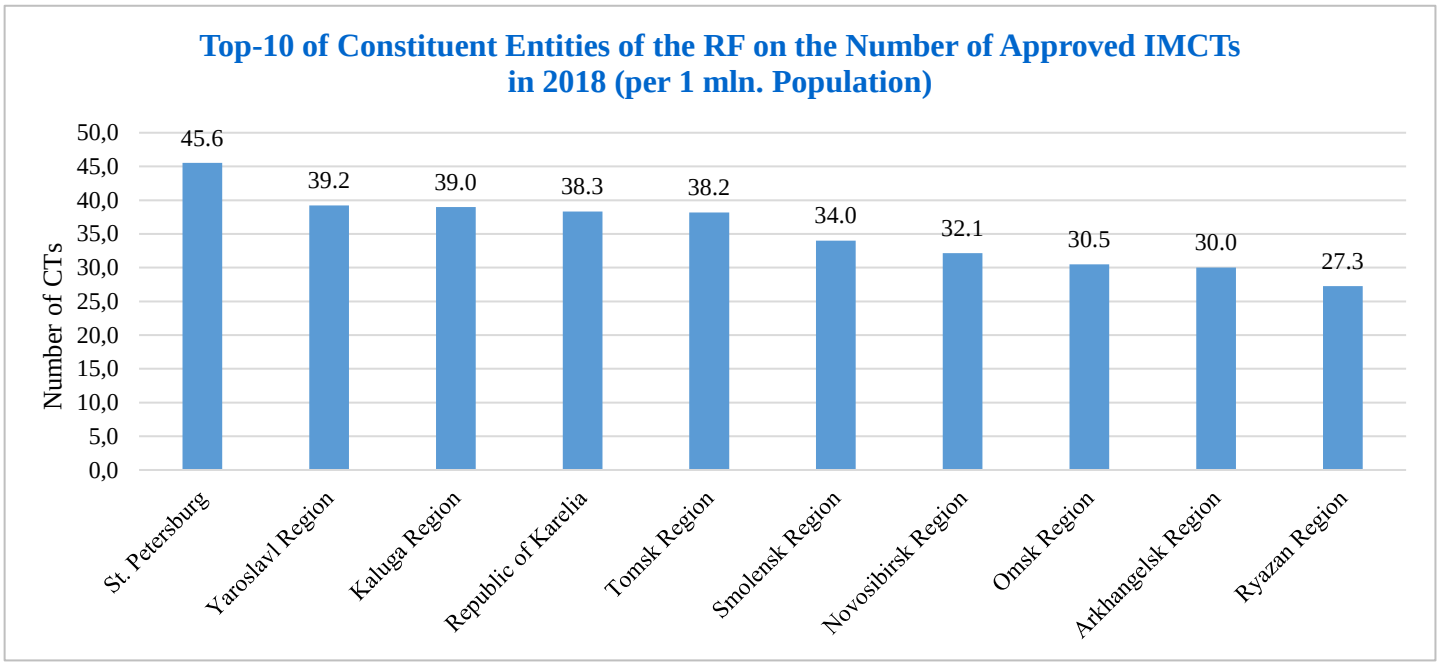
The top 10 subjects of the Russian Federation by number of IMCTs approved in 2018, in absolute and relative terms, are shown in diagrams 8 and 9.

Diagram 8



Data from www.grls.rosminzdrav.ru

Diagram 9



Data from www.grls.rosminzdrav.ru

The following changes in absolute terms (diagram 8) were observed compared with the results for 2017. Moscow and St. Petersburg changed places, the first went around the second one by three trials. Novosibirsk Region, the Republic of Tatarstan, and Samara and Yaroslavl regions have held onto their top 10 positions since 2015. The first three of these federal subjects rose in the rankings, gaining three, two and four IMCTs respectively, while on the other hand Yaroslavl Region saw 24 fewer projects announced, falling from second to tenth place. Something worth noting in the 2018 results is the significant overhaul of the top 10, which this year features four new federal subjects. These are Rostov Region, which appeared in the top 10 in 2016, as well as Stavropol Territory, Omsk Region and Krasnodar Territory, which have not featured in the top 10 since 2015 when ACTO began collecting data.

The ranking based on relative indicators (diagram 9) is more stable. The only federal subject which did not appear on the same diagram in 2017 is the Republic of Karelia, which featured in the ranking in 2015 and 2016, placing sixth and fifth respectively, then fell out of the top 10 in 2017, but jumped straight up to fourth place in 2018. The rest of the changes to the top 10 federal subjects by number of IMCTs per million population concern only the positions within the leaderboard: St. Petersburg moved from third place to first, increasing its figure from 44.7 to 45.6, Yaroslavl Region moved from first to second (the number of trials in the region falling from 59 to 39 IMCTs per million population), Kaluga Region rose from seventh to third place (with respective figures of 32.5 and 39), Tomsk Region fell from second place to fifth (43.7 and 38.2), Smolensk Region fell from fourth to sixth (36.7 in 2017 and 34 in 2018), Novosibirsk Region climbed from eighth to seventh (25.5 and 32.1), Omsk Region rose from ninth to eighth (25.3 and 30.5), Arkhangelsk Region fell from fifth to ninth (34.8 and 30.0) and Ryazan Region, which took sixth place in 2017, now rounds off the top ten (with 34.6 in 2017 and 27.3 in 2018).

***

Table 9 provides an indication of the 20 most active clinics by participation in IMCTs. Since 2015, eight medical institutions have consistently featured in the top 20:

- N. N. Blokhin National Medical Research Centre of oncology in Moscow (has held first place since 2016);
- Pavlov First Saint Petersburg State Medical University (first in 2015 and second in subsequent years);
- Omsk Region Clinical Oncological Dispensary (successively ranked 18th, 16th, sixth and then fourth in 2018);
- Kazan State Medical University (fourth in 2015, third in 2016 and 2017, fifth in 2018);
- N. N. Petrov Research Institute of Oncology (sixth in 2015 and 2016, joint 14th–15th in 2017 and seventh in 2018);
- City Clinical Oncology Center in St. Petersburg (seventh in 2015, 11th in 2016 and 2017, and eighth in 2018);
- I. M. Sechenov First Moscow State Medical University (successively third, fourth, fifth, and joint 11th–13th in 2018);
- National Medical Research Radiological Center in Obninsk (successively 19th, 17th, ninth and once again 17th in 2018).

The Mechnikov North-Western State Medical University has almost constantly featured in the rankings. It placed 17th in 2015, fell out of the top 20 in 2016, returned in 2017, ranking 13th, and placed third in 2018.

Eight more institutions fell out of the rankings in 2018 after featuring in 2017. These are Kemerovo Regional Clinical Hospital (fell from fourth to joint 29th–30th), Nizhny Novgorod Regional Clinical Hospital (from eighth to joint 32nd–35th), Kuzbass Cardiology center (from 12th to 25th), N. V. Solovyov Clinical Emergency Hospital in Yaroslavl (from joint 14th–15th to joint 61st–67th), Tomsk National Research Medical Center of the Russian Academy of Sciences (from 17th to 31st), Regional Clinical Hospital in Barnaul (from 18th

to joint 101st–116th), Ryazan State Medical University (from joint 19th–21st to joint 83rd–97th), and City Multiprofile Hospital No. 2 in St. Petersburg (from joint 19th–21st to joint 83rd–97th).

Table 9

Top-20 Medical Organizations on the Activity of Participation in IMCTs Approved in 2018				
Place in ranking	**Name of medical organization**	**Number of IMCTs approved in 2018 with participation of this medical organization**	**Number of centers approved in 2018 for conducting IMCTs**	**Number of IMCTs and ranking of the centers (on approvals issued in 2017)**
1	N. N. Blokhin Russian Cancer Research Centre, Russian Ministry of Health, Moscow	56	59	52 (1)
2	I. P. Pavlov First St. Petersburg State medical University, Russian Ministry of Health, St. Petersburg	49	50	47 (2)
3	I. I. Mechnikov North-West State Medical University, Russian Ministry of Health, St. Petersburg	42	43	24 (13)
4	Clinical Oncological Dispensary, Omsk	41	48	28 (6)
5	Kazan State Medical University, Russian Ministry of Health, Kazan	39	39	37 (3)
6	Rostov State Medical University, Rostov-on-Don	37	47	18 (22–25)
7	N. N. Petrov Research Institute of Oncology, Russian Ministry of Health, St. Petersburg	36	36	24 (14–15)
8	St. Petersburg City Clinical Oncological Dispensary, St. Petersburg	31	31	26 (11)
9	Federal Almazov North-west Medical Research Centre, Russian Ministry of Health, St. Petersburg	29	30	28 (7)
10	S. M. Kirov Military-Medical Academy, Russian Ministry of Defense, St. Petersburg	29	29	16 (29–30)
11–13	Arkhangelsk Clinical Oncological Dispensary, Arkhangelsk	28	28	16 (31–34)
11–13	I. M. Sechenov First Moscow State Medical University, Russian Ministry of Health, Moscow	28	28	32 (5)
11–13	Moscow Regional Research and Clinical Institute (MONIKI) named after M. F. Vladimirskiy, Moscow	28	28	10 (66–74)
14	State Scientific-Research Institute of Physiology and Basic Medicine, Novosibirsk	27	27	12 (53–55)
15	St. Petersburg Clinical Practical Research Centre for Specialised Types of Medical Aid (Oncological), St. Petersburg	26	27	19 (19–21)
16	Republican Clinical Oncological Dispensary, Kazan	26	26	13 (44–50)
17	National Medical Research Radiological Center, Obninsk	25	30	26 (9)
18	Saratov State Medical University named after V. I. Razumovsky, Russian Ministry of Health, Saratov	24	25	26 (10)
19	Medical University "Reaviz", Samara	24	24	8 (95–106)
20	City Hospital of the Holy Martyr Elizabeth, St. Petersburg	23	24	11 (56–64)

Source: www.grls.rosminzdrav.ru

Seven clinics which featured in 2015 and/or 2016 but fell out of the ranking in 2017 returned to the top 20 ranking in 2018: they are Rostov State Medical University (sixth place), Almazov National Medical Research Centre in St. Petersburg (ninth place), S. M. Kirov Military Medical Academy in St. Petersburg (tenth), Arkhangelsk Regional Clinical Oncological Dispensary (joint 11th–13th), St. Petersburg Clinical Research and Practical Center of Specialized Types of Medical Care (15th), Republican Clinical Oncology Dispensary of the Ministry of Health of the Republic of Tatarstan in Kazan (16th), and Razumovsky Saratov State Medical University (18th place).

Four medical organizations appeared in the top 20 for the first time since ACTO began collecting results. These are M. F. Vladimirsky MONIKI (joint 11th–13th), State Scientific-Research Institute of Physiology and

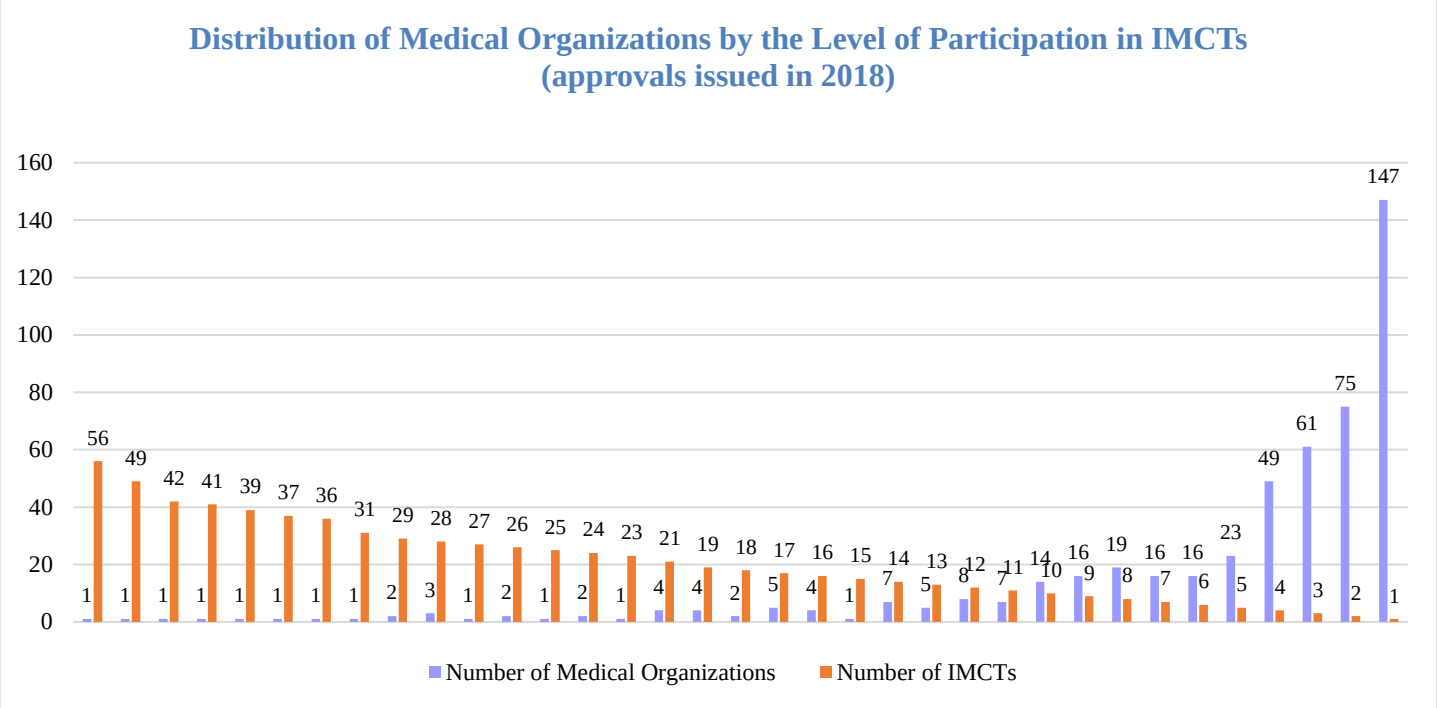
Basic Medicine in Novosibirsk (14th place), Reaviz Medical University in Samara (19th) and City Hospital of the Holy Martyr Elizabeth in St. Petersburg (20th).

The highest jumps in the rankings in 2018 were made by Reaviz Medical University (rising 76 places, with 16 more IMCTs), M. F. Vladimirsky MONIKI (rising 55 places with 18 more IMCTs), Research Institute of Physiology and Basic Medicine (39 places higher with 15 more new projects), City Hospital of the Holy Martyr Elizabeth (36 places higher with 12 extra projects) and the oncology dispensary in the Republic of Tatarstan (28 places higher, a rise of 13 IMCTs).

***

The distribution of IMCT approvals issued in 2018 by medical organizations is shown in diagram 10. Eight clinics received approvals to carry out over 30 new trials, while 147 organizations were given the go ahead to participate in just one international project, 75 in two, and 61 in three. In total, 503 organizations were enlisted to carry out new IMCTs in 2018, which is 17 fewer than in 2017.

Diagram 10



Data from www.grls.rosminzdrav.ru

***

Tables 10 and 11 show the distribution of IMCTs by the various subordinations of the medical organizations in the two most active federal subjects, Moscow and St. Petersburg. Both regions increased their IMCT activity compared to 2017, with Moscow rising from 231 IMCTs to 249 and St. Petersburg from 236 to 246. Let us consider in more detail the categories of clinic that led to this rise, looking at how the activity of medical organizations of various subordinations has changed over the last year.

In Moscow (table 10) the largest number of centres claimed to participatein IMCTs is accounted for by medical organizations belonging to the Ministry of Health of the Russian Federation, accounting for 248 new centres in 2018, 21 more than in the previous year. They are followed by the Moscow Healthcare Department, which had 120 participating centres (three more than in 2017) and federal state bodies (excluding those belonging

to the Ministry of Health) with 76 centres (110 in 2017). Next are non-governmental clinics, which have significantly increased their number of centers of IMCTs, from 26 in 2017 to 66 in 2018. In addition to non-governmental clinics, a noticeable increase in centres was shown by a category of institutions subordinate to the Ministry of Health of Moscow Region, from 13 to 29 (accounted for by M. F. Vladimirsky MONIKI, which jumped from 10 to 28). Only two categories of institutions have bucked the trend of growth in the number of sites: the abovementioned federal state bodies (excluding those belonging to the Ministry of Health of the Russian Federation), and institutions belonging to Russian Railways. The latter saw the number of sites under its subordination fall from 20 to seven. The growth in activity in Moscow in 2018 was chiefly down to the non-governmental healthcare system and organizations belonging to the Ministry of Health of the Russian Federation and the Ministry of Health of Moscow Region.

The non-governmental healthcare system has shown exceptional growth in the number of its organizations involved in conducting IMCTs, rising from 12 in 2017 to 20 in 2018. The number of clinics belonging to the Ministry of Health of Moscow Region remained constant. There have been no significant fluctuations in the number of clinics involved in new international projects in any other categories of medical organization, though in all cases a drop of between one and three institutions was observed.

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 centres approved for IMCTs**		**Activity Coefficient**	
	2018	**2017**	**2018**	**2017**	**2018**	**2017**
Ministry of Healthcare of the Moscow region	2	2	29	13	**14.5**	6.5
Ministry of Healthcare of the Russian Federation	21	23	248	227	**11.8**	9.9
JSC "Russian Railways"	1	2	7	20	**7.0**	10.0
Moscow Department of Healthcare	25	28	120	117	**4.8**	4.2
Federal bodies (except Ministry of Healthcare of the RF)	21	24	76	110	**3.6**	4.6
Non-governmental health system	20	12	66	26	**3.3**	2.2
TOTAL	90	91	546	513	**6.1**	5.6

Data from www.grls.rosminzdrav.ru

In the Newsletter announcing the results for the end of 2017 we noted that the number of IMCT sites in Moscow Heathcare Department clinics fell by a quarter compared with 2016, at the time attributing this to the fact that the Moscow Heathcare Department created additional administrative barriers for its subordinate institutions[2]. The department's policy was less demanding in 2018, though conditions for conducting trials in Moscow Healthcare Department clinics remained more difficult than in organizations with different departmental affiliations. At first glance it would appear that the number of IMCTs stopped falling in 2018: the number of participating sites increased by three compared with 2017. Nevertheless, the number of Moscow Healthcare Department clinics involved in conducting IMCTs continues to fall: in 2017 the figure fell by six, and in 2018 by three more.

The main trend in St. Petersburg (table 11) in 2018 was the increase in the number of new IMCT centres (by 8.4%, from 664 to 720) alongside a small contraction in the number of organizations involved in international projects (a fall of 3.6%, from 115 to 111). That is to say, to use the terminology of our newsletter, the activity coefficient for medical centres increased. The only category to buck this trend was the largest one: medical organizations belonging to the Health Committee of St. Petersburg saw the number of clinics participating in new

2. See ACTO Newsletter № 16, "ACTO counteracting superfluous administration of clinical trials by Moscow Healthcare Department". http://acto-russia.org/files/bulletin_16.pdf#page=48&zoom=100,0,66.

IMCTs remain unchanged at 51, while the number of sites planned fell by 5%, from 277 to 264. Nonetheless, the margin of increase for the remaining types of medical organization compensated for the reduced activity coefficient in this category. The number of clinics involved in IMCTs at institutions belonging to federal bodies (excluding the Ministry of Health of the Russian Federation), the Healthcare Committee of the Leningrad Region, and Russian Railways remained the same (nine, three and one respectively), while the number of approved sites grew from 61 to 69, 32 to 44 and from nine to 13 respectively. There was a reduction in the number of clinics participating in IMCTs among institutions belonging to the Ministry of Health of the Russian Federation, from 13 to 10, while at the same time the number of approvals for sites grew from 169 to 187. An even greater increase in the number of centres was observed among medical organizations representing the non-governmental healthcare system: the number of clinics involved in IMCTs in this category decreased by one, but 27 more centres were approved than in 2017. Overall, St. Petersburg's medical institutions showed increased activity indicators, facilitated mostly in absolute terms by the non-governmental healthcare system and clinics falling under the remit of the Russian Ministry of Health of the Russian Federation and the Healthcare Committee of the Leningrad Region.

Table 11

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 centres approved for IMCTs**		**Activity Coefficient**	
	2018	**2017**	**2018**	**2017**	**2018**	**2017**
Ministry of Healthcare of the Russian Federation	10	13	187	169	**18.7**	13.0
Committee of Health of the Leningrad Region	3	3	44	32	**14.7**	10.7
JSC "Russian Railways"	1	1	13	9	**13.0**	9.0
Federal bodies (except Ministry of Healthcare of the RF)	9	9	69	61	**7.7**	6.8
Health Committee of Saint-Petersburg	51	51	264	277	**5.2**	5.4
Non-governmental health system	37	38	143	116	**3.9**	3.1
TOTAL	111	115	720	664	**6.5**	5.8

Data from www.grls.rosminzdrav.ru

PARTICIPATION OF MEDICAL INSTITUTIONS IN BIOEQUIVALENCE STUDIES

Table 12 provides a ranking of medical organizations by their level of participation in bioequivalence studies. Ten organizations remain in the top 15 from 2017, while six are new entries for 2018: Tomsk National Research Medical Center of the Russian Academy of Sciences, Demikhov City Clinical Hospital of the Moscow Healthcare Department, North-West Public Health Research Center, Institute of the Human Brain of the Russian Academy of Sciences, Clinical Hospital No. 3 in Yaroslavl and Belgorod State National Research University.

Table 12

Top-15 medical organizations on the activity of participation in Bioequivalence Studies (approvals issued in 2018)					
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 center ranking on approvals issued in 2017**
1	Clinical Hospital № 2, Yaroslavl	31	20	11	26 (2)
2	Medical Center Probiotech, Serpukhov	17	16	1	29 (1)
3	Road clinical Hospital at the station Yaroslavl, JSC Russian Railways, Yaroslavl	16	11	5	17 (3–4)
4	Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk	15	12	3	4 (17–19)
5	City Clinical Hospital named after V. P. Demihov, Moscow	14	4	10	n/a
6	Research Center Eco-bezopasnost, St. Petersburg	13	11	2	17 (3–4)
7	North-West Public Health Research Center, St. Petersburg	9	2	7	4 (17–19)
8–11	Family Doctor+ Clinic, Nizhny Novgorod	7	6	1	7 (11–12)
8–11	BioEq, St. Petersburg	7	3	4	12 (7)
8–11	N. P. Bekhtereva Institute of Human Brain of the Russian Academy of Sciences, Saint Petersburg	7	7		n/a
8–11	Clinical Hospital № 3, Yaroslavl	7	5	2	3 (20–22)
12–14	Federal Research and Clinical Centre of Physical-Chemical Medicine, Federal Medical-Biologicall Agency, Moscow	6	1	5	13 (5–6)
12–14	Kazan (Privolzhsky) Federal University, Kazan	6	5	1	8 (8–10)
12–14	Yaroslavl Region Clinical Hospital № 8, Yaroslavl	6	5	1	5 (15–16)
15–16	Belgorod National Research University, Belgorod	5	5		1 (26–52)
15–16	MedFort, St. Petersburg	5	5		8 (8–10)

Data from www.grls.rosminzdrav.ru

MAIN PLAYERS ON THE RUSSIAN CLINICAL TRIALS MARKET – 2018

This section covers the key players on the market and analyses their activity across various types of clinical trials in 2018.

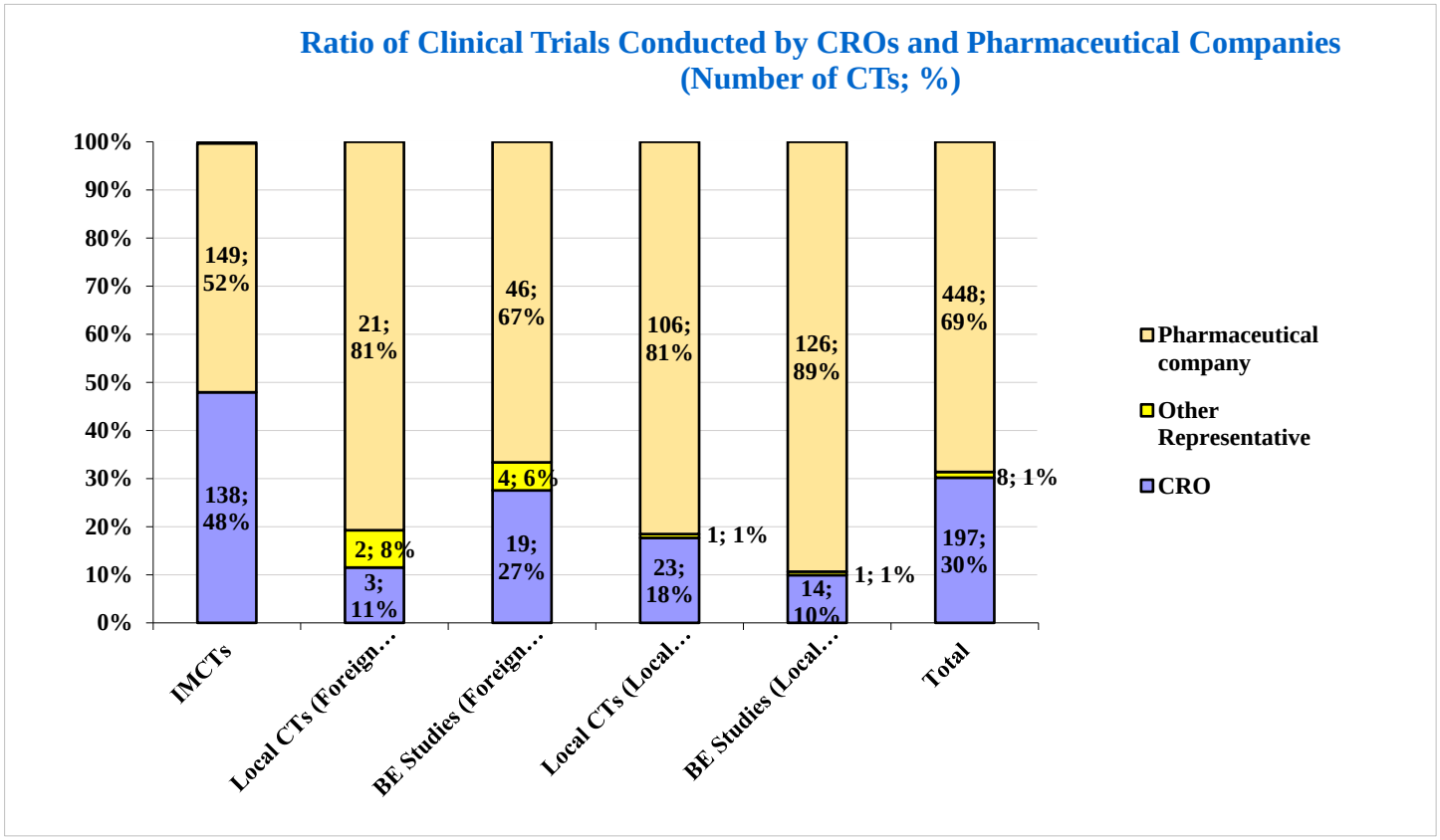
We customarily divide market players into three groups: sponsors, contract research organizations (CROs) and 'other representatives'. The latter are organizations for which conducting clinical trials is not a primary business activity, but which can undertake this task. For example, the most typical case is the launch of a medicinal product on the market, including registration, for which Russian legislation requires local trials to be conducted. (*For more information about criteria for the classification being used see Newsletters № 12 and 14*).

A further preliminary comment concerns CROs and how to account for their activity, which is likely to be higher than the data below suggests. The reason for this is that the Ministry of Health register of approved trials, which serves as the cornerstone of our analysis, does not always provide full information about CROs contracted by sponsors. As a consequence, CRO activity may be hidden from us, as they are not cited in the register in every case.

Sponsors and CROs, general structural distribution

Looking at the distribution of trials between the groups of subjects carrying them out, little has changed since 2017. Overall in 2018, 69% of approvals were issued for trials conducted by the sponsors themselves (67% in 2017), 30% for trials involving CROs (31% in 2017), and 1% for trials involving 'other representatives' (2% in 2017).

Diagram 11



Data from www.grls.rosminzdrav.ru

IMCT is a type of trials where practically no ‘other representatives’ are found. There is usually a 50/50 split between sponsors and CROs for this type of trial, with a small margin in favour of CROs. In 2018 it was 52% to 48%, and for the first time since 2013, with a margin of sponsors.

The share of local trials conducted by the foreign sponsors themselves rose significantly, from 61% in 2017 to 81%. This increase has come about at the expense of trials involving CROs, which saw their share fall from 29% to 11%. The share of approvals for trials with involvement of ‘other representatives’ also shrank, though only marginally, from 10% to 8%. Here it is also worth noting the overall decrease in the number of local trials by foreign sponsors for the year (from 48 to 26): the significantly smaller sample size may have been a factor in the marked changes to the ratio between sponsors and CROs.

An increase in the share of trials carried out by the sponsors themselves – from 73% to 81% – was also observed in the Russian-sponsored local trial sector, also on the back of a reduction in the CRO share, this time from 22% to 18%. The share of trials with ‘other representatives’ remained unchanged at 1%.

A reverse trend – a reduction in the share of trials conducted by the sponsors themselves thanks to an increase in the share of CROs, with the level of activity of ‘other representatives’ remaining the same – was observed in bioequivalence studies. Here, the share of foreign sponsors fell from 73% in 2017 to 67% in 2018, while the share of CROs contracted by foreign sponsors to conduct trials rose from 21% to 27% according to the Ministry of Health register of approved trials. The share of approvals issued for trials with participation from ‘other representatives’ remained unchanged at 6%. The share of Russian sponsors fell from 92% to 89%, while the share of CROs working with them increased from 7% to 10%.

As is clear from a comparison with the 2017 results, compensatory shifts in the distributions between the separate trial types are offsetting minor changes in the overall distribution.

International multicentre clinical trials, sponsors

Table 13 shows a list of the leading sponsors of IMCTs for 2018 (it was not possible to provide a full top 15 list this year, as there were five companies with four approvals, and so we decided not to include them). The final column shows the 2017 results for comparison.

Table 13

Ranking of Pharmaceutical Companies on Approvals for International Multicenter CTs, 2018					
Rating position in 2018	**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 2017**
1	Novartis	32	–	32	24 CTs; 1
2	F. Hoffmann-La Roche	23	–	23	15 CTs; 4
3–4	Pfizer	–	15	15	5 CTs; 13–15
3–4	Janssen Pharmaceutica	10	5	15	8 CTs; 8–9
5–6	AstraZeneca	12	1	13	17 CTs; 2–3
5–6	Merck & Co.	13	–	13	17 CTs; 2–3
7–8	Bristol-Myers Squibb	9	3	12	8 CTs; 8–9
7–8	AbbVie	12	–	12	11 CTs; 7
9	Sanofi	9	–	9	14 CTs; 5
10–11	Allergan	–	8	8	1 CT; 39–98
10–11	Eli Lilly	5	3	8	7 CTs; 10
12–13	GlaxoSmithKline	5	1	6	12 CTs; 6
12–13	Celgene	–	6	6	5 CTs; 13–15
14	Shire	–	5	5	n/a

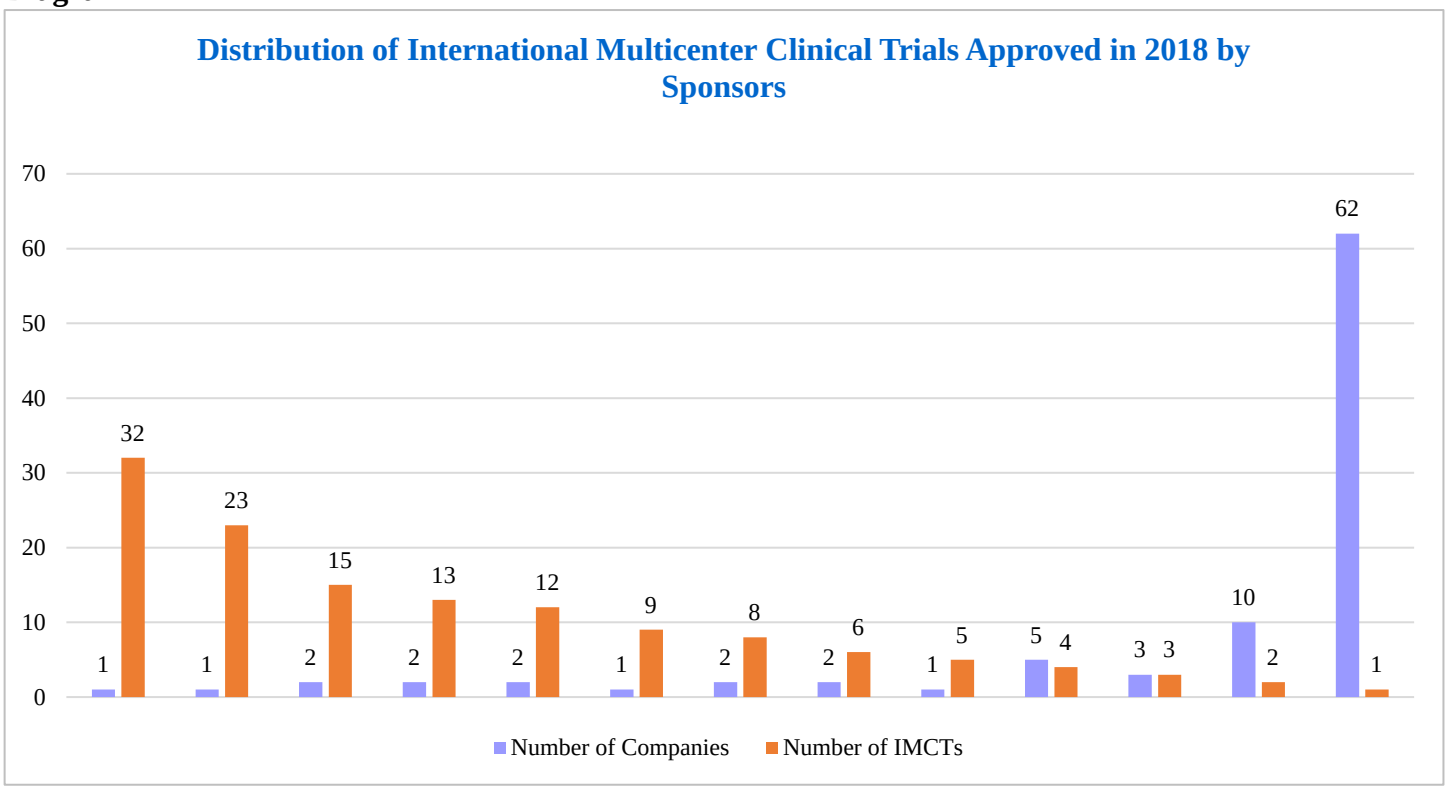
Data from www.grls.rosminzdrav.ru

Novartis has led the ranking for ACTO's entire monitoring period, i.e. since 2013. F. Hoffmann-La Roche placed second, climbing from fourth place the previous year. Pfizer saw an even more spectacular breakthrough in the ranking, from 13–15 place last year to 3–4 this year, a position it shared with Janssen Pharmaceutica, which rose from 8–9 place in 2017. AstraZeneca and Merck & Co. placed 5–6, both down from 2–3 place in the ranking.

Gilead Sciences, Bayer and Octapharma AG dropped out of the top ranking in 2018. They were replaced by Allergan and Shire, the former receiving seven approvals more than in 2017, allowing it to climb from 39–38 place to 10–11.

The distribution of all approvals received by sponsor companies in 2018 is shown in diagram 12. Eight companies received ten or more approvals, while 62 companies received just one approval and ten received two. In total 94 companies received approvals to conduct IMCTs in 2018, four fewer than the previous year.

Diagram 12



Data from www.grls.rosminzdrav.ru

International multicentre clinical trials, CROs

Table 14 shows the top ranking of CROs actively involved in conducting clinical trials in 2018.

For the first time in five years IQVIA vacated the top position, dropping to fifth place. Parexel, which placed first in 2013, returned to the top spot in 2018. PPD placed 2–3, as in 2017, this time sharing the spot with Syneos Health. PSI rose from 5–6 to fourth place.

The changes to the top ranking of CROs were largely down to company mergers. INC Research and inVentiv Health, which took fourth and eighth place respectively in 2017, were ranked 2–3 in 2018 as the newly formed Syneos Health. Covance, which now includes Chiltern, settled at 7–8 (Covance was ranked seventh a year ago, while Chiltern was only ranked 11th). As a result of the mergers, several positions in the top ranking have been freed up for new participants: Synergy Research Group was ranked joint 9th–11th, sharing the position with MB Quest which rose from joint 12th–15th.

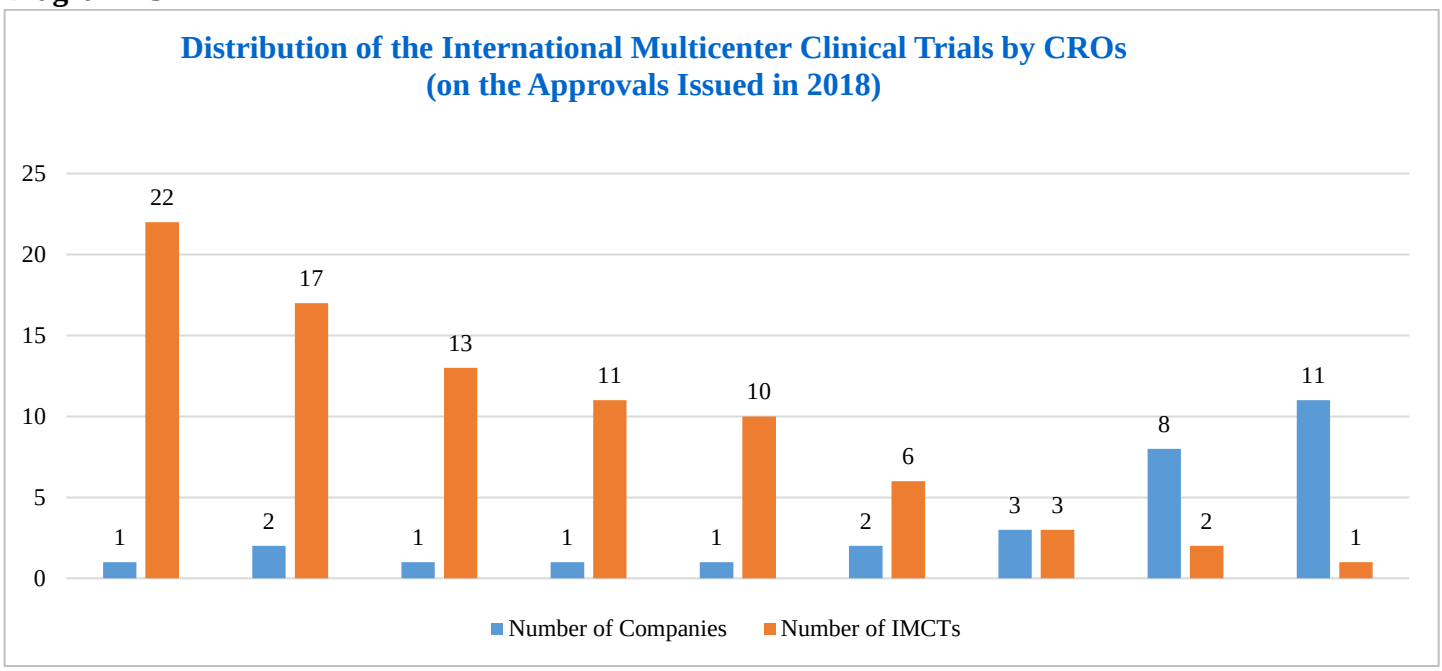
Table 14

Ranking of CROs on Approvals for International Multicenter CTs, 2018				
Ranking in 2018	**Company**	**Number of IMCTs**	**Number of Sponsors**	**Number of IMCTs; Ranking in 2017**
1	Parexel	22	10	9 CTs; 5–6
2–3	PPD	17	10	14 CTs; 2–3
2–3	Syneos Health (INC Research + inVentiv Health Clinical)	17	10	11 CTs; 4 – INC Research; 7 CTs; 8 – inVentiv Health Clinical
4	PSI	13	9	9 CTs; 5–6
5	IQVIA (QuintilesIMS)	11	8	27 CTs; 1
6	ICON	10	4	6 CTs; 9–10
7–8	Covance (incl. Chiltern)	6	5	8 CTs; 7 – Covance; 5 CTs; 11 – Chiltern
7–8	PRA Health Clinical	6	4	14 CTs; 2–3
9–11	Medpace	3	3	6 CTs; 9–10
9–11	Synergy Research Group	3	3	1 CT; 21–27
9–11	MB Quest	3	2	3 CTs; 12–15

Data from www.grls.rosminzdrav.ru

Diagram 13 shows the distribution of new IMCTs among contract research organizations. 30 CROs were active in the IMCT sector in 2018, three more than in 2017. Six CROs (20% of the total number of CROs mentioned in approvals in 2018) participated in ten or more trials, representing 73 new projects in total, or 86% of all CRO-involved projects.

Diagram 13



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, foreign sponsors

Table 15 contains information about the foreign sponsors which initiated the most local trials and bioequivalence studies in 2018.

Table 15

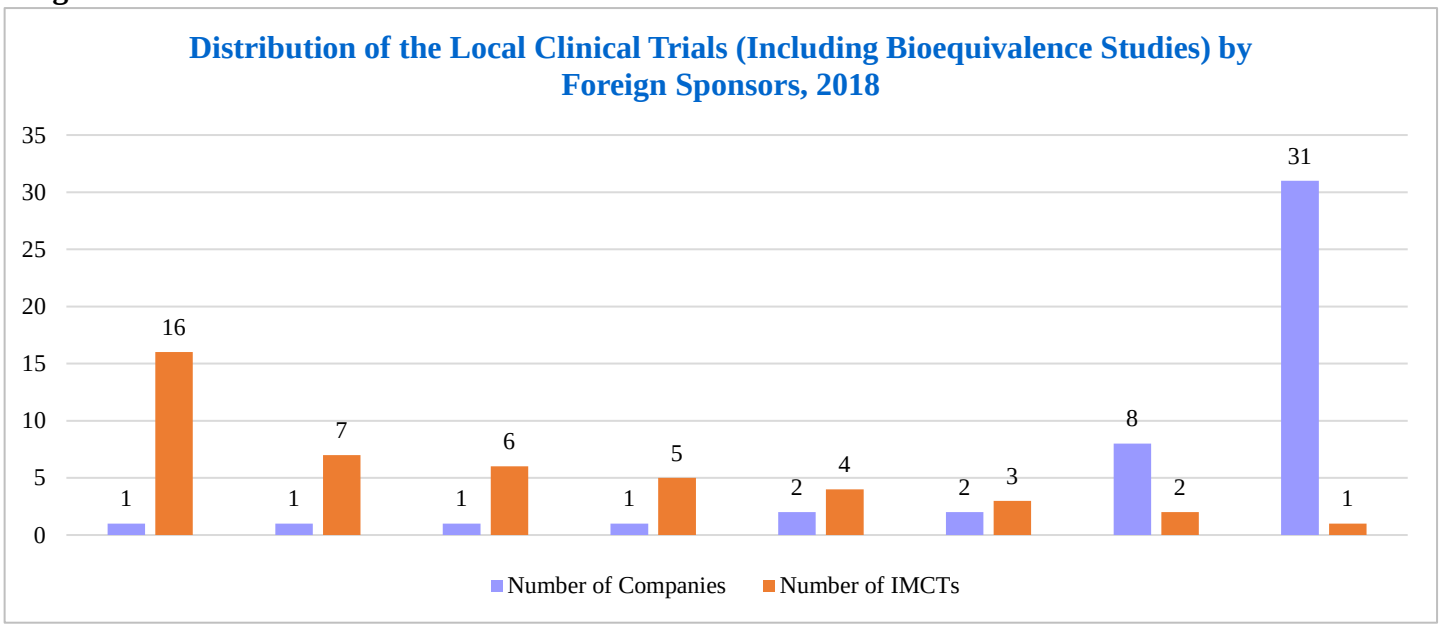
Ranking of Leading Foreign Sponsors on Approvals for Local CTs and Bioequivalence Studies, 2018					
Ranking in 2018	**Company**	**Conducted by themselves**	**Conducted by CROs/other representatives**	**Total**	**Number of CTs; Ranking in 2017**
1	Hetero Labs	16	–	16	13 CTs; 2
2	Polpharma (incl. Medana Pharma)	7	–	7	1 CT; 21–59
3	KRKA	6	–	6	3 CTs; 8–11
4	Pharmtechnology	–	5	5	3 CTs; 8–11
5–6	Teva	4	–	4	5 CTs; 4
5–6	Adamed	–	4	4	2 CTs; 12–20
7–8	Dr. Reddy's Lab.	3	–	3	14 CTs; 1
7–8	Novartis (incl. Sandoz, Gexal, Lek)	3	–	3	1 CT; 21–59

Data from www.grls.rosminzdrav.ru

Dr. Reddy's Laboratories, which took first place in 2016 and 2017, fell to joint 7th–8th, handing the title to 2017's runner-up Hetero Labs. Second place went to Polpharma, which did not even feature in the top ten the previous year. Third place was taken by KRKA, which rose from joint 8th–11th in the 2017 ranking, followed by Pharmtechnology, also ranked 8th–11th the previous year. Another new entry was Adamed, which shared 5th–6th place with Teva Pharmaceutical Industries, itself ranked fourth the previous year. Novartis, which also didn't feature in the top ten in recent years, was on the leaderboard in 2018.

The distribution of new local trials and bioequivalence studies among foreign companies is shown in diagram 14. It is worth noting that the number of sponsors of these types of trials continues to fall: 99 in 2016, 59 in 2017, and just 47 in 2018.

Diagram 14



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, domestic sponsors

The ranking of Russian sponsors by their degree of activity in obtaining approvals to conduct local trials and bioequivalence studies is shown in table 16.

Table 16

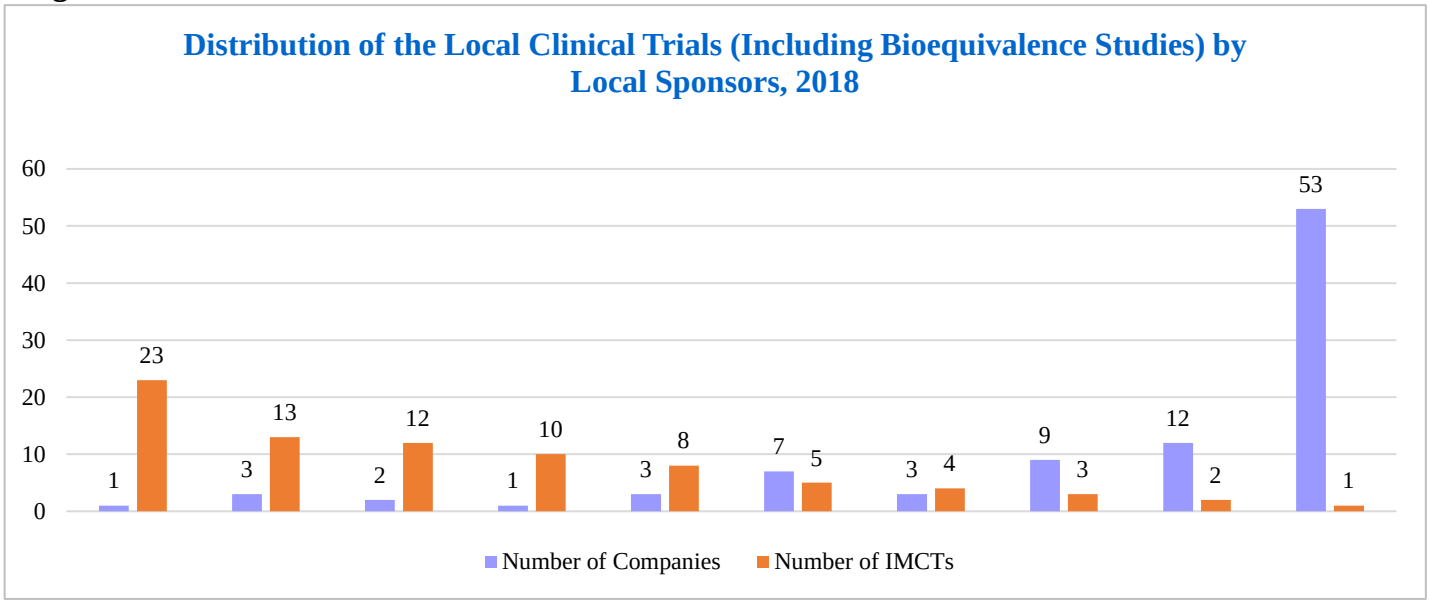
Top-10 Local Sponsors on Approvals for Local Clinical Trials and Bioequivalence Studies, 2018					
Ranking, 2018	**Company**	**Conducted by themselves**	**Conducted by CRO**	**Total**	**Number of CTs; Ranking, 2017**
1	Pharmasyntez (incl.Pharmasyntez-Tyumen and Pharmasyntez-Nord)	23	–	23	12 CTs; 5
2–4	Microgen	13	–	13	14 CTs; 3
2–4	ChemRar (incl. ChemDiv, Research Institute ChemRar, Viriom)	5	8	13	3 CTs; 20–31
2–4	Biocad	13	–	13	18 CTs; 1
5–6	R-Pharm (incl. Medicine Technology LLC)	12	–	12	6 CTs; 14 – Medicine Technology; 4 CTs; 19–22 – R-Pharm
5–6	Atoll	12	–	12	9 CTs; 10
7	Severnaja Zvezda	10	–	10	17 CTs; 2
8–10	Valenta Pharm	8	–	8	3 CTs; 20–31
8–10	Vertex	8	–	8	7 CTs; 12–13
8–10	Pharmstandard (incl. Pharmstandard-UfaVita, Phs-Leksredstva, Lekko, Pharmapark)	8	–	8	1 CT; 47–93

Data from www.grls.rosminzdrav.ru

Atoll, the leader from 2013 to 2016, dropped to tenth in 2017, but began to recover its position in 2018, placing joint 5th–6th in the ranking. The previous year's leader, BIOCAD, dropped to joint 2nd–4th, sharing the position with Microgen (third in 2017) and ChemRar, which did not feature in the top ten in 2017. In 2018 it was Pharmasyntez which came top, with 23 new trials (ranked fifth in 2017). Severnaya Zvezda saw its position weaken, from second in 2017 to seventh in 2018. Canonpharma Production, Promomed Rus, Obolenskoe, Akrikhin and Sotex dropped out of the top ten. In addition to the abovementioned ChemRar, they were replaced by R-Pham, Valenta Pharm, Vertex and Pharmstandard.

Diagram 15 shows the distribution of approvals issued in 2018 to carry out local trials and bioequivalence studies among domestic sponsors. Approvals were issued to 94 companies, one more than in 2017.

Diagram 15



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, CROs

The top ranking of the CROs which participated most actively in conducting local trials and bioequivalence studies in 2018 is shown in table 17.

Table 17

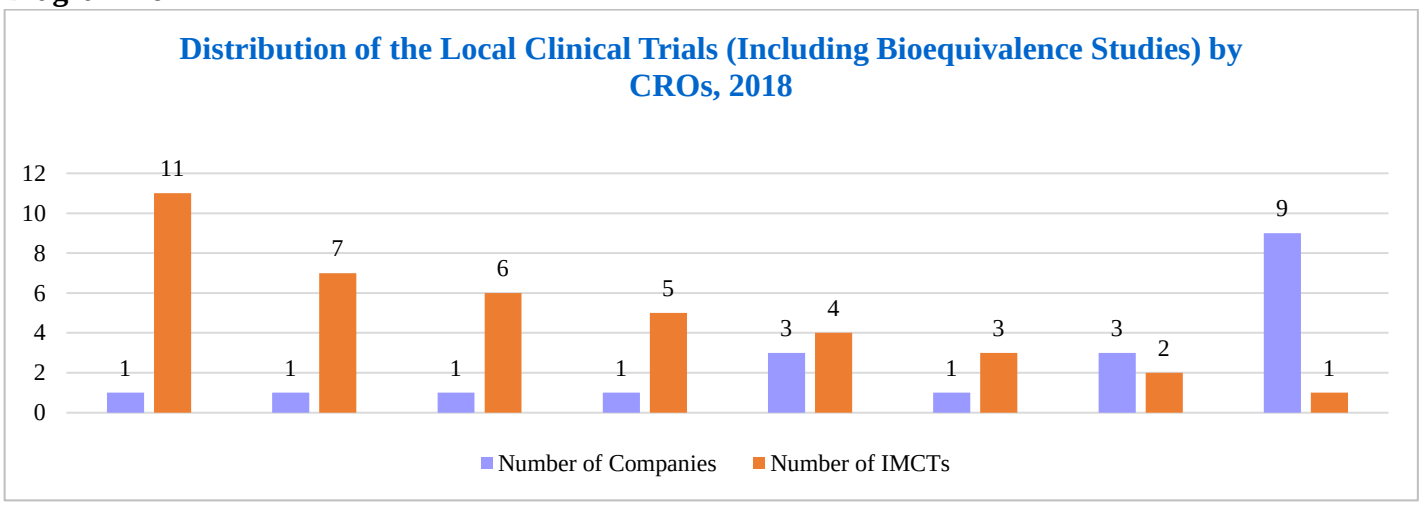
CROs Involved in the Local CTs and Bioequivalence Studies (on Approvals Issued in 2018)						
Ranking	**Company**	**Number of CTs of foreign sponsors**	**Number of CTs of local sponsors**	**Total number of local CTs, 2018**	**Number of sponsors**	**Number of CTs; Ranking, 2017**
1	IPHARMA	1	2	11	3	15 CTs; 1
2	R&D Pharma	–	3	7	3	2 CTs; 12–14
3	Medical Development Agency (MDA)	1	4	6	5	3 CTs; 6–11
4	ClinPharmInvest	1	–	5	1	3 CTs; 6–11
5–7	GLOBALPHARM/GLOBALPHARMA	1	–	4	1	1 CT; 15–21
5–7	X7 Research	1	1	4	2	1 CT; 15–21
5–7	Synergy Research Group	1	1	4	2	12 CTs; 2
8	OCT	–	3	3	3	6 CTs; 3
9–11	Accellena Research and Development	–	1	2	1	n/a
9–11	Probiotech	1	1	2	2	4 CTs; 5
9–11	RegExpert	2	–	2	2	n/a

Data from www.grls.rosminzdrav.ru

IPHARMA maintained its dominance, with 11 approvals. Synergy Research Group and OCT, which took second and third place in 2017, fell down to joint 5th–7th and eighth in the ranking respectively. Medical Development Agency (MDA), ClinPharmInvest and Probiotech held onto their places in the top ten, the former two rising in the rankings and the latter falling. Breaking into the top ten were R&D Pharma, which rose from 12th–14th to second place, Global Pharm and X7 Clinical Research, which both rose from joint 15th–21st to joint5th–7th, as well as Accellena Research and Development and RegExpert, neither of which appeared in last year's ranking.

Diagram 16 shows the distribution of local trials and bioequivalence studies among contract research organizations. In total 20 CROs participated in conducting local trials, one fewer than in the previous year.

Diagram 16



Data from www.grls.rosminzdrav.ru

TIMEFRAMES FOR OBTAINING APPROVALS

ACTO routinely monitors timeframes for obtaining approval documents for conducting clinical trials, and for the last three years has been doing this jointly with the Association of International Pharmaceutical Manufacturers (AIPM). 32 pharmaceutical companies and contract research organizations, which are members of ACTO and AIPM, took part in a survey conducted at the end of 2018. The sample size of basic approvals to conduct trials was 248, which amounts to 86% of all approvals for IMCTs issued in Russia in 2018. The results of the survey are shown in table 18.

Table 18

Timeframes for Issuing Approvals, 2018					
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*	92	52	269	248
To Import Medicines	8/12	14	1	66	449
To Import/Export Biosamples	13/19	21	5	54	963
To Make Amendments to the Protocol	34/48	47	10	85	480
Other Approvals**	25/35	26	4	88	847

Data from timeframes monitoring of ACTO and AIPM

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

** To prolong clinical trials, to include new sites, to enroll additional patients, etc.

The process for calculating the average timeframe for receiving clinical trial approvals should be clarified. It varies depending on the calculation method and in particular on how any time spent on correspondence is accounted for in the event that applicants receive requests from expert bodies. Table 18 shows the average timeframe, calculated on the basis of all applications, including those for which requests were made by expert organizations or the Ministry of Health of the Russian Federation – the figure was 92 days, including response times. Furthermore, the average timeframe for receiving an approval for applications where there were no requests was 65 days. The timeframe for receiving an approval for all applications, excluding the response time where requests were made, was 71 days. The timeframe for receiving approvals for applications where there were requests, including the necessary response time, was 112 days.

It is also worth adding that the share of applications for which no requests or corrections were received was, according to the 2018 survey, just 38.8%. Furthermore, a significant portion of the corrections were made by the Ethics Council of the Ministry of Health. So, if the Ministry of Health filtered out 18.8% of applications on the first attempt when performing document completion checks, and the Scientific Centre for Expert Evaluation of Medicinal Products had questions for 20.1% of applications undergoing protocol evaluations, the Ethics Council either provided corrections or refused applications to conduct IMCTs in 43.9% of cases. And considering the fact that requests and corrections from expert organizations and the Ministry of Health of the Russian Federation can relate to various protocols, the outcome is lamentable: in 61.2% of cases the applications were inhibited at any of the stages. However, the statistics collected on corrections received by applicants are only preliminary in character. In the middle of year ACTO conducts a separate survey analysing the process of passing expert evaluations, and this topic will be dealt with in more detail in the next newsletter.

Let us return to the timeframes. All things considered, we can conclude that changes in the average time for receiving approvals for all types of fillings in 2018 compared to 2017 are insignificant. The average timeframe for receiving a basic approval to conduct a clinical trial decreased by 3.2% (from 95 to 92 days). The timeframe for approvals to make amendments to the protocol grew by 12% (from 42 to 47 days), while the timeframe for

approvals to import/export biological samples grew by 5% (from 20 to 21 days). For approvals to import medicines and for all other types of approval (including approving new sites, enrolling additional patients, extending trials etc.) the average timeframes remained unchanged, at 14 and 26 days respectively.

Statistics about violations of deadlines in issuing approval documents in 2018 were calculated separately and are presented in table 19. A positive growth trend was observed in approvals to conduct trials, and permits for import of medicinal products and for 'other approvals' compared with 2017, with the share of documents issued on time increasing by 10.4 percentage points (from 11.4% to 21.8%), 5.7 percentage points (from 38.6% to 44.3%) and 4.3 percentage points (from 87.2% to 91.5%) respectively. For permits to import/export biological samples and approvals to make protocol changes the percentage of approvals issued on time contracted slightly, by 3.8 percentage points (from 45.5% to 41.7%) and 11 percentage points (from 75.4% to 64.4%) respectively.

Table 19

Violations of Timeframes, 2018 vs 2017								
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*	2018	21.8%	78.2%	73.3%	4.9%	0,0%.	0.0%	0.0%
	2017	11.4%	88.6%	79.8%	7.0%	1.8%	0.0%	0.0%
To Import Medicines	2018	44.3%	55.7%	38.8%	12.0%	4.2%	0.5%	0.2%
	2017	38.6%	61.4%	38.9%	19.4%	2.6%	0.0%	0.5%
To Import/Export Biosamples	2018	41.7%	58.3%	47.7%	9.3%	1.3%	0.0%	0.0%
	2017	45.5%	54.5%	46.2%	7.8%	0.5%	0.0%	0.0%
To Make Amendments to the Protocol	2018	64.4%	35.6%	33.3%	2.3%	0.0%	0.0%	0.0%
	2017	75.4%	24.6%	22.6%	1.6%	0.5%	0.0%	0.0%
Other Approvals**	2018	91.5%	8.5%	7.1%	1.3%	0.1%	0.0%	0.0%
	2017	87.2%	12.8%	12.0%	0.6%	0.0%	0.1%	0.0%

Data from timeframes monitoring of ACTO and AIPM

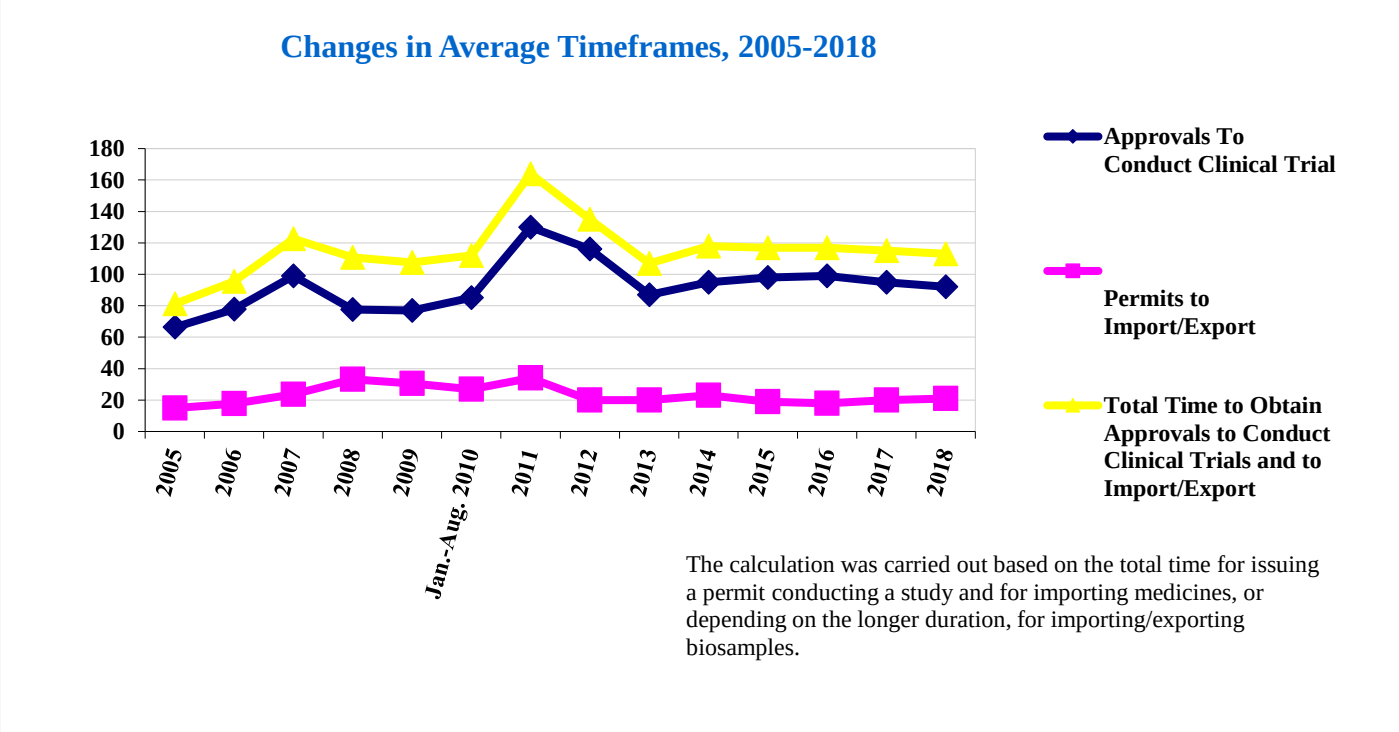
* The calculation of deadlines for clinical trial approvals was carried exclusively those applications where there were no requests from expert organizations or the Ministry of Health.

** To prolong clinical trials, to include new sites, to enroll additional patients, etc.

The ratio of shares of different periods of delay in issuing approvals has slightly changed. For the most significant and at the same time problematic category of approvals – clinical trial approvals (only 21.8% of approvals issued on time) – the situation improved palpably, with a reduction in the share of approvals issued with a delay of 1,5–1,9 times of the timeframe, as well as in the share of approvals with a delay of under 1,5 times. There were no recorded cases where there was a delay of 2–2,9 times of the standard timeframe for applications under review. For other categories of applications the situation was slightly worse. While there was an overall reduction in the proportion of approvals issued with a delay, the share of approvals issued with a delay of 2–2,9 or 3–3,9 times of the timeframe increased for the 'importing medicines' category, and with a delay of 1,5–1,9 times for the 'other approvals' category. Nevertheless, it cannot be said that all the changes identified are significant.

Changes to the timeframes for issuing approvals since 2005 can be seen in diagram 17. The graph shows that for the past six years the situation has remained stable overall, with some minor fluctuations.

Diagram 17



Data from timeframes monitoring of ACTO

IMPORT OF MEDICINAL PRODUCTS FOR CLINICAL TRIALS

Statistics on the import of medicinal products into the Russian Federation for use in clinical trials are shown in tables 20 and 21.

The data on import volumes (table 20) includes not only medicines being tested, but also comparators and in some cases concomitant treatments. A comparison with 2017 shows that, in ruble terms, the overall cost of supplying medicines for use in clinical trials has seen a slight change, with growth of around one percent. In dollar terms the figure decreased by 0.4%. VAT and customs duties, as well as 'VAT, customs duties and custom fees' figures showed growth of less than one percent. Customs fees even decreased slightly.

Table 20

Import of medicinal products to the Russian Federation for clinical trials, 2017–2018		
Parameter	**2017**	**2018**
Total value of shipments, rub.	13 524 110 010	14 456 760 247
Total value of shipments, $	231 874 168	230 850 496
VAT, rub.	1 397 081 825	1 492 894 044
Customs duties, rub.	434 360 335	435 953 057
Customs fees, rub.	15 471 988	14 909 846
VAT + Customs dutie + Customs fees, rub.	1 822 726 648	1 943 756 947

Source: RNC Pharma

Table 21 shows the manufacturers whose medicines had the largest share in the overall volume of imported medicines for conducting clinical trials in 2018. It should be taken into account that not only the sponsors themselves, but also CROs and rival companies using the medicines as comparators or background therapies can import these medicines. The share of deliveries fulfilled by the company itself (whether by a representative or daughter company) is shown in a separate column.

Table 21

Top-10 pharmaceutical companies on import of medicinal products for clinical trials, 2018					
Ranking	**Company**	**Value of shipments, rub.**	**Number of shipments**	**Imported by the companies themselves, %**	**Ranking, 2017**
1	Johnson & Johnson	2 169 919 890	183	47.3%	2
2	Novartis	1 685 708 926	558	86.8%	7
3	Merck & Co.	1 637 903 012	186	90.9%	3
4	F. Hoffmann-La Roche	1 188 294 588	186	62.8%	5
5	Merck Group	619 404 769	31	0.0%	6
6	Pfizer	503 198 238	53	0.1%	4
7	GSK	471 870 856	161	0.0%	12
8	Celgene Corp.	404 653 875	46	0.0%	10
9	Kyowa Corp.	404 555 350	10	0.0%	8
10	Amgen	388 949 921	92	52.2%	9

Source: RNC Pharma

Table 21 shows the results by supplies which could be identified. In addition to the supplies identified in the RNC Pharma database for 2018, there were 229 deliveries which could not identified, representing a total value of RUB 1.4 billion. Some evidence suggests that these supplies include medicines manufactured by Pfizer, AbbVie, Eli Lilly and Company, and Sanofi among others, but without more precise data we are unable to include them in the overall distribution.

INVESTIGATOR INITIATED TRIALS: A VIABLE FUTURE IN RUSSIA?

M.B. Nassonova
MD, PhD, Executive Manager, ALMEDIS

Clinical trials initiated by the investigators themselves, known as Investigator Initiated Trials (IIT) or Investigator Initiated Studies (IIS), are now prevalent in healthcare and pharmaceutical industries throughout the world. In Russia too, IITs are attracting more and more interest among the medical community, with greater opportunities available for conducting trials of this kind, including the legislative framework.

Among the reasons for the growth in IITs currently being observed are the following:

- Qualitative growth in knowledge about the pathogenesis of various diseases in recent decades, improved classification of diseases (for example classification of tumours by mutation type), and the identification of a large number of potential new targets for intervention with medicinal products;

- Limitations of trial programmes for medicines led by pharmaceutical companies, which do not provide complete information about features of medicines for the benefit of a wide pool of potential patients, as they are first and foremost aimed at support regulatory approval for the medicines and rolling them out onto the market. Protocols for trials sponsored by the pharmaceutical industry have design flaws which make it impossible to evaluate the effectiveness of the medicines under real-world conditions, and the clinical development programs are focused on the most commercially appealing market segments/therapeutic areas;

- New level of cooperation and awareness among doctors made possible by contemporary channels of communication (internet, social media and IT), which facilitate collaborative work between geographically remote participants. The introduction of convenient tools for collecting and management of data.

Therefore, in an environment where there are many potential goals of trials as well as numerous technical solutions for various aspects of collaboration, the coordination of efforts and collaborative work on projects between multiple trial centres and groups becomes possible and feasible.

For their part, pharmaceutical companies consider IITs as a significant aid in the life-cycle of their medicines in an environment of fierce competition and increased expenditure on the development of medicinal products, as well as a cost-effective means of seeking out new indications and niche applications.

Almost all international companies have a policy in place for the active involvement of IITs, making budgetary allocations, adopting procedures and developing tools to this end. In supporting IITs, pharmaceutical companies must be satisfied that high ethical standards are in place, as well as ensuring and monitoring compliance with all regulatory requirements, as well as their own standards for IITs.

In practice, major differences in the ways in which medical investigations are conducted continue to exist between pharmaceutical companies on the one hand, and doctors and healthcare research organisations on the other. The former operate in an environment of strict regulation, while the latter work according to the long-established approaches of various institutes and scholarly traditions. In recent years, leading countries in the development of new treatment methods have taken steps to improve the standards of IITs. Regulatory bodies in these countries view their task as consisting of offering support in the development of a methodological framework for IITs and, by the same token, improving their quality.

For one, the US Food and Drug Administration (FDA) is developing guidelines for clinical trials for the benefit of sponsor-investigators (Investigational New Drug Applications Prepared and Submitted by Sponsor-

Investigators, Draft Guidance[3]). The aim of these guidelines is to aid sponsor-investigators in preparing and submitting applications for trial medicines as part of its Investigational New Drug (IND) programme, as investigators who wish to conduct clinical trials often lack the expert knowledge or resources necessary to prepare and submit applications. The guidelines also set out the responsibilities of sponsor-investigators in the process of conducting trials.

According to European Union regulations, IITs are categorised as non-commercial trials. With the introduction of the Clinical Trials Directive (2001/20/EC), which regulates the conduct of non-commercial trials among other types, there has been an increase in the administrative burden of preparing and conducting trials, which has led to a corresponding budget increase. It can be said, however, that the rights of patients of IITs being conducted in the EU are now better protected, and the quality of the results obtained in such trials has tended to increase.

The Russian Federation also has a legal basis for conducting investigator-initiated clinical trials (it should also be noted that there are no obstacles to conducting non-interventional, or observational trials initiated by investigators either, but these are beyond the scope of this article). According to part 3 of article 38 of the Federal Law № 61-FZ "On Circulation of Medicines", dated 12/04/2010, research organisations and higher and/or further vocational education institutions are entitled to conduct clinical trials. It follows from this that only a legal entity can act as sponsor of a clinical trial in the Russian Federation, as opposed to western countries, where individual medical investigators have the right to act as sponsor. At the present time, statutory provisions in Russia with regard to IITs have not been worked out in detail, and in fact all regulations affecting IITs have been extrapolated from those which apply to clinical trials in general. After the introduction of the latest amendments to 61-FZ at the end of 2014 when it became possible to submit local clinical trial applications to the Ministry of Health separately from medicine product registration process, projects of this kind began to appear in the register of approved trials (table 22).

Table 22

IITs approved by the Ministry of Health		
Year	**Number of IITs**	**Therapeutic Areas**
2015	2	Neurology – 1, Narcology – 1
2016	3	Oncology – 1, Cardiology and CVD – 2 (one of the cardiological IIT projects is phase III IMCT)
2017	3	Endocrinology – 1, Cardiology and CVD – 2 (one more cardiological IMCT)
2018	4	Obstetrics and Gynecology – 1 (IMCT), Oncology – 2, Cardiology / Nephrology – 1

Because of the specific requirements in registering information on the website of the Ministry of Health of the Russian Federation it is impossible to say with certainty that all IITs were identified when analysing the material on the website, but information is at least available on 12 studies of this type, covering the period from 2015 to 2018. Over the same period more than 3,500 non-commercial projects were registered in the EU Clinical Trials Register (over 1,100 in 2015, over 900 in 2016, over 800 in 2017 and over 750 in 2018). The FDA website provides data on the number of “research IND” submissions filed. There were over 700 in 2015, and over 800 in 2016. Searching on clinicaltrials.gov for clinical trials (phases I–IV) initiated between 2015 and 2018 gives the following results: around 20,500 projects initiated by the NIH, other US agencies, and other entities (the “others” category in this register includes individuals, universities and organisations). Out of this number, 17,500 trials were initiated by representatives of the “others” category. According to clinicaltrials.gov, 99 of these trials took place, are taking place, or will take place in Russia. It can be assumed that some IITs, for one reason or another, were not identified on the website of the Ministry of Health of the Russian Federation. These may include, while

[3] Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators. Guidance for Industry (Draft Guidance, May 2015) - https://www.fda.gov/downloads/Drugs/Guidances/UCM446695.pdf.

not being limited to, projects which are not subject to review by the ministry and are therefore not published on its website (trials of medical devices and biotechnologies for example), or trials which have not yet reached the launch stage in Russia.

It can therefore be said that there is a legal basis for conducting interventional trials initiated by the investigators, that there is a process in place for the approval of such projects by the Ministry of Health of the Russian Federation, and that practical experience is being gained both through participation in international IITs and through initiation local projects in Russia.

Speaking about the experience of conducting local IITs, it should be noted that the difficulties encountered in Russia have much in common with those recorded in other markets, including those which are more developed. They stem from the significant increase in responsibility falling on sponsor-investigators when conducting IITs as opposed to IMCTs or research. These responsibilities include processes which investigators may be either completely unfamiliar with, or else only very superficially aware of.

The potential sponsor-investigator is expected to prepare a synopsis/protocol for the trial. If they are applying to a pharmaceutical company for a grant, then the company must review and approve the protocol. This requires that the design, aim and objectives, and justification of the choice of variables and methods of their evaluation, as well as the justification or calculation of the sample size are correctly described in the trial protocol in line with the current understanding of the issue at hand at the global level. Unfortunately, a situation is often encountered whereby a potential sponsor-investigator is not in a position either to distinguish between an observational project and an interventional clinical trial, or to align planned aims with realistic capabilities, including the necessary sample size.

The evaluation of clinical trial documents carried out by the expert body of the Ministry of Health of the Russian Federation is an important step in the process. To receive a positive assessment, applicants should comply with both scientific and procedural requirements.

In addition to the specific demands of this kind of research, the sponsor-investigator should be aware of the legislation and actual practice. If the trial falls within the remit of 61-FZ, the sponsor-investigator should be prepared to independently ensure and monitor compliance with the requirements of this law and a range of secondary legislation, including the Order of the Ministry of Health of the Russian Federation № 200n on Approval of Rules for Good Clinical Practice, dated 01/04/2016. The sponsor-investigator should be equipped to assemble a package of trial documents, provide life and health insurance of patients participating in a trial undergo a trial approval procedure with the Ministry of Health of the Russian Federation, ensure the import/purchase of the necessary medicines and materials, and carry out proper reporting on all aspects of the trial.

It is often the case that doctors do not have an adequate understanding of either the current requirements governing the collection and management of clinical trial data, the systems used for this purpose, or the rules of medical terms coding. While western universities and advanced clinics are in possession of such systems and provide them to their investigators, questions about which data management system to use and how to use it are decided at the individual project level for trials in Russia.

Doctors rarely involve qualified biostatisticians in the development of the design concept for the trial, rather calculating the results themselves. This approach leads to difficulties when coordinating initiatives with the headquarters of pharmaceutical companies and when undergoing expertize by the Federal State Budgetary Institution “Scientific Centre for Expert Evaluation of Medicinal Products” (SCEEMP) of the Ministry of Health of the Russian Federation, and can lead to erroneous conclusions in the processing of trial results further down the line.

No less important are the organisational and financial aspects. In most cases, doctors and institutions – especially public ones – may have insufficient experience and inadequate tools at their disposal to draw up a project budget and manage it flexibly, i.e. making various purchases, payments etc.

All things considered, it can be stated unequivocally that the significance and number of investigator-initiated trials of medicinal products in Russia is on the rise. Nevertheless, the methodological framework for conducting them does not always meet current requirements. This must be accounted for when projects of this type come under consideration, and plans should be made in advance to determine the kind of support investigators require in order to realise their research concepts.