ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER № 21

1st Half of 2020

MOSCOW 2020

CONTENTS

SUMMARY

In H1 2020 the Ministry of Health of the Russian Federation issued 302 approvals for clinical trials. A year earlier this indicator stood at 346, i.e. the number of issued approvals went down 12.7% against a similar period of 2019. The reduction was hardly caused by the lockdown, given that in H1 2018, when the entire industry functioned normally, 304 approvals had been issued - almost the same amount as in January-June 2020.

The sector of international multicentre clinical trials (IMCTs) proved most stable, having shrunk only by 2.2% (from 136 approvals in H1 2019 to 133 for the same period of 2020). The number of bioequivalence studies of Russian generics decreased by 15.5% (from 84 to 71); the local trials of Russian medications sagged by 28.2% (from 78 to 56) while the number of local trials by overseas sponsors dropped by 47.4% (from 19 to 10). On the contrary, the segment of bioequivalence studies of foreign-made generics has upped 10.3% from 29 to 32 protocols in H1 2020 year-on-year.

Analysis of the practice of planned trials examination showed that the share of the requests for completeness of documents decreased again and reached 11.9% of the total volume of incoming applications for IMCTs. The contraction was even more significant for the previous period: from 18.5% to 12.7%; but on the whole the positive trend has so far persisted. The share of applications for IMCTs without extra requests for expert evaluation by the FSBI "Scientific Centre for Expert Evaluation of Medicinal Products" (SCEEMP) has dropped from 73.1% based on a survey of ACTO members in 2019 to 67.1% in 2020. A similar indicator for the Ethics Council moved in the opposite direction, though, and has grown from 62.6% to 76.5% which is maximum for eight recent years. 52.8% of all primary applications have passed both expert evaluations without comments, which is higher than both in the previous period (47.3%) and any other period since 2013.

This issue also analysis prevalence of blinding in clinical trials of various types. The comparison shows that the blind method is most often used in IMCTs (72.1%), followed by local trials of Russian sponsors (60.6%), then by local trials of foreign sponsors (26.7%) most of which are so-called "registration" trials.

We could not overlook the rampant pandemic and have prepared a review of anticoronavirus medications trials, for which approvals were issued in H1 2020. During this period the Ministry of Health has issued 26 such approvals which account for 8.6% of all approvals for January-June 2020. Only remedies for oncological diseases (43 clinical trials approvals or 14.2% of all issued in H1), neurological diseases (37 and 12.3%) and cardiac diseases with cardiovascular diseases (32 and 10.6%) stood higher in our rankings.

The pandemic and associated "cutting corners" in clinical trials led us to address the issue of GCP violations that ACTO had to deal with in 2020. In the text titled Critical Testing of Clinical Trial Standards we highlighted only some selected cases - most sensational, bearing highest potential risks and requiring the greatest involvement from the ACTO team. Without claiming the full coverage of the situation, this section seems to give some general idea about the degree of clinical trial standards erosion in Russia in times of crisis.

Another material regards the activity of principal investigators as reflected in the respective Register of the Ministry of Health. Several rankings based on the number of approvals in the capacity of principal investigators (including separate ones for oncologists and clinical pharmacologists) reveal leaders both in terms of the current protocol count and the total number of projects.

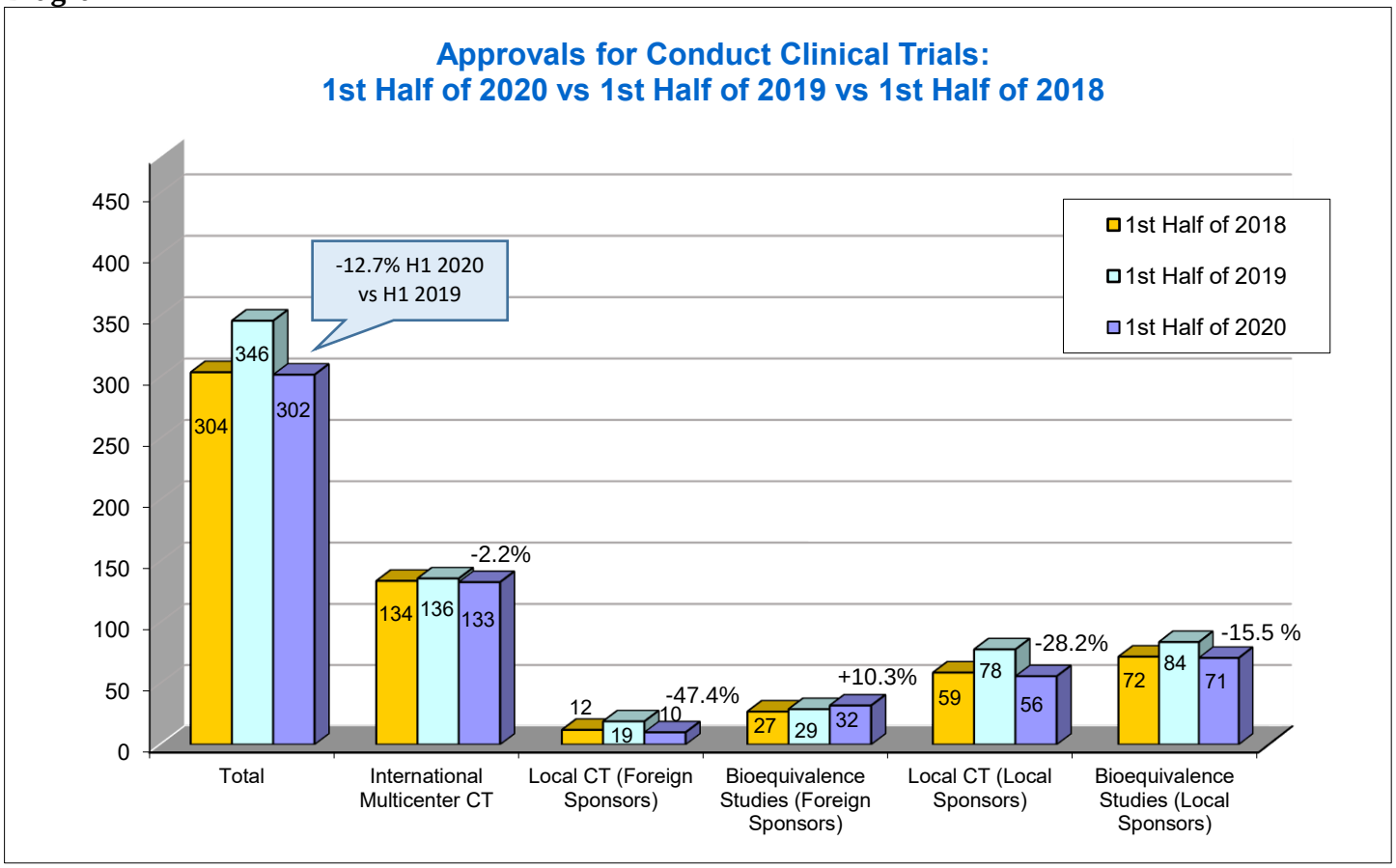
This issue is traditionally crowned with a review of international trials in oncology and oncohaemotology. Tables and diagrams showing information about respective IMCTs for which approvals were issued throughout 2019 are placed in the Annex.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

Despite the still rampant global pandemic that has already affected almost all spheres of our daily life, including the global impact upon clinical trials, we'll traditionally start our issue with general statistical data for H1 2020.

From January to June inclusive the Ministry of Health has issued 302 approvals for clinical trials, which is 12.7% less than a year before, when 346 approvals were issued. One could conjecture that this reduction was caused by the lockdown announced in Russia in mid-March. But this is obviously not quite the case if we take the data for H1 2018 into consideration, when the number of issued approvals was almost the same (304 approvals).

Diagram 1



Data from www.grls.rosminzdrav.ru

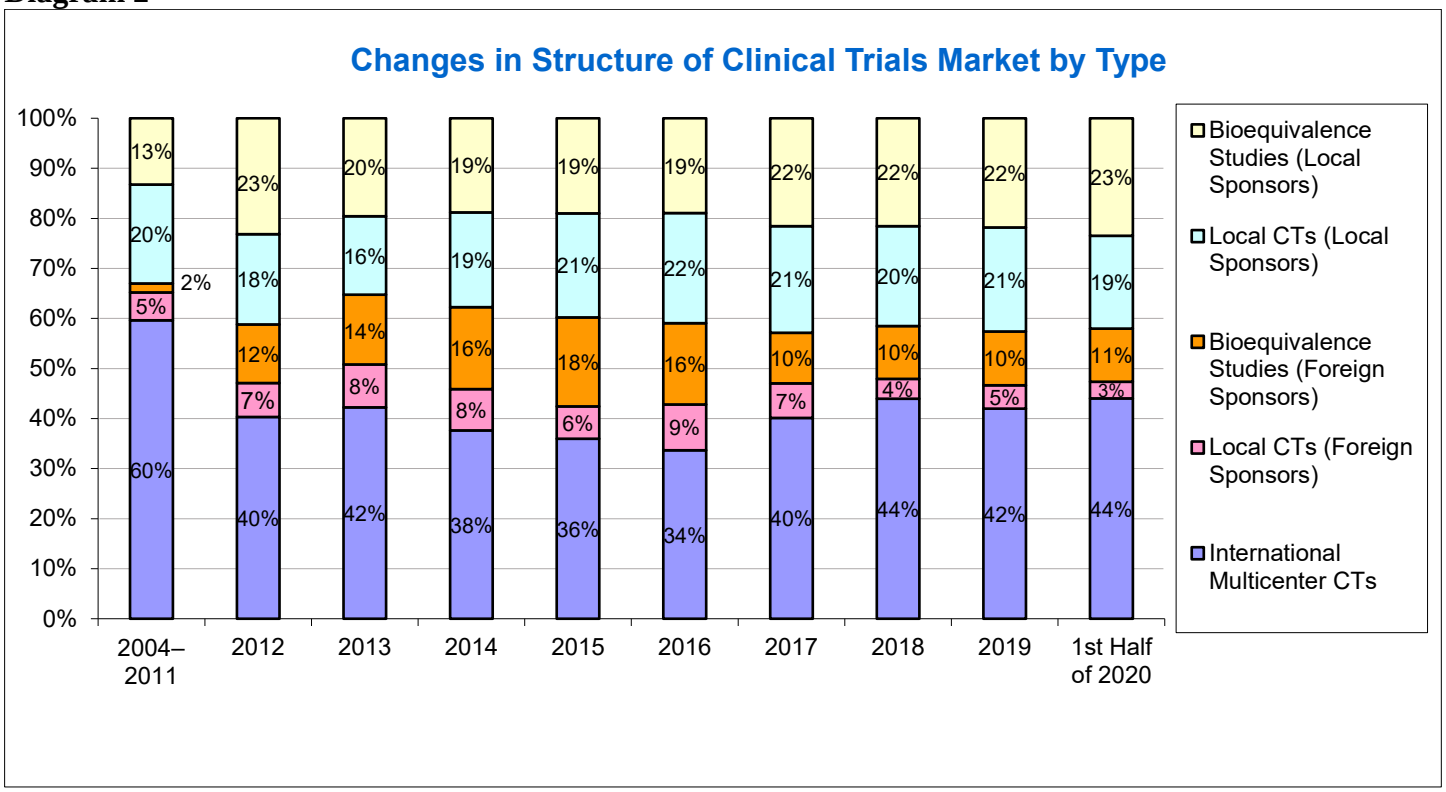
It can be seen from Diagram 1 that most stable was the segment of international multicentre clinical trials (IMCTs), which shrank only by 2.2% against H1 2019 (133 versus 136 approvals).

The number of approvals for bioequivalence studies of Russian generics has gone down by 15.5% (71 approvals versus 84), whereas the number of approvals for other trials of Russian medicinal products has dropped by 28.2% (56 versus 78). The deepest fall (as usual, due a small number of such trials) could be seen in the segment of local trials by foreign sponsors - 47.4% (10 approvals versus 19 in H1 2019).

The only type of trials where the number of approvals has grown year-on-year (by 10.3%) was bioequivalence studies of foreign-made generics: 32 approvals versus 29.

As regards the market structure by types of clinical trials, you can see from Diagram 2 that in H1 2020 it almost remained unchanged as compared with the data for two previous years. We may see more radical changes at the end of the year, but a nearly four-month lockdown in H1 2020 had almost no impact upon the traditional balance between various types of trials.

Diagram 2



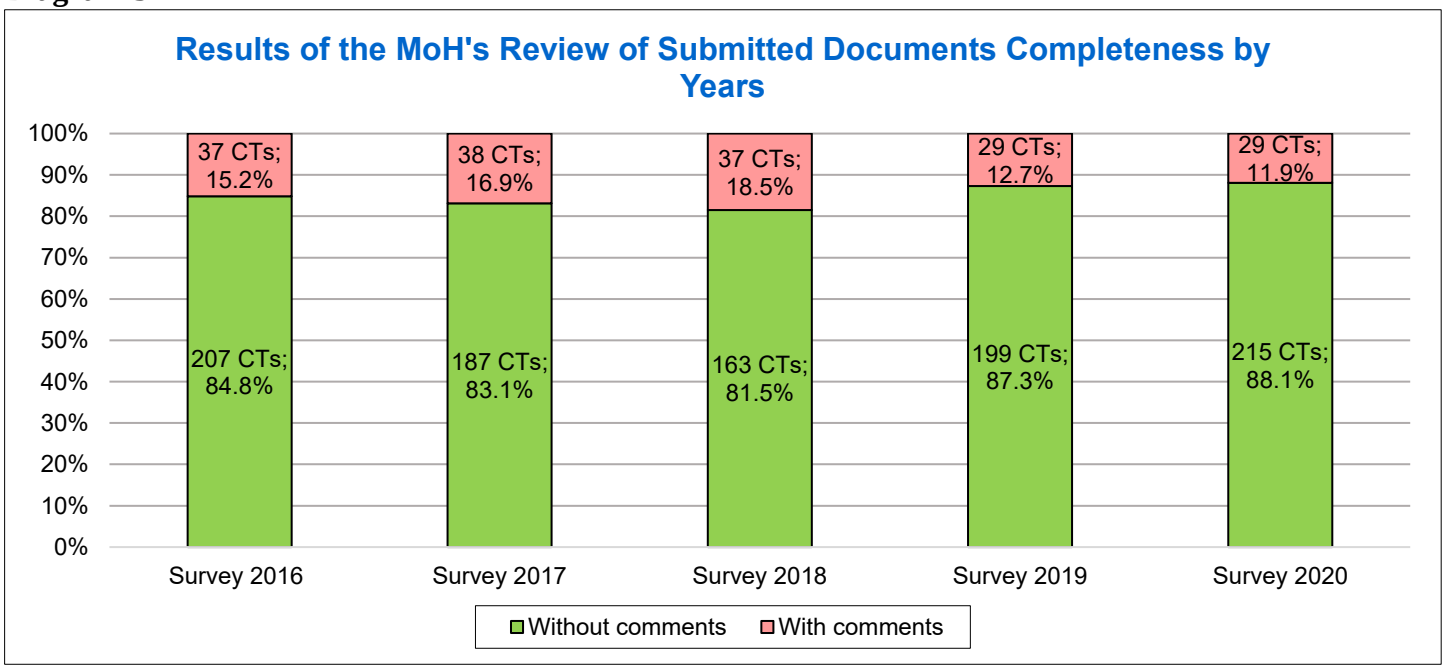
Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

EXPERT EXAMINATION OF PLANNED TRIALS

The next section of our Newsletter has also become quite traditional in the eyes of our loyal readership: reviewing the expert evaluation of documentation for planned trials, based on the annual survey of ACTO member companies. The survey is usually conducted in mid-year and includes the data of primary review of applications for IMCTs for the second half of the previous year and first half of this year. This time 24 ACTO member companies have taken part in the survey.

Diagram 3 shows the data of checking the completeness of documentation by the Ministry of Health. As we can see, the results of the initial stage of documentation review are getting better for the second year in a row: the share of requests relative to the completeness of documents has dropped to 11.9% of all incoming applications for IMCTs. This is certainly not a radical improvement like the one we saw a year ago (from 18.5% to 12.7%), but the trend remains positive anyway.

Diagram 3



Data from www.grls.rosminzdrav.ru

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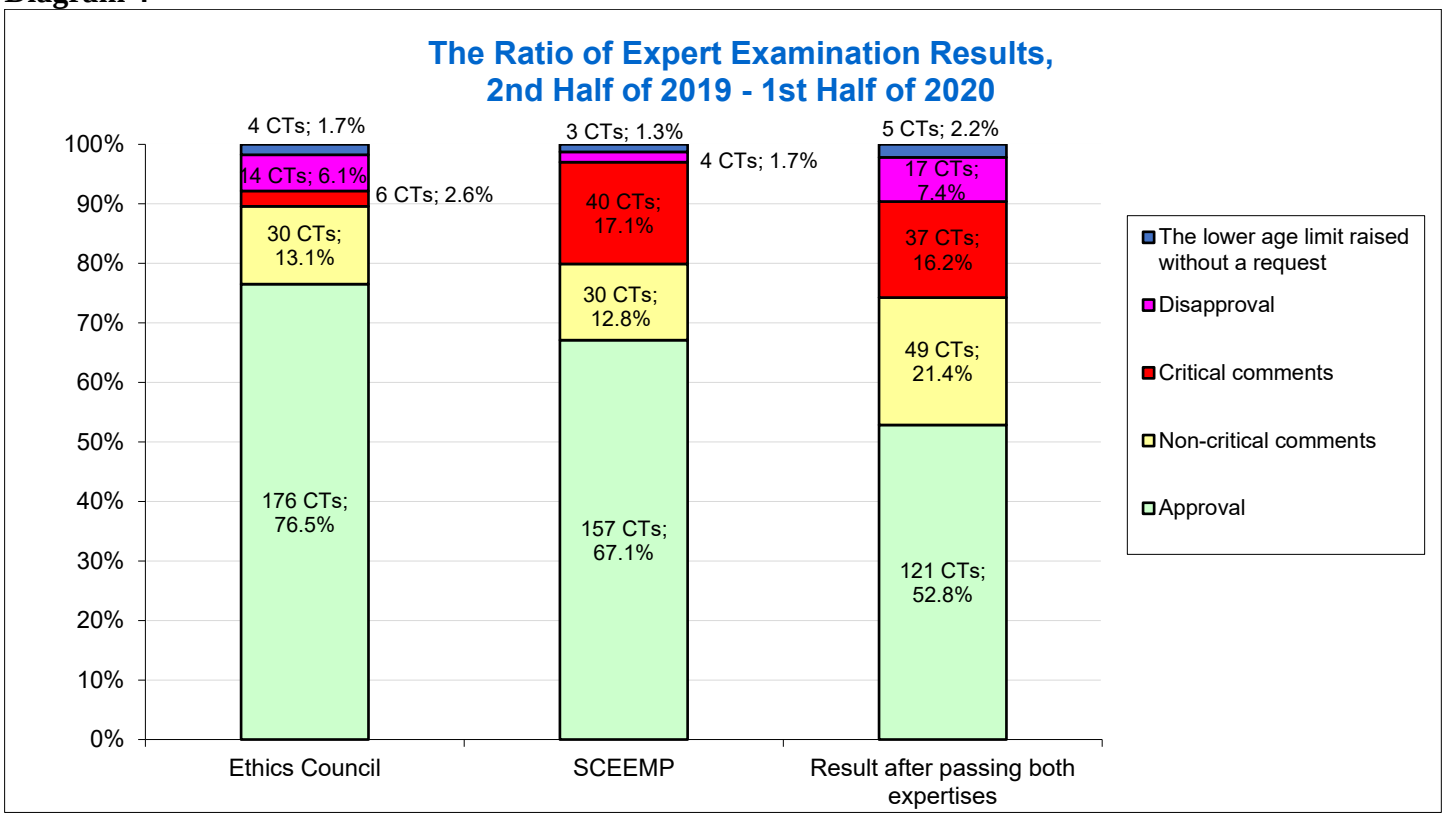
Diagram 4 highlights the results of primary expert evaluation of documentation at the Scientific Centre for Expert Evaluation of Medicinal Products (SCEEMP) and at the Ethics Council separately as well as the results of review by experts from both bodies.

It can be seen that as compared to the previous year, the distribution of requests and comments from SCEEMP and Ethics Council has somewhat changed. While judging by the results of the 2019 survey only 73.1% of planned IMCTs passed the expert evaluation at SCEEMP without further comments, now this indicator has dropped to 67.1%, whereas the last-year's result for the Ethics Council (62.6%) moved in the opposite direction and now stands at 76.5%. Thus the latest survey revealed that the experts of the Ethics Council are a bit more loyal towards the applicant in comparison with SCEEMP experts.

It is rewarding that decreasing the share of cases "without comments" at SCEEMP was mainly due to increasing the share of non-critical comments (12.8% versus 6.6% as per the 2019 survey), whereas the share of critical comments remains at the same level (17.1% versus 17.2% a year earlier). The share of disapprovals and instances of raising the age of trial participants without any notice forwarded to the applicant has also remained practically unchanged (1.7% versus 1.3% and 1.3% versus 1.8%, respectively).

Diagram 4



Data from poll of ACTO members

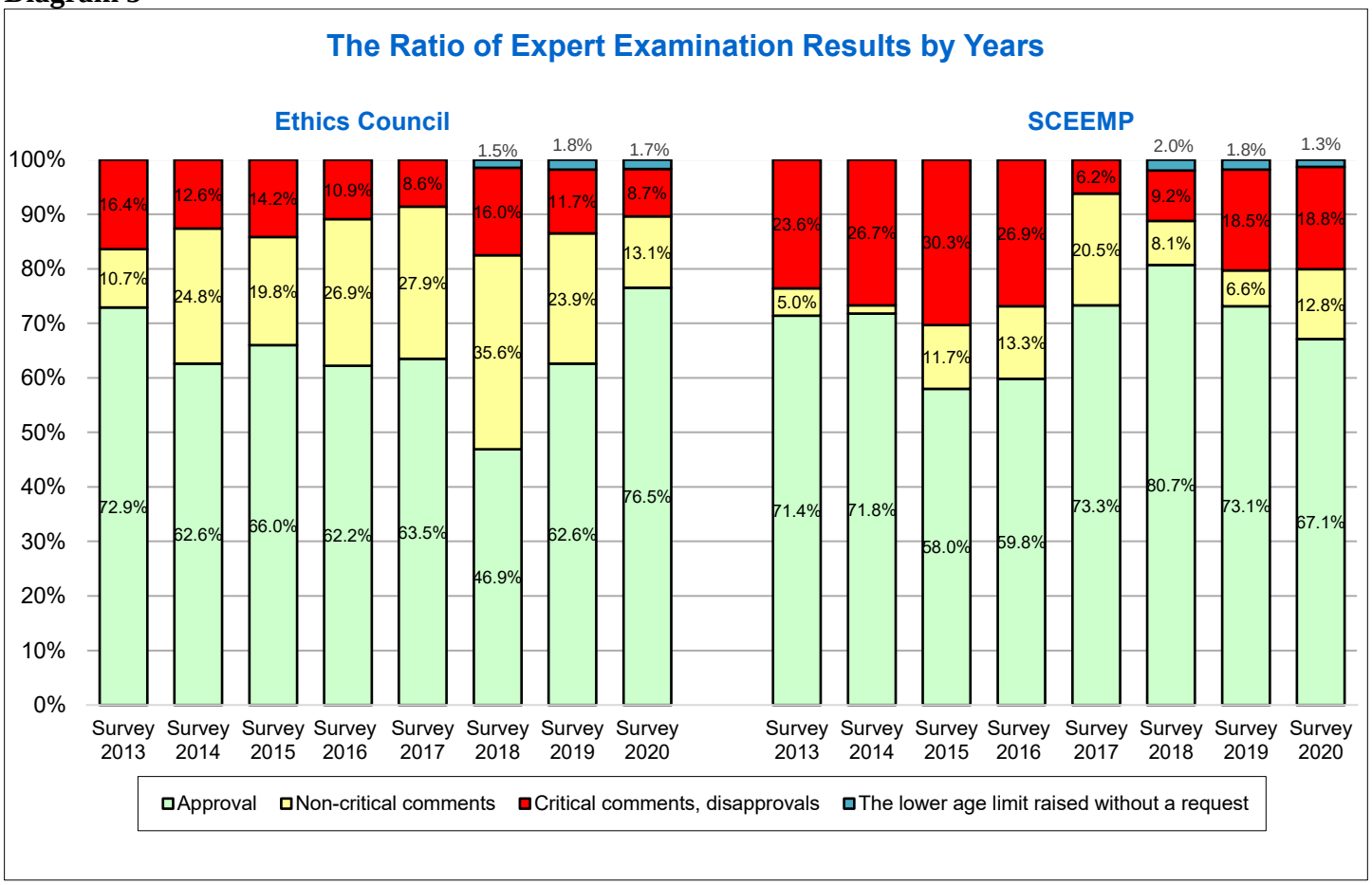
A higher share of IMCTs that passed expert evaluation without any comments from the Ethics Council was caused above all by decreasing the share of cases which received non-critical comments (13.1% versus 23.9% based on the 2019 survey results), which is also true for SCEEMP. Though it should be noted that the share of cases on which critical comments were received has also dropped to 2.6% against 5% a year before. The share of IMCTs with disapprovals as well as those where the age of participants was increased without notifying the applicant has almost remained unchanged, standing at 6.1% versus 6.8% and 1.7% versus 1.8%, respectively.

As regards the cumulative result for both types of expert evaluations, only 52.8% of all primary applications have passed safely. Yet this result proved better than a year before, when it stood at 47.3%. This is caused by decreasing the share of cases with non-critical comments to 21.4% versus 26.1% based on the 2019 survey results. The total share of cases with critical comments insignificantly decreased from 17.1% to 16.2%. The share of disapprovals has sunk even less from 7.7% to 7.4%. While the share of cases where the age of participants was raised without notifying the applicant has grown by a meager 0.4 p.p. (from 1.8% to 2.2%).

Diagram 5 shows the dynamics of results of different expert evaluations by years. It reflects more graphically a remarkable quality progress demonstrated by expert evaluations of the Ethics Council: the share of IMCTs that passed this expert body without comments proved maximum at least for eight recent years monitored. And the share of cases that received critical comments stood almost at minimum (only the survey of 2017 revealed a better result). This trend in the expert body which has raised most flags among the industry operators in several recent years cannot but rejoice.

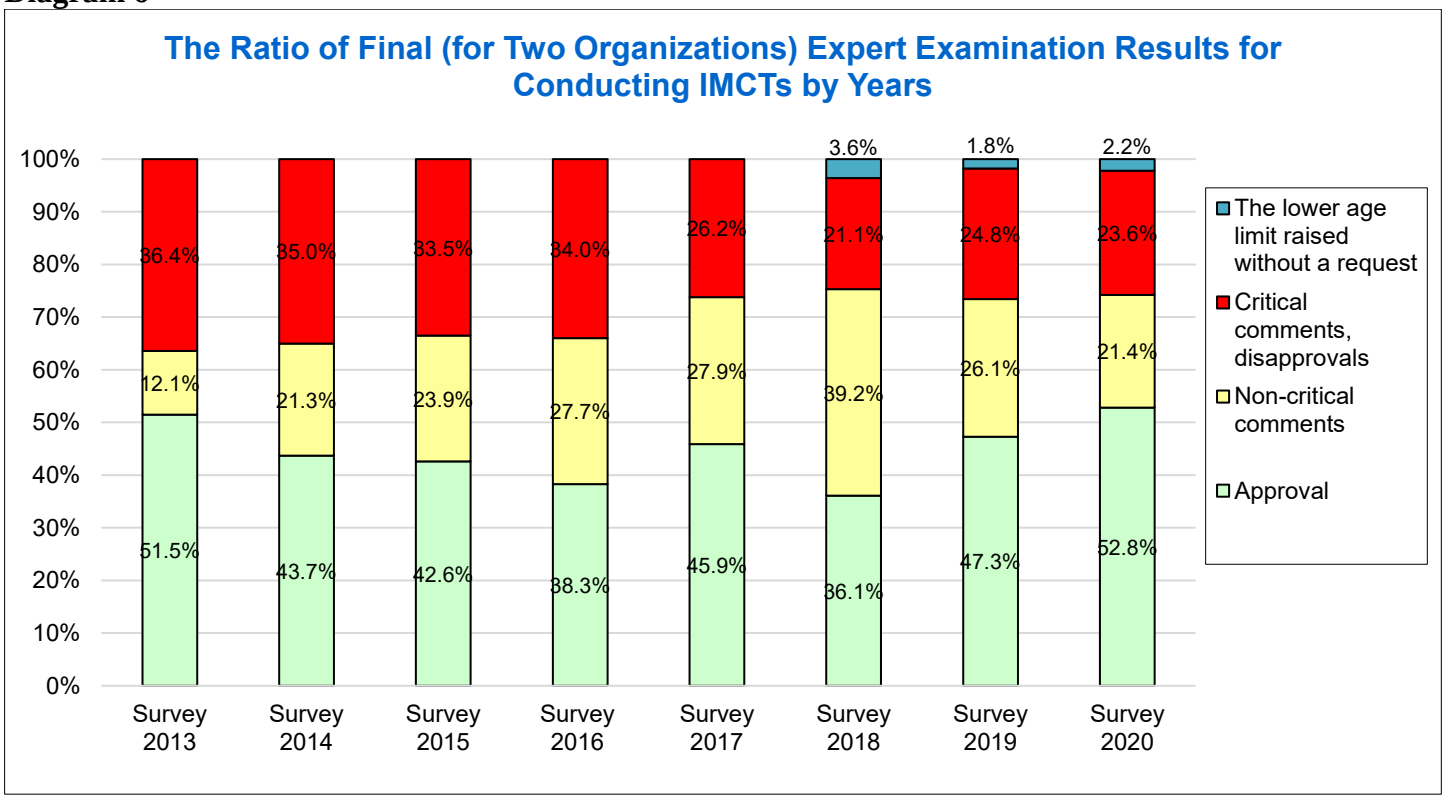
On the contrary, the situation with SCEEMP expert evaluations looks bleak as can be seen from the data collected. Nevertheless, it has not reached the critical levels typical of 2015-16 so far and hopefully it won't reach them in the future.

Diagram 5



Data from poll of ACTO members

Diagram 6



Data from poll of ACTO members

Finally, see Diagram 6 for the annual dynamics of results of reviewing the documentation by both expert bodies. And here the picture is more or less rosy. The share of cases that passed both expert evaluations without comments is at maximum for the entire period of monitoring. But what is no less and maybe even more important is that the share of cases with critical comments is almost at minimum (it was better only in 2018).

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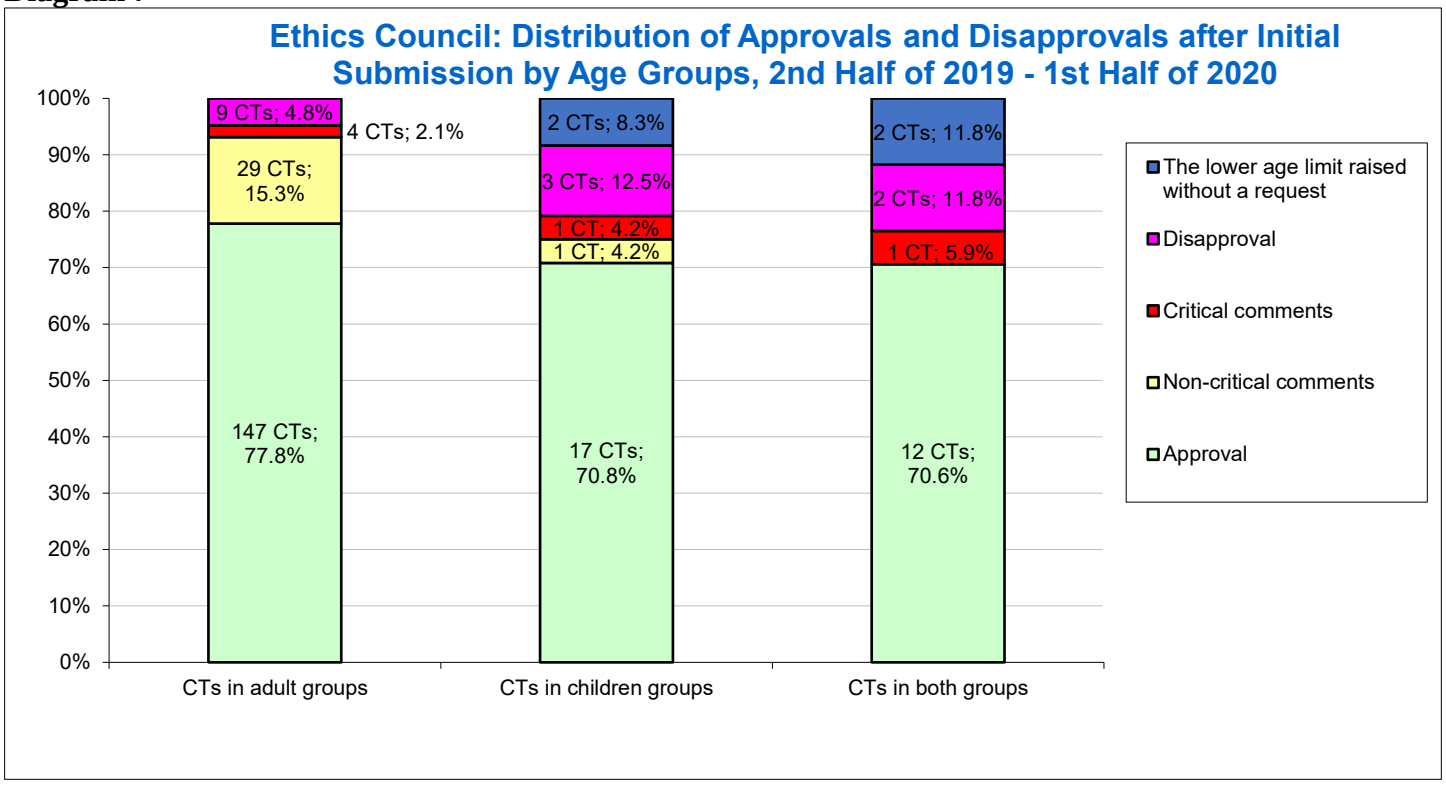
Given below are the results of reviewing the impact of age parameters of trials planned upon the expert body's opinion. We traditionally divide all planned IMCTs into three groups: with adults participating, with only pediatric population participating, and with both groups (adults and children) participating. Diagram 7 reflects the results of reviewing these three groups of protocols drawn by the Ethics Council.

It can be noted straight away that the indicators have improved for all three groups as compared with the 2019 survey. Thus the share of protocols involving adults that passed the expert evaluation without comments has increased from 66.1% to 77.8%. The share of pediatric protocols that have raised no red flags from the Ethics Council's experts has also increased from 50% to 70.8%. Finally, the share of protocols that included the mixed population and passed this barrier without any snags amounted to 70.6% versus 45% a year before. It is gratifying that not only the shares themselves have increased, but the gap between different groups of trials has also narrowed. Thus, if in 2019 it stood at 16.1 and 21.1 p.p. between the first and second as well as the first and third groups of protocols, respectively, this year it stands at 7.0 and 7.2 p.p. This progress gives hope that the apparent bias of the Ethics Council's experts towards pediatric protocols has been overcome to a certain extent[1].

Diagram 7



Data from poll of ACTO members

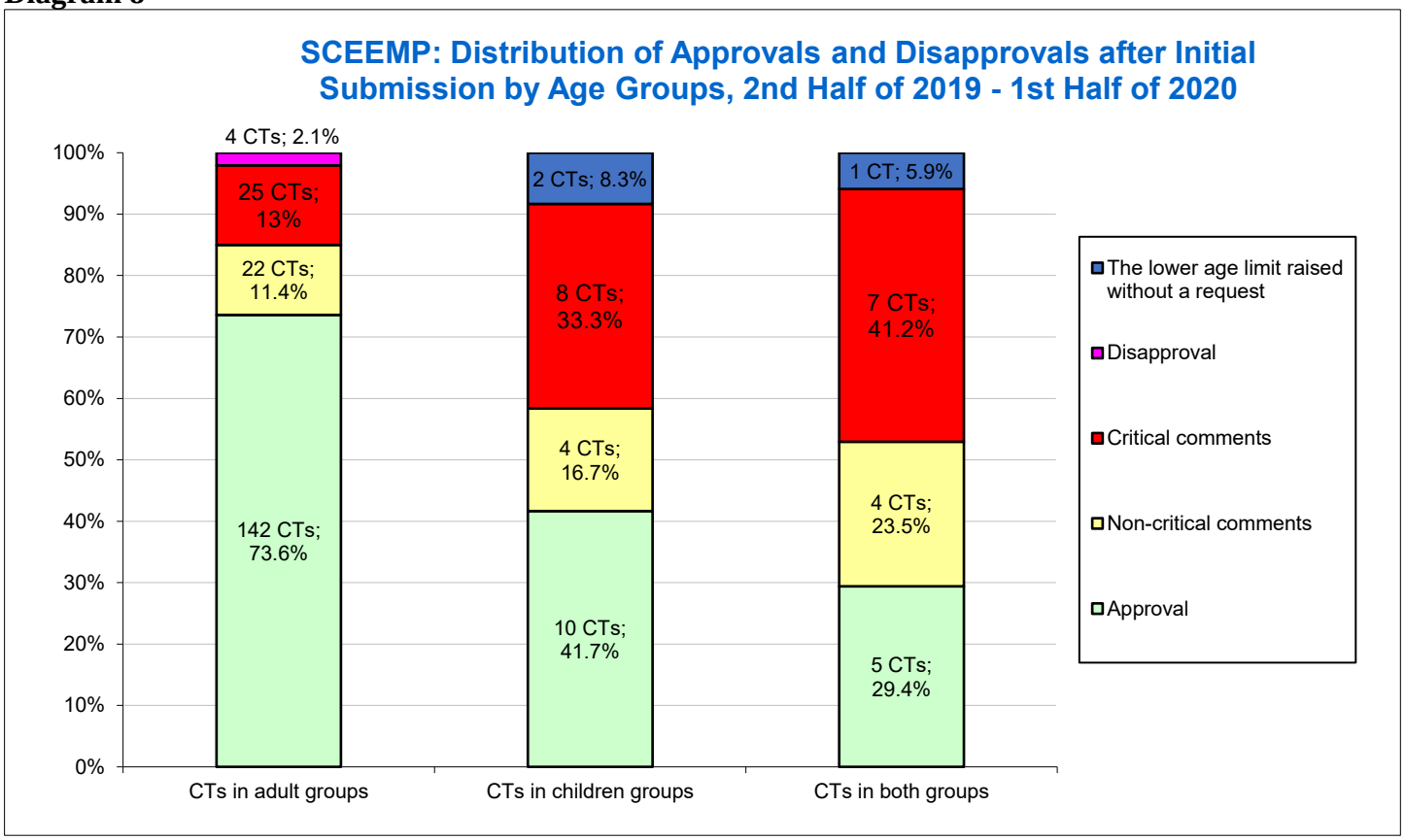
Regrettably, SCEEMP experts do not deserve similar compliments (Diagram 8). Here the results have deteriorated and the gap between the groups is rather obvious. The 2019 survey revealed that 77.6% of the trials with only adult population involved went uncensored, whereas in 2020 their share dropped to 73.6%. The gap is not critical. On the other hand, SCEEMP took a much stricter approach to pediatric protocols: 52.2% of all cases went uncensored in 2019 and only 41.7% in 2020. As for the protocols that involved a mixed population, their lot was unenviable: for them the chance to pass the expert evaluation without comments shrank from 57.2% to

[1] For more detail about the IMCT situation with pediatric population involved see the ACTO Newsletter #20.

only 29.4%! As a result, the gap between the groups has grown from 25.4 and 20.4 p.p. between the first-second and first-third groups to 31.9 and 44.2 p.p., respectively.

It's hard not to mention the fact that the decreasing share of cases that have passed the expert evaluation uncensored was due above all to an increased percentage of cases that received critical comments. Thus solely for pediatric protocols the share of such cases has increased from 26.1% to 33.3% and for mixed protocols - from 19% to 41.2%.

Diagram 8



Data from poll of ACTO members

Given below is the distribution of expert evaluation results depending on a therapeutics area of a trial planned. Table 1 and Diagram 9 show a respective distribution for the Ethics Council. As we can see from the diagram, ophthalmology trials were least lucky in the past year, with only 20% of all protocols approved at first go. Yet this can be caused by a small number of trials in this area. This is perhaps the reason for an unenviable fate of trials in obstetrics and gynecology. Psychiatry traditionally "ostracized" by Ethics experts this time ranked only third in the anti-rating. Nevertheless, this therapeutics area has slightly improved its showing. If, according to the results of the 2019 survey, only 42% of IMCTs in psychiatry had passed the expert evaluation at the Ethics Council without comments on the first try, then this year their number has slightly risen to 47%.

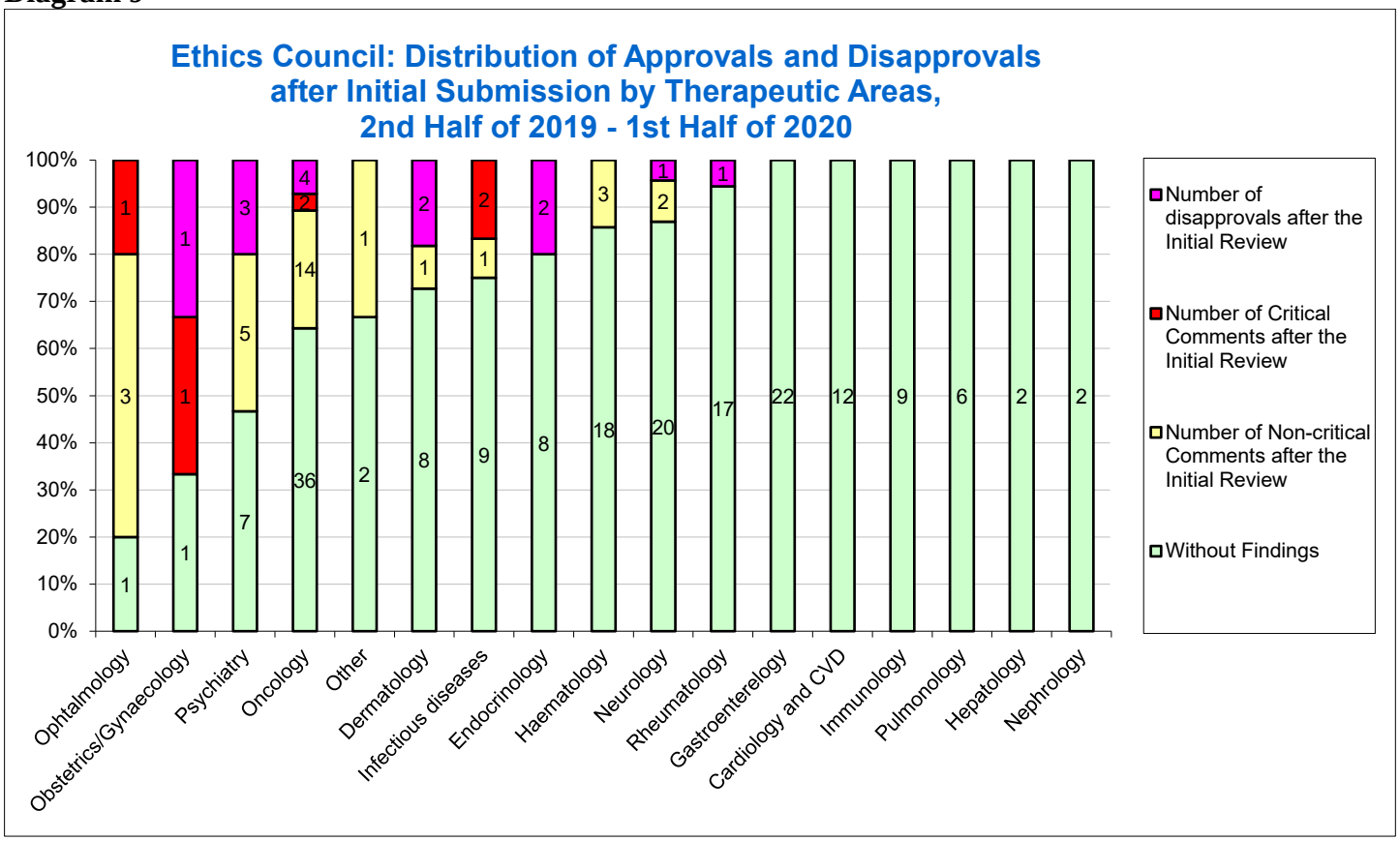
And on the whole it can be stated that by the "share of cases without comments" literally all therapeutics areas with the notable exception of ophthalmology have improved their showing. Most rewarding is that it's also true for the most numerous area – oncology, where the share of expert evaluations without comments has grown from 57% to 64%. For neurology which by the number of stated trials ranked second this indicator has risen from 53% to 87%.

Table 1

Ethics Council: Distribution of Approvals and Disapprovals by Therapeutic Areas									
Therapeutic Areas	**Total Number of Initial Submissions**	**Without Findings**	**Without Findings, % of Total**	**Number of Non-critical Comments after the Initial Review**	**Non-critical Comments after the Initial Review, % of Total**	**Number of Critical Comments after the Initial Review**	**Critical Comments after the Initial Review, % of Total**	**Number of Disapprovals after the Initial Review**	**Number of Disapprovals after the Initial Review, % of Total**
Oncology	56	36	64%	14	25%	2	3.6%	4	7.1%
Neurology	23	20	87%	2	9%	0	0.0%	1	4.3%
Gastroenterelogy	22	22	100%	0	0%	0	0.0%	0	0.0%
Haematology	21	18	86%	3	14%	0	0.0%	0	0.0%
Rheumatology	18	17	94%	0	0%	0	0.0%	1	5.6%
Psychiatry	15	7	47%	5	33%	0	0.0%	3	20.0%
Cardiology and Cardiovascular diseases	12	12	100%	0	0%	0	0.0%	0	0.0%
Infectious diseases (except HIV/HCV/tuberculosis)	12	9	75%	1	8%	2	16.7%	0	0.0%
Dermatology	11	8	73%	1	9%	0	0.0%	2	18.2%
Endocrinology	10	8	80%	0	0%	0	0.0%	2	20.0%
Immunology	9	9	100%	0	0%	0	0.0%	0	0.0%
Pulmonology	6	6	100%	0	0%	0	0.0%	0	0.0%
Ophtalmology	5	1	20%	3	60%	1	20.0%	0	0.0%
Obstetrics/Gynaecology	3	1	33%	0	0%	1	33.3%	1	33.3%
Hepatology	2	2	100%	0	0%	0	0.0%	0	0.0%
Nephrology	2	2	100%	0	0%	0	0.0%	0	0.0%
Other	3	2	67%	1	33%	0	0.0%	0	0.0%
Total	230	180	78%	30	13%	6	2.6%	14	6.1%

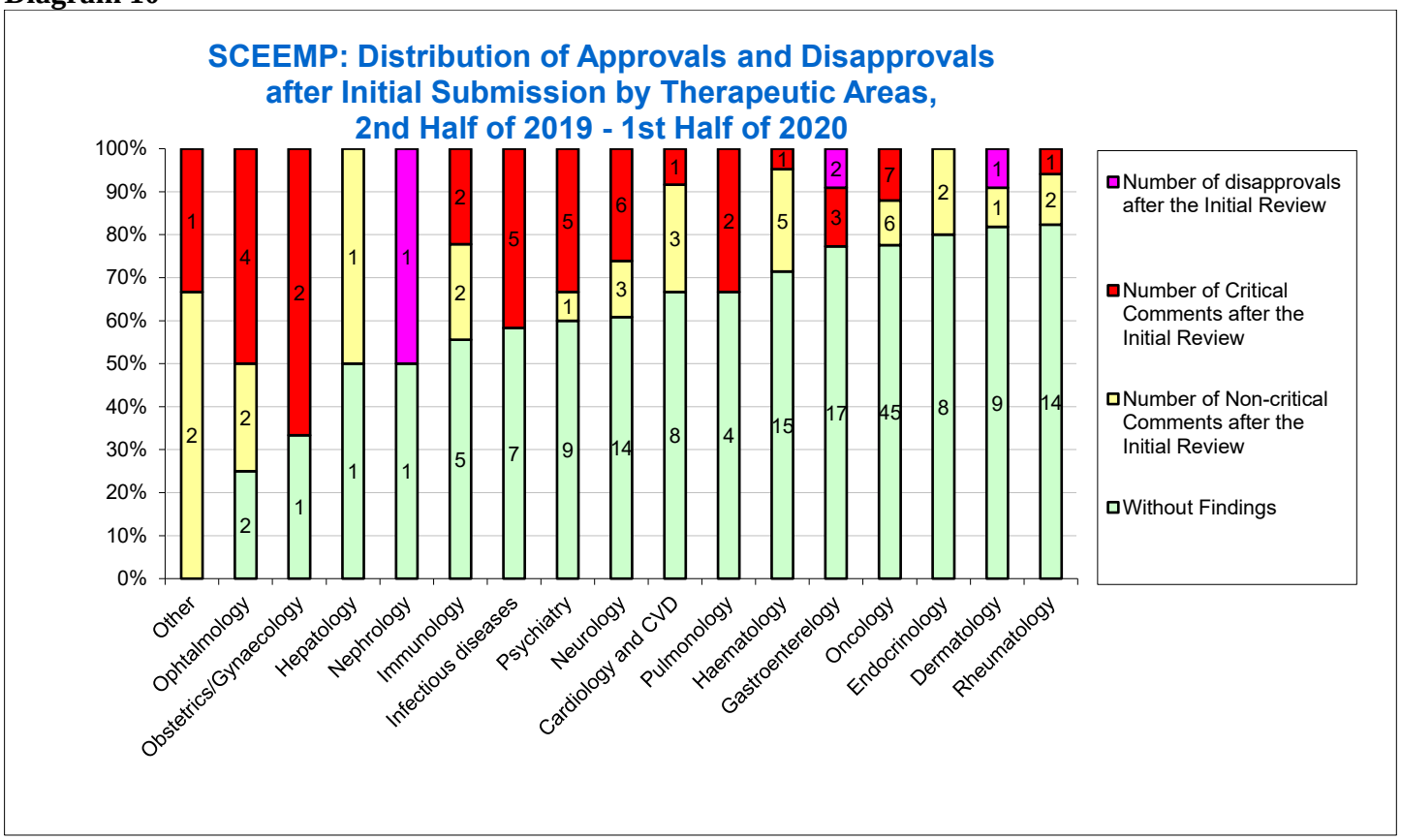
Data from poll of ACTO members

Diagram 9



Data from poll of ACTO members

Diagram 10



Data from poll of ACTO members

Table 2

SCEEMP: Distribution of Approvals and Disapprovals by Therapeutic Areas									
Therapeutic Areas	**Total Number of Initial Submissions**	**Without Findings**	**Without Findings, % of Total**	**Number of Non-critical Comments after the Initial Review**	**Non-critical Comments after the Initial Review, % of Total**	**Number of Critical Comments after the Initial Review**	**Critical Comments after the Initial Review, % of Total**	**Number of Disapprovals after the Initial Review**	**Number of Disapprovals after the Initial Review, % of Total**
Oncology	58	45	77.6%	6	10.3%	7	12.1%	0	0.0%
Neurology	23	14	60.9%	3	13.0%	6	26.1%	0	0.0%
Gastroenterelogy	22	17	77.3%	0	0.0%	3	13.6%	2	9.1%
Haematology	21	15	71.4%	5	23.8%	1	4.8%	0	0.0%
Rheumatology	17	14	82.4%	2	11.8%	1	5.9%	0	0.0%
Psychiatry	15	9	60.0%	1	6.7%	5	33.3%	0	0.0%
Cardiology and Cardiovascular diseases	12	8	66.7%	3	25.0%	1	8.3%	0	0.0%
Infectious diseases (except HIV/HCV/tuberculosis)	12	7	58.3%	0	0.0%	5	41.7%	0	0.0%
Dermatology	11	9	81.8%	1	9.1%	0	0.0%	1	9.1%
Endocrinology	10	8	80.0%	2	20.0%	0	0.0%	0	0.0%
Immunology	9	5	55.6%	2	22.2%	2	22.2%	0	0.0%
Ophtalmology	8	2	25.0%	2	25.0%	4	50.0%	0	0.0%
Pulmonology	6	4	66.7%	0	0.0%	2	33.3%	0	0.0%
Obstetrics/Gynaecology	3	1	33.3%	0	0.0%	2	66.7%	0	0.0%
Hepatology	2	1	50.0%	1	50.0%	0	0.0%	0	0.0%
Nephrology	2	1	50.0%	0	0.0%	0	0.0%	1	50.0%
Other	3	0	0.0%	2	66.7%	1	33.3%	0	0.0%
Total	234	160	68.4%	30	12.8%	40	17.1%	4	1.7%

Data from poll of ACTO members

Table 2 and Diagram 10 show the distribution SCEEMP expert evaluation results by therapeutics areas. Here the "other" category has been least lucky, but it makes no sense to dwell on it because it includes only three protocols. As for the rest of therapeutics areas, ophthalmology has the lowest share of first-go approvals, as is also the case with the Ethics Council's expert evaluations.

It's rewarding to see improvements in an important therapeutics area such as infectious diseases. Protocols in this area are often subjected to a particularly severe inspection by SCEEMP experts, though in 2020 the share of cases approved uncensored has risen to 58.3% from 35.7% based on the 2019 survey. However, the pandemic might have contributed to this outcome: for understandable reasons, most protocols of medicinal candidates for fighting COVID-19 "flew by" expert evaluations without any delays or bureaucratic snags since March 2020. Truly, this was a blessing in disguise.

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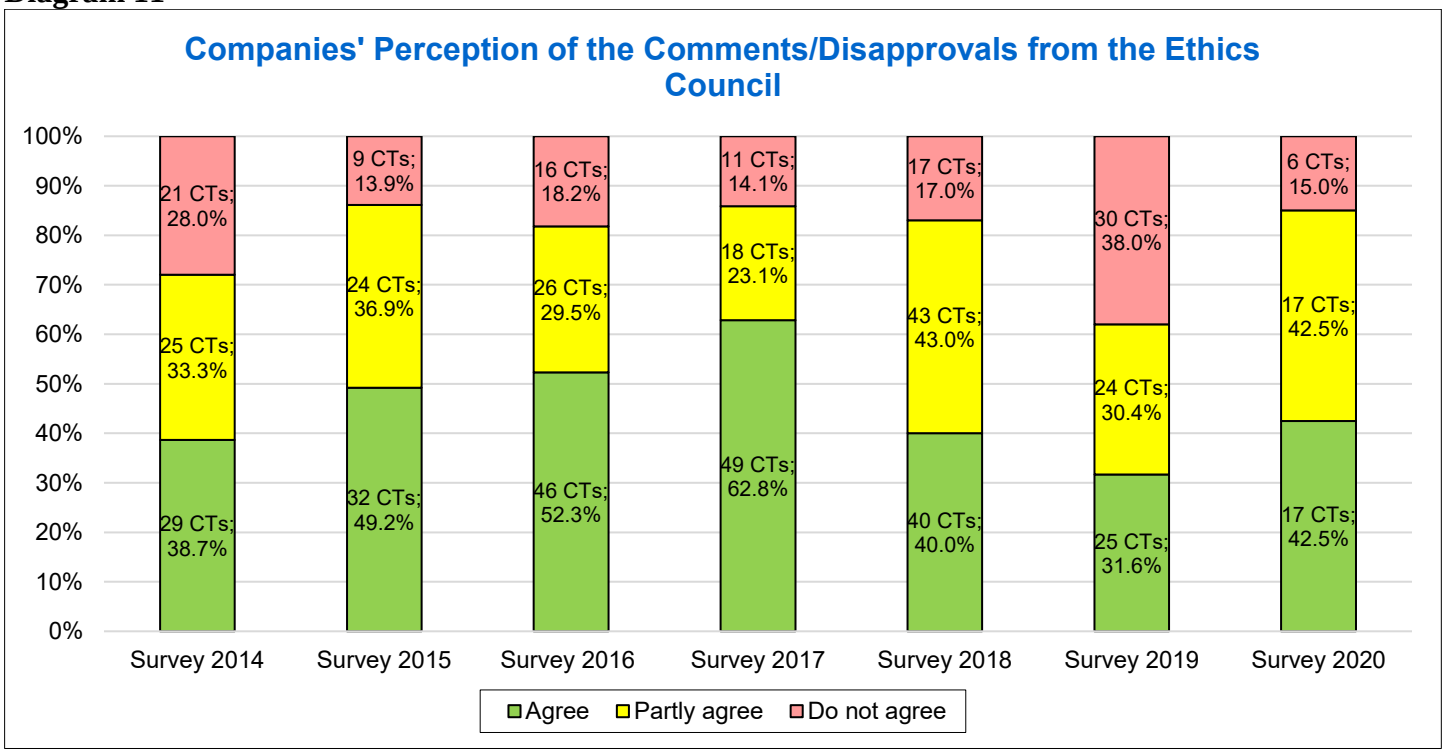
The concluding part of our review traditionally covers more subjective parameters, such as the perception by companies of the fairness of requests and comments addressed to them by expert bodies, and how they responded to those comments.

In particular, you can see on Diagram 11, how the attitude of companies towards the expert evaluations of the Ethics Council has changed year after year. You can see that the level of accord with comments has notably risen based on the latest survey's results, almost by 11 p.p. (from 31.6% to 42.5%). The share of cases where applicants explicitly disagreed with reprimands has significantly decreased from 38% to 15%. This greater loyalty correlates quite well with the "liberalisation" trend so apparent in recent expert evaluations provided by the Ethics Council.

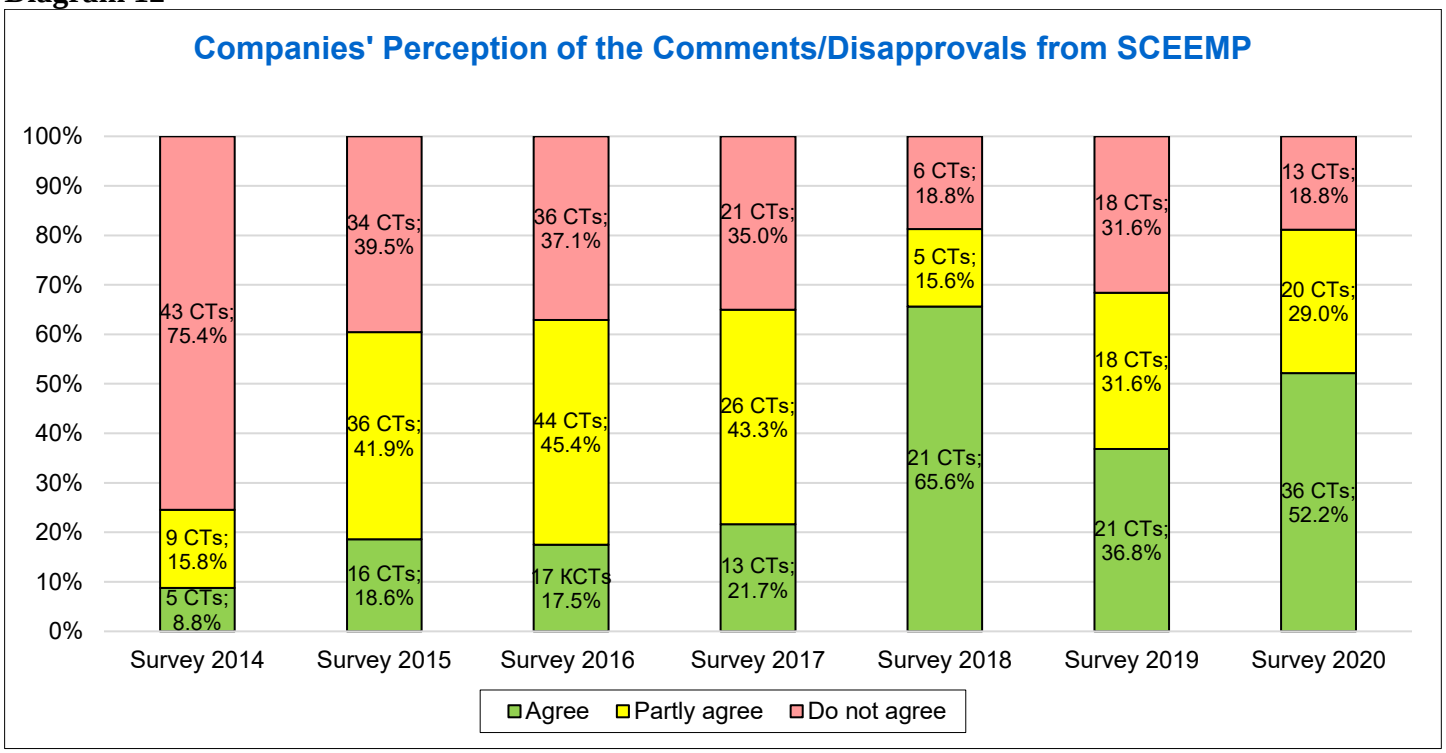
Diagram 11



Data from poll of ACTO members

The situation with SCEEMP evaluations is different. The companies' perception of comments they receive from this expert body has also improved in comparison with the 2019 survey (Diagram 12), although, as we can remember, the expert evaluation has become more rigid towards applicants this year. Nevertheless, applicants agreed with comments received in 52.2% of cases (more often than with the Ethics Council), whereas in 2019 this indicator stood at 36.8% (of all cases). The share of cases receiving comments with which companies disagreed has dropped from 31.6% to 18.8%. We can only express hope that this credit of trust on the part of applicants won't be wasted.

Diagram 12



Data from poll of ACTO members

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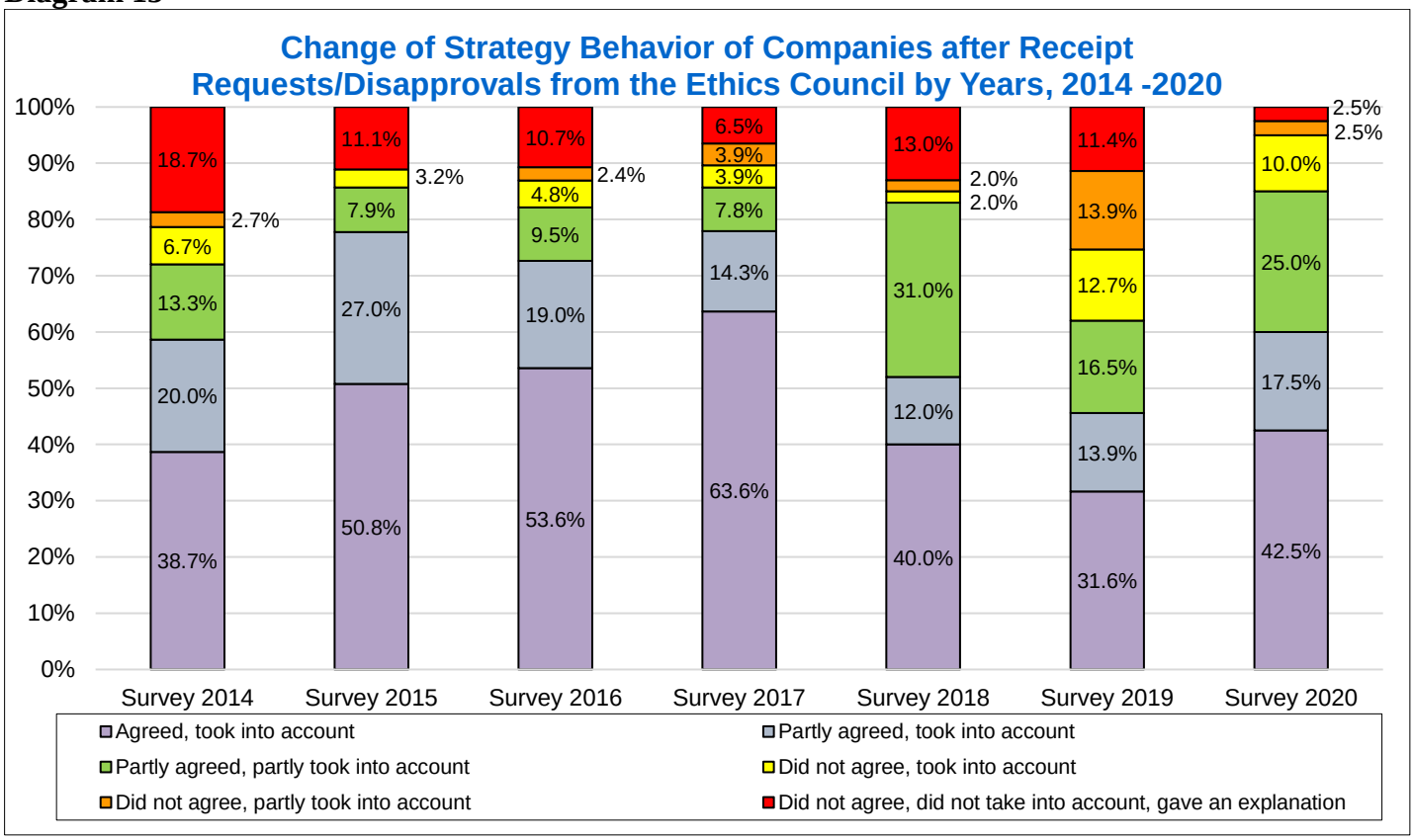
Now let us consider what strategy of conduct has been chosen by companies as they responded to comments about the documents submitted. Diagram 13 shows changes in the yearly response of applicants to the Ethics Council's expert evaluations. As you can see, the option "agreed, took into account" is still most popular. In the 2020 survey applicants chose it in 42.5% of cases, i.e. almost 11 p.p. more often than a year before. The shares of strategies such as "partly agreed, took into account" (17.5%, 3.6 p.p. more) and "partly agreed, partly took into account" (25%, 8.5 p.p. more) have also increased. On the other hand, the share of cases where applicants explicitly disagreed with the expert opinion has shrunk. Companies had to choose the "did not agree, took into account" strategy in 10% of cases. The share of cases where applicants have partly taken into account the criticism despite their general disagreement or totally neglected them after giving respective explanations has dropped to 2.5%.

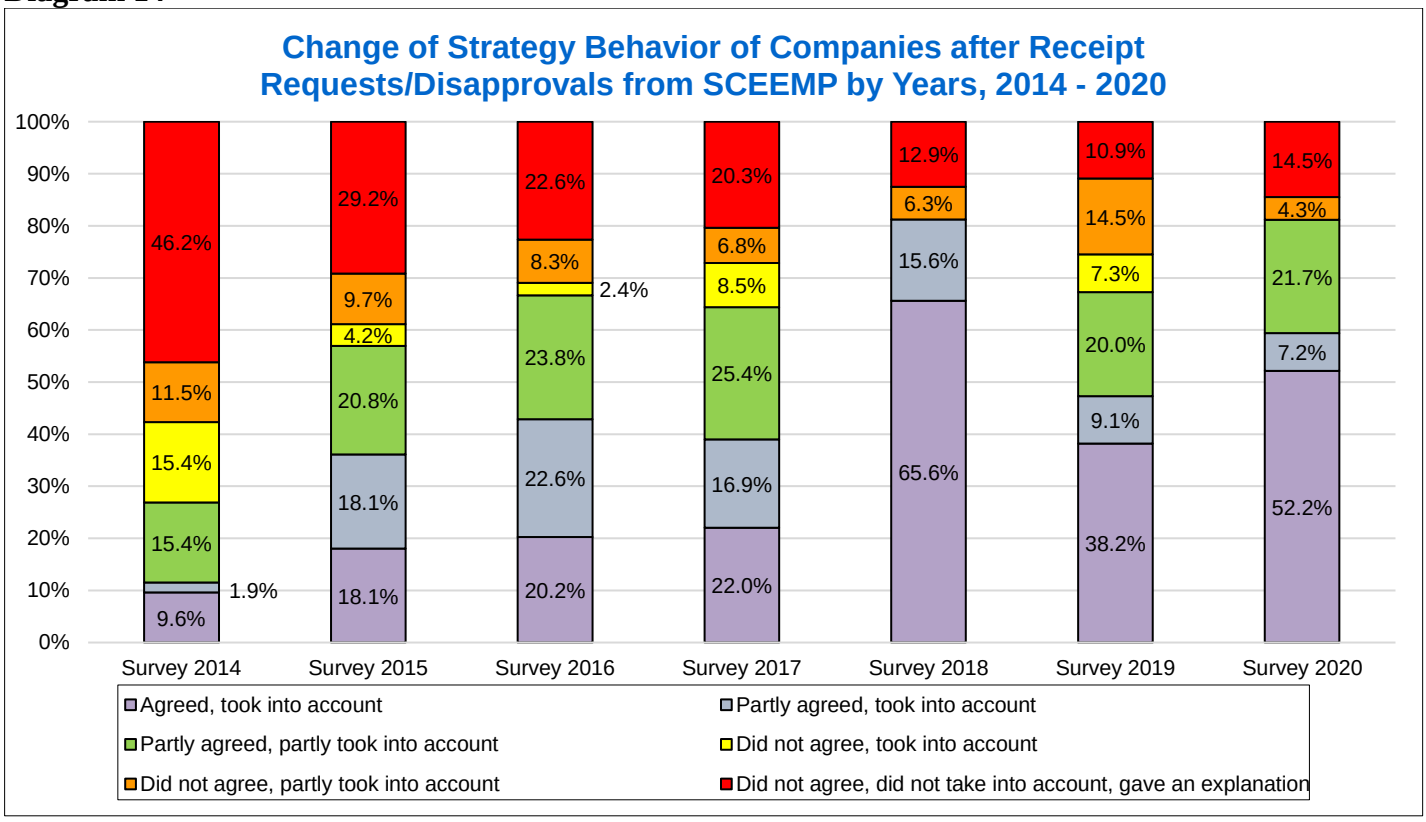
The balance of corporate strategies was somewhat different for interaction with the second expert body: SCEEMP, see Diagram 14. The latest survey reveals that the share of cases where applicants agreed with expert criticisms and worked on them has also grown year-on-year to 52.2%. The strategy "partly agreed, took into account" ranked second in terms of frequency and was used by applicants in 21.7% of cases. The cases where companies resolutely disagreed with the expert opinion so they had to give their explanations and stand for their point of view ranked third, however (14.5%). The share of cases where companies were forced to partly take into account expert criticism despite their disagreement has markedly decreased, as compared to the previous survey results (4.3% versus 14.5% in accordance with the 2019 survey).

Diagram 13



Data from poll of ACTO members

Diagram 14



Data from poll of ACTO members

CORRELATION BETWEEN TYPES OF CLINICAL TRIALS AND DESIGN USED

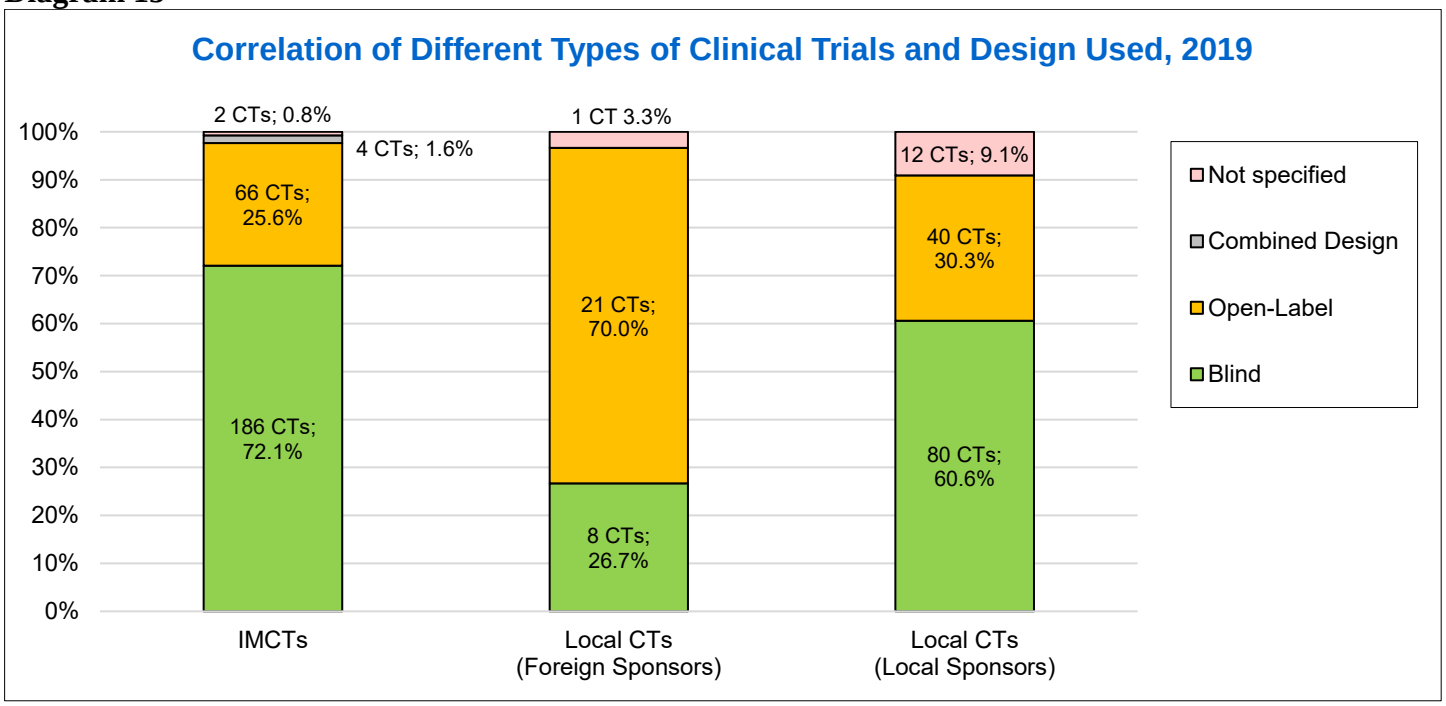
As we followed up with the section that appeared for the first time a year ago, we reviewed the design of clinical trials protocols again, specifically the balance between blind and open trials in approvals issued by Russian Ministry of Health in 2019. Diagram 15 shows the results separately for each type of trials: IMCTs, local trials by foreign and domestic sponsors.

In IMCTs the share of protocols where the blind method is used has somewhat decreased as compared with the same indicator a year ago: 72.1% in 2019 versus 76.3% in 2018. Accordingly, the share of open IMCTs has increased: 25.6% in 2019 versus 21.7% in 2018. Despite this change, IMCTs still surpass local trials by the frequency of the blind method used. The share of combined protocols in IMCTs stood at 2.1% in 2018, but only at 1.6% in 2019. In 0.8% other protocols the use of the blind method was not mentioned in 2019, which does not mean this method was not used.

The balance between blind and open protocols in local trials of Russian sponsors roughly coincides with the data recorded a year before: 60.6% where the blind method was used in 2019 versus 56% in 2018, and 30.3% without blindfolding in 2019 versus 34.7% in 2018. The share of protocols where the use of the blind method is not explicitly stated also remained roughly the same: 9.1% in 2019 versus 9.3% a year earlier. All changes described above can be explained by natural fluctuations, which are in inverse relationship with absolute figures subject to estimation. Thus the total number of local trials by Russian sponsors is less than the IMCT count; accordingly, fluctuations in this group of trials are more pronounced.

This explanation is even truer for the smallest group: local trials by foreign sponsors. Here the share of open protocols was already the largest, but it grew even more to 70% in 2019 versus 52% in 2018. The share of blind trials dropped from 40% in 2018 to 26.7% in 2019. The share of protocols with unclear design stood at 3% in 2019 versus 8% a year earlier (1 and 2 protocols, respectively, in absolute figures). As we already noted a year ago, a large share of open protocols can be related to the fact that foreign sponsors often conduct local trials solely for the purpose of registration, rather than for obtaining new data.

Diagram 15



Data from www.grls.rosminzdrav.ru

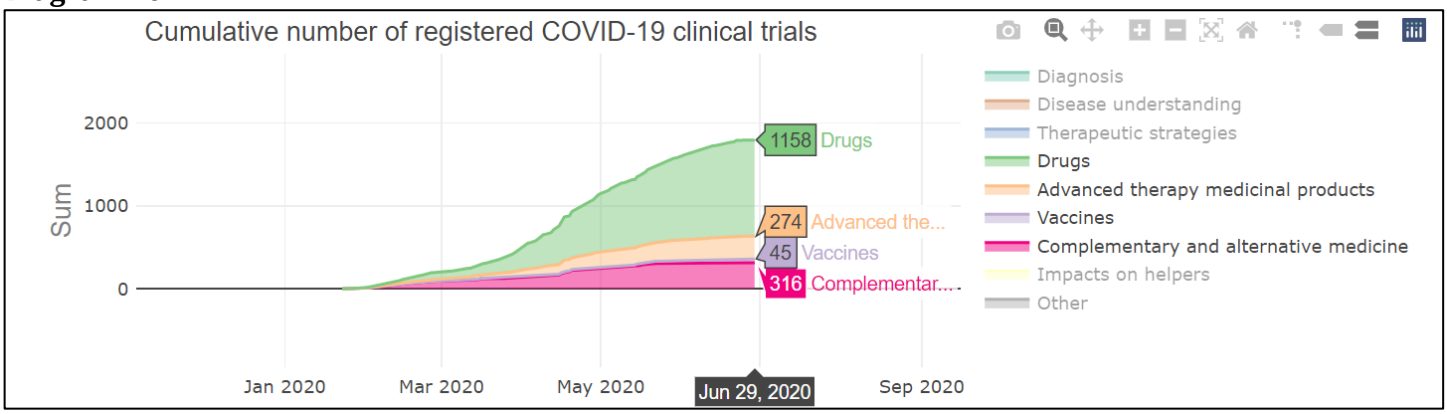
SITUATION WITH CLINICAL TRIALS OF MEDICINAL PRODUCTS FOR COVID-19

In the wake of the COVID-19 pandemic the universal focus has shifted towards the trials of medicinal products used in the treatment of the new coronavirus infection. By the time of the Newsletter release the Ministry of Health had approved the conduct of 43 such trials. But keeping up with our semiannual schedule below, we review the situation with this category of trials in Russia only in the first half year of 2020.

From January to June of 2020 the authorities issued 26 approvals for the trials of medications used in the treatment of COVID-19 (8.6% of all approvals issued in this period). More approvals were issued only in areas such as oncology (43 approvals, 14.2% of all issued in H1), neurology (37 and 12.3% respectively) and cardiology with CVD (32 and 10.6%).

These data can be compared with the Map of Clinical Trials for COVID-19 drawn on the basis of information found in the International Clinical Trials Registry Platform of WHO[2]. As of the late June 2020 the WHO Register included 1,158 trials of medicines, 45 trials of vaccines, in addition to 274 trials of advanced therapy medications that were taken stock separately and 316 trials of alternative medicinal products (see Diagram 16). The ClinicalTrials.gov Register reveals that in the first half of 2020 about 1,200 trials were due to be launched where COVID-19 or SARS-CoV-2 is indicated in the "disease" column. The Russian share in the worldwide volume of clinical trials of remedies for the coronavirus is less than 2% which corresponds with the share of Russia in the global volume of clinical trials in all therapeutics areas.

Diagram 16

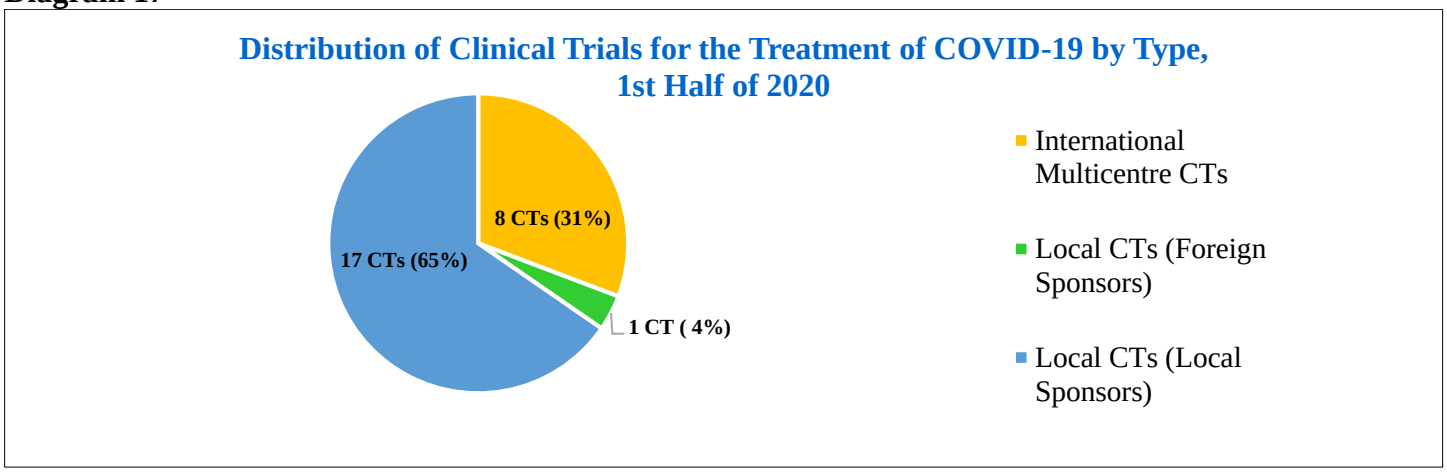


Data from: **https://covid-19.heigit.org/clinical_trials.html**

Diagram 17 shows the distribution of approvals for the testing of medicinal products against COVID-19 by types of trials. As can be seen, two thirds of all protocols are developed by domestic sponsors (17 trials), whereas IMCTs account for only one third of protocols (8 trials). The only trial initiated by a foreign sponsor as local stands out rather uncommon.

[2] https://covid-19.heigit.org/clinical_trials.html

Diagram 17



Data from www.grls.rosminzdrav.ru

Table 3 gives us information about the sponsors who initiated trials. Novartis with three approvals is the leader among IMCTs by the number of trials. Other foreign sponsors were granted one approval each, namely: Apeiron Biologics, Acerta Pharma, Sanofi, F. Hoffmann-La Roche and Eli Lilly that initiated IMCTs as well as Il-Yang Pharmaceuticals which sponsored the local trial.

Among the Russian developers Generium, Pharmasyntez and the Gamaleya National Center have two approvals each. Eleven more domestic sponsors each initiated one trial of medicinal products meant for the treatment of COVID-19.

Table 3

Distribution of Clinical Trials for the Treatment of COVID-19 by Sponsors, 1st Half of 2020

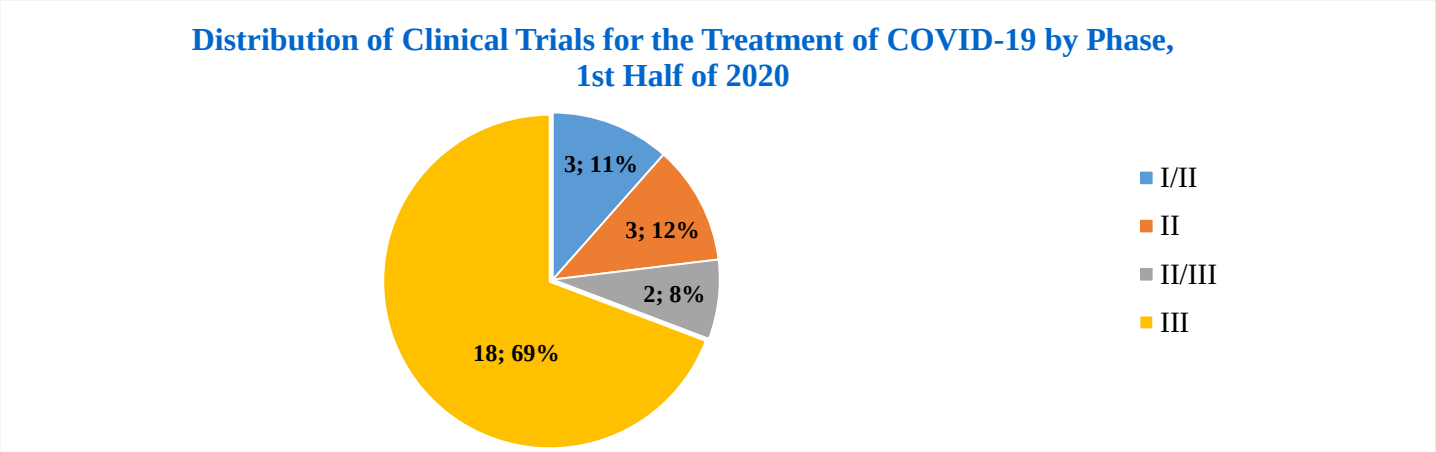
Company	Conducted by themselves	Conducted by CRO	Total	Type of CT
Novartis	3	-	3	IMCT
Generium	2	-	2	Local CT (Local Sponsor)
Pharmasyntez	2	-	2	Local CT (Local Sponsor)
The Gamaleya National Center of Epidemiology and Microbiology under the Ministry of Health of the Russian Federation	2	-	2	Local CT (Local Sponsor)
Allopheron	1	-	1	Local CT (Local Sponsor)
Apeiron Biologics	-	1	1	IMCT
Acerta Pharma B.V. (AstraZeneca)	1	-	1	IMCT
Biocad	1	-	1	Local CT (Local Sponsor)
Biocom	1	-	1	Local CT (Local Sponsor)
Viriom	-	1	1	Local CT (Local Sponsor)
Il-Yang Pharmaceuticals	-	1	1	Local CT (Foreign Sponsor)
Chromis	-	1	1	Local CT (Local Sponsor)
Petrovax Pharm	1	-	1	Local CT (Local Sponsor)
Promomed Rus	1	-	1	Local CT (Local Sponsor)
RSV Therapeutics	-	1	1	Local CT (Local Sponsor)
R-Pharm	1	-	1	Local CT (Local Sponsor)
Sanofi	1	-	1	IMCT
Medicine Technology	1	-	1	Local CT (Local Sponsor)
F. Hoffmann-La Roche	1	-	1	IMCT
Scientific Center of Biomedical Technologies of the FMBA	1	-	1	Local CT (Local Sponsor)
Eli Lilly	1	-	1	IMCT
TOTAL	21	5	26	

Data from www.grls.rosminzdrav.ru

In five cases sponsors involved other organisations in their clinical trials: Research Institute of Chemical Diversity was engaged twice (by sponsors such as Chromis and Viriom); Synergy Research Group (sponsor: RSV Therapeutics), IPHARMA (sponsor: Apeiron Biologics) and R-Pharm that helped to organise a trial for Il-Yang Pharmaceuticals in Russia were involved one time each.

See the distribution of trials of interest to us by phases on the next diagram. 18 out of 26 approvals, i.e. more than a third were issued for the trials of phase III. Three approvals were issued for trials of phases I/II and II each and two approvals for trials of phase II/III.

Diagram 18



Data from www.grls.rosminzdrav.ru

Viriom tested elsulfavirin (one trial) as part of phase I/II, while the Gamaleya National Center tested a two-vector vaccine as an intramuscular solution and as a lyophilizate for preparing a solution (two trials). Acalabrutinib, DFV890 and APN01 passed Phase II trials. Sarilumab and the RPH-104 + olokizumab combination were tested in the protocols of phase II/III. You can get an idea of other medicinal products by referring to Table 4. But on the whole it can be noted that the key products that roused vibrant discussions in the professional community (e.g. hydroxychloroquine and remdesivir) are being tested in Russia.

Table 4

Medicinal products for COVID-19, whose trials were approved in H1 2020			
Name of medicinal product	**Product type**	**Number of trials**	**Company and number of trials**
Favipiravir	antiviral drug	4	Chromis - 1 Medicine Technology - 1 Promomed Rus - 1 Pharmasyntez - 1
Two-vector vaccine preventing the coronavirus infection caused by the SARS-CoV-2 virus	two-vector vaccine	2	The Gamaleya National Center under the Ministry of Health of the Russian Federation
DFV890 (IFM-2427)	inhibitor of the NLPR3 receptor to counter inflammations	1	Novartis – 1
RPH-104 + Olokizumab	interleukin-1 inhibitor and interleukin-6 inhibitor	1	R-Pharm - 1
Azoximer bromide	immunomodulatory agent	1	Petrovax Pharm - 1
Acalabrutinib	antitumor drug, protein kinase inhibitor	1	Acerta Pharma - 1
Allokine-alpha	oligopeptide	1	Allopheron - 1
Baricitinib	antiviral drug	1	Eli Lilly – 1
Hydroxychloroquine	antimalaria drug	1	Biocom - 1
Dalargin	regulatory peptide	1	Scientific Center of Biomedical Technologies of the FMBA - 1
Dornase alpha	mucolytic agent	1	Generium – 1
Canakinumab	interleukin-1-beta inhibitor	1	Novartis – 1
Levilimab	interleukin-6 inhibitor	1	Biocad - 1
Radotinib hydrochloride	antitumor drug	1	Il-Yang Pharmaceuticals

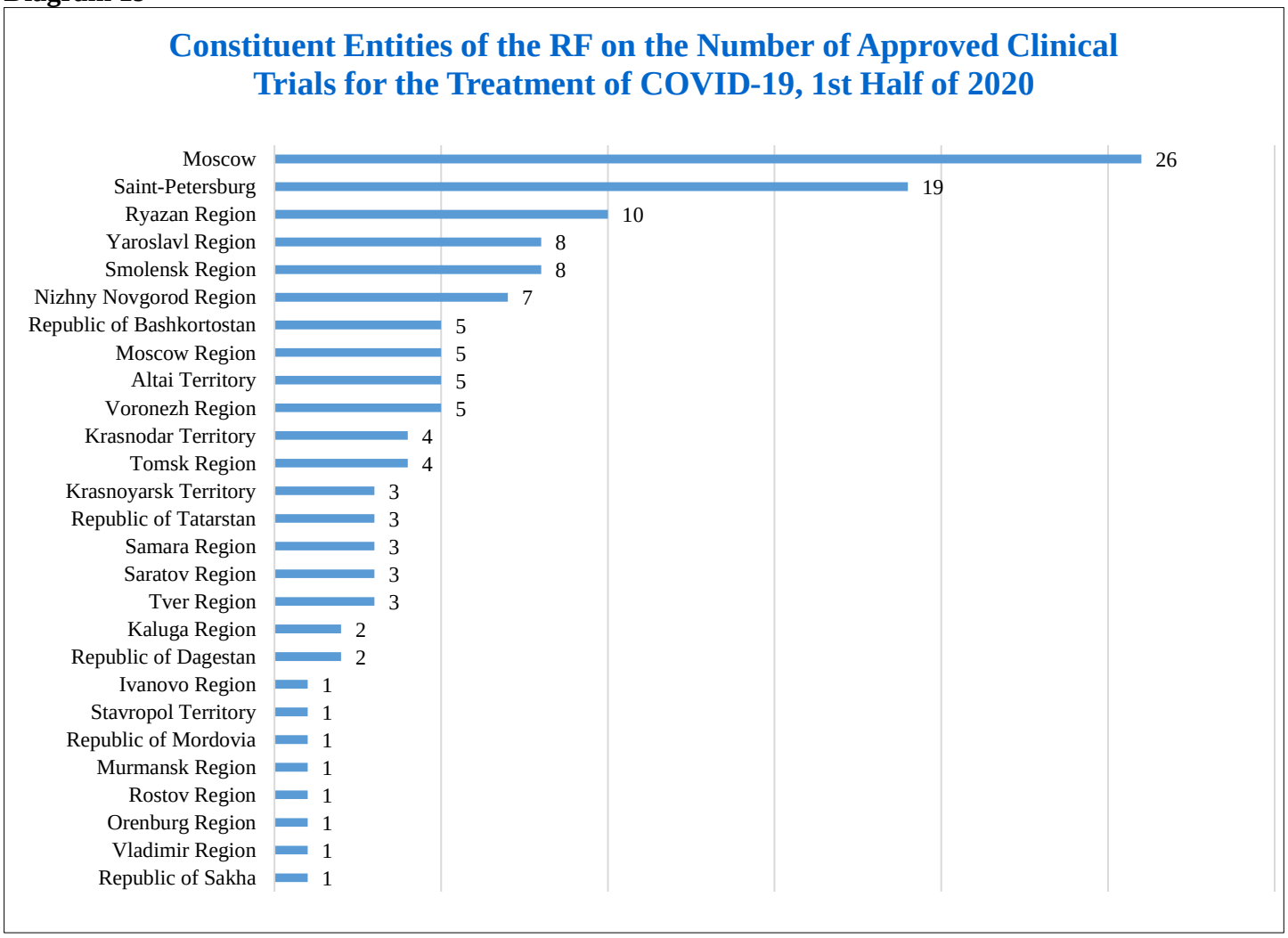
Recombinant human angiotensin transforming enzyme 2 (rhACE2), APN01	recombinant human angiotensin transforming enzyme 2	1	Apeiron Biologics
Remdesivir	antiviral drug	1	Pharmasyntez - 1
Remdesivir + Tocilizumab	antiviral drug, interleukin-6 inhibitor	1	F. Hoffmann-La Roche – 1
Ruxolitinib	inhibitor of tyrosine kinases JAK1 and JAK2	1	Novartis – 1
Sarilumab	blocker of receptors to interleukin-6	1	Sanofi – 1
XC221	antiviral drug	1	RSV Therapeutics - 1
Eculizumab	immunosuppressive agent	1	Generium – 1
Elsulfavirin	antiretroviral drug, non nucleoside reverse transcriptase inhibitor	1	Viriom - 1

Data from www.grls.rosminzdrav.ru

From 40 to 454 participants were involved in the trials of anti-COVID-19 drugs. The plan called for the recruitment of 120 to 250 patients in most protocols (in 15 out of 26).

The next diagram lists the regions of the Russian Federation where sites were to be opened for the 26 trials under review. Both capital cities are far ahead of other regions.

Diagram 19



Data from www.grls.rosminzdrav.ru

And in conclusion of our overview we show in Table 5 ten medical institutions that take the lead by the number of trials approved with their participation.

Table 5

Distribution of Clinical Trials for the Treatment of COVID-19 by Medical Organizations, 1st Half of 2020			
Place in ranking	**Name of medical organization**	**Number of approved clinical trials that involved this medical organization**	**Number of sites approved for conducting clinical trials**
1	Municipal Clinical Hospital No.15 named after O. M. Filatov, Moscow	16	16
2	I. M. Sechenov First Moscow State Medical University, Russian Ministry of Health, Moscow	15	20
3	City Clinical Hospital No. 52, Moscow	15	15
4	City Hospital No. 40 of Kurortny District, St. Petersburg	13	13
5-6	City Clinical Hospital No. 40, Moscow	10	10
5-6	Pokrovskaya City Hospital, St. Petersburg	10	10
7-8	Group of companies "Medsi", Moscow	9	9
7-8	Sklifosovsky Research Institute of Emergency Medicine, Moscow	9	9
9	Clinical Hospital No. 1, Smolensk	8	8
10	S. M. Kirov Military Medical Academy, St. Petersburg	7	9

Data from www.grls.rosminzdrav.ru

CRITICAL TESTING OF CLINICAL TRIAL STANDARDS

Exposed to the pandemic of the new coronavirus in spring and summer of 2020 were not only the health and lives of concrete people, but also far less corporal objects such as industry standards, research ethics, the rule of law and law enforcement practice as well as the goodwill of development teams, research centers and whole nations. Considering all corrections by independent analysts to the official stats, the Russian Federation succeeded in keeping the mortality from COVID-19 at a relatively low level, but unfortunately it failed to keep several major state research institutions and certain health executive authorities from violating the international standards of clinical trials. Given below is a review of most egregious cases which ACTO ran into in spring and summer of 2020.

Chaos in vitro: Government Order No. 441

The basis for the most of the incidents described below is a document that will appear in this text as "Order No. 441", although its full title is much longer: *The specifics of circulation of medicinal products for medical use under the threat of emergency and response thereto and for medical aid to people who suffered as a result of emergencies, prevention and treatment of diseases posing threat to those around, diseases and damage caused by exposure to unfavourable chemical, biological and radiation factors,* approved by Order No. 441 of the Russian Government, dated 03.04.2020.

Clauses 29-35 of this Order mention a certain "use of medicinal products under emergencies following the indications not mentioned in the instructions for medical use for studying their effectiveness in taking preventive and therapeutic measures." The text alternately mentions the "use", "studying the effectiveness of using", "scientific studying of usage efficiency" and even a "low-intervention study", allowing for changes to be entered into package leaflets based on such "studies". In other words, the document authors confused the off label use of drugs, which can be justified in an extreme situation of the global pandemic (and was permitted in the Russian regulation before) with clinical trials, overlooking the fact that organizing and conduct of such trials implies compliance with the GCP standards. This laid a legal route for human drug testing circumventing the international standards of clinical trials and the Russian law "On Circulation of Medicines".

A bypass via Order No. 441 is a lot simpler. The "trial" programme is approved only by the independent ethics committee established under an initiating medical institution, i.e. no approval of the Ministry of Health is needed. No need to get an independent expert opinion about the scientific justification of the hypothesis and statistical analysis methods, no need to confirm the qualification and experience of investigators, no need for independent safety monitoring of the drug used. Any substantial requirements to obtaining an informed consent are cancelled; life and health insurance of participants is no longer mandatory; nor is the expert evaluation of materials at the Ethics Council under the Ministry of Health or publication of results. However, the drug developer is entitled to enter changes to the medical use instructions on the basis of such "results", i.e. to introduce new indications, dosage and treatment regimens to the widespread practice. It should be noted specifically that Order No. 441 does not forbid medicine developers to initiate "efficiency studies" violating the principles of evidence-based medicine. In other words, Order No. 441 made possible to launch some sort of offshore zones on the premises of medical institutions, where the Ministry of Health no longer performs the regulator's functions, the only regulator being the developer's scruples.

The attempts to explain this lawlessness by the fact that the regulator does not cope with its responsibilities have failed. By the time of issuing Order No. 441 the Ministry of Health of the Russian Federation had already issued three clinical trial approvals for anti-COVID-19 medications and at the time of this Newsletter publication the number of such approvals already exceeded 40. Judging by the feedback from our members that obtained approvals for the trials of anti-COVID-19 drugs in spring 2020, even though they were forced to keep the distancing and had to comply with a more complicated procedure of submitting their documents, the Ministry of Health would review their applications at a neck-breaking speed within a week instead of traditional three months.

Early in June, after facing the practice of using Order No. 441 (for more detail see below), ACTO suggested that Prime Minister Mikhail Mishustin should instruct the taskforce to enter amendments to this Order

and to divorce off label usage from clinical trials[3]. By September changes had been entered to the Order indeed, but only to the section concerning the state registration. We were given an opaque hint: "We have more important priorities to worry about, apart from these subtleties." Uncontrolled human experiments seem to be a secondary matter.

Preclinical study: risky "prevention" without legal protection

Early in April 2020, several days before the adoption of Order No. 441, medical staff from some clinics subordinate to the Moscow Healthcare Department complained to the ACTO that their bosses "insisted" on their participation in the so-called COVID-19 "prevention programme" using hydroxychloroquine. Formally there was an option "to refuse taking the drug" on the site of the programme where it was required to fill out a questionnaire, but according to the information that reached ACTO, some department chiefs insisted on their subordinates' consent with taking hydroxychloroquine.

The medical workers who sought our advice were concerned that taking hydroxychloroquine (originally used as an anti-malaria drug) is fraught with collateral damage, including nausea, vomiting, diarrhea and other adverse reactions capable to hamper the work of a person wearing protective overalls during a 12-hour shift in the red zone. They were also concerned by the dosage regimen: 200 mg two times a day during a fortnight, followed by 200 mg x 1 time a day during three months. The dosage appeared excessive and highly likely to cause adverse reactions. To the best of our knowledge, no independent justification of the dosage regimen had been performed. It was proposed to expose healthy and hard-working people to unnecessary risks, although the effectiveness of hydroxychloroquine in COVID-19 prevention was just a hypothesis (that was later proved to be false)[4].

In April ACTO wrote an open letter to Moscow Healthcare Department (MHD)[5]. We paid attention to the uncertain status of the "prevention programme": its description was changed several times on the website as the programme was transformed into a "clinical trial" and backwards. The goals were stated to be research, but the Ministry of Health did not issue a trial approval. And because the Russian law does not provide any protection for participants of "prevention programmes", the medical staff of MHD clinics (more than 4,000 workers agreed to take the drug) took risks having no guarantees of legal protection that they would have had under a clinical trial. Adherence to the voluntary participation and the procedure of obtaining informed consent roused our serious concern: we detected that information about the drug and informed consent form changed quite substantially during the month, but the number of programme participants kept growing. The MHD reply to the ACTO letter contained a couple of lines stating that "they continue studying the effectiveness and safety" indeed, without any further explanations or rationale.

The MHD "prevention programme" could not formally lean on Order No. 441, but was totally true to its spirit: a similar confusion of the medical practice goals (disease prevention) and medical science (obtaining new knowledge about the drug properties), similar prevarication of the regulator and similar divestment of the programme participants of the legal protection adequate to the risk they were exposed to.

Late in May the following statement was published in media[6]: the MHD "research" demonstrated the inefficiency of hydroxychloroquine for COVID-19 prevention. In the meantime MHD representatives affirmed that those who took the drug had a milder form of disease and promised to publish the results soon. The were no publication within the specified time period. And then ACTO again turned to MHD[7] to ask some questions about the programme, whether it continues, and where information can be found about its results. Late in June we received a reply where we were promised that the results would be "presented in the form of printed publications in open access"; yet MHD officials diplomatically neglected to mention the deadline.

[3] See. Letter of ACTO to the Russian Government and Ministry of Health requesting changes to be entered to Russian Government Order No. 441, dated 03.04.2020,on our site in the press release section.
[4] https://www.nejm.org/doi/full/10.1056/NEJMoa2016638
[5] http://acto-russia.org/index.php?option=com_content&task=view&id=393
[6] https://medvestnik.ru/content/news/DZM-Moskvy-podtverdil-neeffektivnost-gidroksihlorohina-dlya-profilaktiki-COVID-19.html
[7] http://acto-russia.org/index.php?option=com_content&task=view&id=402

The same June letter contained for the first time a rational behind the MHD initiative. The initiators referred to Temporary Methodological Recommendations from the Ministry of Health regarding the prevention, diagnostics and treatment of the new coronavirus infection. Hydroxychloroquine appears indeed in their fourth version, dated 27 March 2020, as a possible COVID-19 curative and preventive agent. It remained in the therapeutic regimen recommended by the Ministry of Health at the time of this Newsletter release, although it slightly ceded its positions in the eighth version published early in September, where it was excluded from the list of curative agents for complicated forms, whereas for other cases it was recommended in smaller dosages.

For better understanding of the questions raised in connection with hydroxychloroquine prescription, we should probably go beyond the sheer Russian context and take into account a broader international experience. Hydroxychloroquine became perhaps the most disputed potential anti-COVID drug after it had been advertised by Donald Trump. Already in spring 2020 any assessment of its safety and effectiveness in view of COVID-19 turned from a neutral opinion in a scientific discussion into a resounding political statement. Along with challenges provoked by the pandemic itself (organizing trials in no time and hence serious flaws in their design, a particularly tricky recruitment and therefore small groups of participants, etc.), political overtones markedly impeded the task of reaching consensus in the international expert community over the drug use.

Late in March, when the "prevention programme" using hydroxychloroquine kicked off, this drug seemed promising to some major experts. It was then that the drug was included in the recommendations of the Ministry of Health of the Russian Federation for the treatment of coronavirus infection. Gradually evidence against its use were being accumulated[8], but in mid-June, judging by the site of the "prevention programme"[9], while medical personnel in MHD clinics no longer used this drug, hydroxychloroquine was still recommended by the Ministry of Health and on the whole its status as an anti-COVID agent could still be considered disputed. Taking this into account, studying the efficiency of hydroxychloroquine as a COVID-19 preventive agent could have become a source of valuable data in case of compliance with all standards of clinical trials. Regrettably, the "prevention programme" organizers took a different route.

Notwithstanding the promises, we did not discover any publications highlighting the results of "studying the drug effectiveness" prior to this Newsletter release.

Phase I: promulgation of results before recruitment completion

Another team – from the Research & Production Centre Pharmzashchita at Russia's Federal Medical-Biological Agency (FMBA) – was inspired by one more anti-malaria drug mefloquine. On 28 March 2020 FMBA announced the development of the coronavirus infection treatment regimen on its basis. As per the departmental press release[10], interference with triggering an inflammatory response was corroborated on cell cultures. Yet FMBA Chief Executive Veronika Skvortsova proposed an immediate implementation of this development in Methodological Recommendations of the Ministry of Health of the Russian Federation for the prevention, diagnostics and treatment of the new coronavirus infection. Mefloquine was indeed included in the coronavirus infection treatment and prevention regimens already in the next version of the Recommendations (Version 5 dated 8 April 2020).

On the first business day after the passing of Order No. 441, which was 06 April 2020, FMBA launched "comparative clinical trials" of hydroxychloroquine, mefloquine and a combination of lopinavir with ritonavir in three groups of patients with different severity. Without getting any approval from the Ministry of Health, independent expert evaluations and other boring bureaucratic formalities. The press release[11] issued on this occasion clearly referred to Order No. 441 and was intended to remove all questions.

Questions were still raised - e.g. by ACTO - when just 2.5 weeks later Ms. Skvortsova announced preliminary results[12]: 78% of patients having moderately severe conditions and taking mefloquine show positive

[8] See our review in the article https://vademec.ru/news/2020/05/28/minzdrav-ukazal-na-obosnovannost-primeneniya-gidroksikhlorokhina-pri-covid-19/
[9] https://doc-covid.ru/
[10] https://fmba.gov.ru/press-tsentr/novosti/detail/?ELEMENT_ID=38052
[11] https://fmba.gov.ru/press-tsentr/novosti/detail/?ELEMENT_ID=38196
[12] https://fmba.gov.ru/press-tsentr/novosti/detail/?ELEMENT_ID=38468

clinical dynamics with no serious adverse events recorded. In its letter addressed to FMBA[13] ACTO remonstrated against publicly describing dubious experiments that do not comply with GCP standards as "clinical trials" and called at least to get close to the standards of conducting the latter by publishing a protocol, information for the patient and then a report on the results. We also asked the Head of FMBA to abstain from bombastic public statements about the drug effectiveness before completion of its clinical development.

Two weeks later Ms. Skvortsova declared at a press conference: *"On mefloquine by the end of the course, i.e. by the end of the first week of treatment, 70% are guaranteed not to have virus already."*[14]. This 70% figure was much trumpeted by media. This figure was touted as a result of "clinical trials" without mentioning a preliminary nature of the data received. ACTO remonstrated again[15], having noted that mefloquine investigation by FMBA is not a clinical trial, that the quality of obtained and promulgated results rouses great doubts and that any conclusions about the drug effectiveness are premature, given that according to FMBA Head herself, the recruitment of participants had not been fully completed. Responding to ACTO protests, FMBA referred to Order No. 441 as the legal ground of its activities.

In April FMBA promised[16] to promulgate the results of studying mefloquine before late May 2020, but never did that. At the end of June ACTO sent another inquiry to the Agency wondering if the report will be published and forwarded to the Ministry of Health, as Order No 441 prescribes. Neither the reply nor the report itself, if it was ever prepared, have been sent to us. A peculiar point in this story was the complete disappearance of mefloquine from the Health Ministry's Methodological Recommendations for the treatment of coronavirus infection in their eighth version dated 3 September 2020, even though the chemically related hydroxychloroquine remained in the document. Whatever was the ground for this decision by the Health Ministry's expert group, it is confined to this narrow group.

Phase II which is also phase III and phase IV: registration acceleration to escape velocity

The Gamaleya National Center engaged all eyes in mid-May when its Director Alexander Ginzburg, answering a journalist's question, why scientists aren't testing the COVID-19 vaccine on themselves, answered during his interview for Russia-1 TV Channel: *"Who told you we are not doing that? Well, just nobody publicizes that"*[17]. At that time, the trial of phase I was still being planned to be launched. A transcript of this interview with the eccentric confession was soon published on the Health Ministry's website[18] without any explanations, remarks and especially without refuting human trials prior to the official start. A couple of days later leading national news agencies hyped this newsfeed as sensational information about a successful trial of an anti-COVID-19 vaccine, even if informal[19]. It is from these news items that the general public first heard about the future Russian vaccine Sputnik V.

The story about "informal trials" attracted great public attention including in the expert community where the ethical aspect of testing the little-known drug on the personnel of the Gamaleya National Center was heatedly debated. ACTO published an open statement[20], where it pointed out that representatives of a vulnerable group were recruited for the experiment (who might have been explicitly or implicitly pushed towards participation by their bosses), for whom the Declaration of Helsinki demands special protection. In experiments at the Gamaleya National Center even standard requirements were apparently not met: insurance, a full-fledged procedure of informed consent, etc., not to mention the fact that the Ministry of Health gave no permission to those interventions.

Early in June it became known that at subsequent development stages the Gamaleya Center would collaborate with the Russian Direct Investment Fund (RDIF) which, as far as we can judge, launched a rather

[13] http://acto-russia.org/index.php?option=com_content&task=view&id=396
[14] https://fmba.gov.ru/press-tsentr/novosti/detail/?ELEMENT_ID=38807
[15] http://acto-russia.org/index.php?option=com_content&task=view&id=399
[16] https://fmba.gov.ru/press-tsentr/novosti/detail/?ELEMENT_ID=38468
[17] https://russia.tv/video/show/brand_id/65067/episode_id/2391350/video_id/2299521/
[18] https://minzdrav.gov.ru/news/2020/05/18/13979-aleksandr-gintsburg-rasskazal-v-intervyu-telekanalu-rossiya-1-o-hode-razrabotki-vaktsiny-ot-koronavirusa
[19] https://tass.ru/obschestvo/8536967
[20] http://acto-russia.org/index.php?option=com_content&task=view&id=400

aggressive PR campaign of the vaccine. Furthermore, it was announced that one of the sites would be opened at the Ministry of Defense's Hospital, with contracted professional soldiers to become participants of the vaccine trials[21]. Their preparation for the trial was highlighted on federal TV channels in the pieces [22], close to the reality show format. Roughly at the same time (prior to phase I trials, we'd emphasize) Vice Premier Tatyana Golikova mentioned the tentative time of the vaccine's state registration (August) and launch of its industrial production (September)[23]. A trial of the combined phase I-II started on 17 June 2020 and this time they complied with the formal requirements: the Ministry of Health's approval was obtained, the insurance of the trial participants and obtaining their informed consent were reported, etc. A week after the trial was launched the Director of the Gamaleya Center Alexander Ginzburg said in his interview that the coronavirus vaccine (despite the virus being first detected only six months earlier) would protect from contagion during two years[24]. Items about the condition of volunteers kept popping up in media outlets[25], the Health Minister reporting in public on the course of data collection[26] and promising that the results would become known already in August [27].

In July the Ministry of Defense first reported on the immune response of volunteers[28], then on the safety of the vaccine[29]; the Director of the Gamaleya National Center announced that its use may start in mid-August[30], while the Ministry of Industry and Trade listed the production facilities which were already being equipped at the moment[31]. Officially the data collection for the trial of phase I-II had not been over yet. The sort of reality show went on on national TV channels as well[32]. Without waiting for the expert opinion (it is the experts who were to assess the data and take a registration decision) Russian officials and media had actually decided everything for them in advance, cutting off the path to retreat: there simply could not be a failure.

In late July - early August another row flared up around the vaccine development: Bloomberg stated that the Russian elite had been vaccinated against the coronavirus since spring. The government officials denied everything. However, the Editor-in-Chief of a well-known Moscow radio station narrated that his friends from the government offered him such a vaccination [33]. Still later it became known that one of the President's daughters was also vaccinated and this information came directly from the President[34].

Because statements about the imminent registration and subsequent wide use of the vaccine developed by the Gamaleya Center persistently popped up in the news field (both in media and in informal talks), ACTO published an open letter to the Ministry of Health of the Russian Federation, calling for postponement of vaccine registration and introduction into civil circulation until the completion of phase III trials[35]. We gave the following rationale: (1) the vaccine is new; it was tested in small groups, less than 100 recruits in total, young and healthy, which disables adequate assessment of its safety profile; (2) the unclear safety profile is particularly troubling first of all because, as had been announced, COVID-19 risk groups would be the first to get vaccinated, including elderly people with weaker immune response as compared to younger ones; (3) finally, it is the end product, not

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[21] https://ria.ru/20200603/1572376596.html
[22] For instance, https://tvzvezda.ru/news/vstrane_i_mire/content/20206141916-BCn2T.html?utm_source=tvzvezda&utm_medium=longpage&utm_campaign=longpage&utm_term=v1https://www.vesti.ru/article/2417438
[23] https://www.interfax.ru/russia/713011
[24] https://www.kommersant.ru/doc/4389401
[25] For instance: https://www.1tv.ru/news/2020-06-18/387954-pervaya_otechestvennaya_vaktsina_protiv_koronavirusa_vvedena_dobrovoltsam и https://www.rbc.ru/society/07/07/2020/5f0378dc9a7947253bf10e51
[26] https://tass.ru/obschestvo/8777875
[27] https://www.interfax-russia.ru/koronavirus-v-rossii/rezultaty-klinicheskih-ispytaniy-vakciny-ot-koronavirusa-poyavyatsya-v-avguste
[28] https://www.rbc.ru/rbcfreenews/5f07c7e49a79474e5e57c745?fromtg=1
[29] https://www.rbc.ru/rbcfreenews/5f0ed3129a794710ff3bff2f
[30] https://rg.ru/2020/07/13/nazvany-sroki-postupleniia-rossijskoj-vakciny-ot-koronavirusa-v-oborot.html
[31] https://tass.ru/ekonomika/8984347
[32] https://www.1tv.ru/news/2020-07-19/389729-otechestvennaya_vaktsina_ot_koronavirusa_vse_blizhe_k_zapusku_v_proizvodstvo
[33] https://www.znak.com/2020-08-07/glavred_eha_moskvy_rasskazal_pochemu_ne_stal_stavit_sebe_rossiyskuyu_vakcinu_ot_covid_19
[34] https://tass.ru/obschestvo/9171305
[35] http://acto-russia.org/index.php?option=com_content&task=view&id=411

a fundamental development, that is normally liable to registration; but it's impossible to assess the end product whose manufacturing has not been streamlined yet. On the next day after ACTO published its appeal, Russian President personally announced about registration of the Gamaleya Center's vaccine. The trade name under which the vaccine was registered in Russia is Gam-COVID-Vac[36] (Sputnik V could be described as a sort of stage name). The issued certificate is valid till 1 January 2021, though there are few doubts that it will be automatically prolongated after that.

In the media, not only Russian, immediately after registration a PR war unfolded, otherwise it is difficult to call it. The arguments of its opponents and proponents could be trivialized down to the following maxims. Those who opposed radical registration acceleration emphasized insufficient knowledge of the vaccine, with its efficiency data totally missing (these can be obtained only through phase III) while the design of the first trial, even though it was considered a combined I-II phases trial was much more similar to the design of phase I, because of limited volunteer sampling, too young average age of those volunteers, and the lack of blinding. It was also noted that neither the results of preclinical trials, nor the results of phase I-II did not appear articles in scientific journals. The registration proponents vigorously used argumentum ad hominem, explaining the very fact of criticism by the interests of critics. Perhaps most discouraging was the statement that the business of those who organize clinical trials bogs down to the testing of new drugs; therefore, they need as many sick people as possible and for this reason they oppose the new vaccine production: they need more people ill in order to test their medicines on them. Other arguments appear trivial against this backdrop: foreign pharmaceutical firms try to eliminate competition, foreign regulators hamper the entry of Russian medicinal products to their national markets, and the West is averse to recognizing the grandeur of Russia and Russian science, etc.

On 4 September 2020 The Lancet published an article on the results of phase I-II trials and on 7 September 2020 an independent group of scientists asked the authors to explain some cases of data duplication in their publication, since the existing matches seemed "highly unlikely" to them. While discussions were under way in the academic community, first batches of the vaccine were delivered to Moscow outpatient clinics and registration of those who would like to get vaccinated was opened on a special site. A parallel start of two processes was announced[37]: a clinical trial of phases III-IV and vaccination of people at risk for COVID-19 (where they included medical staff, workers of education, policemen, students and conscripts[38]). The plan called for the recruitment of 40,000 volunteers, whereas the number of massive vaccination participants was not limited. In response to numerous public expression of concern the doctors and teachers will be forcibly vaccinated public officials assured that vaccination would be done solely voluntary. According to surveys, 52% of medical workers were not ready to get vaccinated with the vaccine created in the Gamaleya Center[39].

In late August - early September the PR media campaign to promote Sputnik V continued as media informed that some prominent government officials had got vaccinated, such as Moscow Mayor, Minister of Defense, one of Vice Premiers, Prime Minister of Belarus, and others. It should be noted that these statements appeared, when the trial of phase I-II had already been completed, whereas the trial of phase III-IV had not been officially launched.

Routinely the drug registration and its introduction into civil circulation can be considered the finale of its development, since post-registration trials seldom have any appreciable impact upon the market fate of a medicine. Obviously, this rule does not work for the vaccine developed by the Gamaleya Center. Formal registration of their vaccine coincided with the very beginning of human trials. So it's too early to draw the line in the story of Sputnik V. Especially given the promise of the Gamaleya Center to develop its lite version for children, to release a similar "live" vaccine based on weakened viruses, and to create a multivalent flu and coronavirus vaccine. Inspired by their success, the developers decided to look beyond vaccines, having requested state financing for a new anti-COVID-19 agent based on monoclonal antibodies. One can only recall the lyrics of rock band Nautilus Pompilius: "this music will last forever."

Post-registration: excessive activation of PR service

[36] http://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=f6e6d4fe-374c-43af-805f-75a07ad108b9&t
[37] https://www.interfax.ru/russia/725214
[38] https://www.interfax.ru/russia/724572
[39] https://www.rbc.ru/society/14/08/2020/5f35d9579a79471d249e8374

In our narrative on the Gamaleya Center's vaccine we mentioned the Russian Direct Investment Fund (RDIF) as the party which was probably responsible for an aggressive promotional campaign of Sputnik V where the reality show format (a media version of transparency) was called to substitute an independent evaluation of all procedures and data (transparency proper). RDIF is a suspect because of its activity related to another drug called favipiravir.

For the first time in the Russian media space the name of this medicine was mentioned late in March 2020. It was postulated that according to the data provided by Chinese researchers, favipiravir demonstrated fair clinical effectiveness in the treatment of the new-type coronavirus[40]. Almost immediately it was announced that RDIF would invest in the manufacturing of favipiravir[41]. In Version 4 of Temporary Methodological Recommendations on the new coronavirus infection prevention, diagnostics and treatment that saw light in late March favipiravir was also mentioned as a medicine being tried, whose effectiveness had not been proved yet, but which could well be prescribed at the decision of a medical panel.

Early in April Japan intended to triple its stock of favipiravir and to approve it as an anti-COVID-19 agent[42]. It should be noted that this drug was approved in Japan as a remedy for the flu in 2014, but with significant restrictions: only for the treatment of strains resistant to antiviral drugs. The teratogen effect manifest in animal experiments was the ground for such constraints. The drug never went on open sale in Japan and was never approved in Europe or the US. Favipiravir got the chance to break free from the narrow market niche after the outbreak of SARS CoV-2 pandemic, RDIF actively facilitating its promotion.

RDIF co-founded a favipiravir production line with ChemRar Group and announced its readiness to ensure its output by May for hospital patients[43]. On 23 April 2020 the recently founded joint venture was granted an approval for "Adaptive multicentre randomized open comparative clinical trial of Favipiravir effectiveness and safety in hospitalized patients with COVID-19". The news of this approval issue was suddenly published on the website of the Health Ministry, although routine bureaucratic procedures of this sort are never supported by special press releases. Favipiravir was the seventh anti-COVID-19 drug approved for testing by the Ministry of Health since the beginning of the pandemic; it was then followed by quite a few other drugs and yet favipiravir was privileged to be presented on the regulator's site. This was definitely a great PR luck, since a multitude of non-specialised journalists who are not used to constantly checking of the Ministry of Health register of approved trials spread this news as though the favipiravir trial was the first trial of an anti-Covid-19 agent, approved in Russia.

Powerful PR support also assumed other forms at this stage: media outlets, including regional ones, began publishing articles about the start of trials, excellent results of previous stages and soon launching of the production line[44]. Against this background more skeptical opinions were very scarce[45]. Close collaboration with the Ministry of Health deepened early in May, when Russian Health Minister argued at the online session of the State Duma Committee on Healthcare that favipiravir trials "encourage and give hope that this drug may work indeed"[46]. This remark was then widely replicated by the media.

In May the collaboration of RDIF and ChemRar had competitors. First of all, Drugs Technology (affiliated with R-Pharm Group) started investigating its own version of favipiravir, and secondly the pharmaceutical company Promomed along with Biohimik plant developed their proprietary full-cycle production technology, and they were also granted an approval for a clinical trial. In June PharmaSyntez JSC was also added to this list. A higher number of players meant a more frequent mention of the drug in the media space.

RDIF and ChemRar announced about the interim results of the clinical trial in mid-May and the phrase "shortening of disease duration from 11 to 4-5 days" infiltrated federal media and spread there like a forest fire.

[40] https://tass.ru/obschestvo/8011397
[41] https://tass.ru/obschestvo/8080609
[42] https://tass.ru/obschestvo/8165291
[43] https://ria.ru/20200409/1569788232.html
[44] https://www.niann.ru/?id=551446
[45] https://news.ru/health/rossijskie-farmakologi-ne-vysoko-ocenili-yaponskij-preparat-ot-covid-19/
[46] https://vademec.ru/news/2020/05/06/murashko-schitaet-obnadezhivayushchimi-pervye-rezultaty-ki-favipiravir-ot-covid-19/

The headlines stated: "The Russian drug speeds up the recovery of COVID-19 patients twice"[47]. The PR team of the developers successfully collaborated with regional media as well: in the cities which hosted sites of this trial materials were published about successful trying out of the drug (as if the trial had already been completed) on residents of their region. Meanwhile the official time of the trial completion, indicated in the register of issued approvals, is 31 December 2020. However, nobody was going to wait that long. On 22 May 2020 RDIF published another press release where their brainchild under the trademark of Avifavir was already declared "the first Russian direct-acting antiviral agent that showed effectiveness in clinical trials"[48]. The conclusions were based on a 10-day follow-up of 60 patients.

Late in May new sites were included in the trial and new patients were recruited (the plans called for the recruitment of 390 people), which was accompanied by a new flurry of articles in regional media about the opportunity to take part in testing the "80% effective drug", whatever this meant[49]. Meanwhile federal TV channels cheerfully reported: "The first and most powerful anti-COVID-19 drug has been produced in Russia"[50] and once again, using recognizable cold-war rhetoric ploys, they extolled impressive effectiveness of the "domestic" drug, far surpassing the results of "American" remdisivir.

On 30 May 2020 favipiravir from RDIF and ChemRar was approved by the Ministry of Health of the Russian Federation, but with a caveat that the drug is registered on the basis of limited data on its use under the emergency, and that it can be used only in day and night clinics. On 3 June 2020 it was included in the next version of the Ministry of Health's recommendations on how to treat COVID-19 patients, topping that list (with the same caveat that it can be used only in day and night clinics). Favipiravir was recommended for moderate to severe forms of this disease.

Its registration and inclusion in the Recommendations provoked a minor splash of reminders that it's premature to talk about the effectiveness of the product which is still being tried[51]. Yet they drowned in wild PR celebrations that broke out after registration. Odes in prose dedicated to Avifavir were daily published in federal and regional media. Here are just several quotes and headlines: "It has been proven that Avifavir blocks the coronavirus replication, so the sooner it is taken, the lesser the threat of severe complications"[52], "Avifavir becomes the golden standard: Russia shores up its leadership in fighting COVID"[53], "Remedy for coronavirus found"[54]. Avifavir supplies to each particular city of Russia were always supported by articles about this event in local newspapers ("Samara Region gets a remedy for COVID-19... We are tackling the treatment of COVID patients and this means saved lives and a high pace of recovery"[55], and suchlike). Chief Physician of district clinical hospital in Ryazan Dmitry Khubezov said on his page in Vkontakte: "Already today this drug is referred to as a 'hope pill', because it was developed for most severe cases"[56], while media, both federal[57], and regional[58], eagerly quoted him.

Late in June the Ministry of Health registered favipiravir from another manufacturer and the articles about Avifavir in the spirit of those quoted above were complemented with articles about Areplivir titled "Now we have this medicine and people do not die"[59], "Russia gets a coronavirus medication with almost no side effects" and humbler ones like "The trials of coronavirus drug in Smolensk went fine."[60] (all texts were published half a year

[47] https://rg.ru/2020/05/14/rossijskij-preparat-uskoril-vyzdorovlenie-bolnyh-covid-19-v-dva-raza.html
[48] https://iz.ru/1014318/2020-05-22/pervyi-effektivnyi-rossiiskii-preparat-ot-covid-19-nazvali-avifavir
[49] https://live24.ru/v-strane/25152-rfpi-zapuskaet-finalnuju-stadiju-ispytanija-preparata-ot-koronavirusa.html
[50] https://www.vesti.ru/article/2413216
[51] https://thebell.io/v-rossijskie-bolnitsy-postupit-eksperimentalnyj-preparat-ot-covid-19
[52] https://www.1tv.ru/news/2020-06-11/387529-novye_metodiki_i_razrabotki_v_borbe_s_koronavirusom_obsuzhdali_na_zasedanii_pravitelstva
[53] https://www.vesti.ru/video/2200069
[54] http://indolgoprud.ru/novosti/zdorove/lekarstvo-ot-koronavirusa-naydeno
[55] https://ria.ru/20200616/1573032804.html
[56] https://vk.com/wall472917533_459
[57] https://www.interfax.ru/russia/713162
[58] https://www.ryazan.kp.ru/online/news/3901742/
[59] https://stolica-s.su/archives/268406
[60] https://readovka67.ru/news/58899

before official completion of the trial). On the other hand, the registration of a generic from R-Pharm in early July was not accompanied by the same violent advertising.

Early in July RDIF requested the Ministry of Health to permit the outpatient use of Avifavir. ACTO came up with another open letter[61], where it warned the Ministry of Health against taking this step. We argued that the current trial is: (1) open, whereas the golden standard of evidence-based medicine is blind design, (2) comparative, but it was not specified what the comparison was made with; (3) the criterion of inclusion was the admission of patients, i.e. the matter mainly regards severe cases, whereas outpatients were not included in the trial; (4) no publications on the results of the RDIF trial are available; (5) there are no data about the results of other trials of acceptable quality either; (6) the drug possesses a proven teratogenic and embryotoxic effect as well as a number of other adverse reactions. In our letter we also referred to the latest data at the moment: Fujita Health University in Japan presented interim testing results stating that their investigators failed to discover any advantages of favipiravir treatment.

During a relative lull in mid-August the exuberant advertising campaign of the RDIF generic nearly faded away. The latter can be attributed to the fact that the Fund had to invest all resources into the PR campaign of Sputnik V vaccine. Media reported that Avifavir would be supplied to 50 countries[62] and updated its agenda.

Early in September favipiravir became the only therapy for severe cases of COVID-19 according to the eighth version of the Ministry of Health recommendations for the new coronavirus treatment (used with tocilizumab or sarilumab). And in mid-September the Ministry of Health, after prolonged reflections, still permitted the outpatient use of favipiravir, albeit only from two manufacturers: Coronavir from R-Pharm and Areplivir from Promomed. But while it is at least mentioned in the name of the R-Pharm protocol that COVID-19 patients with milder conditions were involved in the drug testing (there is even a publication[63] in a Russian journal about its effectiveness in outpatients), this cannot be said about the trial by Promomed. This did not hinder Promomed from fixing the retail price of its drug package at 12,320 rubles, i.e. at the minimum subsistence level for able-bodied population (12,392 rubles). R-Pharm lagged slightly behind and fixed the price at 11,550 rubles, which coincides with per capita subsistence level (11,468 rubles). The sale of RDIF-made favipiravir in pharmacies had just been announced at the time of this Newsletter release[64], which means this story is not yet complete.

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What we stated above is far from being a full list of clinical trial standards violations which we could observe after the outbreak of the pandemic. We've omitted a story of First Deputy Chairman of the Federation Council's Committee on Budget and Financial Markets Sergey Ryabukhin who tried "on himself, friends, loved ones and relatives, 50 people already" an immunomodulatory agent against the coronavirus infection, developed by a group of Saratov-based virologists[65]. We've also omitted the "trial" of triazavirine in the Urals, initiated by Governor's decree, rather than the Ministry of Health's approval (or at least the notorious Order No. 441). Initially the Governor just ordered to buy a new development of the regional university and use it as a "therapy" for medical doctors and only several months later he instructed that its effectiveness and safety should better be "investigated"[66]. There were also "human trials of methylene blue's water solution"[67] without the Ministry of Health's approval or oversight of Roszdravnadzor, but with results sent to the Nature Medicine, as was assured by media. Or what would you say about Surfactant-BL - a medicinal product derived from cattle lungs that allegedly has no side effects, well tolerated and well-suited even for newly born babies[68]? It was used to treat at least 120 people without regulatory oversight.

[61] http://acto-russia.org/index.php?option=com_content&task=view&id=410
[62] https://rg.ru/2020/07/14/pervyj-rossijskij-preparat-ot-covid-19-budet-postavliatsia-v-50-stran.html
[63] https://issuu.com/proffopponent/docs/_____mo_1_2020_____./50
[64] https://echo.msk.ru/news/2713775-echo.html
[65] https://www.pnp.ru/social/ryabukhin-oproboval-na-sebe-novyy-preparat-protiv-koronavirusa.html
[66] https://www.znak.com/2020-08-21/v_ekaterinburge_nachalis_klinicheskie_issledovaniya_preparata_kotorym_s_aprelya_lechili_covid
[67] https://nauka.tass.ru/nauka/8816933
[68] https://www.gazeta.ru/social/2020/09/08/13241378.shtml

All of these cases bring us back to the idea that COVID-19 is not only capable of damaging the lung tissue; it can also affect immaterial substances, such as legal norms and ethical standards. One of the most important functions of regulatory bodies - protecting citizens against unnecessary medical risks - became its victim in Russia. Instead the attempts to mollify all residents by building the image of a strong state capable of coping with any challenge were given undeservedly much attention. Which is a very important task as well unless it becomes an end in itself.

We sincerely hope that excesses like the ones described above will gradually fade away along with the pandemic. For its part, ACTO will continue putting all of its efforts for preserving the culture of conducting clinical trials in Russia. In this endeavour we are backed by numerous conscientious players of the local market whose work standards have not been affected by the virus.

RANKINGS OF PRINCIPAL INVESTIGATORS

A year ago we published for the first time the ranking of principal investigators. In this issue we present it to our readership once again.

While interpreting, please, bear in mind that the register of principal investigators[69], whence we draw information, lives its own and rather enigmatic life: certain trials vanish from it and reappear there some time later; for this reason the statistics is liable to fluctuations, even if insignificant. Therefore, not only a source of information is indicated under each table, but also the time when it was downloaded from the register. Discrepancies between our tables/diagrams and the register of principal investigators are partly caused by the manual purge of duplications, when the same person was entered into the register several times because his first and last name or even date of birth were misspelled.

The position in the TOP-100 rankings depends on the number of appointments as Principal Investigator. Table 6 reflects both the total number of appointments as PI and the number of current protocols. The data in the upper quarter of Table 6 are additionally generalized in Diagram 20 "Top-25 PIs by total number of clinical trials conducted".

Because the rankings in Table 6 do not take specializations into account, clinical pharmacologists specializing in bioequivalence studies predictably take the lead. Presented below for greater clarity are TOP-20 principal investigators by current trials in oncology (Table 7) and clinical pharmacology (Table 8), to supplement the general rankings, as well as TOP-50 principal investigators by current trials exclusive of oncologists and clinical pharmacologists (Table 9).

Finally, in conclusion of this overview we give the distribution of TOP-100 PIs by cities of Russia (Diagram 21).

Table 6

TOP-100 of Principal Investigators by Total Number of Trials Conducted from November 2010 to H1 2020						
Ref. No.	**Principal investigator's full name**	**Total number of CTs**	**Number of ongoing CTs**	**Specialization**	**City**	**Ranking and Number of CTs in 2019**
1	Aleksandr Leonidovich Khokhlov	**504**	61	cardiology, clinical pharmacology, oncology, pulmonology, therapy	Yaroslavl	1 (473)
2	Sergey Mikhailovich Noskov	**256**	48	rheumatology, clinical pharmacology, therapy	Yaroslavl	2 (227)
3	Alina Sergeevna Agafyina	**203**	79	clinical pharmacology, neurology, pulmonology, therapy	St. Petersburg	5 (169)
4	Olga Borisovna Yershova	**192**	53	rheumatology, cardiology, therapy	Yaroslavl	3 (179)
5	Anna Nikolaevna Galustyan	**191**	42	allergology and immunology, infectious diseases, clinical pharmacology, oncology, pediatrics, pulmonology, therapy	St. Petersburg	4 (176)
6	Ivan Gennadyevich Gordeev	**181**	55	cardiology, therapy	Moscow	8 (156)
7	Vladimir Ivanovich Vladimirov	**168**	57	oncology, urology	Pyatigorsk	7 (161)
8	Olga Vilorovna Reshetko	**157**	48	rheumatology, clinical pharmacology, therapy	Saratov	11 (143)

[69] http://grls.rosminzdrav.ru/CIExperts.aspx?moduleId=2

9	Olga Leonidovna Barbarash	**157**	46	cardiology, endocrinology	Kemerovo	9 (150)
10	Konstantin Konstantinovich Laktionov	**155**	84	oncology, surgery, thoracic surgery	Moscow	10 (148)
11	Elena Anatolyevna Smolyarchuk	**154**	41	rheumatology, clinical pharmacology, therapy, ophthalmology	Moscow	12 (139)
12	Marina Leonidovna Stanislav	**151**	34	rheumatology	Moscow	6 (167)
13	Yuri Grigoryevich Shvarts	**145**	51	cardiology, nephrology, rheumatology, therapy	Saratov	13 (133)
14	Dmitry Petrovich Udovitsa	**144**	72	hematology, oncology	Sochi	21 (117)
15	Sergey Vladimirovich Orlov	**143**	61	oncology	St. Petersburg	15 (124)
16	Mikhail Vladimirovich Dvorkin	**135**	104	oncology, surgery	Omsk	23 (112)
17	Vasily Ivanovich Trofimov	**135**	29	gastroenterology, pulmonology, therapy	St. Petersburg	14 (127)
18	Guzel Zinnurovna Mukhametshina	**130**	59	oncology	Kazan	19 (120)
19	Daniil Lyvovich Stroyakovsky	**128**	87	oncology, neurology	Moscow	20 (118)
20	Vladimir Mikhailovich Moiseenko	**127**	38	oncology	St. Petersburg	17 (121)
21	Artyom Yurievich Vorobyov	**127**	36	neurology	MR, Serpukhov	29 (100)
22	Konstantin Anatolyevich Zakharov	**125**	59	infectious diseases, clinical pharmacology, therapy, general medical practice (family medicine)	St. Petersburg	33 (97)
23	Sergey Yurievich Martsevich	**125**	4	cardiology	Moscow	16 (122)
24	Viktor Vasilievich Shilov	**122**	4	therapy, toxicology	St. Petersburg	18 (121)
25	Natalya Nikolaevna Varnakova	117	28	therapy	Nizhny Novgorod	25 (106)
26	Anton Sergeevich Yedin	**116**	32	dermatovenerology, clinical pharmacology, therapy	St. Petersburg	27 (104)
27	Vladimir Ilyich Simanenkov	**116**	32	gastroenterology, clinical pharmacology, therapy	St. Petersburg	22 (115)
28	Vladimir Valentinovich Yakusevich	**116**	30	clinical pharmacology, therapy	Yaroslavl	30 (100)
29	Ivan Surenovich Sardanyan	**115**	32	clinical pharmacology	St. Petersburg	40 (89)
30	Aleksandr Yurievich Malygin	**115**	24	anesthesiology-intensive care medicine, clinical pharmacology	Yaroslavl	28 (104)
31	Natalya Vladimirovna Fadeeva	**114**	48	oncology	Chelyabinsk	24 (110)
32	Oleg Aleksandrovich Gladkov	**114**	42	oncology	Chelyabinsk	26 (104)
33	Igor Dmitrievich Lifirenko	**111**	64	oncology	Kursk	31 (99)
34	Marina Fedorovna Osipenko	**111**	51	gastroenterology, pulmonology, clinical pharmacology, therapy	Novosibirsk	34 (97)
35	Marina Nikolaevna Nechaeva	**109**	86	oncology	Arkhangelsk	42 (88)
36	Veronika Borisovna Popova	**106**	27	pulmonology, therapy, clinical pharmacology	St. Petersburg	38 (90)
37	Grigory Vladimirovich Rodoman	**105**	30	clinical pharmacology, surgery	Moscow	32 (99)
38	Rodion Aleksandrovich Oseshnyuk	**99**	11	clinical pharmacology, therapy	St. Petersburg	35 (95)

39	Tatyana Alekseevna Raskina	**98**	31	cardiology, rheumatology, therapy	Kemerovo	36 (94)
40	Sergey Stepanovich Yakushin	**97**	26	cardiology, rheumatology, nephrology, therapy	Ryazan	44 (87)
41	Nadezhda Vitalyevna Kovalenko	**95**	58	oncology	Volgograd	52 (79)
42	Olga Petrovna Ukhanova	**95**	44	allergology and immunology, therapy	Stavropol	48 (81)
43	Nina Alekseevna Karaseva	**94**	46	oncology	St. Petersburg	37 (92)
44	Elena Valentinovna Borodulina	**93**	15	clinical pharmacology, obstetrics and gynaecology, therapy	Tomsk	47 (82)
45	Arkady Lyvovich Vertkin	**92**	7	clinical pharmacology, therapy	Moscow	41 (89)
46	Petr Aleksandrovich Chizhov	**91**	15	cardiology, pulmonology, rheumatology, therapy	Yaroslavl	39 (89)
47	Elena Alekseevna Shumetova	**91**	12	cardiology	Ivanovo	43 (88)
48	Andrey Petrovich Rebrov	**88**	22	cardiology, rheumatology, therapy	Saratov	45 (85)
49	Olga Sergeevna Samoylova	**87**	55	hematology, oncology	Nizhny Novgorod	56 (76)
50	Vladimir Vitalyevich Rafalsky	**87**	38	cardiology, clinical pharmacology, therapy	Kaliningrad	50 (80)
51	Sergey Valentinovich Cheporov	**87**	9	oncology	Yaroslavl	49 (81)
52	Sergey Alekseevich Tyulyandin	**86**	25	oncology	Moscow	46 (84)
53	Natalya Nikolaevna Maslova	**85**	29	neurology	Smolensk	65 (71)
54	Zhanna Davidovna Kobalava	**85**	19	cardiology, endocrinology, therapy	Moscow	51 (80)
55	Viktor Borisovich Shunkov	**84**	21	cardiology, clinical pharmacology, therapy	St. Petersburg	53 (78)
56	Natalya Petrovna Shilkina	**83**	22	rheumatology, cardiology, therapy	Yaroslavl	54 (78)
57	Boris Yakovlevich Alekseev	**81**	55	oncology, urology	Moscow	55 (76)
58	Evgeny Arsenyevich Gotovkin	**81**	36	oncology	Ivanovo	57 (76)
59	Evgeniya Isaakovna Shmidt	**80**	32	rheumatology	Moscow	58 (76)
60	Galina Lyvovna Ignatova	**79**	14	pulmonology	Chelyabinsk	60 (75)
61	Aleksey Georgievich Manikhas	**77**	22	oncology	St. Petersburg	59 (76)
62	Vadim Borisovich Shirinkin	**76**	42	oncology	Orenburg	66 (70)
63	Oleg Nikolaevich Lipatov	**76**	39	oncology	Ufa	62 (71)
64	Galina Aleksandrovna Chumakova	**76**	26	gastroenterology, cardiology, therapy	Barnaul	63 (71)
65	Gadel Maratovich Kamalov	**75**	9	cardiology, therapy	Kazan	74 (68)
66	Aleksey Vladimirovich Smolin	**74**	57	oncology, radiology	Moscow	89 (63)
67	Aleksandr Voleslavovich Gordienko	**74**	39	gastroenterology, cardiology, therapy	St. Petersburg	72 (68)
68	Olga Viktorovna Bugrova	**74**	37	nephrology, rheumatology, therapy	Orenburg	61 (71)
69	Natalya Nikolaevna Vezikova	**74**	23	rheumatology, therapy	Petrozavodsk	80 (66)
70	Natalya Grigoryevna Astafyeva	**74**	13	allergology and immunology, pulmonology	Saratov	82 (66)

71	Aleksandr Yurievich Vishnevsky	**73**	28	anesthesiology-intensive care medicine, cardiology	St. Petersburg	93 (63)
72	Vasily Bogdanovich Vasilyuk	**73**	25	clinical pharmacology, therapy	St. Petersburg	107 (58)
73	Natalya Evgenyevna Nikulenkova	**73**	24	rheumatology	Vladimir	77 (67)
74	Lyudmila Gennadyevna Lenskaya	**73**	13	oncology, surgery, clinical pharmacology, therapy	Tomsk	78 (67)
75	Nikolai Viktorovich Kislov	**72**	61	oncology	Yaroslavl	102 (59)
76	Yuri Pavlovich Uspensky	**72**	36	gastroenterology, therapy	St. Petersburg	86 (64)
77	Svetlana Anatolyevna Protsenko	**71**	41	oncology	St. Petersburg	76 (67)
78	Ildar Rishatovich Akhmetov	**71**	20	anesthesiology-intensive care medicine, toxicology, clinical pharmacology	Moscow	108 (58)
79	Mikhail Yurievich Byakhov	**71**	19	oncology	Moscow	64 (71)
80	Svetlana Borisovna Yerofeeva	**70**	17	cardiology, therapy, clinical pharmacology	Moscow	100 (60)
81	Ekaterina Yurievna Valuiskikh	**69**	47	gastroenterology, therapy	Novosibirsk	84 (64)
82	Anna Valerievna Alyasova	**69**	37	oncology	Nizhny Novgorod	91 (63)
83	Elena Pavlovna Ilivanova	**69**	28	rheumatology	St. Petersburg	83 (65)
84	Diana Nodarievna Alpenidze	**69**	22	endocrinology, therapy	St. Petersburg	96 (61)
85	Georgy Moiseevich Manikhas	**69**	21	hematology, oncology	St. Petersburg	68 (69)
86	Leysan Ildarovna Myasoutova	**69**	15	rheumatology	Kazan	73 (68)
87	Natalya Aleksandrovna Yeremina	**69**	11	ophthalmology, therapy	Nizhny Novgorod	81 (66)
88	Grigory Pavlovich Arutyunov	**69**	7	cardiology, rheumatology, therapy	Moscow	75 (68)
89	Irina Valentinovna Sidorenko	**69**	6	allergology and immunology, pulmonology	Moscow	70 (69)
90	Vsevolod Borisovich Matveev	**68**	45	oncology	Moscow	95 (61)
91	Aleksandr Valerievich Luft	**68**	43	oncology, surgery	St. Petersburg	85 (64)
92	Olga Polikarpovna Alekseeva	**68**	33	gastroenterology, therapy	Nizhny Novgorod	92 (63)
93	Farit Akhatovich Khabirov	**68**	29	neurology	Kazan	98 (60)
94	Nadezhda Vladimirovna Izmozherova	**68**	12	cardiology, clinical pharmacology, therapy	Ekaterinburg	69 (69)
95	Valery Mikhailovich Chistyakov	**67**	43	oncology, clinical pharmacology, therapy	Pyatigorsk	90 (63)
96	Olga Vladimirovna Vorobyova	**67**	18	neurology	Moscow	105 (59)
97	Lyubov Anatolyevna Shpagina	**67**	15	hematology, cardiology, pulmonology, clinical pharmacology, therapy	Novosibirsk	88 (64)
98	Elena Vladimirovna Zonova	**66**	35	rheumatology, therapy	Novosibirsk	103 (59)
99	Oleg Raisovich Ziganshin	**66**	31	dermatovenerology, cosmetology, urology	Chelyabinsk	126 (53)
100	Anton Sergeevich Povzun	**66**	25	nephrology, rheumatology, therapy	St. Petersburg	87 (64)

**The data are given as of July 2020*

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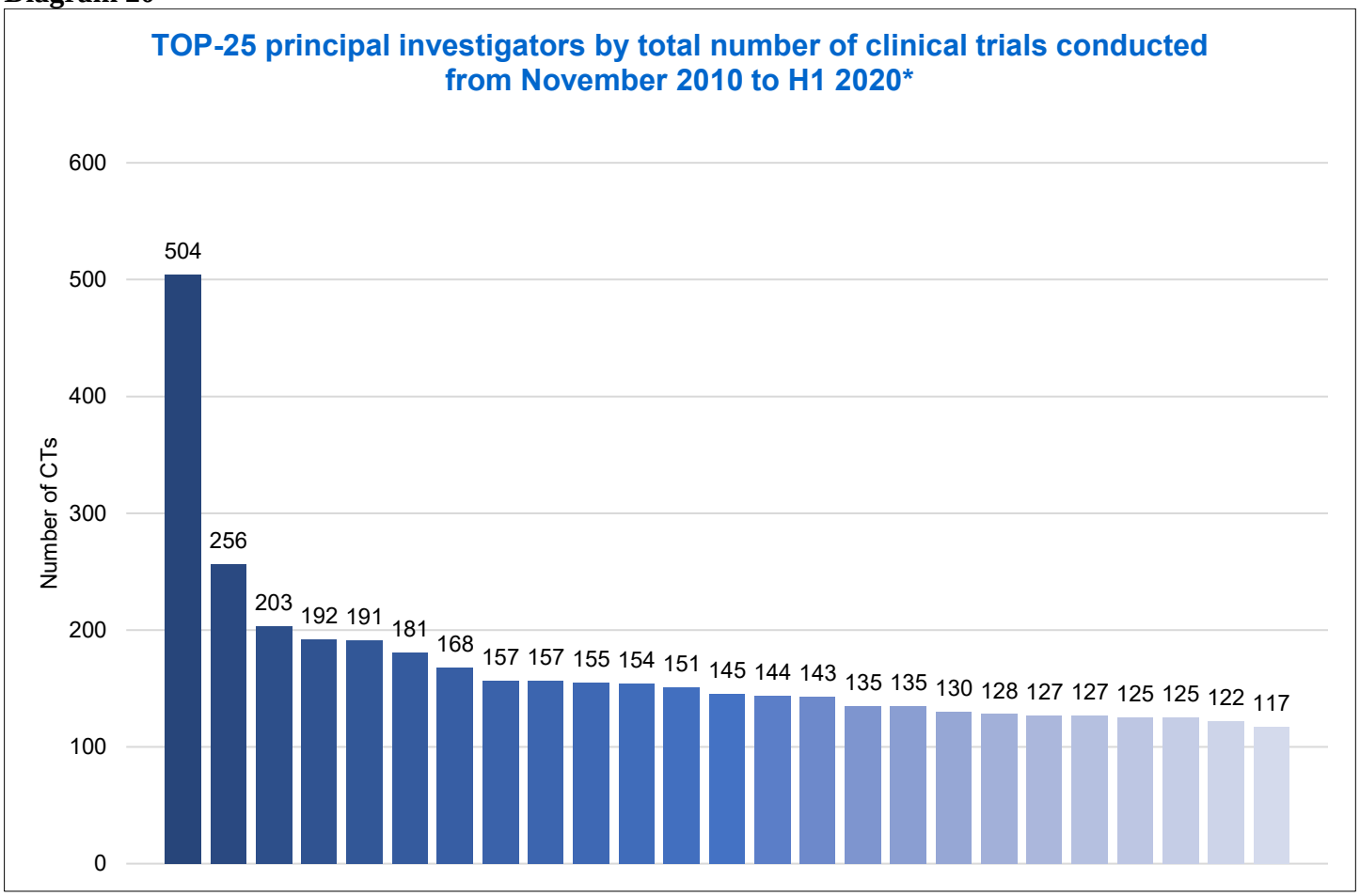
Diagram 20



**The data are given as of July 2020*

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Table 7

Top-20 of Principal Investigators in Oncology by Number of Ongoing Trials*						
Reference number	**Principal investigator's full name**	**Number of ongoing CTs**	**Total number of CTs**	**Specialization**	**City**	**Ranking and Number of CTs in 2019**
1	Mikhail Vladimirovich Dvorkin	**104**	135	oncology, surgery	Omsk	1 (90)
2	Daniil Lyvovich Stroyakovsky	**87**	128	oncology, neurology	Moscow	2 (86)
3	Marina Nikolaevna Nechaeva	**86**	109	oncology	Arkhangelsk	6 (73)
4	Konstantin Konstantinovich Laktionov	**84**	155	oncology, surgery, thoracic surgery	Moscow	3 (81)
5	Dmitry Petrovich Udovitsa	**72**	144	hematology, oncology	Sochi	7 (68)
6	Igor Dmitrievich Lifirenko	**64**	111	oncology	Kursk	8 (68)
7	Sergey Vladimirovich Orlov	**61**	143	oncology	St. Petersburg	13 (54)
8	Nikolay Victorovich Kislov	**61**	72	oncology	Yaroslavl	16 (52)
9	Guzel Zinnurovna Mukhametshina	**59**	130	oncology	Kazan	10 (61)
10	Nadezhda Vitalyevna Kovalenko	**58**	95	oncology	Volgograd	18 (45)
11	Vladimir Ivanovich Vladimirov	**57**	168	oncology, urology	Pyatigorsk	4 (76)
12	Aleksey Vladimirovich Smolin	**57**	74	oncology, radiology	Moscow	17 (50)

13	Olga Sergeevna Samoylova	**55**	87	hematology, oncology	Nizhny Novgorod	15 (52)
14	Boris Yakovlevich Alekseev	**55**	81	oncology, urology	Moscow	14 (54)
15	Natalya Vladimirovna Fadeeva	**48**	114	oncology	Chelyabinsk	9 (64)
16	Nina Alekseevna Karaseva	**46**	94	oncology	St. Petersburg	12 (58)
17	Vsevolod Borisovich Matveev	**45**	68	oncology	Moscow	24 (41)
18	Aleksandr Valerievich Luft	**43**	68	oncology, surgery	St. Petersburg	20 (43)
19	Oleg Aleksandrovich Gladkov	**42**	114	oncology	Chelyabinsk	11 (59)
20	Vadim Borisovich Shirinkin	**42**	76	oncology	Orenburg	19 (44)

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Table 8

Top-20 of Principal Investigators in Clinical Pharmacology by Number of Ongoing Trials*						
Reference number	**Principal investigator's full name**	**Number of ongoing CTs**	**Total number of CTs**	**Specialization**	**City**	**Ranking and Number of CTs in 2019**
1	Alina Sergeevna Agafyina	**79**	203	clinical pharmacology, neurology, pulmonology, therapy	St. Petersburg	2 (71)
2	Aleksandr Leonidovich Khokhlov	**61**	504	cardiology, clinical pharmacology, pulmonology, oncology, therapy	Yaroslavl	1 (85)
3	Konstantin Anatolyevich Zakharov	**59**	125	infectious diseases, clinical pharmacology, therapy, general medical practice (family medicine)	St. Petersburg	3 (56)
4	Sergey Mikhailovich Noskov	**48**	256	rheumatology, clinical pharmacology, therapy	Yaroslavl	5 (51)
5	Olga Vilorovna Reshetko	**48**	157	rheumatology, clinical pharmacology, therapy	Saratov	4 (53)
6	Valery Mikhailovich Chistyakov	**43**	67	oncology, clinical pharmacology, therapy	Pyatigorsk	8 (39)
7	Anna Nikolaevna Galustyan	**42**	191	allergology and immunology, infectious diseases, clinical pharmacology, oncology, pediatrics, pulmonology, therapy	St. Petersburg	6 (49)
8	Elena Anatolyevna Smolyarchuk	**41**	154	rheumatology, clinical pharmacology, therapy, ophthalmology	Moscow	7 (41)
9	Vladimir Vitalyevich Rafalsky	**38**	87	cardiology, clinical pharmacology, therapy	Kaliningrad	9 (38)
10	Anton Sergeevich Yedin	**32**	116	dermatovenerology, clinical pharmacology, therapy	St. Petersburg	11 (33)
11	Ivan Surenovich Sardanyan	**32**	115	clinical pharmacology	St. Petersburg	19 (20)
12	Grigory Vladimirovich Rodoman	**30**	105	clinical pharmacology, surgery	Moscow	12 (28)
13	Vladimir Valentinovich Yakusevich	**30**	116	clinical pharmacology, therapy	Yaroslavl	10 (35)
14	Vasily Bogdanovich Vasiluk	**25**	73	clinical pharmacology, therapy	St. Petersburg	15 (23)

15	Aleksandr Yurievich Malygin	**24**	115	anesthesiology-intensive care medicine, clinical pharmacology	Yaroslavl	17 (21)
16	Viktor Borisovich Shunkov	**21**	84	cardiology, clinical pharmacology, therapy	St. Petersburg	13 (28)
17	Svetlana Borisovna Yerofeeva	**17**	70	cardiology, clinical pharmacology, therapy	Moscow	24 (15)
18	Elena Valentinovna Borodulina	**15**	93	clinical pharmacology, obstetrics and gynaecology, therapy	Tomsk	22 (17)
19	Petr Aleksandrovich Chizhov	**15**	91	cardiology, pulmonology, rheumatology, therapy	Yaroslavl	18 (20)
20	Lyubov Anatolyevna Shpagina	**15**	67	hematology, cardiology, pulmonology, clinical pharmacology, therapy	Novosibirsk	18 (20)

**The data are given as of July 2020*
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Table 9

Top-50 of Principal Investigators (Excluding Oncologists and Clinical Pharmacologists) by Number of Ongoing Trials*

Reference number	Principal investigator's full name	Number of ongoing CTs	Total number of CTs	Specialization	City	Ranking and Number of CTs in 2019
1	Ivan Gennadyevich Gordeev	**55**	181	cardiology, therapy	Moscow	8 (40)
2	Olga Borisovna Yershova	**53**	192	rheumatology, cardiology, therapy	Yaroslavl	3 (56)
3	Yuri Grigoryevich Shvarts	**51**	145	cardiology, nephrology, rheumatology, therapy	Saratov	4 (49)
4	Marina Fedorovna Osipenko	**51**	111	gastroenterology, pulmonology, clinical pharmacology, therapy	Novosibirsk	6 (44)
5	Ekaterina Yurievna Valuiskikh	**47**	69	gastroenterology, therapy	Novosibirsk	5 (45)
6	Olga Leonidovna Barbarash	**46**	157	cardiology, endocrinology	Kemerovo	2 (57)
7	Olga Petrovna Ukhanova	**44**	95	allergology and immunology, therapy	Stavropol	10 (39)
8	Aleksandr Voleslavovich Gordienko	**39**	74	gastroenterology, cardiology, therapy	St. Petersburg	14 (35)
9	Olga Viktorovna Bugrova	**37**	74	nephrology, rheumatology, therapy	Orenburg	11 (39)
10	Artyom Yurievich Vorobyov	**36**	127	neurology	MR, Serpukhov	9 (39)
11	Yuri Pavlovich Uspensky	**36**	72	gastroenterology, therapy	St. Petersburg	15 (35)
12	Elena Vladimirovna Zonova	**35**	66	rheumatology, therapy	Novosibirsk	16 (35)
13	Marina Leonidovna Stanislav	**34**	151	rheumatology	Moscow	1 (66)
14	Igor Gennadyevich Bakulin	**34**	64	gastroenterology, therapy	St. Petersburg	21 (33)
15	Olga Polikarpovna Alekseeva	**33**	68	gastroenterology, therapy	Nizhny Novgorod	20 (33)

16	Vladimir Ilyich Simanenkov	**32**	116	gastroenterology, clinical pharmacology, therapy	St. Petersburg	7 (41)
17	Evgeniya Isaakovna Shmidt	**32**	80	rheumatology	Moscow	19 (33)
18	Tatyana Alekseevna Raskina	**31**	98	cardiology, rheumatology, therapy	Kemerovo	17 (34)
19	Oleg Raisovich Ziganshin	**31**	66	dermatovenerology, cosmetology, urology	Chelyabinsk	28 (28)
20	Vasily Ivanovich Trofimov	**29**	135	gastroenterology, pulmonology, therapy	St. Petersburg	18 (33)
21	Natalya Nikolaevna Maslova	**29**	85	neurology	Smolensk	44 (21)
22	Farit Akhatovich Khabirov	**29**	68	neurology	Kazan	30 (27)
23	Natalya Nikolaevna Varnakova	**28**	117	therapy	Nizhny Novgorod	37 (23)
24	Aleksandr Yurievich Vishnevsky	**28**	73	anesthesiology-intensive care medicine, cardiology	St. Petersburg	31 (26)
25	Elena Pavlovna Ilivanova	**28**	69	rheumatology	St. Petersburg	24 (31)
26	Veronika Borisovna Popova	**27**	106	pulmonology, therapy, clinical pharmacology	St. Petersburg	45 (20)
27	Sergey Stepanovich Yakushin	**26**	97	cardiology, rheumatology, nephrology, therapy	Ryazan	22 (32)
28	Galina Aleksandrovna Chumakova	**26**	76	gastroenterology, cardiology, therapy	Barnaul	23 (31)
29	Anton Sergeevich Povzun	**25**	66	nephrology, rheumatology, therapy	St. Petersburg	26 (29)
30	Natalya Evgenyevna Nikulenkova	**24**	73	rheumatology	Vladimir	25 (29)
31	Natalya Nikolaevna Vezikova	**23**	74	rheumatology, therapy	Petrozavodsk	46 (20)
32	Andrey Petrovich Rebrov	**22**	88	cardiology, rheumatology, therapy	Saratov	12 (37)
33	Natalya Petrovna Shilkina	**22**	83	cardiology, rheumatology, therapy	Yaroslavl	43 (21)
34	Diana Nodarievna Alpenidze	**22**	69	endocrinology, therapy	St. Petersburg	33 (25)
35	Viktor Avenirovich Kostenko	**21**	66	cardiology, therapy	St. Petersburg	41 (22)
36	Ildar Rishatovich Akhmetov	**20**	71	anesthesiology-intensive care medicine, toxicology, clinical pharmacology	Moscow	54 (17)
37	Zhanna Davidovna Kobalava	**19**	85	cardiology, endocrinology, therapy	Moscow	40 (22)
38	Olga Vladimirovna Vorobyova	**18**	67	neurology	Moscow	51 (18)
39	Leysan Ildarovna Myasoutova	**15**	69	rheumatology	Kazan	38 (23)
40	Galina Lyvovna Ignatova	**14**	79	pulmonology	Chelyabinsk	53 (17)
41	Tatyana Ivanovna Martynenko	**14**	65	pulmonology	Barnaul	72 (10)
42	Konstantin Nikolaevich Zrazhevsky	**14**	64	cardiology, therapy	St. Petersburg	39 (23)

43	Natalya Grigoryevna Astafyeva	**13**	74	allergology and immunology, pulmonology	Saratov	76 (8)
44	Elena Alekseevna Shumetova	**12**	91	cardiology	Ivanovo	58 (15)
45	Anastasia Aleksandrovna Bagretsova	**11**	64	therapy	Arkhangelsk	59 (15)
46	Gadel Maratovich Kamalov	**9**	75	cardiology, therapy	Kazan	61 (14)
47	Natalya Leonidovna Shaporova	**8**	64	cardiology, general medical practice, therapy, pulmonology	St. Petersburg	70 (10)
48	Grigory Pavlovich Arutyunov	**7**	69	cardiology, rheumatology, therapy	Moscow	64 (12)
49	Irina Valentinovna Sidorenko	6	69	allergology and immunology, pulmonology	Moscow	66 (11)
50	Viktor Vasilievich Shilov	4	122	therapy, toxicology	St. Petersburg	77 (7)

**The data are given as of July 2020*
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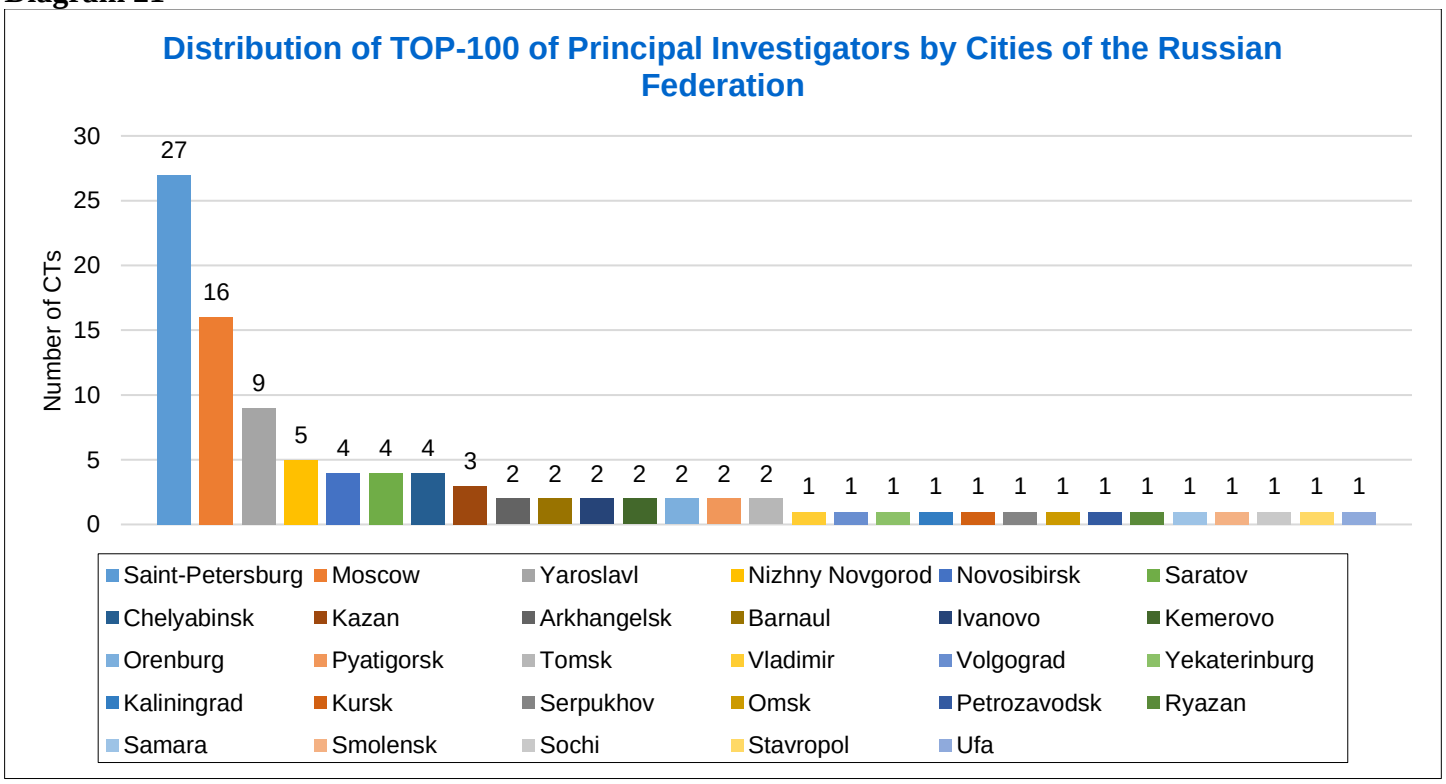
Diagram 21



**The data are given as of July 2020*
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Annex

IMCT STATISTICS FOR ONCOLOGY AND ONCOHAEMATOLOGY, 2019

Table 10

Distribution of IMCTs by Therapeutic Areas, 2019			
Therapeutic area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**
Oncology and oncohaematology	91	29.1%	6407
Neurology	33	10.5%	1836
Rheumatology	29	9.3%	2306
Psychiatry	21	6.7%	2216
Haematology	18	5.8%	413
Infectious Diseases (except HIV/HCV/tuberculosis)	18	5.8%	2204
Gastroenterology	17	5.4%	1396
Endocrinology	16	5.1%	1637
Ophthalmology	15	4.8%	707
Dermatology	12	3.8%	746
Pulmonology	10	3.2%	1223
Cardiology and CVD	9	2.9%	1737
Allergology	4	1.3%	320
Urology	4	1.3%	715
Nephrology	4	1.3%	307
Hepatology	3	1.0%	120
Obstetrics/Gynaecology	2	0.6%	165
Immunology	2	0.6%	270
HIV/HCV	2	0.6%	25
Surgery	2	0.6%	900
Otorhinolaryngology	1	0.3%	360
TOTAL	313	100.0%	26010

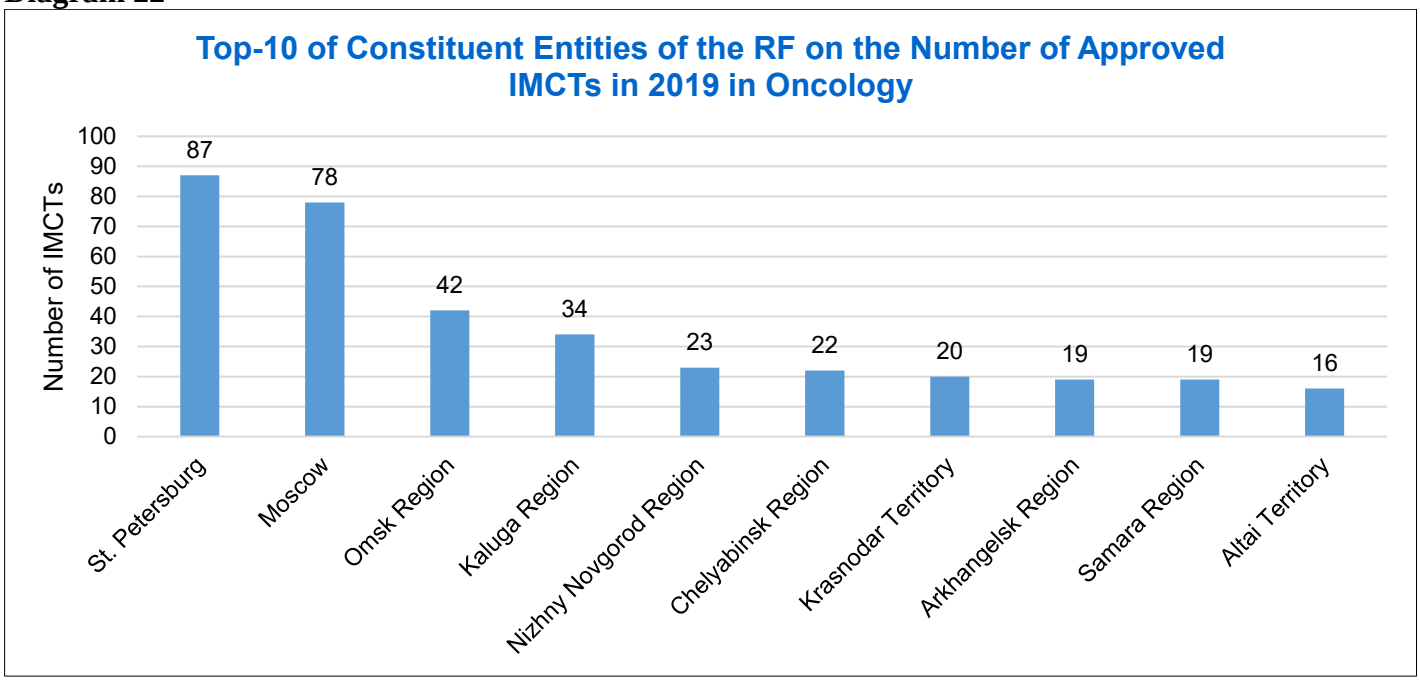
Data from www.grls.rosminzdrav.ru

Table 11

IMCT Distribution in Oncology and Oncohaematology, 2019			
No.	**Disease type**	**Number of IMCTs**	**Claimed number of subjects**
1	Lung and pleural cavity tumours	25	2085
2	Breast tumour	9	946
3	Leukemia	5	342
4	Kidney and genitourinary system tumors	9	412
5	Tumours without known localisation	9	293
6	Gastrointestinal tumours	3	165
7	Female reproductive system tumours	2	180
8	Multiple myeloma	1	75
9	Melanoma, cutaneous squamous cell carcinoma	3	217
10	Liver tumours and biliary tract cancer	6	488
11	Head and neck tumours	1	28
12	Glioma	1	20
13	Thyroid tumor	1	35
14	Lymphoma	8	282
15	Prostate tumour	8	839
	TOTAL	91	6407

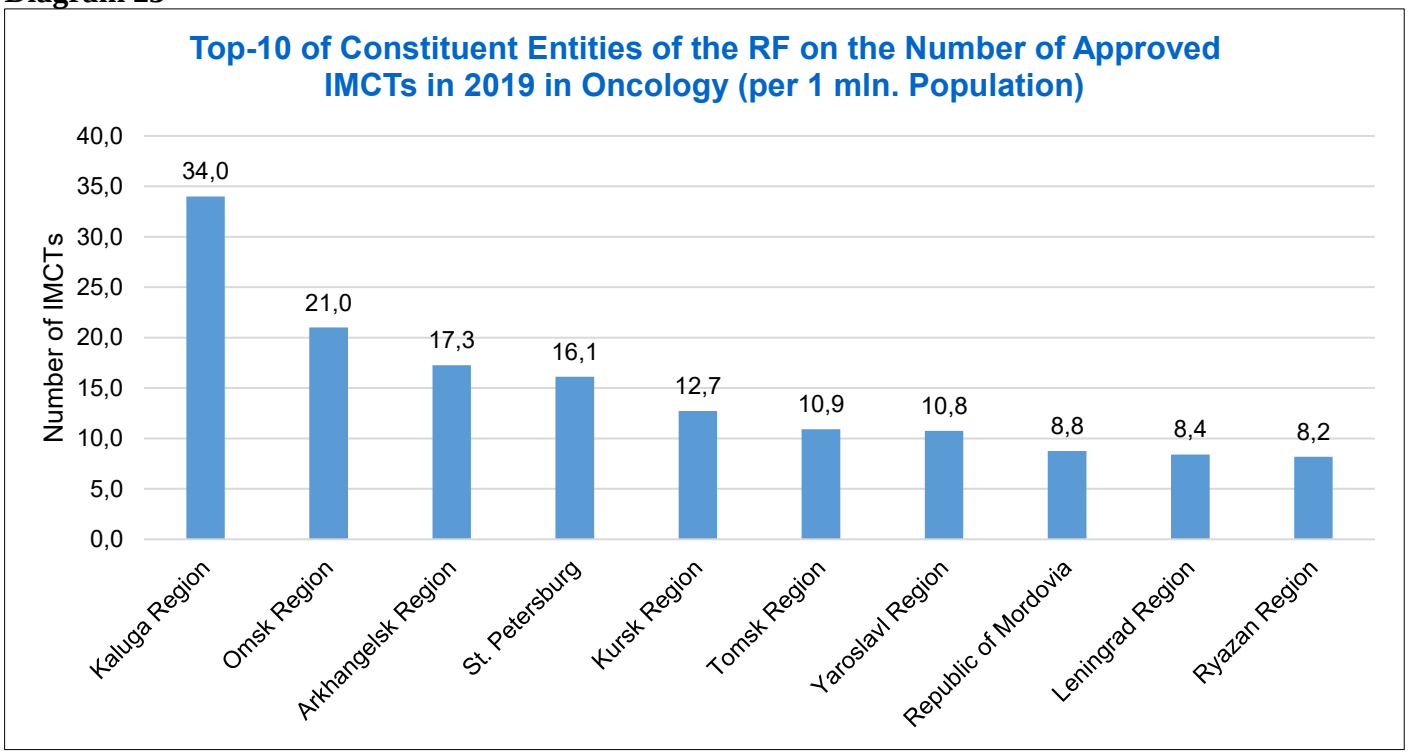
Data from www.grls.rosminzdrav.ru

Diagram 22



Data from www.grls.rosminzdrav.ru

Diagram 23



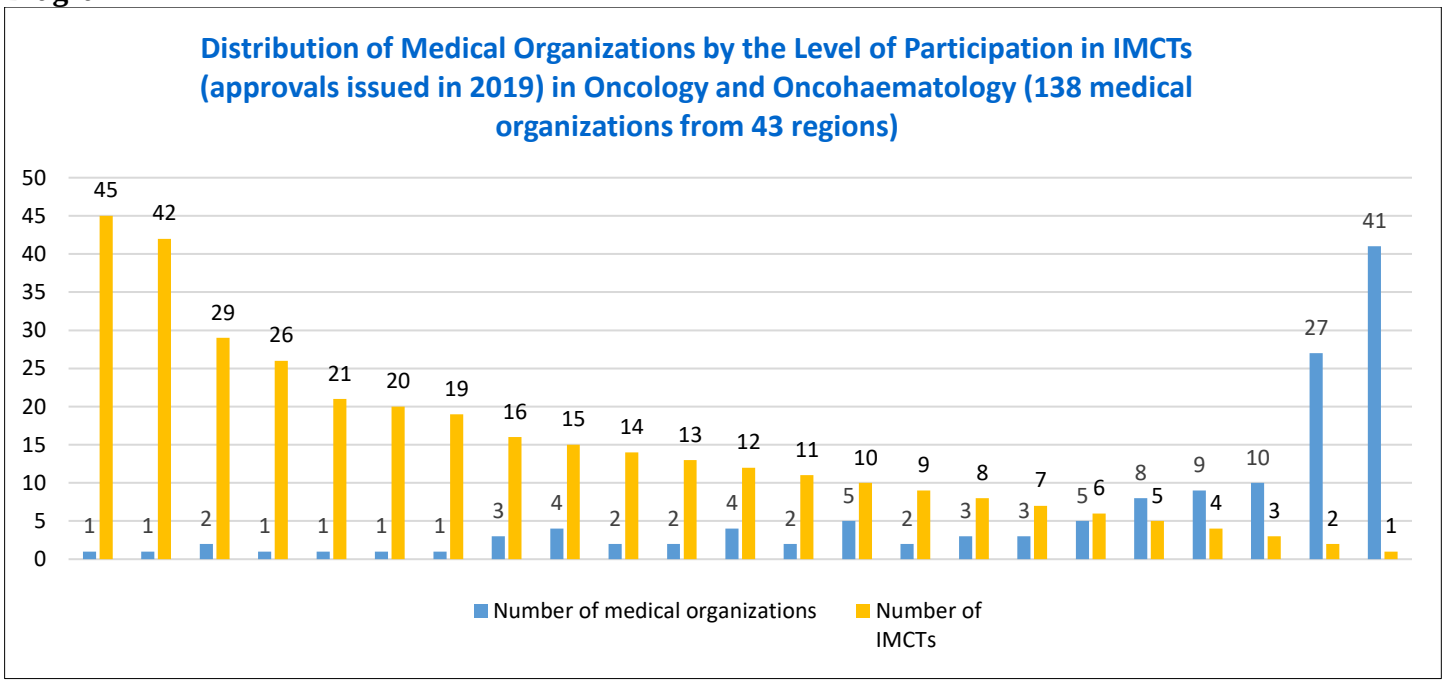
Data from www.grls.rosminzdrav.ru

Table 12

Ranking of Medical Organizations on the Activity of Participation in IMCTs in Oncology and Oncohaemotology Approved in 2019			
Place in ranking	**Name of medical organization**	**Number of IMCTs approved in 2019 with participation of this medical organization**	**Number of sites approved in 2019 for conducting IMCTs**
1	N. N. Blokhin Russian Cancer Research Centre, Russian Ministry of Health, Moscow	45	49
2	Clinical Oncological Dispensary, Omsk	42	43
3	National Medical Research Radiological Center, Obninsk	29	32
4	St. Petersburg City Clinical Oncological Dispensary, St. Petersburg	29	29
5	N. N. Petrov Research Institute of Oncology, Russian Ministry of Health, St. Petersburg	26	26
6	St. Petersburg Clinical Practical Research Centre for Specialised Types of Medical Aid (Oncological), St. Petersburg	21	21
7	I. P. Pavlov First St. Petersburg State medical University, Russian Ministry of Health, St. Petersburg	20	20
8	Arkhangelsk Clinical Oncological Dispensary, Arkhangelsk	19	19
9-11	Leningrad Regional Oncology Center, Leningrad region	16	16
9-11	Oncological Dispensary No. 2, Sochi	16	16
9-11	Treatment and rehabilitation center, Russian Ministry of Health, Moscow	16	16

Data from www.grls.rosminzdrav.ru

Diagram 24



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