ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

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MOSCOW 2019

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SUMMARY

In H1 2019 the Russian market of clinical trials has moderately grown. The Ministry of Health of the Russian Federation provided 13.8% more approvals year-on-year and yet this performance (346 approvals) is below the results in H1 2017 (358) and H1 2016 (450). The sector of local trials by foreign sponsors showed fastest growth – by 58.3%. Nevertheless, very modest absolute figures stand behind the impressive relative change: 19 approvals versus 12 in H1 2018. The sector of local trials by domestic sponsors (78 versus 59 approvals) increased by 32.2%. The number of bioequivalence study approvals also went up by 16.7% (84 versus 72) for Russian generics and by 7.4% (29 versus 27) for foreign-made generics. The sector of international multicentre clinical trials (IMCTs) has been most stable in four recent years. 136 IMCT approvals have been provided in January–June 2019, up 1.5% year-on-year (134).

We annually collect data from ACTO members on the work of Health Ministry's expert bodies whose conclusions underlie the approval issue decision. This time 22 companies answered the questions about their experience of passing expert evaluations on 228 applications for IMCTs. The share of approvals without comments following the initial review by the Ethics Council has markedly grown this year to 62.6% versus 46.9% a year before. The expert evaluations by the Scientific Centre for Expert Evaluation of Medicinal Products (SCEEMP) are less rosy than last year. The share of primary reviews without comments accounted for 73.1% versus the record high 80.7% a year before. Yet on the whole the SCEEMP expert evaluation statistics still look better as compared to those of the Ethics Council. The complicacy of the expert evaluation procedure differs depending on the specific therapeutic areas. The highest number of disapprovals from the Ethics Council fall to the share of applications for trials in psychiatry (41.7%), while SCEEMP experts mostly censure protocols in the field of infectious diseases, out of all proportion (64.3%).

For the first time the blind method penetration in clinical trials conducted in Russia is assessed in the ACTO bulletin. It was somewhat unexpected that the share of blind protocols submitted by foreign sponsors in local trials was smaller compared to those submitted by Russian sponsors (40% versus 56%). We believe that some Russian developers are motivated to use the blind method by their desire to enter foreign markets in the future.

We tried to revive the section highlighting the results of inspections made by Federal Service for Surveillance in Healthcare (Roszdravnadzor). The reform of surveillance activities in Russia altered the methods used by inspecting bodies as well as the format of submitting information on the results of inspections. Therefore, interpretation of the data for 2018 requires some elucidation and comments; furthermore, they cannot be checked against the earlier ones.

The situation with clinical trials of medicines for the treatment of neurological and psychiatric diseases is highlighted in the bulletin's separate section. A comparison by three diseases reveals that in 2013–2018 Russia accounted roughly for 13% of all antiepileptic drug trials in the world, 6% of all Alzheimer drug trials and 2% of Parkinson medication trials.

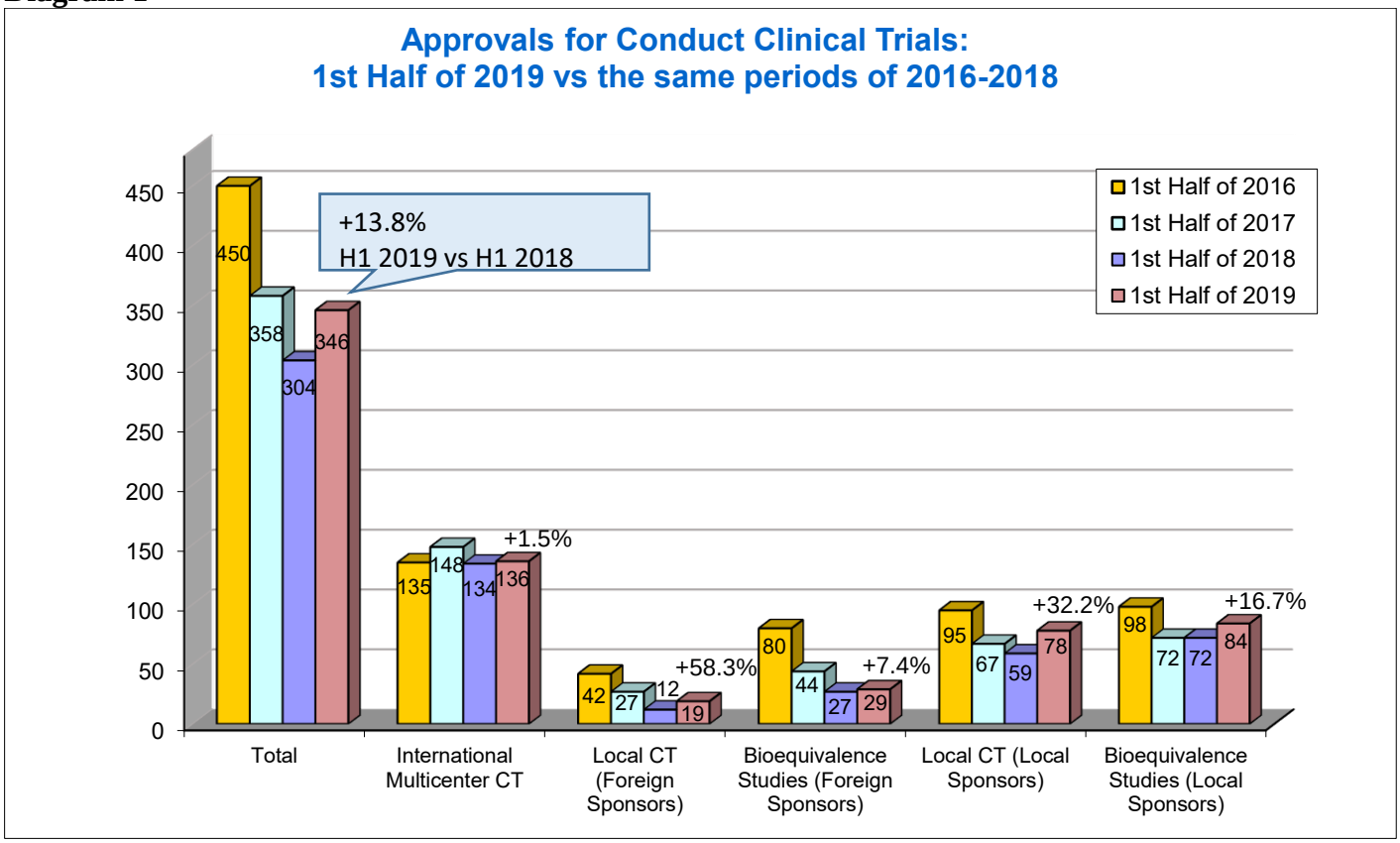
We've never touched the work of principal investigators in our analytics before. So, we decided to remedy this omission. Relying on the data of the Health Ministry's registry, we've ranked experts by the number of approvals they garnered as principal investigators.

Like a year ago, we conclude this issue with a selection of tables and diagrams with the IMCT statistics in oncology and oncohaematology, for this once for 2018.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In H1 2019 the Ministry of Health of the Russian Federation has issued 346 licenses for clinical trials. Up 13.8% year-on-year (42 licenses more), but still fewer than in 2017 and 2016 (Diagram 1).

Diagram 1



Data from www.grls.rosminzdrav.ru

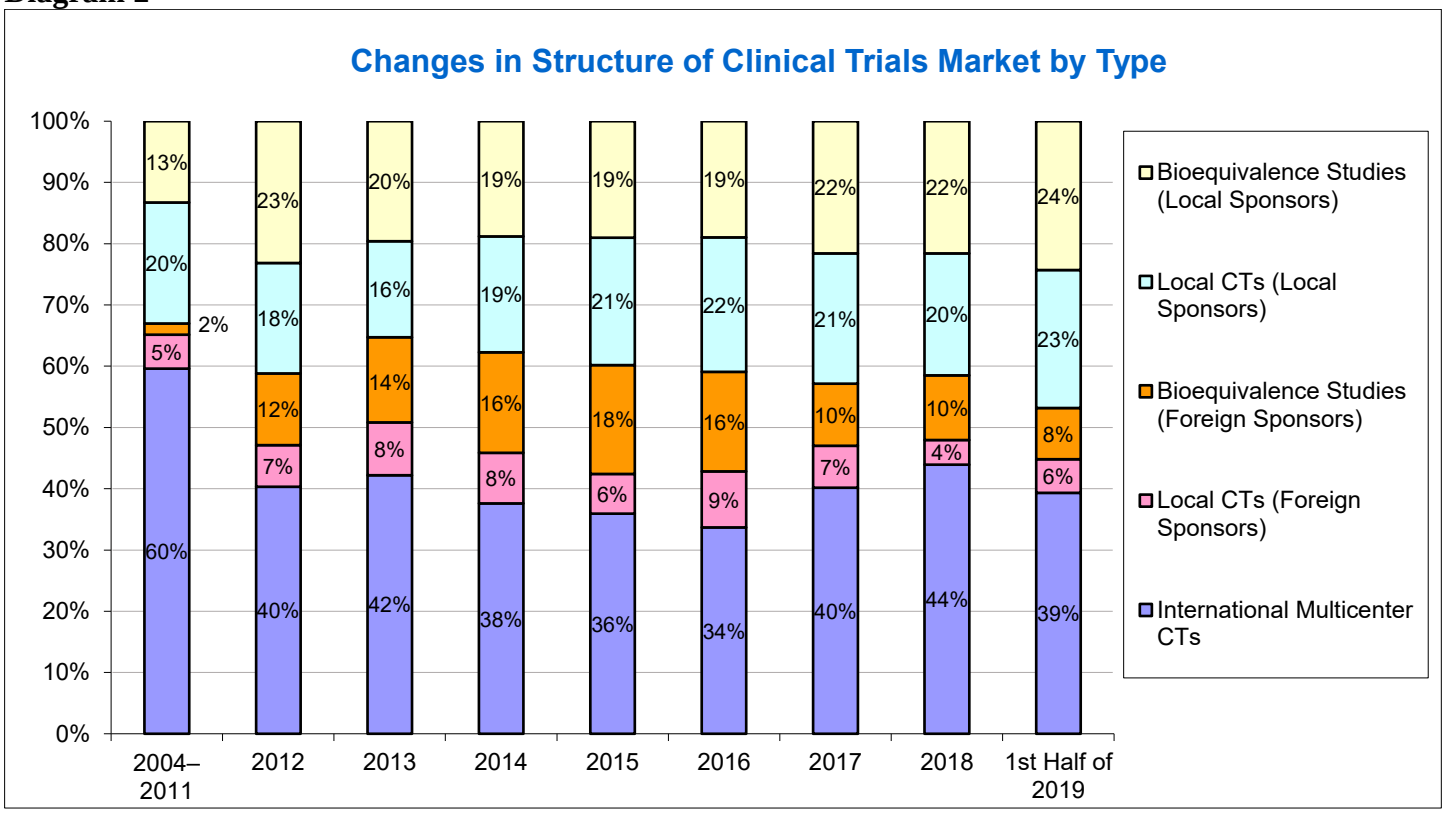
The sector of international multicenter clinical trials (IMCTs) has been most stable not just relative to the data for 2018, but also in all four recent years. In H1 2019 the total of 136 IMCT approvals have been provided, as compared to 134 a year earlier (the growth was limited to 1.5%).

The sector of local trials by foreign sponsors (19 approvals versus 12 in H1 2018) has boasted the largest growth of 58.3%; however, this can solely be explained by a small absolute number of such approvals. The sector of local trials by domestic sponsors (78 versus 59 approvals) has grown by 32.2%.

All other sectors have also recorded some growth, albeit a lot more modest. The number of bioequivalence study approvals also went up by 16.7% (84 versus 72) for Russian generics and by 7.4% (29 versus 27) for foreign-made generics.

The growing number of approval issues was mainly the result of local trials and bioequivalence studies, which inevitably led to a change in the ratio between various trial types and loss of share of IMCTs (Diagram 2). Thus, compared to the data for 2018, in H1 2019 the share of international projects went down by 5 percentage points (39% versus 44% in H1 2018).

Diagram 2



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

As we can see from the diagram, this occurred mainly due to a growing share of trials by Russian manufacturers. So, the sector of their local trials has grown by 3 percentage points (23% versus 20%), with the sector of bioequivalence studies of domestic generics accounting for two more percentage points (24% versus 22%).

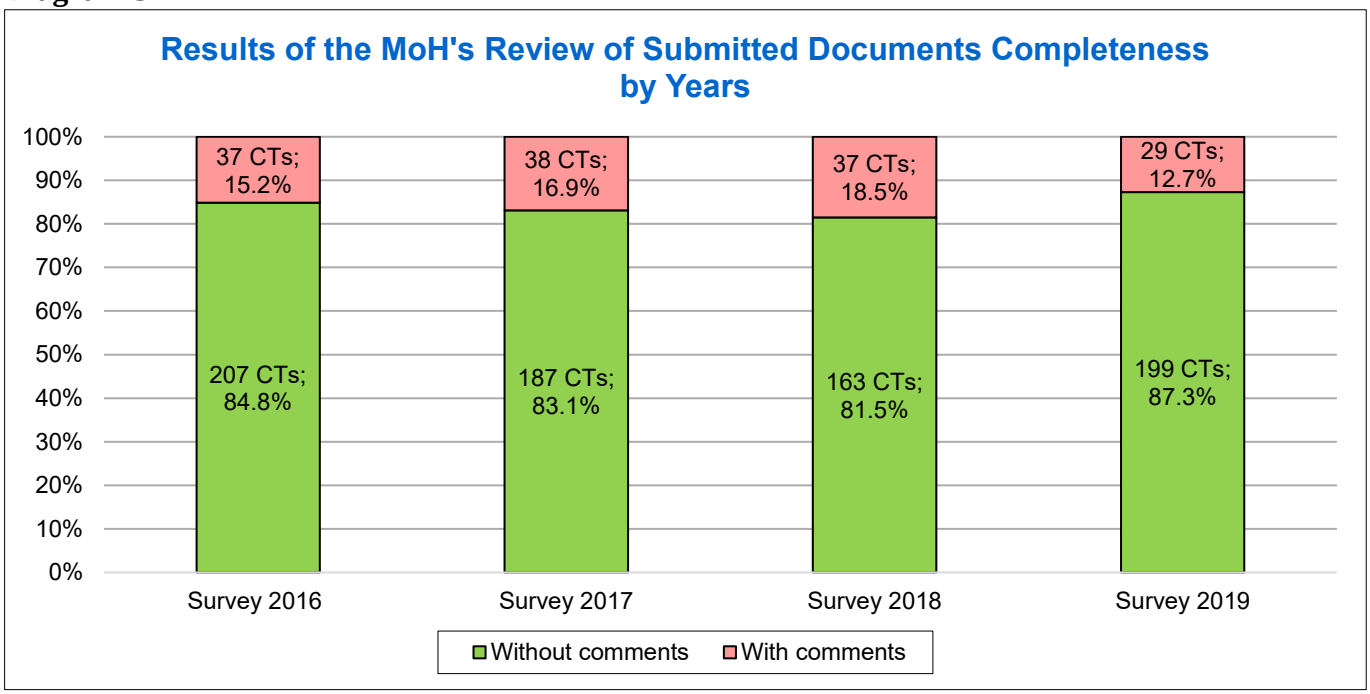
The picture is somewhat different in the sector of local trials by foreign sponsors. The share of bioequivalence studies went down 2 percentage points (8% versus 10% in 2018), whereas the share of efficacy and safety trials grew up by the same 2 percentage points (6% versus 4%).

EXPERT EXAMINATION OF PLANNED TRIALS

In this section we traditionally publish the results of the ACTO members survey regarding the expert evaluation by Scientific Centre for Expert Evaluation of Medicinal Products (SCEEMP) and the Ethics Council as far as the obtaining of approvals for the conduct of clinical trials is concerned. The analysis includes data on the applications reviewed in H2 2018 and H1 2019. Overall 22 companies took part in the survey, and we factored in 228 IMCT applications.

As usual, we start with the results of passing the first stage of the regulatory procedure where the Ministry of Health of the Russian Federation checks the completeness of documents. The results of the latest survey as well as those of previous three surveys are shown in Diagram 3. As we can see, in the last period the number of Ministry of Health's requests in view of missing documents (so-called Request 1) has sunk to 12.7% of all applications versus 18.5% in the 2018 survey.

Diagram 3



Data from www.grls.rosminzdrav.ru

We should remind that most problems at this stage involving the difficulties of providing a GMP-certificate issued by a "regulatory authority of the country of origin of the medicinal product", since not all countries provide this paper. Therefore, the reduction of the Ministry's requests, even if only by 6 percentage points, is a good trend. It should be noted that applicants recently observe a hardly perceptible mitigation of the Ministry's approach indeed. To all appearances, the complete prohibition on trials is not the key objective of public officials. Failing to find the above-mentioned GMP-certificate in the dossier submitted, they are nevertheless willing to consider other papers the applicant can provide to prove the due quality of the investigational product. Sometimes a company has to take some pains before a suitable way-out can be found, but there are still not too many direct losses at this stage. Based on the results of the recent survey, only one sponsor refused conducting a trial in Russia due to being unable to submit a GMP-certificate of the manufacturing country. The sponsor withdrawal was influenced by its successful patient recruitment in other countries, so it did not make much sense to continue a discussion with the Russian regulator.

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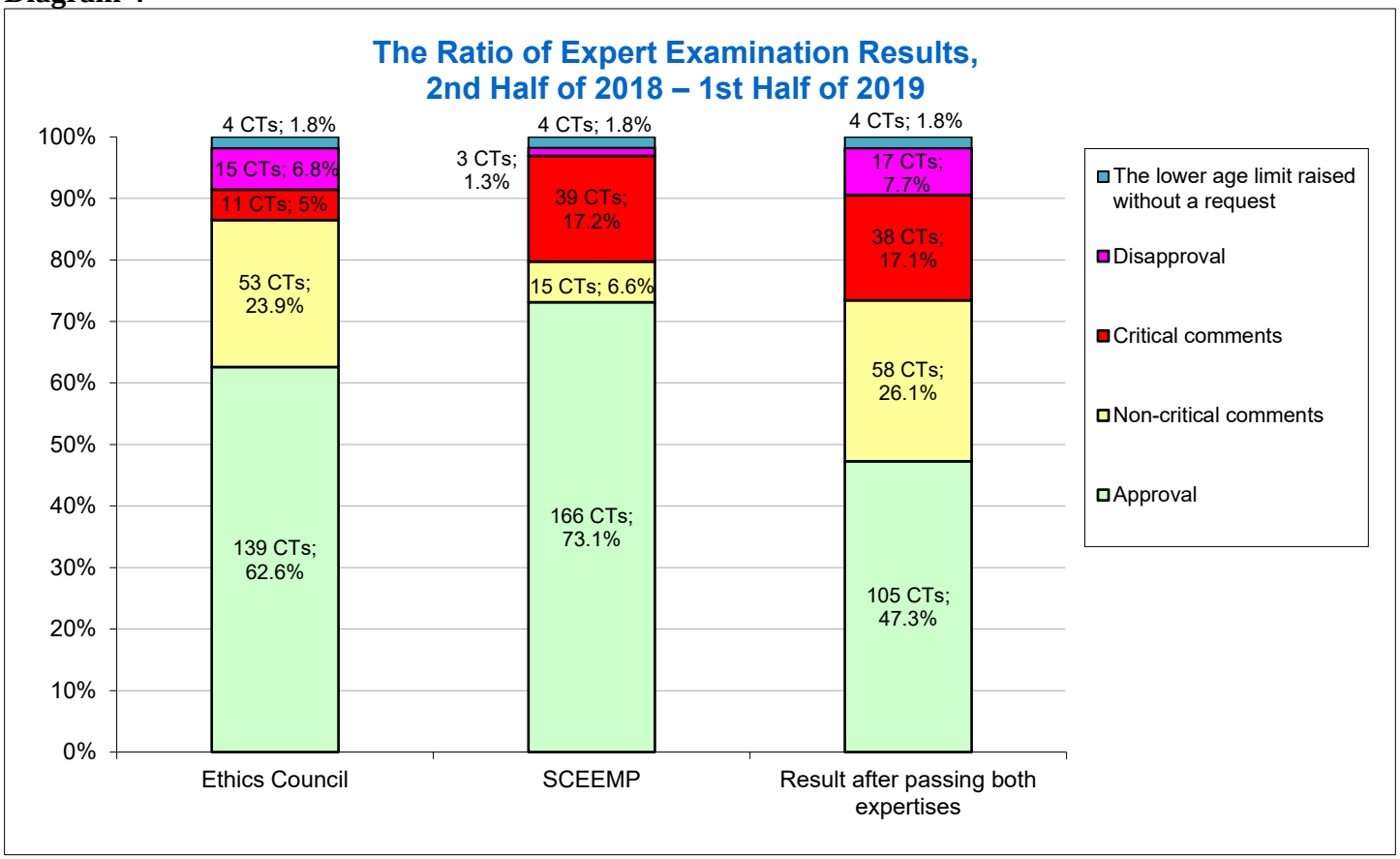
Diagram 4 shows the results of applicants passing the expert evaluation by two bodies: The Ethics Council and SCEEMP as well as the summary results following the expert evaluation by both bodies. Comparing the data obtained with the results of the 2018 survey, we noticed that the share of positive outcomes following the Ethic Council's reviews has grown to 62.6% versus 46.9% a year before. It cannot but rejoice, since the work of this

particular expert body has been causing an increasing concern among members of the ACTO recently. The shares of both non-critical comments (23.9% versus 35.6% a year before) and critical comments (5% versus 13.9%) have decreased. Regrettably, the share of disapprovals has risen to 6.8% (15 IMCTs were given unfavorable primary evaluations by the Ethics Council) versus 2.1% (4 IMCTs) a year earlier. Finally, in 1.8% of all cases reviewed by the Ethics Council (4 trials) the lower age limit of potential participants was raised arbitrarily without any preliminary request or notification of an applicant. The applicant would learn about this outcome already after getting the Ministry's approval. We first encountered this innovative approach after the last year's survey, when the share of the Ethics Council's reviews with this outcome stood at 1.5% (3 trials). Now we can state that this practice has stricken root.

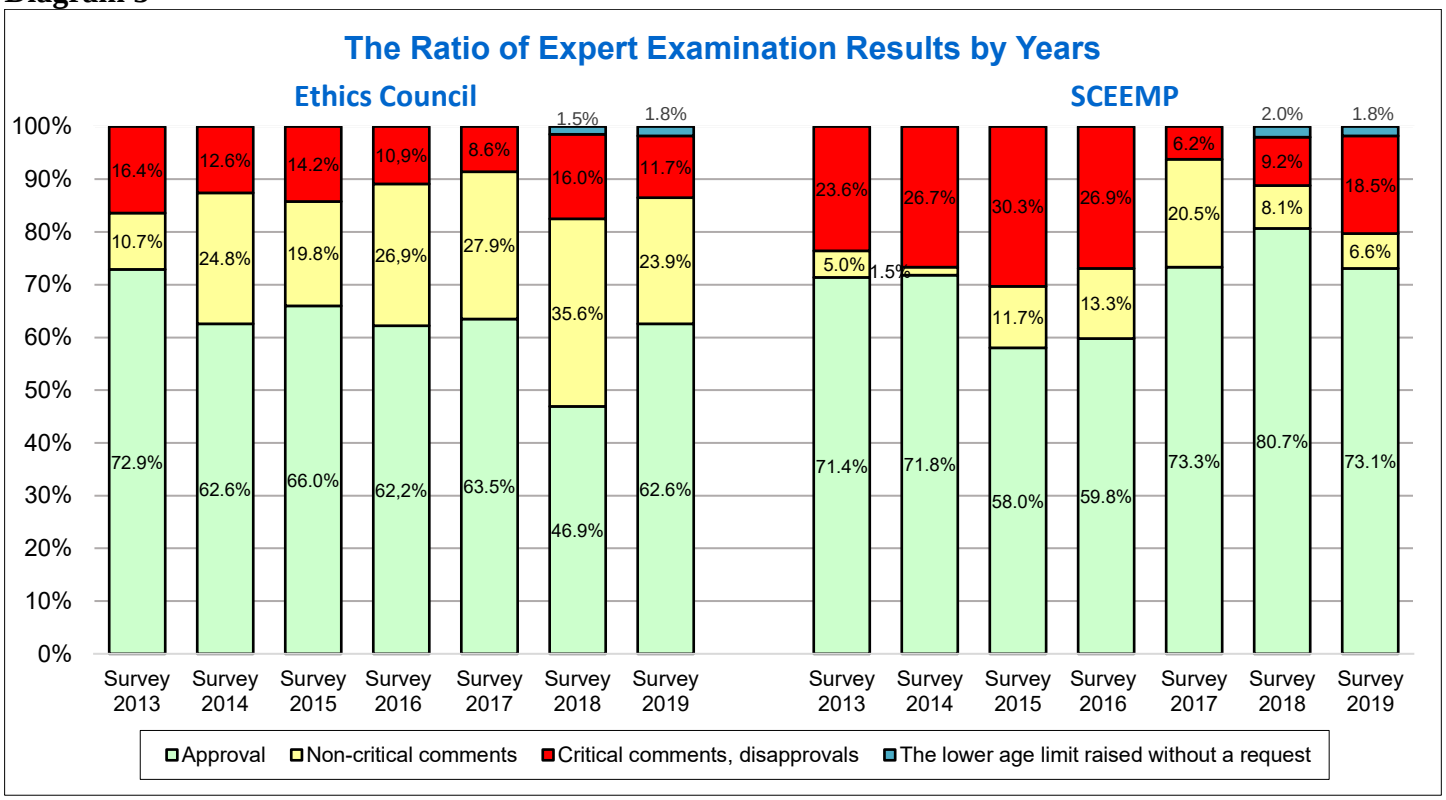
Diagram 4



Data from poll of ACTO members

The results of SCEEMP's expert evaluation slightly deteriorated if compared with the previous survey. Thus, the share of cases without comments amounted to 73.1% versus 80.7% based on the 2018 survey. But it should be noted for the sake of justice that this was the record high figure for the entire time of our monitoring (see Diagram 5). The share of non-critical comments has slid down from 8.1% to 6.6%, whereas the share of critical comments has grown from 8.6% to 17.2% of all cases. What's more, there were three disapprovals (1.3%). Judging by the last year's survey, however, there were no disapprovals from SCEEMP. The share of cases in which, as with the examination of the Ethics Council, the lower age limit for potential participants was increased without preliminary request to the applicant, remained almost the same.

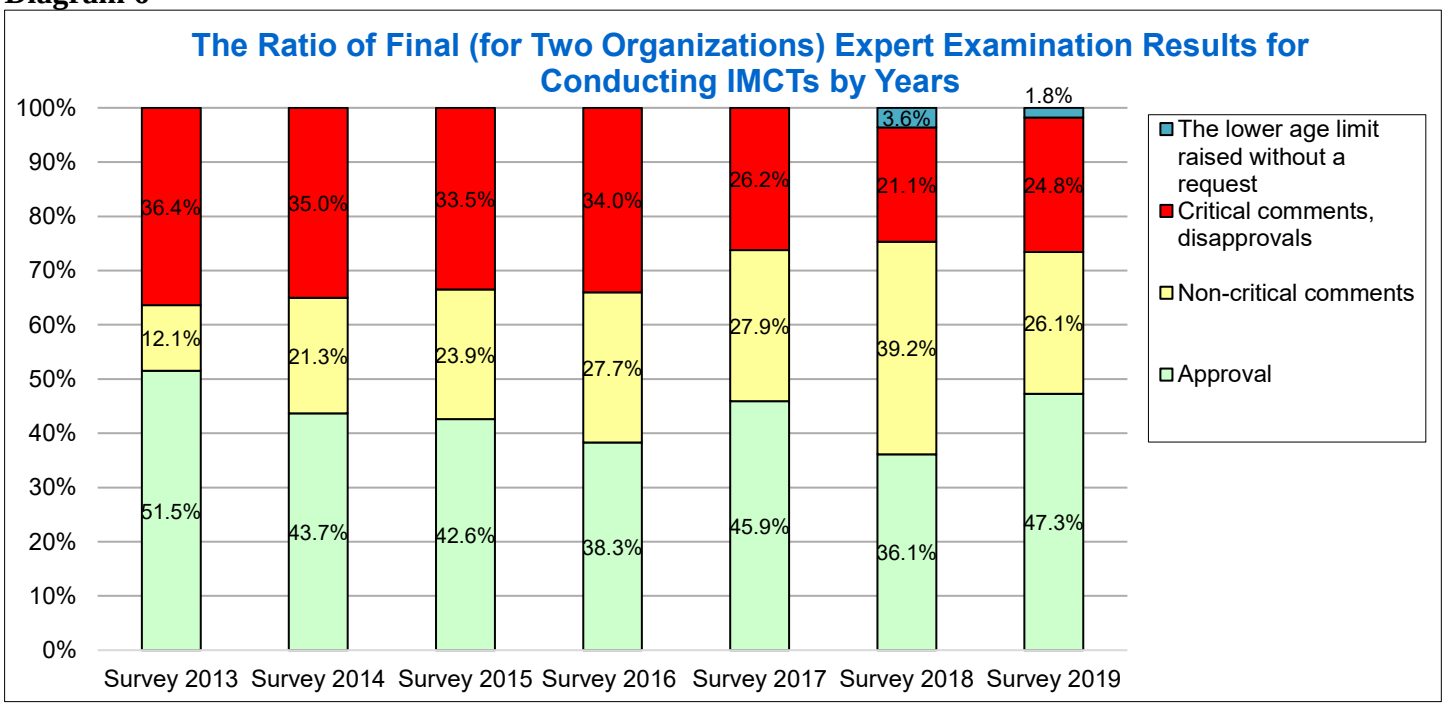
Diagram 5



Data from poll of ACTO members

We'll also review the final results of both expert evaluations (third column in Diagram 4) as well as their dynamics by years (Diagram 6). Despite a relatively small share of cases approved without any requests or comments from any given expert bodies (47.3% of all cases), this share has notably risen, nevertheless, if compared with the last year's result – by 11.2 percentage points. As we can see, this happened primarily due to a sinking share of non-critical requests/comments from 39.2% based on the 2018 survey to 26.1% as per the latest data. This parameter was apparently influenced by a better situation with non-critical comments from the Ethics Council.

Diagram 6



Data from poll of ACTO members

On the contrary, the share of critical comments and disapprovals has risen from 21.1% to 24.8%. This is due to a higher number of disapprovals. Overall, following the results of both expert evaluations, 17 IMCTs were disapproved (7.7% of all cases reviewed). There were only five (2.6%) in the last year's survey. The main reason for a higher number of disapprovals has regrettably been the expert evaluation by the Ethics Council. Just to remind: this body accounted for the lion's share of disapprovals – 15 versus three IMCTs turned down by the SCEEMP expert evaluation. It's not difficult to guess that one trial was disapproved by both expert bodies (yet the Ministry of Health finally issued an approval after the repeated submission).

Finally, the share of protocols where the lower age limit was raised, came to 1.8% (four IMCTs) versus 3.6% a year before.

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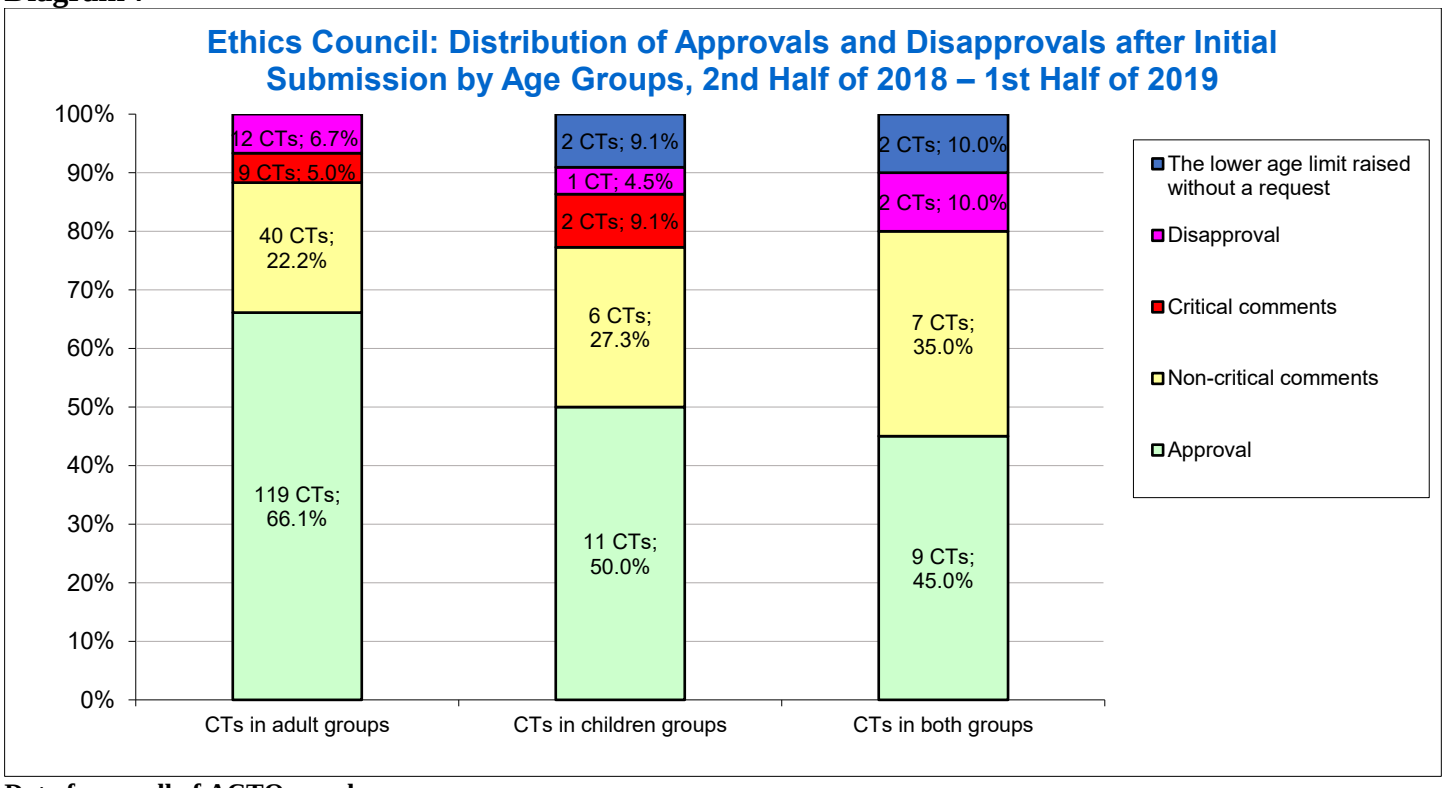
In Diagrams 7 and 8 the reader may see how much the results of expert evaluation by the Ethics Council and SCEEMP depend on the age group of trials subjects (adults, children or both). This dependency is quite explicit in both expert bodies.

So, at the Ethics Council (Diagram 7) a protocol with only adult patients participating had a 66.1% chance of being approved without comments; yet the odds of a protocol being approved stood only at 50% every time pediatric population was involved. Protocols with both age groups involved had an even lower likelihood of passing the expert evaluation of this body smoothly – 45%. Meanwhile most comments of the Ethics Council on all three protocol types are inconsequential, although the total share of cases with critical comments and disapprovals as well as an arbitrary change of the population's age in pediatric protocols are notably higher (22.7%) than in mixed protocols (20%). In trials with the adult population involved this share stood only at 11.7% – 9 IMCTs with critical comments and 12 disapprovals.

Diagram 7

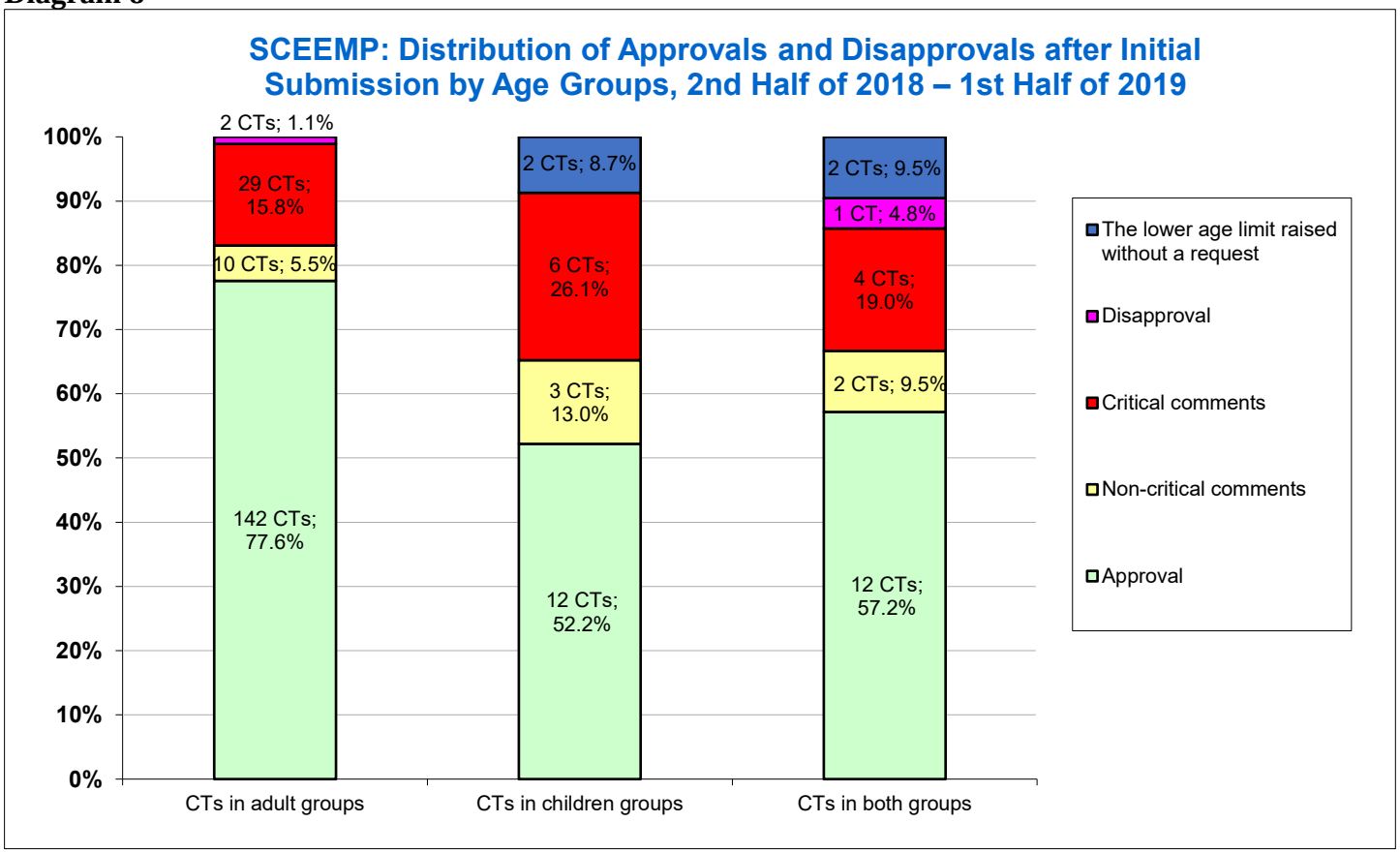


Data from poll of ACTO members

The situation is slightly different with SCEEMP expert evaluation, even though the "age factor" had even a greater impact here. Thus, without any extra request by the expert body, only 77.6% of "adult" protocols were reviewed, as compared to only 57.2% protocols with both age groups involved and 52.2% with only children participating. As we remember, most SCEEMP requests are critical, i.e. they more often regard the protocol or information in the investigator's brochure, whereas the Ethics Council's requests mainly regard minor matters

and are normally related to wording in the informed consent form. The total share of cases receiving critical requests or disapprovals from the SCEEMP in IMCTs with adult population involved stands at 16.9%; in trials with both age groups involved – at 33.3%; as for those where only children were involved the share was 34.8% (the latter also includes protocols where the age range of trial subjects was changed without the applicant being notified).

Diagram 8



Data from poll of ACTO members

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The next aspect we always pay attention to in the course of our analysis is distribution of the expert evaluation's results depending on the therapeutics areas of trials planned. See Table 1 and Diagram 9 where the given distribution is shown for the expert evaluation of the Ethics Council.

As usual, psychiatry trials are least favoured, with disapprovals received on five out of 12 protocols. This is a third of all IMCT disapprovals by the Ethics Council, taken into account in our survey. In one case even a repeated application did not help, ending in a disapproval as well. After that the sponsor decided to give up on Russian centers, and because this sponsor planned to extend the first trial by another (two sequential protocols had been initially announced), our country lost two international trials in psychiatry. Three other protocols disapproved were eventually approved after repeated submittal. And finally, critical and non-critical comments were received on one protocol; after they were addressed, the trial was approved. Yet the general picture looks rather grim, with only 42% of all psychiatry protocols getting approvals at first go.

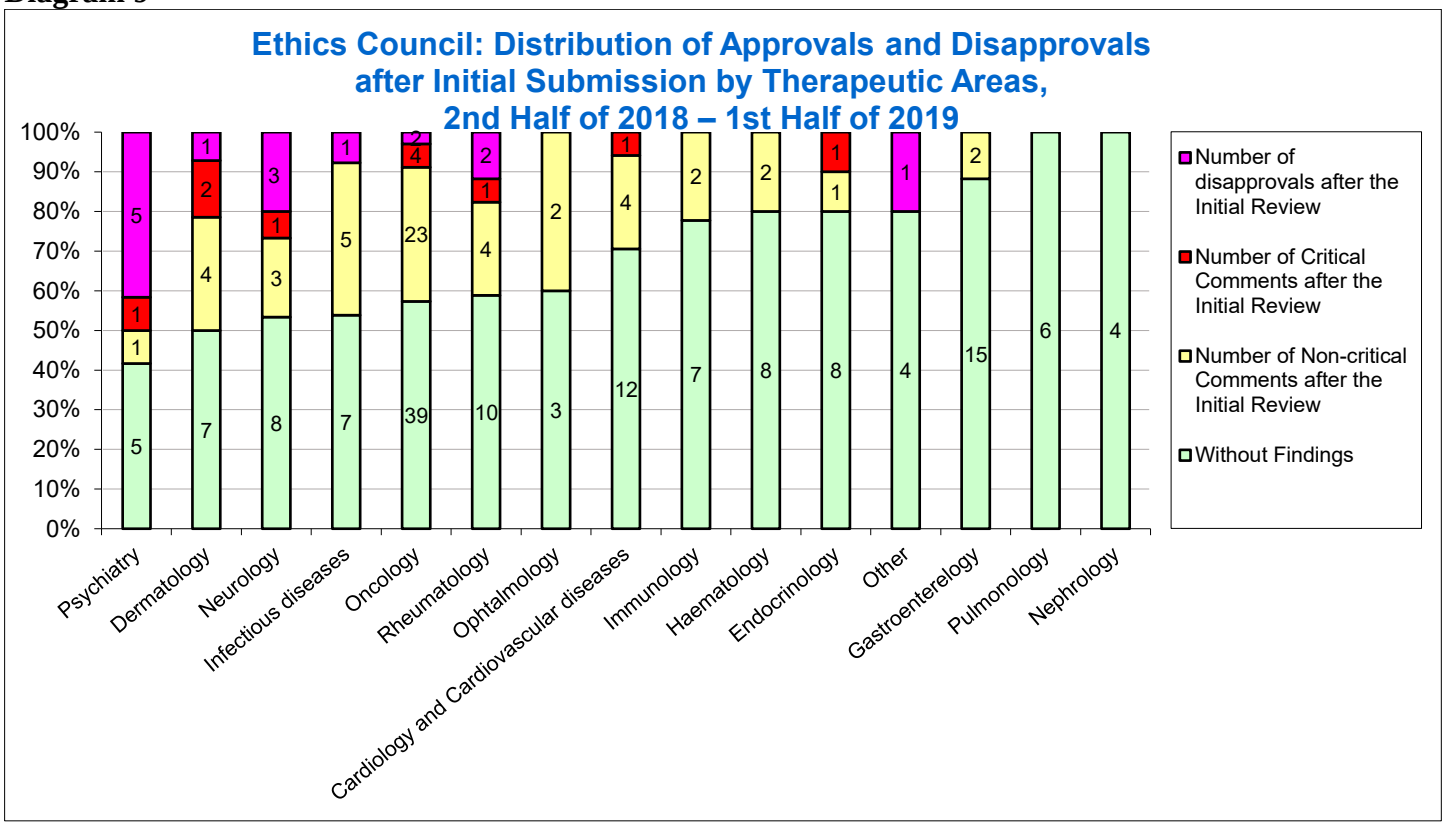
Slightly larger but also low were the shares of approved at first attempt trials in dermatology (50%), in neurology (53%), in infectious diseases (54%) and in oncology (57%). We also keep a watchful eye over oncology in view of the Ethics Council's activities – above all, because of importance and weight of this area for the Russian market of clinical trials. And while the number of applications in oncology, approved at first go, is higher than a year before, this result obviously leaves much to be desired.

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	**68**	**39**	**57%**	**23**	**34%**	**4**	**5.9%**	**2**	**2.9%**
Gastroenterelogy	**17**	**15**	**88%**	**2**	**12%**	**0**	**0.0%**	**0**	**0.0%**
Rheumatology	**17**	**10**	**59%**	**4**	**24%**	**1**	**5.9%**	**2**	**11.8%**
Cardiology and Cardiovascular diseases	**17**	**12**	**71%**	**4**	**24%**	**1**	**5.9%**	**0**	**0.0%**
Neurology	**15**	**8**	**53%**	**3**	**20%**	**1**	**6.7%**	**3**	**20.0%**
Dermatology	**14**	**7**	**50%**	**4**	**29%**	**2**	**14.3%**	**1**	**7.1%**
Infectious diseases (except HIV/HCV/tuberculosis)	**13**	**7**	**54%**	**5**	**38%**	**0**	**0.0%**	**1**	**7.7%**
Psychiatry	**12**	**5**	**42%**	**1**	**8%**	**1**	**8.3%**	**5**	**41.7%**
Haematology	**10**	**8**	**80%**	**2**	**20%**	**0**	**0.0%**	**0**	**0.0%**
Endocrinology	**10**	**8**	**80%**	**1**	**10%**	**1**	**10.0%**	**0**	**0.0%**
Immunology	**9**	**7**	**78%**	**2**	**22%**	**0**	**0.0%**	**0**	**0.0%**
Pulmonology	**6**	**6**	**100%**	**0**	**0%**	**0**	**0.0%**	**0**	**0.0%**
Ophtalmology	**5**	**3**	**60%**	**2**	**40%**	**0**	**0.0%**	**0**	**0.0%**
Nephrology	**4**	**4**	**100%**	**0**	**0%**	**0**	**0.0%**	**0**	**0.0%**
Other	**5**	**4**	**80%**	**0**	**0%**	**0**	**0.0%**	**1**	**20.0%**
Total	**222**	**143**	**64%**	**53**	**24%**	**11**	**5.0%**	**15**	**6.8%**

Data from poll of ACTO members

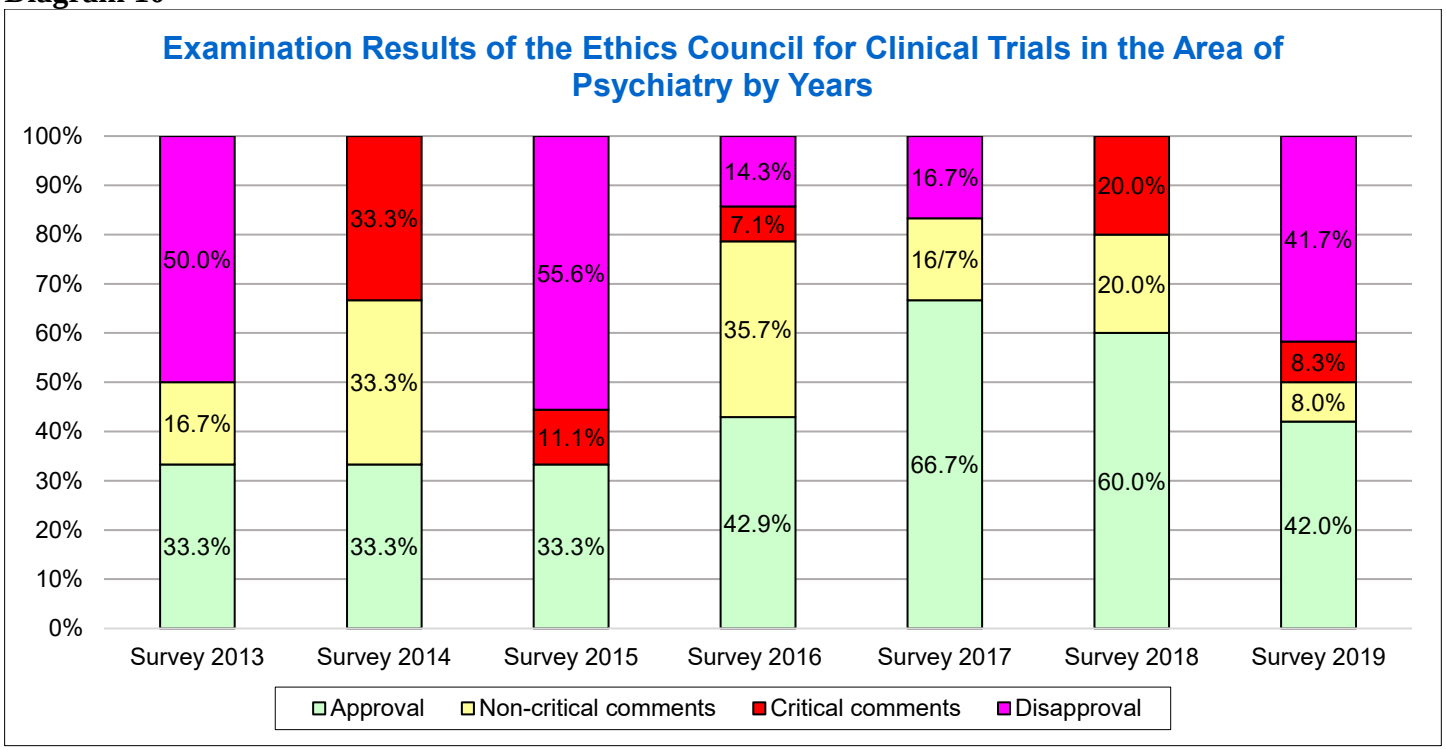
Diagram 9



Data from poll of ACTO members

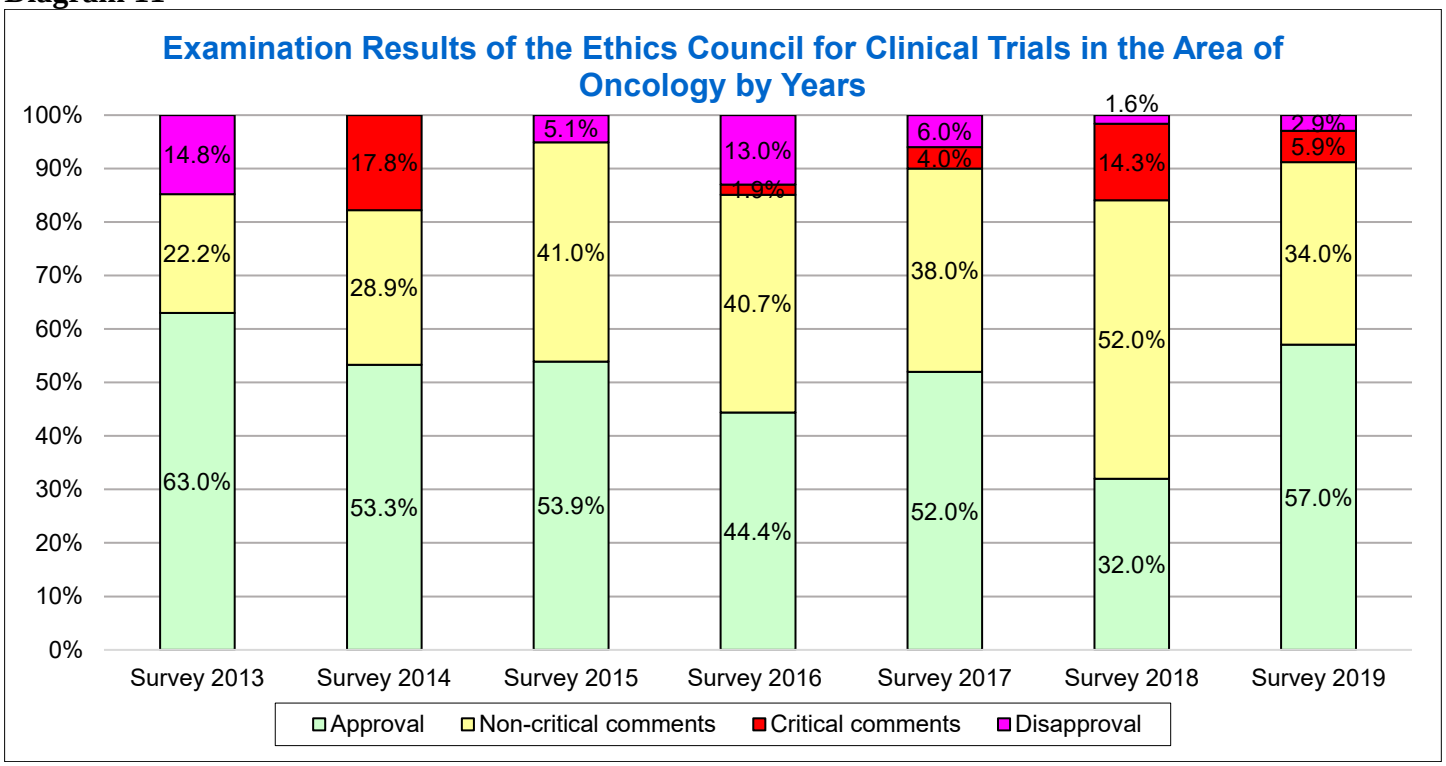
In Diagrams 10 and 11 you may track the distribution of the Ethics Council's "verdicts" in two areas of concern to us, namely psychiatry and oncology, by years.

Diagram 10



Data from poll of ACTO members

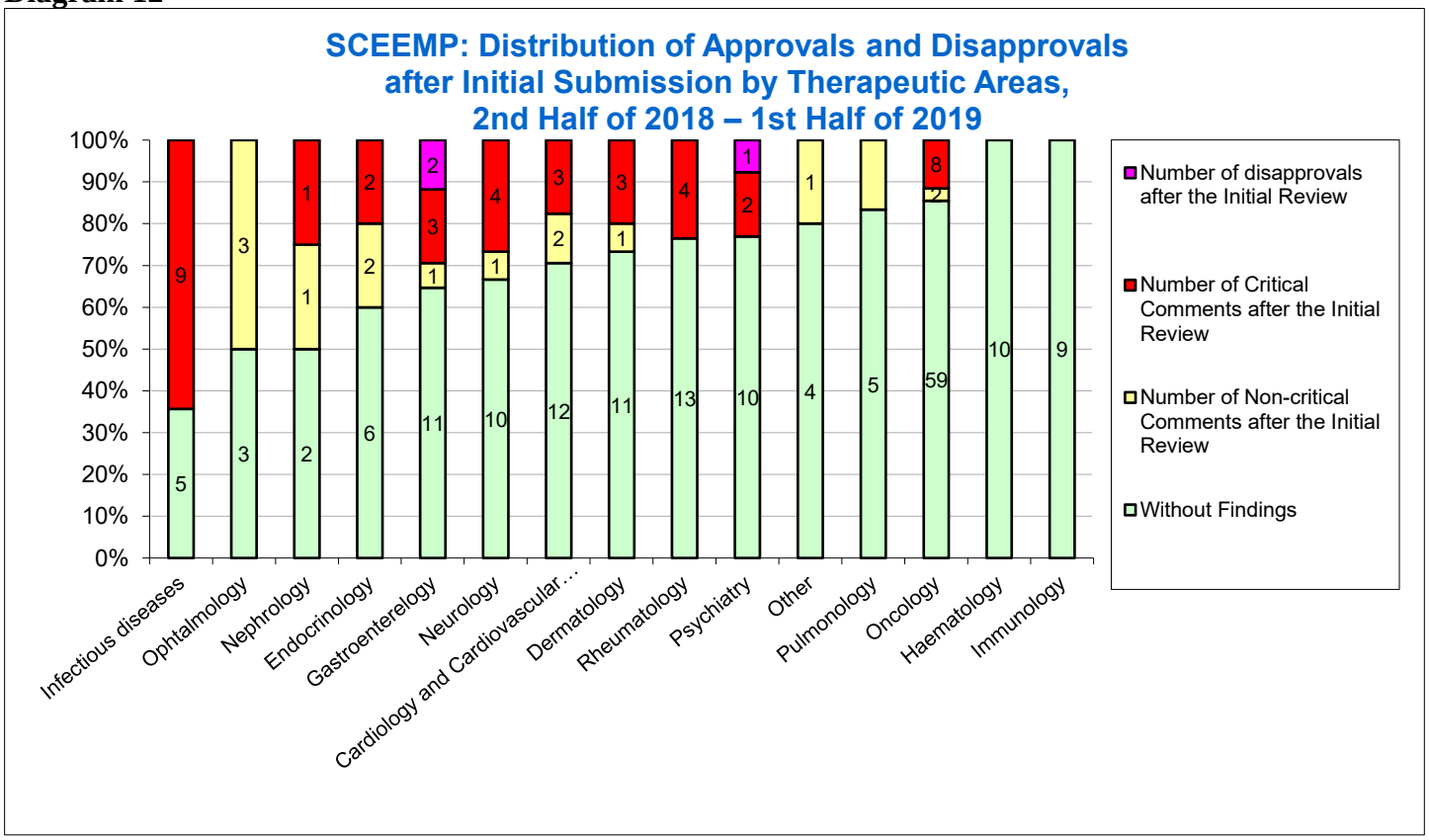
Diagram 11



Data from poll of ACTO members

Table 2 and Diagram 12 show the distribution of SCEEMP expert examination results by therapeutic areas. Once again, like in previous years, infectious diseases remain the most problematic area for this expert body. Only 35.7% of all applications (five out of 14 protocols) could pass the expert evaluation without any requests from the SCEEMP. As in case of the Ethics Council, we decided to show the distribution of SCEEMP decisions in the given therapeutic area by years (Diagram 13).

Diagram 12



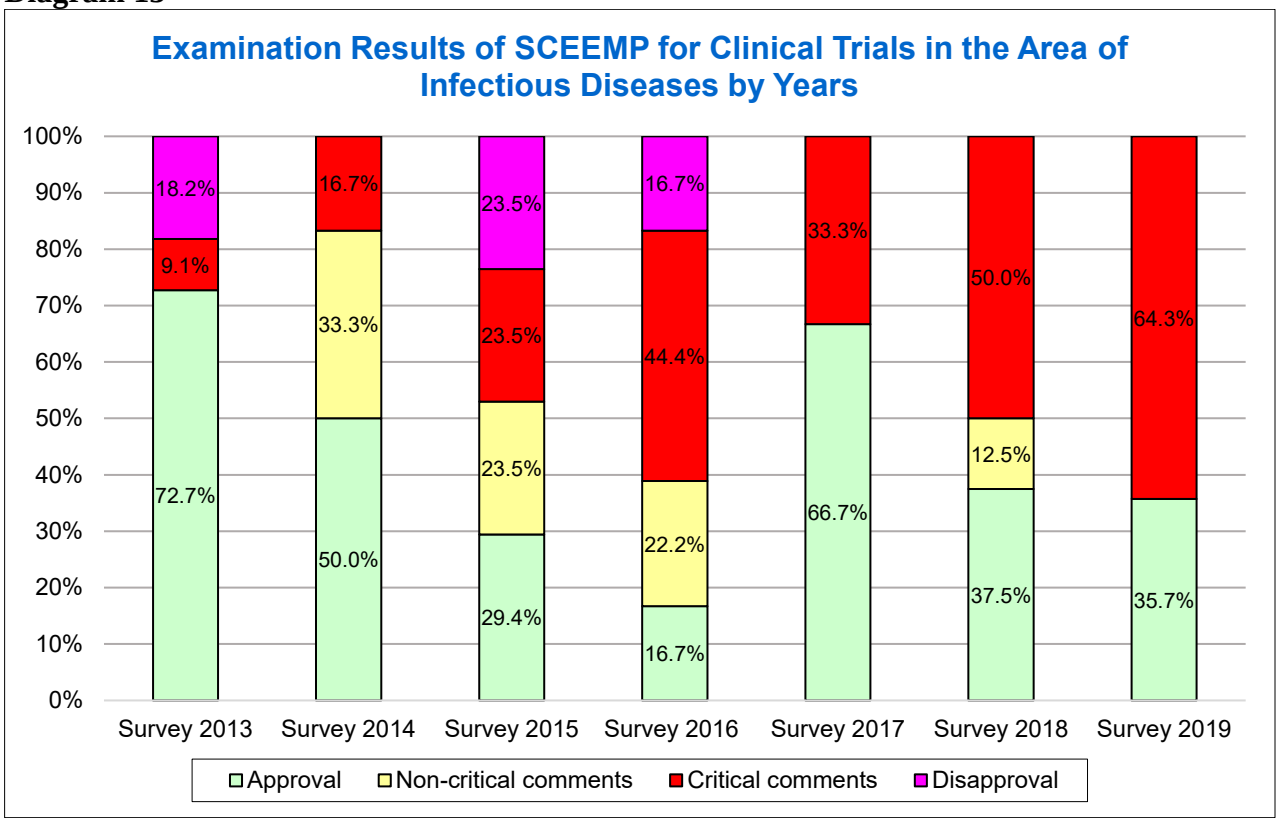
Data from poll of ACTO members

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	**69**	**59**	**85.5%**	**2**	**2.9%**	**8**	**11.6%**	**0**	**0.0%**
Gastroenterelogy	**17**	**11**	**64.7%**	**1**	**5.9%**	**3**	**17.6%**	**2**	**11.8%**
Rheumatology	**17**	**13**	**76.5%**	**0**	**0.0%**	**4**	**23.5%**	**0**	**0.0%**
Cardiology and Cardiovascular diseases	**17**	**12**	**70.6%**	**2**	**11.8%**	**3**	**17.6%**	**0**	**0.0%**
Dermatology	**15**	**11**	**73.3%**	**1**	**6.7%**	**3**	**20.0%**	**0**	**0.0%**
Neurology	**15**	**10**	**66.7%**	**1**	**6.7%**	**4**	**26.7%**	**0**	**0.0%**
Infectious diseases (except HIV/HCV/tuberculosis)	**14**	**5**	**35.7%**	**0**	**0.0%**	**9**	**64.3%**	**0**	**0.0%**
Psychiatry	**13**	**10**	**76.9%**	**0**	**0.0%**	**2**	**15.4%**	**1**	**7.7%**
Haematology	**10**	**10**	**100.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**
Endocrinology	**10**	**6**	**60.0%**	**2**	**20.0%**	**2**	**20.0%**	**0**	**0.0%**
Immunology	**9**	**9**	**100.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**
Pulmonology	**6**	**5**	**83.3%**	**1**	**16.7%**	**0**	**0.0%**	**0**	**0.0%**
Ophtalmology	**6**	**3**	**50.0%**	**3**	**50.0%**	**0**	**0.0%**	**0**	**0.0%**
Nephrology	**4**	**2**	**50.0%**	**1**	**25.0%**	**1**	**25.0%**	**0**	**0.0%**
Other	**5**	**4**	**80.0%**	**1**	**20.0%**	**0**	**0.0%**	**0**	**0.0%**
Total	**222**	**166**	**74.8%**	**14**	**6.3%**	**39**	**17.6%**	**3**	**1.4%**

Data from poll of ACTO members

Diagram 13



Data from poll of ACTO members

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Let's consider the ways companies assess the fairness of requests and comments they receive from the expert bodies. The parameter is undoubtedly subjective, but it appears to reflect the applicants' attitude quite well. The dynamics of those attitudes during the years of our monitoring, rather curious, can be tracked in Diagrams 14 and 15.

We should remind that we used three variants of answer: "agree", "partly agree", "disagree". In those cases where several critical comments were received on one protocol, a company agreeing with some of these and disagreeing with others, the given case has been included in the "partly agree" category. But where a company disagreed with the main comment, with others being ancillary, such cases were included in the "disagree" category.

Before setting to the analysis of the results, we'd like to mention two points. To begin with, we'd like to remind that historically applicants have been more loyal towards the expert evaluations of the Ethics Council, rather than SCEEMP, since it is usually easier to work on comments of the former. As a rule, they do not affect the protocol and researcher's brochure, but rather call for more detailed information for the patient, being "non-critical" as per our classification. The attitude towards non-critical comments is usually more loyal, which undoubtedly influences the applicant's subjective assessment. Moreover, very often respondents at the emotional level confuse the "agree" assessment with another aspect, which will be analyzed in the next subsection: whether or not the company took into account the comments received. So, according to the responses, it is noticeable that the answer "taken into account" often increases the degree of agreement. Although, if you think about it, this kind of connection is not necessary at all: you often have to take into account those comments which validity is doubtful.

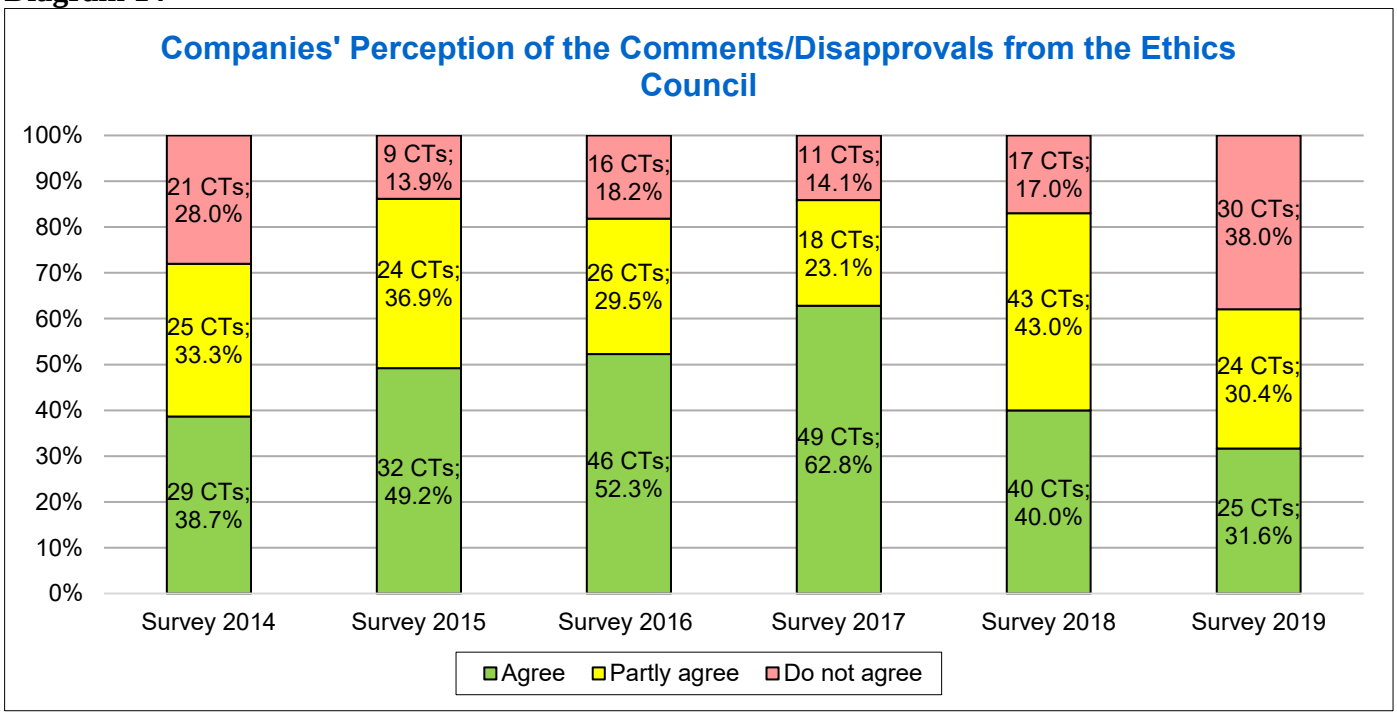
For instance, the requirement to complement information for the patient with a "list of permitted and forbidden medicines pursuant to the protocol" has become quite typical of the Ethics Council in recent years. This section may take 3–5 pages in the protocol. And information for the patient normally contains standard wording that new medicines cannot be taken without consulting an investigator. Yet the Ethics Council keeps pressing for reprinting of the entire information while neglecting the flip side to the coin: it's impossible to

infinitely increase the informed consent form without any detriment to its clarity. The capability to perceive information in a written form is limited, after all a patient is asked to put his or her signature to confirm careful reading of the entire document. Already now the average size of the informed consent form reaches 25–30 pages, so complementing them with yet another 3–5 pages of text is a disputable requirement, especially because the decision to prescribe or permit the use of some or other medicines lies within the investigator's competence. Nevertheless, some companies, after receiving this warrant, obediently write "agreed and taken into account.". Perhaps they took into account. But what about "agree"? There are some doubts that the central project team might well have overlooked a certain issue so important for the participant while preparing a global version of the informed consent form.

There is a second thing we've noticed during six years of our observations. Suppose an expert body lays a certain requirement which is not quite fair, but not cumbersome for an applicant (in other words, there is a surmountable barrier in the way). When this requirement only emerges, the standard reaction is "disagree". But if it is repeated from one expert evaluation to another, adaptation takes place. An increasing number of respondents react to it with "partly agree" or even "agree". It's not for us to judge whether we are dealing with the "Stockholm syndrome" or some other psychological phenomenon here. We can just state that we've noticed this phenomenon which undoubtedly affects the final results.

Let's start with applicants assessing the activities of the Ethics Council (Diagram 14). It can be seen that the share of "agree" responses was highest in the 2017 survey (62.8%), dramatically decreasing in the 2018 survey by 22.8 percentage points. This year's survey has seen an even deeper dive, since now applicants agree with critical comments obtained only in 31.6% of cases. On the other hand, the share of cases where applicants disagree with the stance taken by the Ethics Council has reached its historical maximum at 38%. Curiously enough, these figures are a bit divergent with changes in the results of expert evaluation by the Ethics Council by years (Diagram 5). As we remember, the 2018 survey was notable for the least share of requests approved without comments, whereas the 2019 survey has shown positive dynamics. Yet this improvement has not influenced the answers of applicants. For now, we see only mounting distrust and dissatisfaction about the quality of expert evaluation provided by the Ethics Council.

Diagram 14

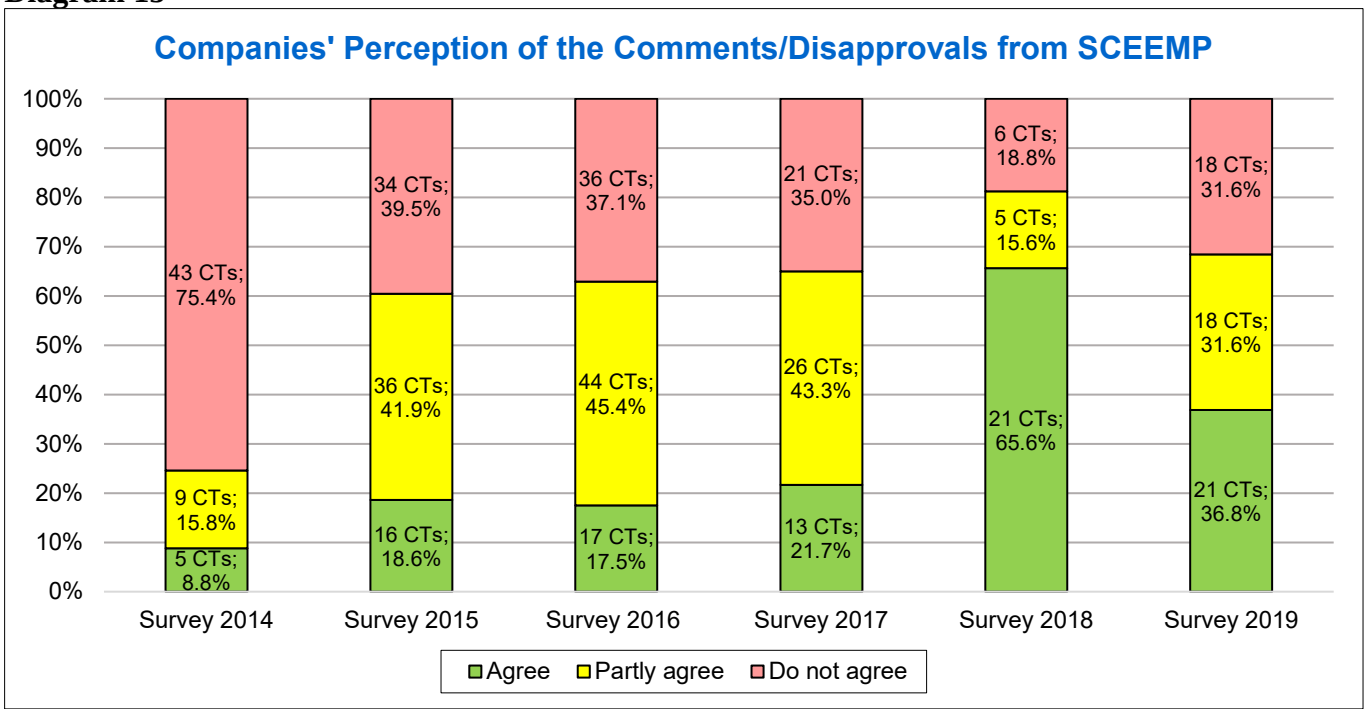


Data from poll of ACTO members

A different pattern can be seen, if we look at the prevailing opinion about SCEEMP evaluations (Diagram 15).

We saw the lowest level of trust in this expert body expressed in the 2014 survey (about the results of H2 2013 and H1 2014), where applicants agreed with expert comments only in 8.8% of cases, whereas in 15.8% of cases they expressed their partial disagreement and in 75.4% of cases they totally disagreed. But then a quality leap occurred and during the following three years the situation obviously improved, even though the share of cases where applicants would agree with expert opinions remained rather low in the 17.5–21.7% bracket. Growing trust can most likely be attributed to the fact that prior to 2014 SCEEMP had had no right to send a request to an applicant, but could only approve or disapprove a trial. Later a request option was added, which allowed at least some feedback and therefore slightly raise the level of mutual understanding between applicants and the expert body. Yet there are still many questions regarding the quality of SCEEMP expert evaluations, which we repeatedly highlighted in our bulletins (*see ACTO Bulletin issues No. 9 and 11*) as well as in our *ACTO* open letter to Russian Minister of Health Ms. V. Skvortsova.

Diagram 15



Data from poll of ACTO members

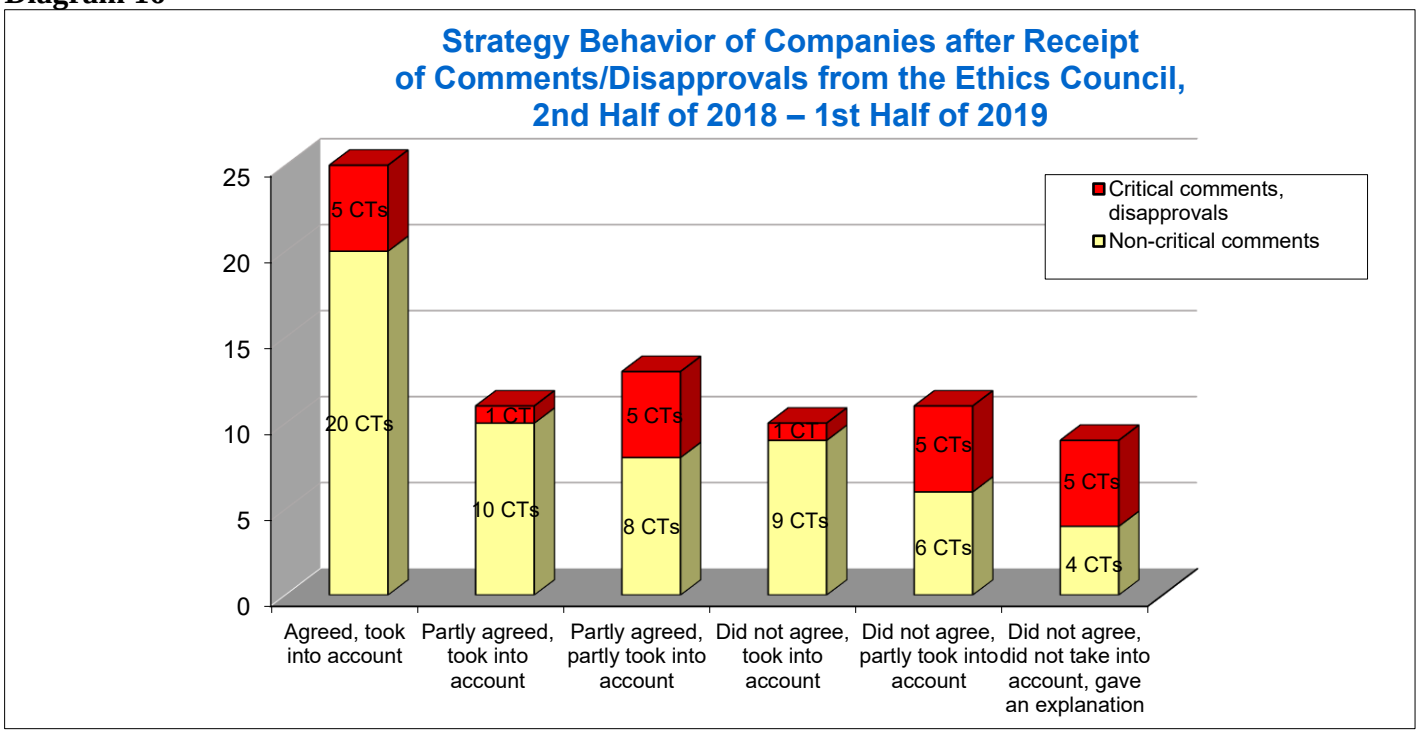
A significant event for the market took place in 2016: a change in the expert body's administration. Given a retrospective nature of our surveys (covering the second half of the previous year and the first half of the current year), necessary time for reforming the system, duration of the very expert evaluation process and certain market inertia, we saw a quality leap only in the 2018 survey, when the level of trust in SCEEMP grew by more than 40 percentage points to 65.6%, whereas the share of cases where applicants disagreed with expert evaluation's results fell from 35% to the record low 18.8%. The latest survey rebalanced the situation as trust in SCEEMP evaluations went slightly down again; nevertheless, even this result seems rather decent: the share of cases where applicants have agreed with the expert opinion now amounts to 36.8%, whereas the shares of cases where companies partly agree or totally disagree turned out equal, standing at 31.6% each. It should also be noted that the expert evaluation quality assessments we've collected are in harmony with the results of SCEEMP expert evaluations in different years, shown in Diagram 5.

***

You may see in Diagram 16 how applicants acted after they got comments or disapprovals from the Ethics Council. The most common strategy (as usual) was "agreed, taken into account" - in 25 of all cases. Other behavioral responses were more or less evenly distributed. These data are hard to assess without considering their dynamics. Diagram 17 shows a changing pattern in the companies' response to criticisms of the Ethics Council. We saw a similar picture in Diagram 14, especially since one of the parameters – the rate of consent with a critical remark – remains the same. Yet here we also see how companies prefer to respond to criticism. As we can see

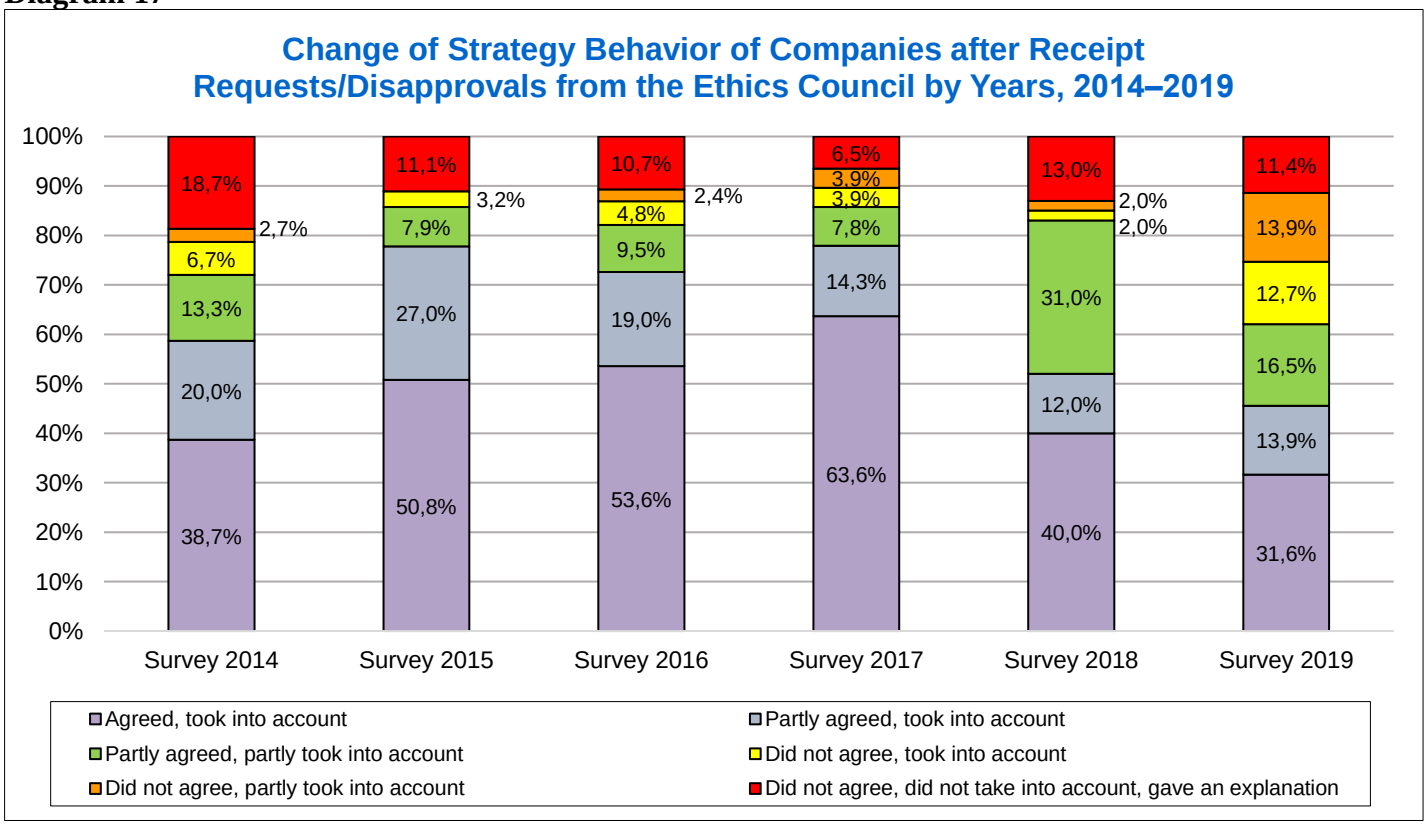
from the recent survey, the share of cases where applicants are unconditionally consonant and address the regulator's rebukes is on the wane, whereas the share of cases with a high level of discord is on the rise; nevertheless applicants are compelled to address the critical comments of the Ethics Council fully or partly. Thus, the sectors such as "did not agree, took into account" (yellow) and "did not agree, partly took into account" (orange) have risen from 2% in the 2018 survey to 12.7% and 13.9%, respectively, in this year's survey.

Diagram 16



Data from poll of ACTO members

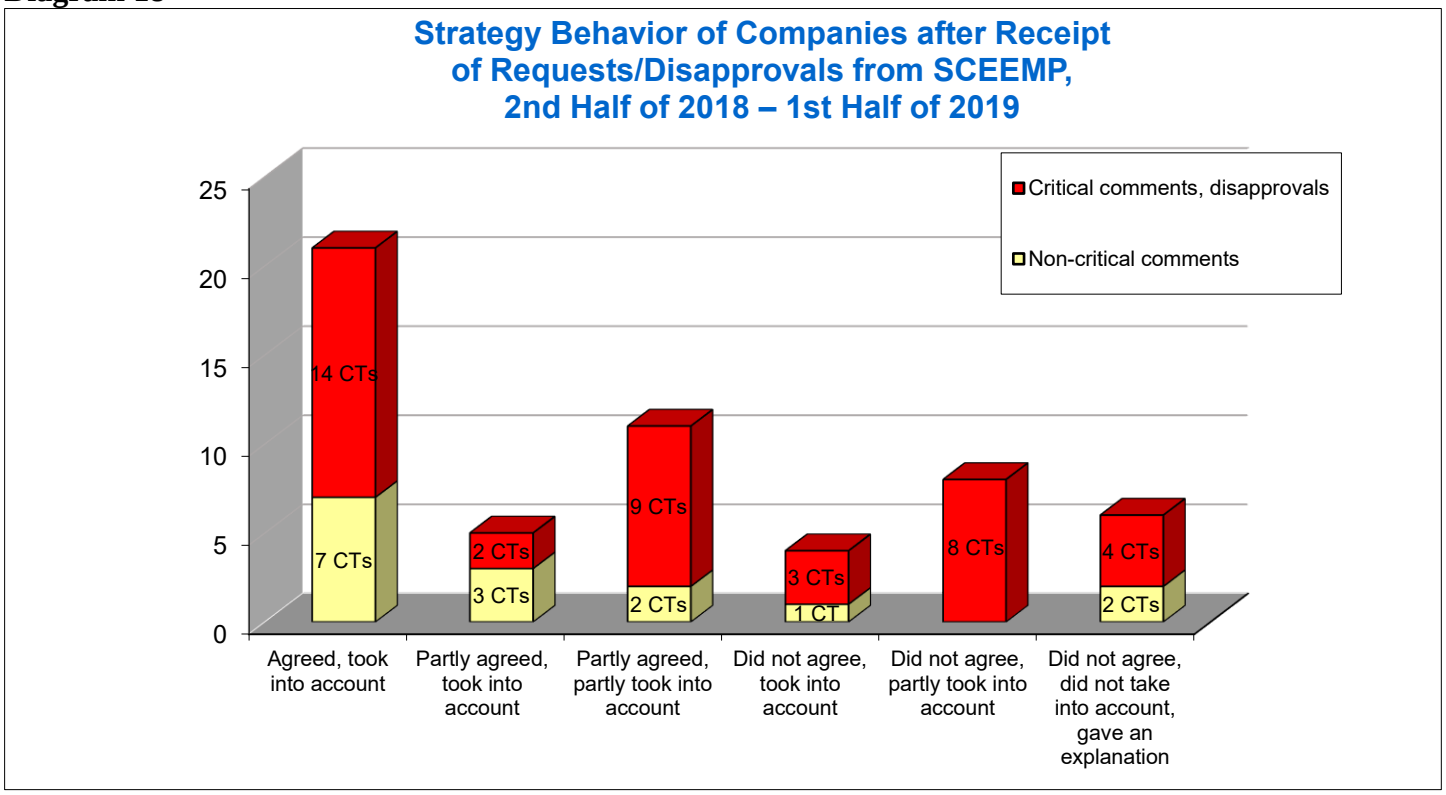
Diagram 17



Data from poll of ACTO members

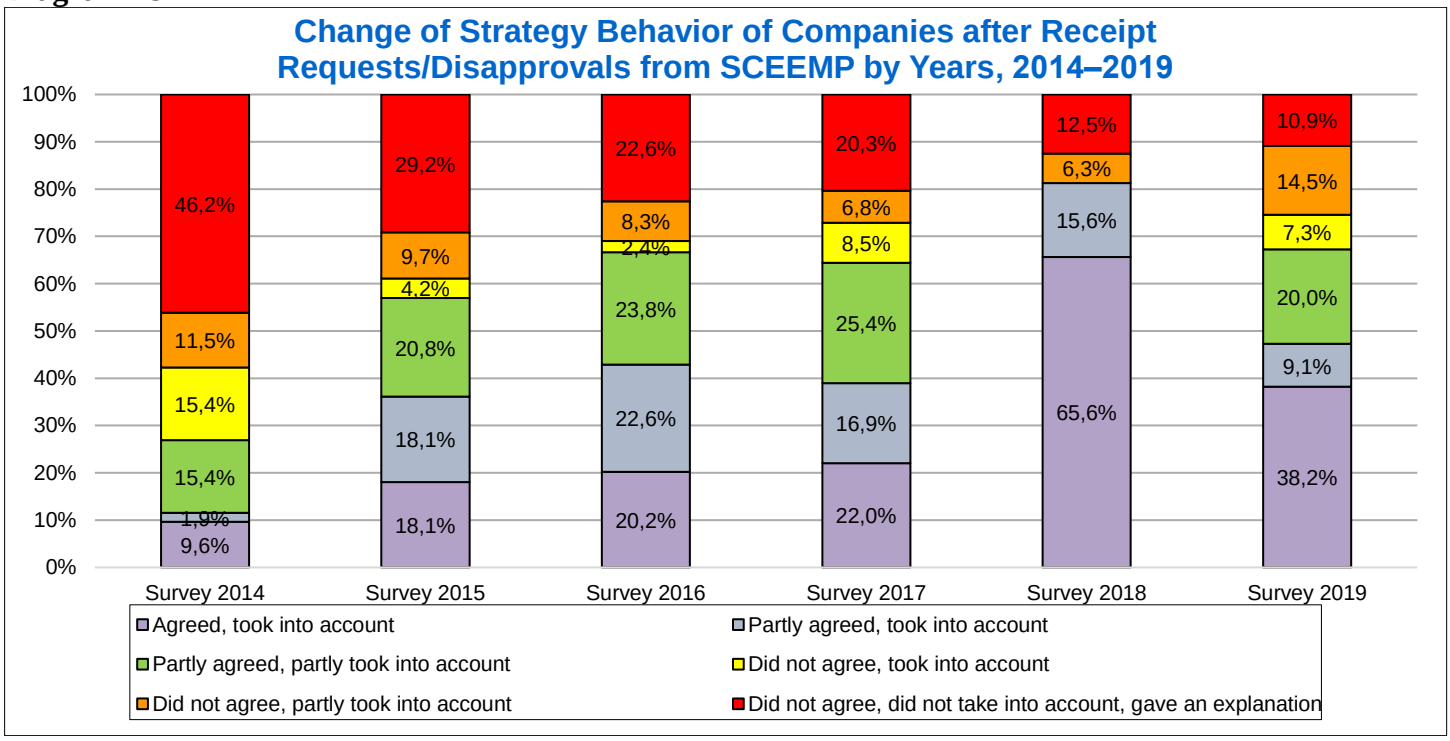
In Diagrams 18 and 19 you may see the companies' strategy as per the data of the recent survey and accordingly year-on-year changes in this pattern after they get critical comments from the SCEEMP. Here, as per the data of the 2019 survey, the strategy "agreed, took into account" prevails, like also in the applicants' relationship with the Ethics Council; however, as can be seen from the diagrams, this has not always been the case. Assessing the general situation and bearing in mind that most SCEEMP requests, unlike those coming from the Ethics Council, are "critical", it can be stated that now engagement with this expert body runs smoother.

Diagram 18



Data from poll of ACTO members

Diagram 19



Data from poll of ACTO members

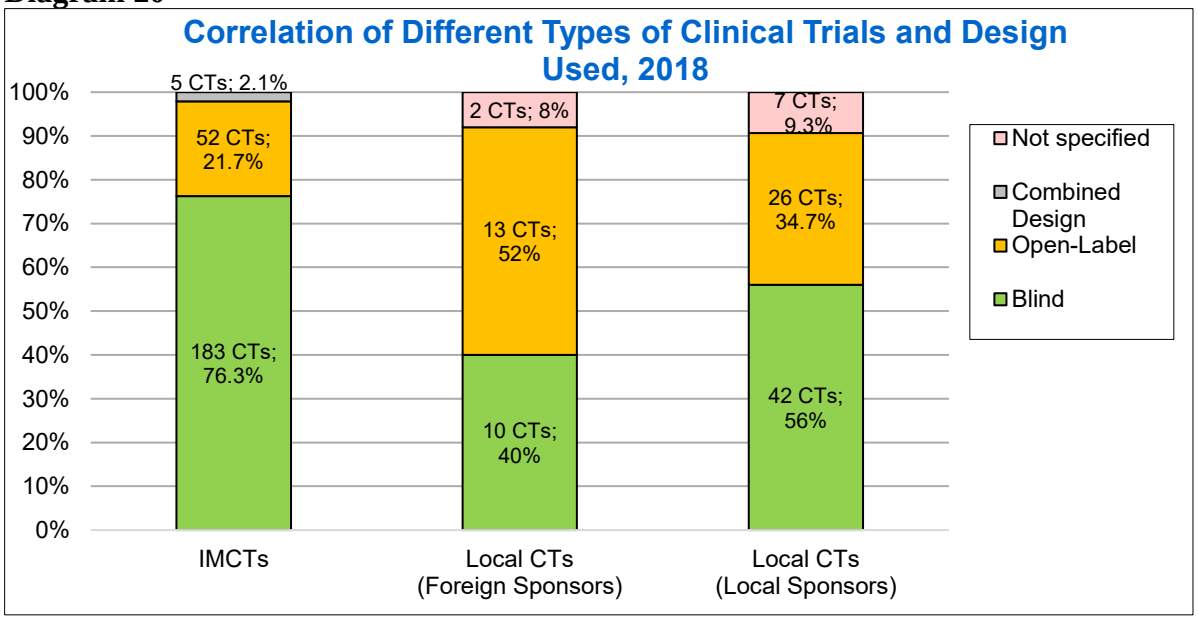
CORRELATION BETWEEN TYPES OF CLINICAL TRIALS AND DESIGN USED

This time we've decided to submit new analytics to the approval of our readership as we looked at the Russian market of clinical trials at yet another angle: we try to come up with general even if rough assessment of the design of clinical trials planned in Russia. We study the practice of using the blind method in various trial types, to be more exact.

It's clear that using a blinding for reducing a bias in the trial results depends on various factors: medicinal product development stage, trial's objectives and other parameters of design, specific disease, its treatment methods, etc. However, we presume that with other things being equal the ratio of blind to open trials in international and local projects should (ideally) be equal. We also realize that most likely this is not the case in real practice. To check this assumption, we've again reviewed the registry of clinical trial approvals issued by the Ministry of Health. We took a sample of approvals dated from 2018, leaving out all bioequivalence studies, all trials of the phase I as well as all non-comparative studies. Then we divided the remaining sample into blind and open trials. Our usual reference point was the protocol name while in case of IMCTs we also checked with international databases. This option was unavailable for local trials; therefore, a small part of trials is unidentified.

The final results are shown in Diagram 20.

Diagram 20



Data from www.grls.rosminzdrav.ru

Frankly speaking, at first, we were somewhat surprised at the results. We surely supposed that the share of open trials would be higher in local trials as compared to IMCTs. Yet we did not expect that in local trials the share of protocols with an open design submitted by foreign sponsors will be higher, compared to Russian sponsors. So much higher actually. For foreign-made medicinal products it stood at 52% – more than half of the entire sample – whereas for domestic drugs it was 34.7%. We could not but feel proud of Russian manufacturers. Since if we presume that the ratio of open to blind trials in IMCTs is a conventional "benchmark", then domestic sponsors are not so much different in terms of open trial shares - by 13 percentage points. The gap between the shares of projects with open design in IMCTs and local trials by foreign sponsors is a lot wider: 30.3 percentage points.

Nevertheless, upon some reflection, we found a rationale behind this pattern. Russian sponsors or at least some of them, while planning local trials, nevertheless keep in mind the prospect of entering foreign markets. In this case they have to be more elaborate in the trial design. This is not a concern for foreign sponsors who resolve to proceed with local trials in Russia, however. Their key goal is to satisfy the Russian regulator. Once the regulator is satisfied, why making things more difficult? At this point we feel like sending our best to the regulator who imposed mandatory local registration trials.

RESULTS OF ROSZDRAVNADZOR INSPECTIONS FOR 2018

In 2017 we were compelled to interrupt the traditional monitoring of Federal Service for Surveillance in Healthcare (Roszdravnadzor) inspection results, since the reform of control and supervision activities in Russia entailed a number of substantial changes in the operation of inspecting bodies. Unfortunately, we possess only incomplete data about the results for 2018, which cannot be correlated with the data for previous years to boot, given that the very approach to inspections has changed. In 2018 inspectors started using checklists – in particular, a special checklist to assess compliance with clinical trial requirements. On the whole, sections on the checklist match the stakeholders involved in a trial as per GCP: sponsor, investigator, independent ethics committee (IEC). What's more, some of the checklist's questions regard the liabilities which the Russian legislation imposes upon a medical firm as a separate legal entity (obtaining accreditation, appointing the principal investigator by the clinic administration, etc.).

Overall, according to our data, in 2018 Roszdravnadzor inspected 127 legal entities that organize clinical trials and/or actually conduct them. Among them are 23 pharmaceutical companies as well as contract research organizations, 97 medical institutions, and 7 other research centers combining the role of a clinic and trial sponsor. The inspectors found at least 383 violations, their distribution by categories of those being inspected shown in Table 3.

In data interpretation it is necessary to take into account that sections of the checklist have different sizes. A large number of breaches by sponsors are caused by the fact that the section covering their responsibilities comprises 40 clauses, whereas the section highlighting the operation of IEC has only 10. In other words, the structure of findings generally mirrors the structure of the checklist.

A division of labour between the central office and territorial bodies of Roszdravnadzor may also cause a gap in the number of findings, depending on a particular administrative entity. The former focuses on sponsors/CROs and nationwide medical institutions. The latter mainly visit ordinary clinics. As for medical institutions, the inspecting bodies do not only check their compliance with clinical trial requirements, but also all lines of their activity; in other words, inspectors from territorial bodies more often work with several checklists at one time.

Table 3

Stats for Inspections of Compliance with Clinical Trial Requirements Conducted by Roszdravnadzor in 2018		
Category of Those Inspected	**The number of inspections***	**The number of violations**
Clinical Trial Organizer (pharmaceutical companies and contract research organizations)	30	198
Medical institutions	104	
Principal investigator and a research team		114
IEC		39
medical institution as a separate legal entity		32
TOTAL	**127****	**383**

**The table shows the total number of inspections, not only those where violations were found. We do not know how many inspections went without comments.*

***Seven institutions assume the double role of a medical institution and a sponsor.*

When reading Table 3 and subsequent ones in this section, it is necessary to bear in mind that the checklist set-up in some cases enables the recording of several findings, despite one actual violation. Thus a sponsor lacking an approved plan of the clinical trial audit and resultant absence of the audit per se prompts inspectors to register two breaches and, unless auditors are appointed (which can be expected in the lack of an approved plan), even three violations.

Furthermore, there are clauses in the checklist, which play the role of summary or wrap-up assessment, i.e. their violations are recorded in the event a number of breaches are found in other clauses. One example is clause 2.9. "Whether IEC makes sure the rights, safety and well-being of clinical trial participants are protected".

The given clause is called to enable the inspector to assess the IEC operation at large, upon a review of all breaches, should they be found.

There is one more summarizing clause in the checklist, which we did not include in general stats. This is clause 4.34 "Whether a clinical trial of a medicinal product is conducted in compliance with the Rules of Good Clinical Practice and regulatory requirements of the Russian Federation, as regards the circulation of medicinal products." The inspector fixes its breach in the event of other clauses being violated. In 2018 at least 25 violations of clause 4.34. were recorded. This actually means that the majority of all breaches were discovered in the course of 25 inspections (14 sponsors/CROs were inspected, in addition to 7 trial sites and 4 medical institutions assuming both roles). Because the breach of clause 4.34 was actually the summary of breaches by all stakeholders responsible for the conduct of a clinical trial, we decided to exclude them from our distribution in Summary Table 3.

Sponsor's Violations

The sponsor's violations which were discovered by inspectors in 2018, as per our data, are shown in Table 4.

The greatest number of findings (40) are related to monitoring. They were found in all clauses of the checklist, dealing with this subject matter (clauses 3.36–3.40 of the checklist), save for the last one, 3.40 (regarding the compliance with monitoring report requirements). Their leadership is largely caused by the bulky clause 3.38 comprising 14 sub-clauses. Clause 3.38 accounts for 31 findings of which in six cases, in the opinion of inspectors, adequate measures for removal and prevention of repeated violations were not taken; in five cases monitoring did not ensure compliance with the sponsor's standard operation procedures (SOPs), whereas in five more cases monitoring did not provide for inspecting the appropriateness, fullness and deadlines of the clinical trial data registration. Other finds are scattered over the sub-clauses of clause 3.38. Relatively many findings (6) are found in clause 3.36 that is rather bulky actually: "Whether the clinical trial monitoring is conducted in accordance with the protocol, SOPs and legal requirements?".

The audit ranks second by the number of rebukes from inspectors. We were so much surprised at the figure of 29 findings that even suspected inspectors of a wrong interpretation of the legislation and the requirement to audit all clinical trials, rather than auditing them selectively. As we investigated this issue, it turned out that most rebukes regarded the lack of an audit plan (nine findings in nine inspected entities), the lack of auditor assignment (nine finds at the same entities) and the resultant absence of the very audit (same nine inspected entities plus two rebukes of other legal entities for non-compliance with the approved audit plan, 11 findings overall).

Table 4

Violations by Clinical Trial Organizer, Discovered by Roszdravnadzor in 2018			
Recorded are violations of requirements for...	**Checklist clauses**	**Number of violations**	**Share of the total number (%)**
... organization and conduct of the clinical trial monitoring	3.36 – 3.39	40	20,2%
... organization and conduct of the clinical trial audit	3.41 – 3.43	29	14,7%
... reporting safety information	3.31 – 3.35	21	10,6%
... informing the Ministry of Health on the trial completion, suspension or termination	3.47	15	7,6%
... operation with clinical trial's medicinal products	3.23 – 3.25, 3.28	14	7,1%
... implementation and support of quality assurance and control systems (compliance with the sponsor's SOPs)	3.8	12	6,1%
... using electronic trial data systems	3.17	8	4%
... distribution of rights and responsibilities between all parties of the trial	3.4	7	3,5%
... the trial organizer getting confirmation of the IEC operation compliance with the Russian Rules of GCP	3.22	7	3,5%
... submittal of the trial results report to the Ministry of Health	3.49	7	3,5%

... appointing skilled and qualified professionals to consult investigators	3.10	6	3%
... forming an independent data monitoring committee	3.13	6	3%
... receipt of written consents from the investigator and a medical institution's authorized person	3.19	4	2%
... ongoing assessment of safety of the investigational medicinal product.	3.29	4	2%
... revision of the investigator's brochure and (or) providing an updated version for the investigator and IEC	3.6 – 3.7	4	2%
... developing a CRF allowing the collection of required data from all medical institutions	3.48	3	1,5%
... compliance with the trial protocol	3.2	2	1%
... organizer's SOP (content, approval)	3.5	2	1%
... providing an investigator and medical institution with a protocol of a clinical trial and a brochure prior to signing of an agreement to conduct clinical trial	3.18	2	1%
... ensuring an opportunity to make a clinical trial suspension or termination of clinical trial if the life and health of participants are threatened	3.46	2	1%
... storing clinical trial documentation	3.14	1	0,5%
... qualification of individuals involved in a trial	3.16	1	0,5%
... the trial participant insurance policy term (matching the trial conduct times)	3.21	1	0,5%
TOTAL		198	100%

Rebukes regarding the safety data reporting are ranked third. In eight cases inspectors mentioned violations in submitting a periodic safety report to Roszdravnadzor (clause 3.32), in four cases – a failure to notify Roszdravnadzor of serious unexpected adverse reaction (clause 3.31, second sub-clause); in three cases – a failure to notify Roszdravnadzor within seven days of lethal and(or) life-threatening conditions (clause 3.33). Two finds were recorded per each of the rest unnamed clauses of this thematic block.

Inspecting bodies recorded 15 failures to keep within the deadline of notifying the Ministry of Health of the trial completion; in 14 cases there were questions regarding the investigational medicinal products and documenting of their handling; in 12 cases the matter regarded the quality assurance and control systems. Other checklist blocks replete with findings regard the trial data systems (8 comments), formalizing the distribution of responsibilities, confirming the compliance of the IEC operation with the Russian Rules of Good Clinical Practice, providing a report on the trial results to the Ministry of Health (7 comments on each).

We'd like to say a few words about seven finds related to confirmation that the IEC is guided in its activities by the Russian Rules of Good Clinical Practice. This responsibility is imposed on the trial organizer by clause 27 of Order No. 200n by the Ministry of Health of the Russian Federation, dated 01.04.2016, "On Approving the Rules of Good Clinical Practice." However, it is not clarified how the receipt of such confirmation should look in practice, and how it should be documented. In other words, the comments made by inspecting bodies are not so much about sponsor's carelessness, but rather about the process of establishing a law enforcement practice, aligning expectations and opportunities of all parties, when in specific situations both the sponsor and inspectors work out optimal algorithms.

Another group of findings is directly related to regulatory imperfections, in our opinion. These are seven cases, when after the trial completion the results were not submitted to the Ministry of Health within three months, as required by the law. The point is that rather bulky and meaty requirements are endorsed for reports on the results of the trials for which applications were submitted on 4 September 2016 and later (see clause 9 of the Rules of Good Clinical Practice approved by Order No. 200n by the Ministry of Health of the Russian Federation, dated 01.04.2016), generally complying with the international statute ICH E3. It is technically impossible to prepare a report with such contents within three months after completion of an international project, on which ACTO has informed[1] the Ministry of Health and Roszdravnadzor in March 2019. Their response shows that the problem is understood and work is under way to change this situation. For now, as far as we know from the practice of our members, no violation is registered, if the trial organizer notifies the Ministry of Health within the due deadline that a full-fledged report will be provided later.

Other groups of violations by trial organizer do not seem to require special explanations.

[1]See our correspondence with the Ministry of Health and Roszdravnadzor on the ACTO website in the section Analytics / Discussing Practical Issues: http://acto-russia.org/index.php?option=com_content&task=view&id=379

Violations by principal investigator

The second largest section of the checklist regards the work of principal investigator and his/her team. At least 114 finds in 104 medical institutions in 2018 had to do with this area, according to our data. Just to remind: we do not know how many of these 104 inspections went without comments.

The most popular claim of inspectors was incomplete informing of the trial participants about the terms of their participation. It should be clarified that this is the largest clause on the checklist that includes 20 sub-clauses, with most of them eliciting no questions from inspectors at all. Only three sub-clauses caused some problems. In ten cases there was no evidence that the participants were informed about the planned payments, although other documents of these trials indicated such payments. In seven cases inspectors were concerned that the participants had not been notified of future expenses. We know that such comments were made for trials with complex logistics, for example, that implied trips to other medical institutions or even to other cities for the sake of special examinations. For all that, inspectors failed to find any warning about transportation expenses to be incurred by patients in the information materials approved by the IEC.

Table 5

Violations by Principal Investigator and the Research Team Found by Roszdravnadzor in 2018			
Recorded are violations of requirements for...	**Checklist clauses**	**Number of violations**	**Share of the total number (%)**
... informing the trial participants or their legal representatives	4.18	21	18,4%
... taking stock of investigational medicinal products and (or) comparators	4.15 – 4.17	16	14%
... the procedure of getting the informed consent	4.22 – 4.23	16	14%
... maintaining the trial-related documentation	4.30	12	10,5%
... investigator and co-investigators' familiarization with the trial documentation	4.2	11	9,6%
... informing the IEC	4.10	8	7%
... providing the safety information for the sponsor	4.24 – 4.25	5	4,4%
... providing additional information on the death of the trial participant on demand of the sponsor/IEC/Ministry of Health/Roszdravnadzor	4.26	5	4,4%
... documenting and reporting of any deviations from the protocol	4.8 – 4.9	4	3,5%
... compliance with the trial protocol	4.7	3	2,6%
... breaking of the randomized code	4.13 – 4.14	3	2,6%
... informing participants, providing them with appropriate follow-up and treatment in case of premature termination or suspension of the trial	4.28	2	1,8%
... informing IEC and the sponsor in case of premature termination or suspension of a trial	4.29	2	1,8%
... an investigator possessing all necessary resources for the conduct of a trial	4.5	1	0,9%
... notifying of primary physicians of the trail subjects of their participation in the trial	4.6	1	0,9%
...use of the investigational medicinal products	4.11	1	0,9%
... informing the head of a medical institution and the sponsor in case the participant's life or health are threatened.	4.27	1	0,9%
... informing the head of a medical institution about the trial completion	4.32	1	0,9%
... preparing a report on the trial completion and its submittal to the sponsor and IEC	4.33	1	0,9%
TOTAL		114	100%

16 findings regard the inventory of medicinal products used in a trial. As we discovered, violations in these clauses of the checklist were not recorded because of slipshod recordkeeping per se, since there is a special clause (4.30) reserved for these purposes, but in those cases, where records diverged with the real number of available and administered units of medicinal product.

Another 16 findings are related to violating the procedure of getting the informed consent. These are generally pediatric trials where the consent was not signed by parents, but rather by relatives who actually assumed the child care, such as grandmas. In this context employees of Roszdravnadzor's territorial bodies in such situation several times recorded a violation of clause 4.23, referring to the ban on participation of vulnerable groups of subjects in trials, including legally free children.

Now a few words about certain entries in the table. In 11 cases inspecting bodies failed to find sufficient evidence confirming the research team acquaintance with the trial documents. To the best of our knowledge, any documented evidence of a training course conducted for co-investigators is sufficient evidence for inspectors. As regards the principal investigator, the latter needs to sign all necessary papers not later than the trial commencement date.

It seems advisable to comment on three other lines or entries of Table 5. The first rebuke is that the requirement "to provide additional information on the death of the trial participant on demand of the sponsor/IEC/Ministry of Health/Roszdravnadzor" was not met. We took an interest in these five findings, since we could hardly imagine the principal investigator ignoring a query from the Ministry of Health. It turned out that inspectors recorded a violation in this paragraph of the checklist in those cases, when the investigator failed to timely respond to the sponsor's question.

The second rebuke is that the requirement "to notify the primary physicians of the trial subjects of their participation in the trial" was not met – one finding. It turned out that it's not the notification of the primary physicians that stands behind fixing of a violation in this clause. The actual violation came down to the fact that patients were denied the participant cards envisaged in the trial, which could serve as a source of extra information for ambulance doctors, should a trial participant suddenly faint outdoors.

Finally, we'd like to pay attention to the last line in the table, where there is only one violation that regards the trial completion. This is part of the above-mentioned requirement for the sponsor to report the results to the Ministry of Health within three months upon the trial completion. Part 11, Article 40 of Federal Law No. 61-FZ, dated 12.04.2010 "On Circulation of Medicines" specifies that this report shall be based on the reports of medical institutions. We should reiterate that in the industry's opinion this is an unfeasible requirement, so the Ministry is contemplating the possibilities of its removal, whereas the practice of its execution and control has not been settled yet.

IEC's Violations

In 2018, according to our data, at least 39 breaches were recorded in the work of IECs of various organizations, of which three violations of clause 2.9 are the summary assessment of IECs' activities. In other words, in the opinion of inspectors, three IECs out of 104 inspected in 2018 do not cope with their obligations to protect the rights, safety and well-being of clinical trial participants.

Table 6

Violations by IECs Discovered by Roszdravnadzor in 2018			
Recorded are violations of requirements for...	**Checklist clauses**	**Number of violations**	**Share of the total number (%)**
... a set of documents reviewed by the IEC	2.4	9	23%
... IEC compliance with the SOPs endorsed	2.2	8	20%
... with the IEC SOP content	2.3	8	20%
... admission of the experts attracted to debates/voting	2.8	8	20%
... IEC ensuring the protection of the trial subjects' rights, safety and well-being	2.9	3	8%
... qualification of the IEC members	2.1	1	3%
... informing the investigator and the sponsor on the IEC decisions	2.6	1	3%
... approval of the protocol amendments	2.7	1	3%
TOTAL		39	100%

The most typical breach by IEC in 2018 was reviewing an incomplete set of documents (nine findings). Hera are included those cases where an incomplete set of documents for review was listed in SOP, and when an inspector discovers an incomplete set in folders with the actually reviewed documents as well as those that contained information materials for participants among the documents of the investigators, which were not submitted for review and, accordingly, did not get any IEC approval.

Ranked second in terms of the frequency of findings in IECs are two sets of violations: deviations from their own SOPs (eight cases) and violations in SOP content (also eight). As for the latter, as far as we can judge,

inspectors checked the compliance of these documents with clause 12 of Order 200n that lists sections to be reflected in SOP: membership qualification and composition requirements, information about the founder, the procedure of meeting organization and conduct as well as decision-making. In other words, availability of separate SOPs or SOP provisions covering these subjects was inspected.

Eight more findings regarded the admission of invited experts to debates and (or) voting. Other violations were recorded in very few cases.

Violations by a medical institution as a separate legal entity

Violations concerned of administration of the process by medical institutions were fewest in number. The matter regards stipulations of the Russian law alone, lying beyond the responsibility of principal investigator as per GCP.

Accordingly, most breaches here are rather formal, to our mind, since they have little impact upon the safety of trial participants and the quality of data obtained. This is the case with 12 breaches of clauses 1.3–1.4 covering the trial conduct contract. As per our data, inspectors were usually unhappy about the fact that the contract did not contain the entire information stipulated by part 2 of article 41 of the Federal Law "On Circulation of Medicines". This is information about the terms and times of a trial, total cost of the programme and, separately, the amount to be paid to the clinical trial team (no specific information on each team member was required) as well as the form of reporting the trial results to the Ministry of Health (here inspectors did not only expect references to the form, but also to the legal entity in charge of submitting the results). The same group of violations includes situations when the period of the trial was extended and the contract with the clinic was not changed.

Many findings in clause 4.1: notifying the Ministry of Health about the trial commencement (seven findings), the obsolete order on appointing a clinical trial team (six findings) – were mere formality. "The obsolete order" implies that the team composition has actually changed, while the order has not been updated, this being construed as the lack of team appointment.

There are also serious breaches in the same clause 4.1, directly affecting the safety issues. In five cases, in the opinion of inspectors, the life and health of patients were threatened, so the trial had to be submitted. Yet the trial was not suspended, which was interpreted as a violation. Unfortunately, we do not know all details of this incident.

Table 7

Violations by a Medical Institution as an Autonomous Legal Entity found by Roszdravnadzor in 2018			
Recorded are violations of requirements for...	**Checklist clauses**	**Number of violations**	**Share of the total number (%)**
... the content and (or) execution of a clinical trial conduct contract	1.3 – 1.4	12	37%
... informing the Ministry of Health on the trial commencement	4.1	7	22%
... appointing the principal investigator and co-investigators	4.1	6	19%
... making the decision to submit a trial in case the patient's life and/or health are endangered	4.1.	5	16%
... accreditations for the conduct of clinical trials	1.1	1	3%
... storage of clinical trial documentation	4.31	1	3%
TOTAL		32	100%

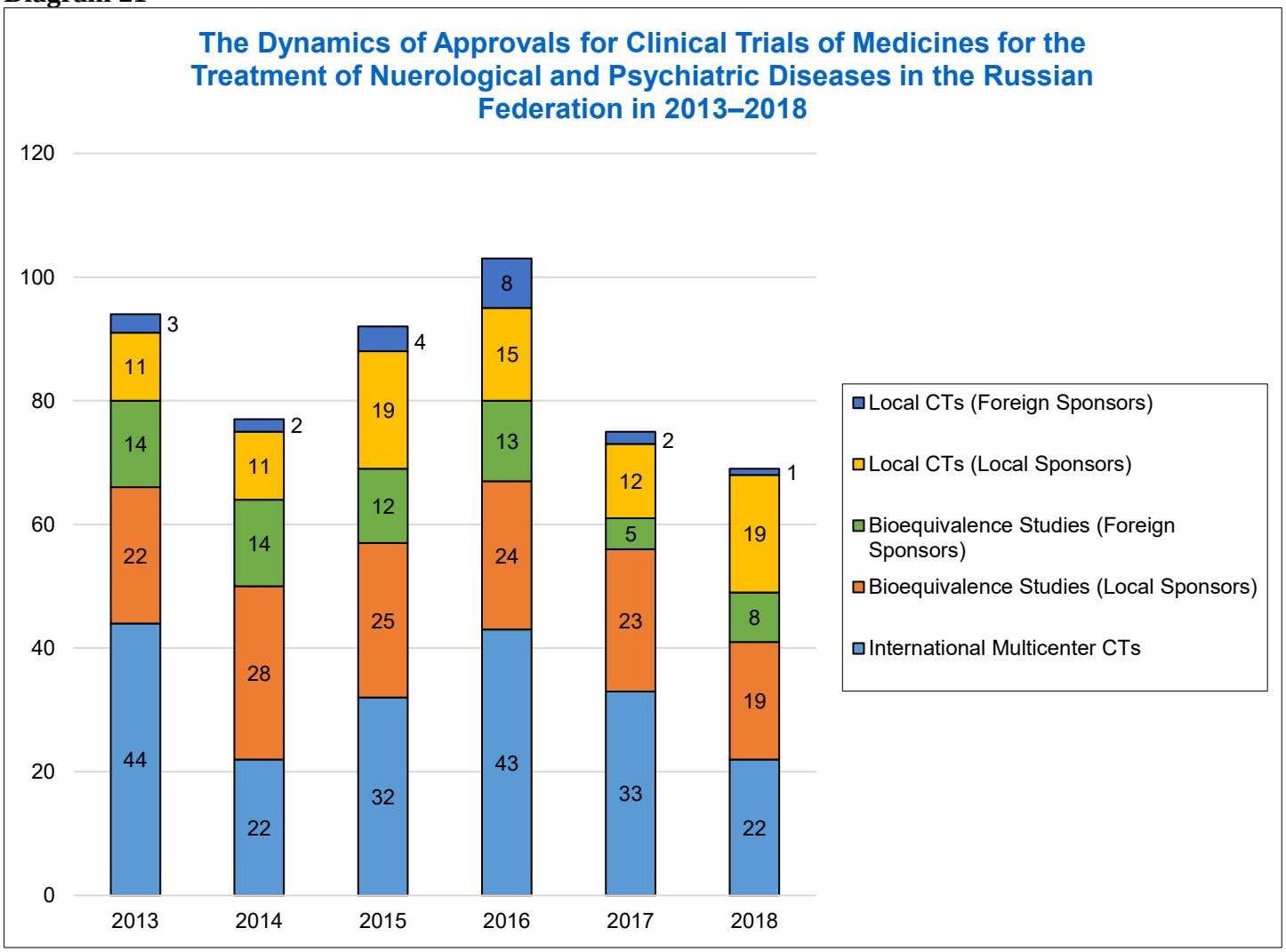
We are aware that the data provided do not give a complete picture of the violations identified. For example, we cannot analyze the number and nature of findings separately for pharmaceutical companies and contract research organizations, or for Russian and foreign sponsors. The current reform of control and surveillance activity also transforms both information sources and the very data available to us. So for now it's impossible to guarantee that the monitoring of inspection results will again become a permanent section of the ACTO Newsletter. But we do hope that even these incomplete stats will prove helpful for the stakeholders involved in clinical trials.

SITUATION WITH CLINICAL TRIALS OF MEDICINAL PRODUCTS TO TREAT NEUROLOGICAL AND PSYCHIATRIC DISEASES

We continue publishing overviews of clinical trials of medicinal products used in a specific therapeutic area. After analyzing the trials of HIV/AIDS, Hepatitis C and Tuberculosis[2] as well as autoimmune diseases medications[3], we decided to review the trials of medicinal products drugs used in neurology and psychiatry. The merging of these two therapeutics areas is caused by the fact that it is difficult to clearly pigeonhole some diseases in any particular area (e.g. brain disorders causing dementia). Sampling trials, we were geared at the ICD code / disease mentioned in the protocol; in the lack of any reference, when the already registered medicinal product was studied, we were guided by the indications.

The overview covers the trials to which approvals were issued by the Ministry of Health of the Russian Federation in 2013–2018 – see Diagram 21 for a general idea about the market structure. Overall 510 clinical trial licenses were issued in the period under review, of which 196 (38%) were provided for IMCTs, 107 (21%) - local trials, 207 (41%) - bioequivalence studies. These three trial groups are described in more detail below.

Diagram 21



Data from www.grls.rosminzdrav.ru

[2]ACTO Newsletter No. 16, pages 24-29.
[3]ACTO Newsletter No. 17, pages 27-34.

IMCTs

In different years neurology and psychiatry accounted for 8% to 14% of all IMCTs approvals issued in Russia (see table 8). In the list of therapeutics areas ranked by the number of IMCTs approvals issued neurology and psychiatry (as one therapeutics area) ranked second in 2013, 2015, 2016 and 2017, sixth in 2014 and third in 2018[4]. The stats collected by ACTO show that in 2013–2018 the only therapeutics area where the Ministry of Health has always issued more approvals than for neurology and psychiatry trials combined was oncology.

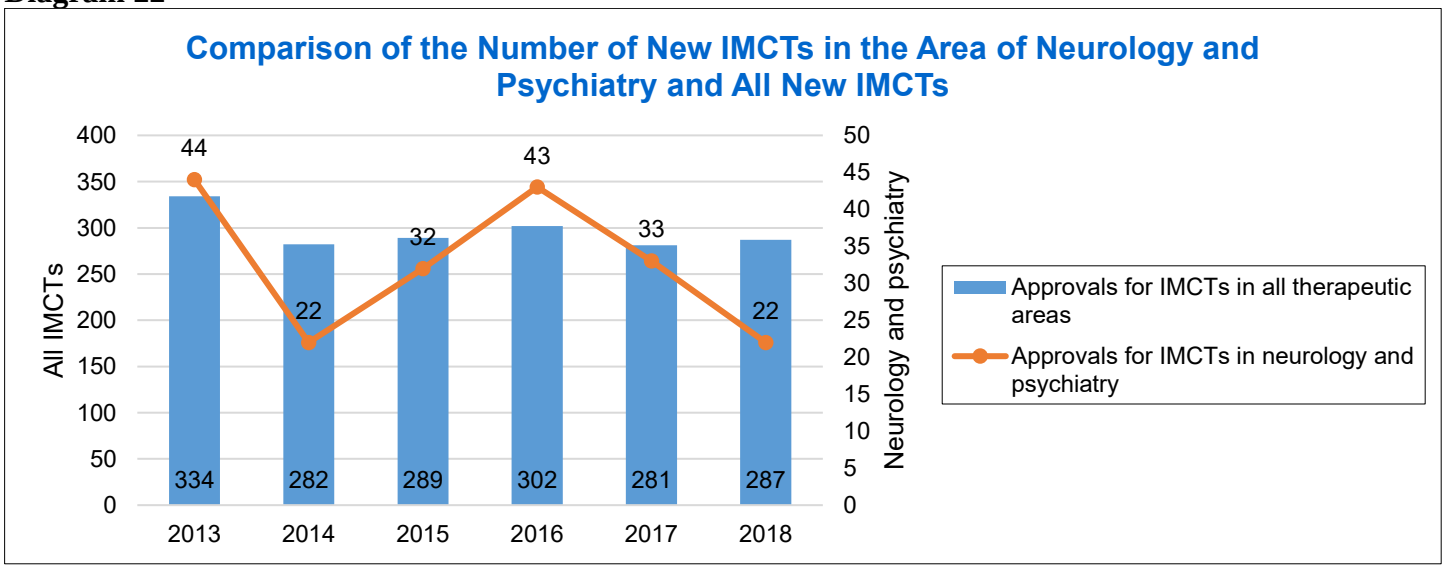
Table 8

Ratio of IMCTs Approvals in All Therapeutics Areas to IMCTs Approvals in Neurology and Psychiatry in the Russian Federation, 2013-2018.					
	The number of IMCTs approvals in all therapeutics areas	**The number of IMCTs approvals in neurology and psychiatry**	**The share of neurology and psychiatry in new IMCTs**	**Rank in the therapeutics area rating by the number of approvals issued**	**Therapeutics areas with the highest share of IMCTs approvals**
2013	334	44	13%	II	oncology
2014	282	22	8%	VI	oncology endocrinology rheumatology cardiology and CVD pulmonology
2015	289	32	11%	II	oncology
2016	302	43	14%	II	oncology
2017	281	33	12%	II	oncology
2018	287	22	8%	III	oncology gastroenterology

Data from www.grls.rosminzdrav.ru

Diagram 22 allows the comparison of changes in the total number of IMCTs approvals and IMCTs approvals in neurology and psychiatry in six recent years.

Diagram 22



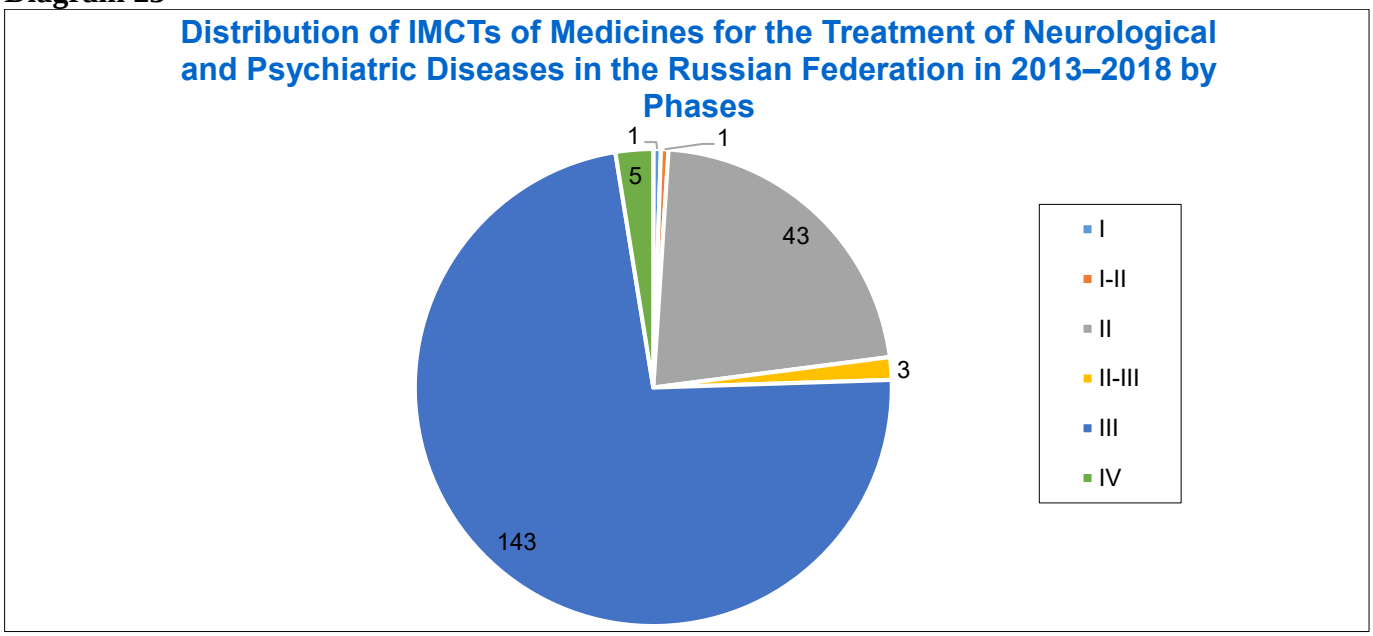
Data from www.grls.rosminzdrav.ru

The trials of second and third phases account for 96% of all IMCTs approvals in neurology and psychiatry during the reporting period. The third phase accounts for 143 (73%) of trials out of 196 IMCTs approvals

[4]See the Structure of Clinical Trials Market by Therapeutics Areas section in the issues of ACTO Newsletter for different years.

provided. The second phase accounts for 43 (22%). In three trials (2%) phase II-III was indicated. The rest 4% are five trials of phase IV, one of phase I and another one of phase I-II.

Diagram 23



Data from www.grls.rosminzdrav.ru

Phase I trials were about studying pharmacokinetics, safety and the tolerance of schizophrenic teenagers to multiple cariprazine dozes, organized by Gedeon Richter. The trial approval in Russia was provided in late 2016; in the second half of 2017 cariprazine was approved in the USA and EU, and in early 2019 it was registered in the State Registry of Medical Products at the Ministry of Health of the Russian Federation. Phase I-II is claimed for studying the primary use of branaplam to babies with spinal muscular atrophy, sponsored by Novartis. The approval was granted in February 2018, the medicinal product study is still ongoing.

The number of patients to participate in neurology and psychiatry IMCTs, as follows from the approvals, fluctuates from three to 1,263, their average number standing at 100 and the median value – at 67 individuals.

Table 9 shows specific diseases and symptoms, remedies for which were most often tested in the course of neurological and psychiatric IMCTs. The list is topped by medicinal products used in multiple sclerosis therapy (including those used to treat some symptoms typical of this disease, such as bladder control problems), which were studied in 50 IMCTs. Following next are remedies for schizophrenia – 32 trials. Medicinal products used in the treatment of major depressive disorders ranked third in terms of frequency of mentions in protocols – 17 IMCTs.

Table 9

Diseases and Their Symptoms Most Often Referred to in IMCTs Protocols of Medicinal Products to Treat Neurological and Mental Diseases, RF 2013–2018.		
Rank	**Disease/symptom**	**Number of IMCTs**
1	multiple sclerosis (including symptomatic treatment)	50
2	schizophrenia	32
3	major depressive disorder	17
4	epilepsy	15
5	Alzheimer disease (including symptomatic treatment)	14
6	bipolar disorder	8
7–8	spasticity	5
7–8	migraine	5
10–11	Parkinson disease	4
10–11	pain of various etiology, localization and intensity	4
10–11	spinal muscular atrophy	4
	Other 21 diseases and their symptoms	***totaling to 38***

Data from www.grls.rosminzdrav.ru

The molecules mentioned in the protocols proved rather diverse. Those tested in five or more trials are shown in Table 10. Four medicinal products of those not included in the table were studied in four trials each, another 11 – in three trials, 25 – in two trials and 56 – in one IMCTs.

Table 10

Molecules in IMCTs of Medicinal Products to Treat Neurological and Mental Diseases, RF 2013-2018.				
Rank	**Molecules**	**Number of IMCTs**	**Disease/symptom and number of IMCTs**	**Sponsor and number of IMCTs**
1	Botulinic toxin	13	spasticity - 5	Allergan – 5
			infantile cerebral paralysis - 3	Merz – 3
			sialorrhea - 2	Merz – 1
				Solstice Neurosciences – 1
			multiple sclerosis - 2	Allergan – 1
				Ipsen – 1
			spastic hemiparesis - 1	Ipsen – 1
2	Lurasidone	10	schizophrenia - 6	Sunovion – 5
				Lundbeck – 1
			bipolar disorder - 3	Dainippon Sumitomo Pharma – 2
				Sunovion – 1
			major depressive disorder - 1	Sunovion – 1
3	Brexpiprazole	8	schizophrenia - 3	Lundbeck – 2
				Sunovion – 1
			major depressive disorder - 3	Lundbeck – 2
				Otsuka – 1
			Alzheimer disease - 2	Otsuka – 2
4–5	Lacosamide	5	epilepsy - 5	UCB Biopharma – 5
	Ofatumumab	5	multiple sclerosis - 5	Novartis – 5
	The rest 96	*155*		

Data from www.grls.rosminzdrav.ru

Table 10 already gives some idea about the companies studying medicinal products to treat neurological and psychiatric in Russia. As can be seen from Table 11, Lundbeck, Novartis and Teva are among the leaders for the conduct of IMCTs in this area.

Table 11

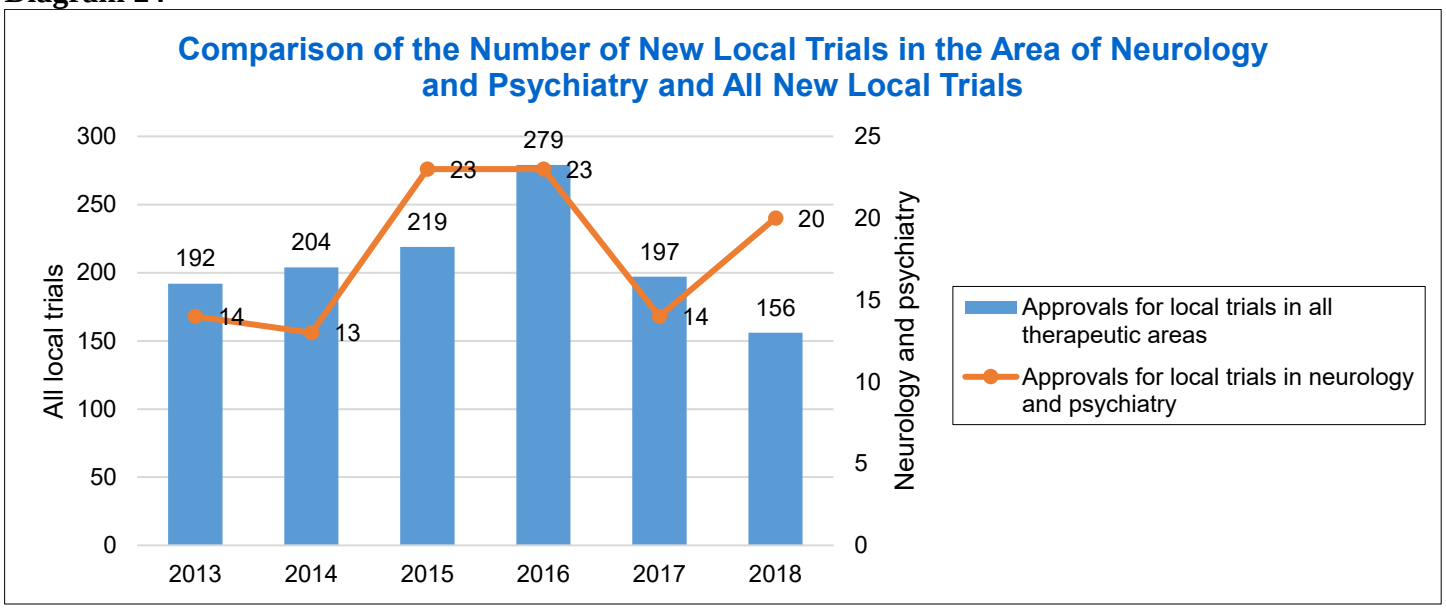
Companies Conducting IMCTs of Medicines for the Treatment of Neurological and Psychiatric Diseases in Russia, 2013–2018		
Ranking	**Company**	**Number of IMCTs**
1	Lundbeck	12
2–3	Novartis	11
2–3	Teva	11
4	Sunovion	10
5–6	Allergan	9
5–6	F. Hoffmann-La Roche	9
7–10	Servier	6
7–10	Biogen	6
7–10	Genzyme	6
7–10	Janssen Pharmaceutica	6
	The remaining 59 companies	***110 total***

Data from www.grls.rosminzdrav.ru

Local trials

Medicinal products to treat neurological and psychiatric diseases accounted for 6% to 13% of all local trial approvals in Russia during 2013–2018. See Diagram 24 for more detail about the number of licenses provided.

Diagram 24

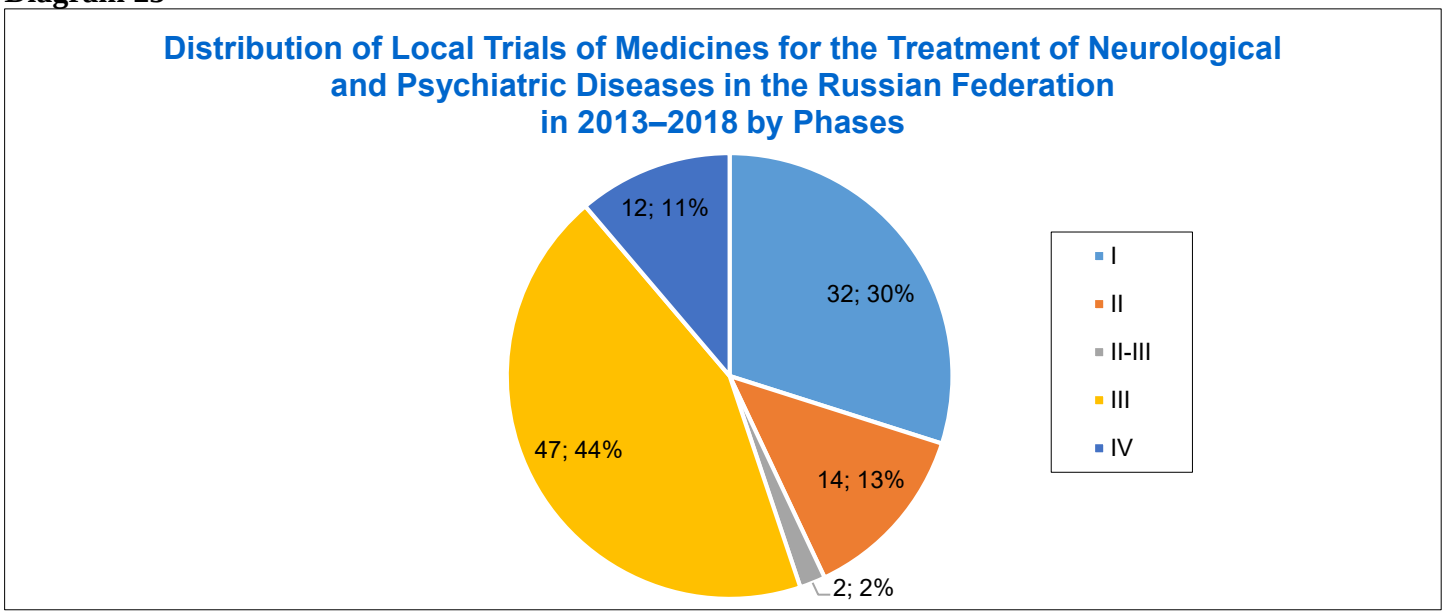


Data from www.grls.rosminzdrav.ru

The number of participants declared in applications for local trial approvals varied between 16 and 498, the average being 119 and the median – 100 individuals.

The distribution of local trials by phases is reflected in Diagram 25. The number of first-phase trials is close to a third (30%). The share of second-phase trials stood at 13%. Approvals for third-phase trials were granted most often (47%). Fourth-phase trial approvals accounted for 11%.

Diagram 25



Data from www.grls.rosminzdrav.ru

Given that promising developments may potentially stand behind first-phase trials, we'll enlarge upon them a bit more. Among 32 first-phase trials three have foreign sponsors. Abbot was twice granted the approval (September 2015 and August 2016) to study Betaserc Forte – a new modification of the medicinal product for

vertigo that has been used for quite some time. In October 2016 Abbott was granted an approval for a third-phase trial of the same medicinal product. Besides Abbott, Cyprus-based Delcroston Management Limited conducted a first-phase trial of Brainmax nootropic in 2016-2017.

Of 29 first-phase trials by Russian sponsors, in nine cases medicinal products based on well-known molecules (alpha-lipoic acid, fampridine and others) were studied, whereas six protocols featured new formulae of well-known substances (melatonin+memantin and others). The rest 14 trials were related to new developments, including rather extravagant ones (Table 12). One example is "Skulachev ions" – mitochondrial-oriented antioxidants, as the developers explain.

Table 12

New Developments by Russian Sponsors in Local Trials of Medicinal Products to Treat Neurological and Psychiatric Disorders, Russian Federation, 2013–2018

No.	Name of the medicinal product	Characteristic of the medicinal product	Sponsor
1	AVN-211 (CD-008-0173, avisetron)	selective inhibitor of serotonin 5-HT6 receptors for schizophrenia treatment	SRI ChemRar
2	AQU-005	low-molecular inhibitor of matric metalloproteinases for the treatment of neuropathic pain	NeuroMax
3	BP101 (Libicore)	medicinal product based on the signal peptide - a modulator of limbic-hypothalamus-pituitary disorders to treat female sexual dysfunction	Ivix
4	AdeVasc	medicinal product for genetic therapy of amyotrophic lateral sclerosis	NTpharma
5	GB-115	dipeptide anxiolytic for treatment of anxiety disorders	Maluna - Pharm
6	Gimantan (N (2 adamantyl) hexamethyleneimine hydrochloride)	antiparkinsonian medicinal product	V.V. Zakusov Pharmacology SRI
7	Innervin	genetic medicine based on a non-viral addressing construct, nerve growth stimulant	MSU
8	Creamid (ethyl (2-[2-(1-methylcarbamimidamido)acetamido]acetate) (2E-but-2-endioat)	neuroprotective medicinal product for prevention and therapy of stroke, heart attack and ischemia aftereffects, registered in 2015.	Vertex
9	Cortexin	medicinal product based on polypeptides of cattle brain cortex, registered in 2009.	Geropharm
10	Plastomitin	Anti-age medicinal product based on Skulachev ions (mitochondrial-targeted antioxidants)	Mitotech
11	Tropoxin (3-(3,4,5-trimethoxibenzoiloxiimino)-8-methyl-8-azabicyclo[3,2,1]hydrochloride octane)	antimigraine	V.V. Zakusov Pharmacology SRI
12	Cellex	medicinal product based on polypeptides extracted from swine embryo brain	Pharm-Synthez
13 & 14	Emopag (6-methyl-2-ethylpyridine-3-ol (2S)-2-acetaminopentadionic acid)	neurotropic drug	PharmFirm Sotex

Data from www.grls.rosminzdrav.ru

Summarizing the data on all trial phases for the period under review, we see that in 53 out of 107 (49.5%) of local trials of neurological and psychiatric generics and biosimilars were studied. Most popular of these are shown in Table 16, together with medicinal products from the protocols of bioequivalence studies. Among the rest 54 medicinal products Emopag was tested more often than others (four trials). The above-mentioned original Russian developments – AdeVasc, GB-115, Gimantan, Innervin and Cellex – were studied in two trials. In addition, nootropic Ampasse (calcium hydroxinicotineilglutamate), two-blade ginkgo biloba extract, a mixture of peppermint oil, motherwort tincture and ethylbromisovalerinate (Corvalol variety) as well as homeopathic agents Divaza and Tenoten were also included in two protocols each. Another 30 medicinal products were studied in one trial each.

Tested most often in local trials were nootropics (17 trials), followed by multiple sclerosis therapy medicinal products (10), by remedies for cerebral blood flow disorders (9).

Table 13

Diseases and Their Symptoms Most Often Referred to in Local CT Protocols of Medicinal Products to Treat Neurological and Psychiatric Diseases, RF 2013–2018.		
Rank	**Disease/symptom/pharmacology group**	**Number of CTs**
1	nootropics[5]	17
2	multiple sclerosis	10
3	cerebral blood flow disorder	9
4–5	generalized anxiety disorder	6
4–5	depressive disorder /depression	6
6–8	Parkinson disease	5
6–8	vestibular vertigo	5
6–8	spasticity	5
9	dementia	4
10	schizophrenia	3
	Other 32 diseases	***totaling to 37***

Data from www.grls.rosminzdrav.ru

Valenta Pharm with its 15 trials took the lead among sponsors in 2013-2018 by the number of local trial approvals in the neurology and psychiatry area. Followed by Materia Medica and Sotex with six approvals each, by Microgen with 4 approvals.

Table 14

Companies Conducting Local Trials of Medicines for the Treatment of Neurological and Psychiatric Diseases in Russia, 2013–2018		
Ranking	**Company**	**Number of trials**
1	Valenta Pharm	15
2–3	Materia Medica	6
2–3	Sotex	6
4	Microgen	4
5–8	Biocad	3
5–8	Research Zakusov Institute of Pharmacology	3
5–8	Abbott	3
5–8	Evalar	3
	The remaining 51 companies	***64 total***

Data from www.grls.rosminzdrav.ru

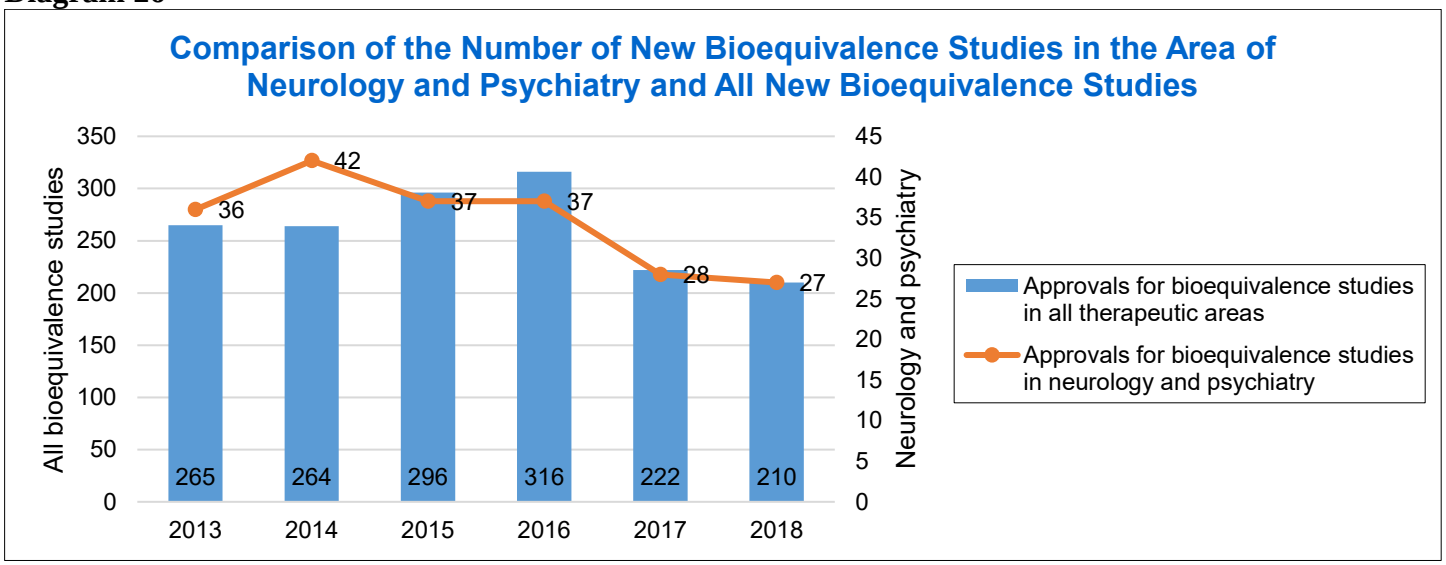
Bioequivalence studies

In 2013–2018 from 12% to 16% of all approvals to bioequivalence studies were issued for medicinal products used in the treatment of neurological and psychiatric diseases. Diagram 26 shows the number of approvals issued by years.

The number of participants claimed in applications for bioequivalence studies in neurology and psychiatry is typical of bioequivalence studies per se. This number ranged from 18 to 120 individuals, the average being 38 and the median standing at 32.

[5]Nootropics are separately reviewed by ACTO because of their non-specific nature, given that a long and versatile list of ICD codes / diseases is often cited in their indications.

Diagram 26



Data from www.grls.rosminzdrav.ru

Given that participants of bioequivalence studies are normally healthy and protocols seldom mention the ICD code / disease which would imply the future use of the medicinal product studied; so for this category of studies we use a distribution by pharmacology groups of products tested, rather than by ICD codes / diseases (see Table 15).

Table 15

Distribution of Bioequivalence Studies in Neurology and Psychiatry by Pharmacology Groups of Tested Medicinal Products, Russian Federation, 2013–2018

Pharmacology group	Number of CTs
→ Nootropics	**152**
→ Antiepileptic drugs	38
→ Neuroleptics	28
→ Nootropics (neurometabolic stimulants)	21
→ Other nootropics	17
→ Antidepressants	16
→ Drugs impacting neuromuscular transmission	9
→Antiparkinsonian drugs	8
→Sleeping aids	7
→Anxiolytics	4
→Sedatives	4
→Immunotropic medicinal products	**16**
→Immune depressants	16
→Intermediates	**15**
→Hystaminergic drugs	9
→Serotoninergic drugs	6
→Vegetropic drugs	**13**
→Adrenomimetic and sympatomimetic agents	1
→ Holinolytic agents: m-, n-holinolytics	3
→Holinomimetic agents	9
→Metabolics	**9**
→ Antihiyoxic drugs and antioxidants	4
→Other metabolics	5
→Organotropic drugs	**2**
→Cardiovascular drugs, vasolidators	2

Data from www.grls.rosminzdrav.ru

Listed in Table 16 are most popular molecules mentioned more often than others in the protocols of generics medicinal products (both in local trials and in bioequivalence studies).

Table 16

Most Popular Molecules Tested in Generic Medicinal Products for the Treatment of Neurological and Psychiatric Diseases, Russian Federation, 2013–2018.				
Molecules	**Number of foreign-sponsored CTs**	**Number of Russian-sponsored CTs**	**Total number of CTs**	**Pharmacology group**
Pregabalin	10	7	17	Antiepileptic drugs
Memantin	12	4	16	Other nootropics
Betagistin (separately and in combos)	6	5	11	Hystaminergic drugs
Aminophenylbutyric acid	1	8	9	Nootropics
Fingolimod	2	7	9	Immune depressants
Levetiracetam	4	4	8	Antiepileptic drugs
Melatonin (separately and in combos)	-	8	8	Sleeping aids
Tolperizon	1	7	8	Drugs impacting neuromuscular transmission
Teriflunomid	1	6	7	Immune depressants
Escitalopram	2	5	7	Antidepressants
78 more medicinal products	***160 CTs in total***			

Data from www.grls.rosminzdrav.ru

The sponsors who initiated five and more bioequivalence studies in neurology and psychiatry during 2013–2018 in Russia are listed in the table below.

Table 17

Companies Conducting Bioequivalence Studies of Medicines for the Treatment of Neurological and Psychiatric Diseases in Russia, 2013–2018		
Ranking	**Company**	**Number of trials**
1	Atoll	23
2	Canonpharma Production	11
3	Polpharma	10
4	Severnaja Zvezda	9
5	Hetero Labs	8
6	Teva	7
7	Medisorb	6
8–9	KRKA	5
8–9	Nativa	5
	The remaining 69 companies	***123 total***

Data from www.grls.rosminzdrav.ru

Comparing the Russian and world markets

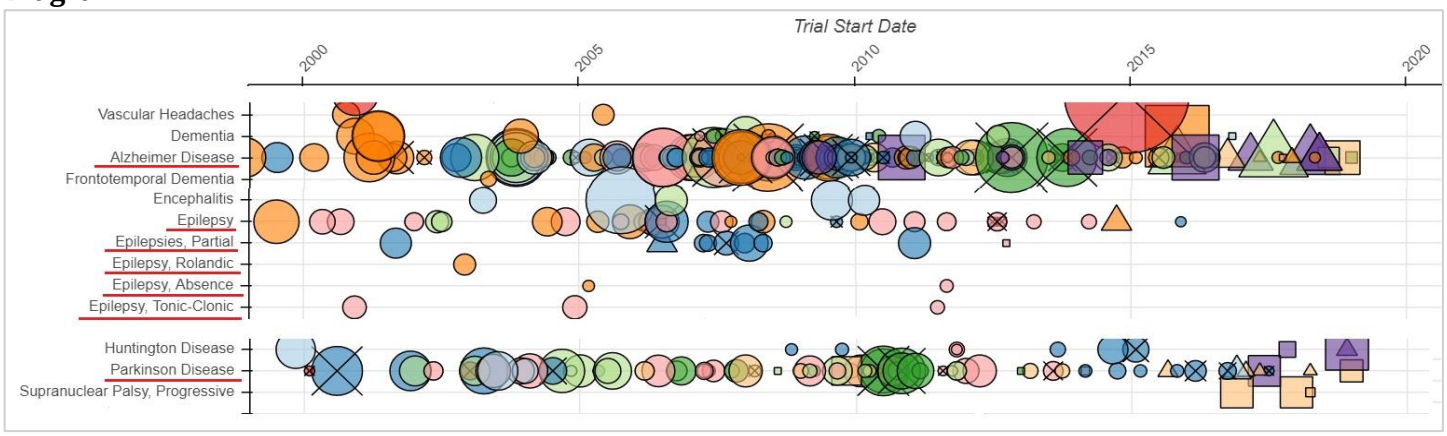
We do not have generalized statistical data on clinical trials in neurology and psychiatry, which are conducted the world over. Whereas trial information processing in all ICD codes / diseases would have been an awesome challenge for us. Therefore, we stayed our choice on comparing the trials of medicinal products for the treatment of randomly selected diseases: epilepsy, Alzheimer and Parkinson diseases.[6]

The Diagram of Aero Data Lab that taps into information posted on ClinicalTrials,gov, regarding 13,749 clinical trials by ten biggest pharmaceutical companies in 20 recent years, gives an idea about the intensity of developing remedies for these diseases. A gigantic interactive diagram is available on the project site, Diagram 27 being its small fragment containing diseases of interest to us. Each sponsor on the diagram has its

[6]See also a similar comparison for the MS diagnosis in ACTO Newsletter No. 17.

corresponding colour, the shape indicating the status (completed, recruitment is under way, etc.), whereas the size shows the number of participants (for details you still have to turn to the source).

Diagram 27



Data from www.aerodatalab.org/birds-eye-view-of-research-landscape

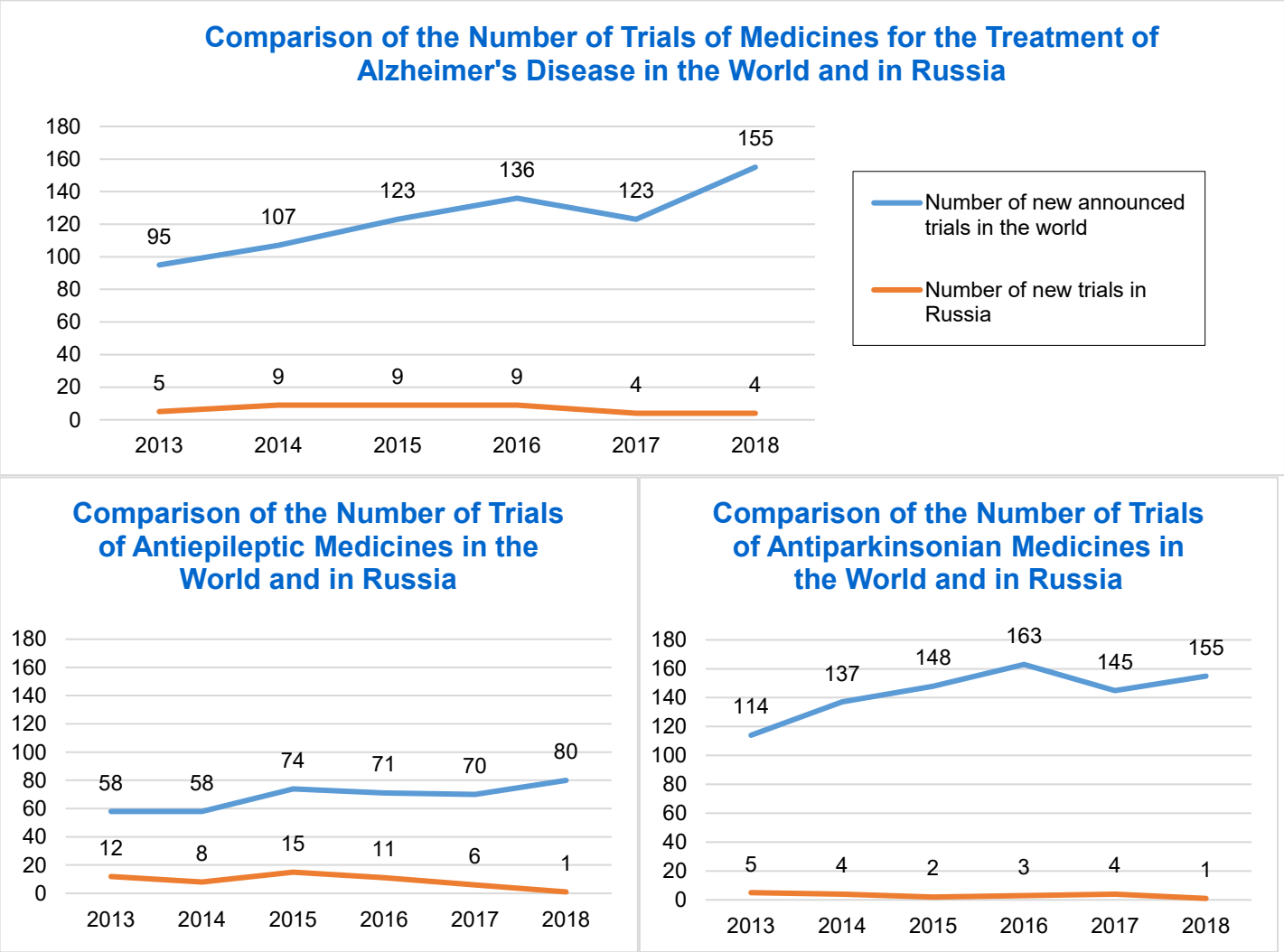
The diagram shows that during 20 recent years medicinal products used to treat the Alzheimer disease roused the interest of developers: more companies out of the top ten care about them than about antiepilepsy or antiparkinsonian medicinal products. The density of trials being high, just slightly on the wane in recent years. Among the three ICD codes / diseases under review fewest trials were conducted for antiepileptic drugs – probably because the already existing medicinal products are adequate to the task of relieving the symptoms, so we should not anticipate another scientific breakthrough in this area. The trials of antiparkinsonian drugs are somewhere in between.

Charts 28–30 comparing the number of respective trials announced on ClinicalTrials.gov with the number of approvals issued in Russia will help to roughly estimate the ratio of trials conducted for these three groups of medicinal products in the world and in Russia.

The trials of antiepileptic medicinal products are notable for the smallest gap between the lines. But as we remember, fewer trials of these medicinal products are conducted in the world, as compared to trials of the medicinal products from two other ICD codes. The gap between lines on the chat of medicinal products from these two ICD codes is wider, with trials about to start in Russia accounting for 1–8% of those announced on ClinicalTrials.gov.

The trials of generics and biosimilars account for a notable share of Russian trials: 70% for the trials of antiepileptic medicinal products, 60% for the trials of medicinal products against the Alzheimer disease, and 47% for antiparkinsonian medicinal products. Unfortunately, we don’t know how many trials conducted worldwide fall to the share of generics and biosimilars.

Diagram 28–30



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

In 20 recent years the development of medicinal products to treat the Alzheimer disease was very intensive, but often brought disappointment to their sponsors. After 2003 only a combination of the already known memantin and donepezil was approved, but not a single new medicinal product entered the market. At the turn of 2018 media reported[7] that Pfizer gave up on further effort in this area. In 2018 the trial of verubecestat conducted by Merck ended in a failure as well as the trials of lanabecestat by Eli Lilly and AstraZeneca. Early in 2019 Roche refused to continue testing crenezumab, because it was dissatisfied with interim data.

Yet despite the disappointments, the quest goes on. According to UsAgainstAlzheimer's[8], third-phase trials of 26 medicinal products are underway in 2019 (down 16% year-on-year). Nine of these are remedies for symptoms, seven impact amyloid proteins, and another 12 – affect neurotransmission. Another 72 medicinal products, as counted by experts, are undergoing second-phase trials. Tested in Russia during 2013–2018 were 11 medicinal products for Alzheimer's, which lack approval in the USA, EU or Japan as of September 2019. Trials of two of them (crenezumab and lanabecestat) were halted by their sponsors. Two medicinal products were tested in local trials: CD-008-0045 developed by Chemrar and estotylin developed by Angelini. For more detail see Table 18.

[7] «Pfizer ends research for new Alzheimer's, Parkinson's drugs», Reuters, 07.01.2018 (https://www.reuters.com/article/us-pfizer-alzheimers/pfizer-ends-research-for-new-alzheimers-parkinsons-drugs-idUSKBN1EW0TN), «Pharma giant Pfizer pulls out of research into Alzheimer's», BBC, 10.01.2018 (https://www.bbc.com/news/health-42633871).

[8] "A Devil of a Disease": The Current Alzheimer's Pipeline", BioSpace, 07.08.2019 (http://www.biospace.com/article/-a-devil-of-a-disease-the-current-alzheimer-s-pipeline/)

Table 18

Trials of Alzheimer's Medicinal Products, the Russian Federation, 2013–2018					
Molecules	**IMCTs**	**Originators in local trials**	**CTs of generics**	**Total number of CTs**	**Medicinal product status**
Memantine	-	-	16	16	approved in Germany, 1989; in USA in 2003
Galantamine	-	-	3	3	has been used in countries of the Soviet bloc since 1958, approved in the USA in 2001
Donepezil	-	-	3	3	approved in the USA in 1996
Crenezumab	3	-	-	3	trials were terminated in 2019
Brexpiprazole	2	-	-	2	approved in the USA for schizophrenia in 2015, has no approval for Alzheimer's
Gantenerumab	2	-	-	2	under trial
Leuco-methylthionine bihydromethanesulfonate	2	-	-	2	under trial
CD-008-0045	-	1	-	1	under trial
Elenbecestat	1	-	-	1	under trial
Lanabecestat	1	-	-	1	trials were terminated in 2018
ORM-12741/DB105	1	-	-	1	under trial
S47445	1	-	-	1	under trial
Masitinib	1	-	-	1	under trial
Melatonin + Memantin	-	-	1	1	Melatonin has been licensed in the EU since 2007, in Australia since 2011; memantin - see above
Rivastigmine	-	-	1	1	approved in Switzerland in 1997; in USA in 2000
Estotiline	-	1	-	1	under trial

Data from www.grls.rosminzdrav.ru

The trials of antiparkinsonian medicinal products were more successful: in 2016 pimavanserin was given a nod in the USA, in 2017 safinamide and amantadine were approved, while in August 2019 istradefilline was given green light. The latter was not tested in Russia[9], but the other three were (amantadine - in 2006–2009), as well as new combinations with levadopa: levadopa+carbidola, levadopa+benserazide, also the earlier combination levodopa+entacapone+carbidola. For more detail see Table 19.

Table 19

Trials of Antiparkinsonian Medicinal Products in the Russian Federation, 2013–2018					
Molecules	**IMCTs**	**Originators in local trials**	**CTs of generics**	**Total number of CTs**	**Medicinal product status**
Pramipexole	-	-	4	4	approved in the USA in 1997
Levodopa+Carbidola	2	-	-	2	the combo was approved in the USA in 2014
Levodopa+Benserazide	-	-	2	2	the combo was approved in the UK and Canada in 2010
Biperiden	-	-	2	2	approved in Germany in 1953; in USA in 1957
Gimantan	-	2	-	2	under trial
Pimavanserin	1	-	-	1	approved in the USA in 2016
Piribedil	-	-	1	1	had been used since the 1970s in the countries of the Soviet bloc
Rasagiline	-	-	1	1	approved in the EU in 2005; in the USA in 2006
Safinamide	1	-	-	1	approved in the EU in 2015; in the USA in 2017

[9]In 2013 NewVac was issued an approval for istradefilline trials, but as an antitumor medicinal product.

Levodopa+Entacapone+Carbidola	-	1	-	1	the combo was approved in the USA in 2003
Trihexyphenidyl	-	-	1	1	approved in the USA in 2003
Entacapone	--	1	-	1	approved in the USA in 1997

Data from www.grls.rosminzdrav.ru

After 2013 the stock of antiepileptic medicinal products was mainly enriched with analogues of well-known anticonvulsant medicinal products: vigabatrin (Sabril, Teva, 2019[10]), carbamazepine (Carnexiv, Lundbeck, 2016), midazolam (Nayzilam, UCB, 2019) and others. The medicinal products earlier approved for other ICD codes, such as everolimus, were given the nod as antiepileptic medicines. Novartis studied its safety and efficiency for patients suffering from refractory partial seizures in the backdrop of tuberous sclerosis, including in the Russian Federation.

Among the new substances approved by regulators in recent years are: brivaracetam (in 2016 this medicinal product was approved in the USA and EU) and cannabidiol (late in June 2018 it was approved by FDA for kids aged two and older, suffering from Dravet and Lennox-Gastaut syndromes, the approval in the EU expected till the end of 2019). Neither brivaracetam nor cannabidiol were tested in Russia from 2013 to 2018. Another new anti-seizure medication, cenobamate by SK Life Science, has the high odds of being approved by FDA till the end of 2019[11]: this medicinal product was tested with Russian patients participating. See Table 20 for a complete overview of antiepileptic medicinal product trials in Russia from 2013 to 2018.

Table 20

Trials of Antiepileptic Medicinal Products in the Russian Federation, 2013–2018				
Molecules	**IMCTs**	**CTs of generics**	**Total number of CTs**	**Medicinal product status**
Pregabalin	2	17	19	approved in the USA in 2004, patent protection expiring in 2019
Levetiracetam	-	8	8	approved in the USA in 1999, patent protection expired in 2011
Lacosamide	5	-	5	approved in the USA in 2008
Valproic acid	-	4	4	approved in the EU in 1960; in the US in 1978
Topiramate	1	3	4	approved in the USA in 1996
Eslicarbazepine acetate	3	-	3	approved in the EU in 2009; in the USA in 2013
Ganaxolone	2	-	2	under trial
Lamotrigine	-	2	2	approved in the UK in 1991; in the USA in 1994
Carbamazeline	-	1	1	approved in the UK in 1965; in the USA in 1974
Clonazepam	-	1	1	approved in the USA in 1975
Oxcarbazepine	-	1	1	approved in Denmark in 1990; by 1999 - in all EU nations; in the USA in 2000
Ethosuximide	-	1	1	approved in the USA in 1960
Everolimus	1	-	1	in the USA market since 2009; approved by FDA in 2018 as a remedy for partial-onset seizures
Cenobamate	1	-	1	under review of FDA

Data from www.grls.rosminzdrav.ru

A problem related to the access of Russian patients to antiepileptic medicinal products made big news in 2018–2019[12]. When three mothers buying unregistered in Russia anti-seizure medicinal products for their children were indicted for illicit trafficking of psychotropic substances (in one case, a woman was selling surplus of the medicinal product): diazepam in small enemas and clobazam. Diazepam was brought onto the world market back in 1963, whereas clobazam has been sold as an anti-seizure medicinal product since 1984. One could reproach medicinal product producers for their unwillingness to have them registered in Russia, but it should be borne in mind that some administrative barriers exist in the country for those eager to enter the local market. One

[10]In all three cases the year of getting an FDA approval is indicated.
[11] «FDA Accepts NDA Submission of Cenobamate for Partial-Onset Seizures», Neurology Live, 07.02.2019 (https://www.neurologylive.com/clinical-focus/fda-accepts-nda-submission-cenobamate-partial-onset-seizures)
[12]"We are very happy that at least the procurement of these 10,000 packs will be carried out," Kommersant, 22.08.2019 (https://www.kommersant.ru/doc/4067592)

of them is the requirement to conduct "registration trials" of medicines already approved in Europe and United States (those of them for which Russian centers were not included in IMCTs). Weighing all pros and cons, a pharmaceutical company may give up registration if the domestic market for a given medicinal product is limited, which means the outlay on additional trials won't pay off quickly. The cancellation of registration trials would eventually facilitate the access to modern medicinal products for patients. Therefore, one cannot but rejoice at the statement published in August 2019, which says that the Federation Council "is developing a bill proposing the cancellation of clinical trials for registration of innovative medicinal products in the Russian Federation which were earlier tried and tested abroad under international standards"[13]. Let's hope that not just innovative medicinal products, but also well-known effective medicines will fall under the simplified registration regulation.

[13] "Federation Council Suggests that Innovative medicinal products Be Registered without CTs", TASS, 22.08.2019 (https://tass.ru/obschestvo/6788772)

RANKINGS OF PRINCIPAL INVESTIGATORS

Another idea occurred to us as we were working on this issue: to rank principal investigators by their participation in clinical trials. The Register of the Ministry of Health of the Russian Federation, this time the registry of principal investigators[14], was used as the primary source of information, like in many other cases. Unfortunately, the register has some shortfalls which disable immediate access to information in due form. It took us more time to compile these rankings. Yet basically, this is not a very demanding exercise, so interested readers can do it by themselves.

The only warning, we would like to give is that the register data somewhat change with time. And we do not mean their natural updating. The database may slightly shrink and all of a sudden you can no longer find a project that was assigned to this or that investigator just yesterday. Yet if you look into the register after a while, you may rediscover the lost information. We do not know the reason for such occasional data "drifting". Similar things happen to western registers as well. For instance, this occasionally occurred in the registry of FDA inspections. That's why we always try to mention the date when the data are taken off, when publishing references to a source.

Overall, the register has 4,216 entries at the moment of writing this article, though some of them are duplicates. Duplicates can be caused by mistaken spelling of investigators' names or dates of birth. As a result, the same individual may be entered into the register twice. We had to remove explicitly mistaken entries by hand. At the time of counting 3,790 investigators were in the register.

To begin with, we ranked investigators by the number of all trials attributed to them in the register. Table 21 shows the TOP-100 doctors ranked by this attribute. It should be added that we filled out the "specialization" column according to the specializations of this or that investigator indicated in the register across the entire list of trials assigned to them.

After compiling this ranking, we stopped to think. The point is that the rating takes into account all trials since November 2010, regardless of whether they are still going on or have been completed. No wonder that the list is topped by clinical pharmacologists mainly specializing in "quick-firing" bioequivalence studies.

Given that the principle we used in drafting the first ranking (total trial count) is open up to criticism, we decided to also look at how the ranks are distributed between investigators involved in current or ongoing trials. This was not a trivial task. We had to study the list of trials conducted by each investigator and pick out projects going on at the present moment. It was immediately clear that oncologists were leading. And then we realized that it's not quite correct to present data as a general list because trials have various durations. For example, trials in oncology can take quite some time. Thus, when death is the endpoint, a trial may last more than ten years. It appears that oncologists "accumulate" a large number of ongoing trials, where the period of active treatment has long passed and we are dealing with the follow-up period. Furthermore, oncology is the therapeutics area with most active trials.

An idea emerged to divide investigators by their specializations. But here too, not everything was so simple because aside from narrowly focused experts, a lot of multiple-discipline doctors also get involved in clinical trials. For instance, how can we pigeonhole an investigator who indicates gastroenterology, cardiology and therapy as his/her specializations?

Eventually, we came up with three groups of investigators. Table 22 shows the top 20 oncologists. Table 23 reveals the top 20 investigators, most having a broad spectrum of specializations (down to aviation and space medicine), but who are mainly active in clinical pharmacology. Finally, in Table 24 we show the top 50 of all other specialists who were not included in the first or second group. We'd like to draw your attention to the fact that doctors from the latter group also have several specializations quite often, including clinical pharmacology. When we could see in the course of our analysis that most of their trials were conducted within one specialization,

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

we placed them in the third group. For example, if a doctor participated in 40 trials as gastroenterologist and only in two as a clinical pharmacologist, we included him/her in the third list.

Table 21

TOP-100 of Principal Investigators by Total Number of Trials Conducted from November 2010 to H1 2019					
Ref. No.	**Principal investigator's full name**	**Total number of CTs**	**Number of ongoing CTs**	**Specialization**	**City**
1	Aleksandr Leonidovich Khokhlov	**473**	85	cardiology, clinical pharmacology, pulmonology, therapy	Yaroslavl
2	Sergey Mikhailovich Noskov	**227**	51	rheumatology, clinical pharmacology, therapy	Yaroslavl
3	Olga Borisovna Yershova	**179**	56	rheumatology, cardiology, therapy	Yaroslavl
4	Anna Nikolaevna Galustyan	**176**	49	allergology and immunology, infectious diseases, clinical pharmacology, oncology, pediatrics, pulmonology, therapy	St. Petersburg
5	Alina Sergeevna Agafyina	**169**	71	aviation and space medicine, clinical pharmacology, neurology, therapy	St. Petersburg
6	Marina Leonidovna Stanislav	**167**	66	rheumatology	Moscow
7	Vladimir Ivanovich Vladimirov	**161**	76	oncology, urology	Pyatigorsk
8	Ivan Gennadyevich Gordeev	**156**	40	cardiology, therapy	Moscow
9	Olga Leonidovna Barbarash	**150**	57	cardiology, endocrinology	Kemerovo
10	Konstantin Konstantinovich Laktionov	**148**	81	oncology, surgery	Moscow
11	Olga Vilorovna Reshetko	**143**	53	rheumatology, clinical pharmacology, therapy	Saratov
12	Elena Anatolyevna Smolyarchuk	**139**	41	rheumatology, clinical pharmacology, therapy, ophthalmology	Moscow
13	Yuri Grigoryevich Shvarts	**133**	49	cardiology, nephrology, rheumatology, therapy	Saratov
14	Vasily Ivanovich Trofimov	**127**	33	gastroenterology, pulmonology, cardiology, therapy	St. Petersburg
15	Sergey Vladimirovich Orlov	**124**	54	oncology	St. Petersburg
16	Sergey Yurievich Martsevich	**122**	8	cardiology, clinical pharmacology, pulmonology, therapy	Moscow
17	Vladimir Mikhailovich Moiseenko	**121**	76	oncology	St. Petersburg
18	Viktor Vasilievich Shilov	**121**	7	therapy, toxicology	St. Petersburg
19	Guzel Zinnurovna Mukhametshina	**120**	61	oncology	Kazan
20	Daniil Lyvovich Stroyakovsky	**118**	86	oncology, neurology	Moscow
21	Dmitry Petrovich Udovitsa	**117**	68	hematology, oncology	Krasnodar
22	Vladimir Ilyich Simanenkov	**115**	41	gastroenterology, clinical pharmacology, therapy	St. Petersburg
23	Mikhail Vladimirovich Dvorkin	**112**	90	oncology	Omsk
24	Natalya Vladimirovna Fadeeva	**110**	64	oncology	Chelyabinsk
25	Natalya Nikolaevna Varnakova	**106**	23	therapy	Nizhny Novgorod
26	Oleg Aleksandrovich Gladkov	**104**	59	oncology	Chelyabinsk
27	Anton Sergeevich Yedin	**104**	33	dermatovenerology, clinical pharmacology, therapy	St. Petersburg

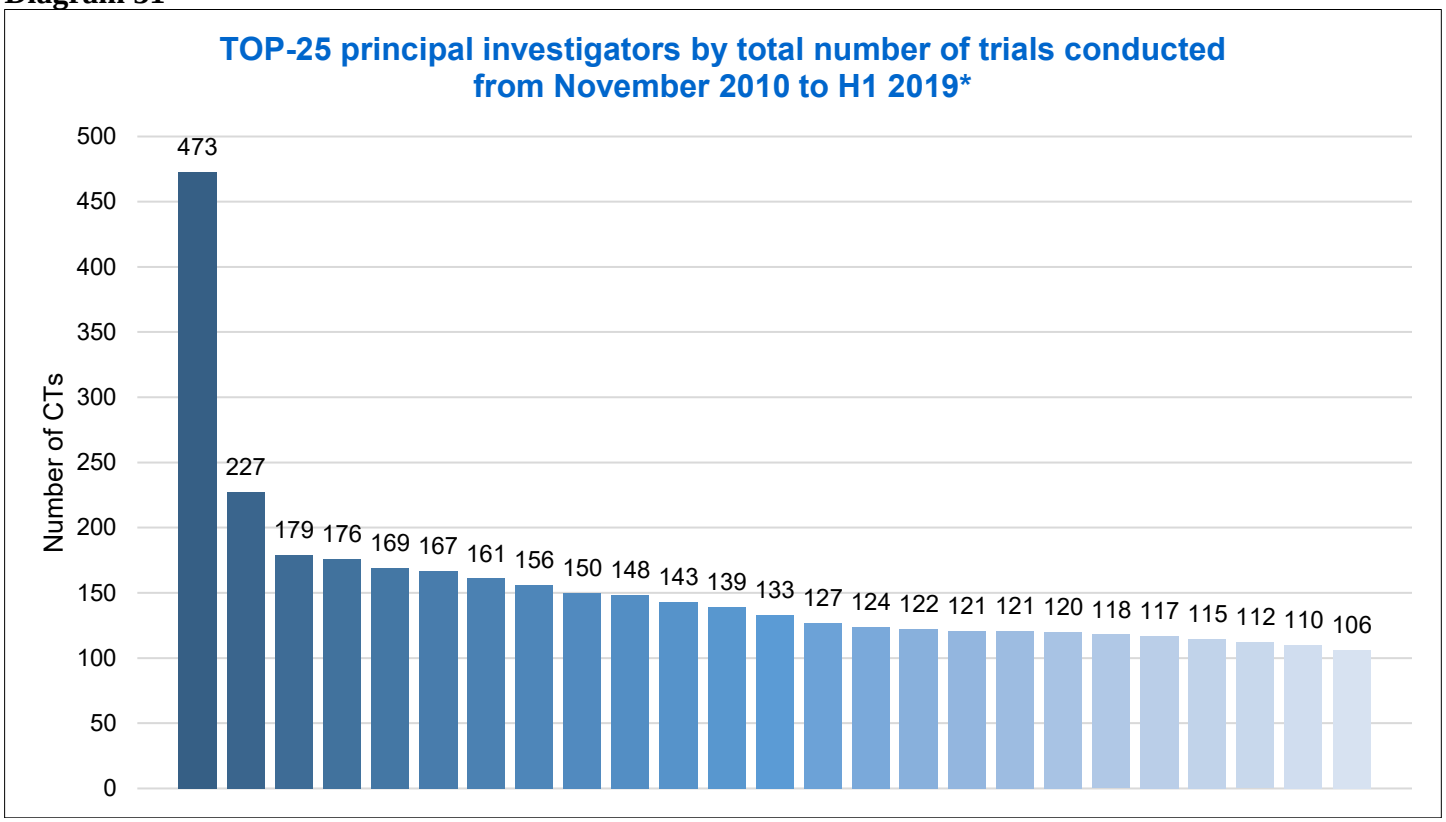
28	Aleksandr Yurievich Malygin	**104**	21	anesthesiology-intensive care medicine, clinical pharmacology	Yaroslavl
29	Artyom Yurievich Vorobyov	**100**	39	neurology	MR, Serpukhov
30	Vladimir Valentinovich Yakusevich	**100**	28	clinical pharmacology, therapy	Yaroslavl
31	Igor Dmitrievich Lifirenko	**99**	68	oncology	Kursk
32	Grigory Vladimirovich Rodoman	**99**	35	clinical pharmacology, surgery	Moscow
33	Konstantin Anatolyevich Zakharov	**97**	56	infectious diseases, clinical pharmacology, therapy	St. Petersburg
34	Marina Fedorovna Osipenko	**97**	44	gastroenterology, pulmonology, clinical pharmacology, therapy	Novosibirsk
35	Rodion Aleksandrovich Oseshnyuk	**95**	12	clinical pharmacology, therapy	St. Petersburg
36	Tatyana Alekseevna Raskina	**94**	34	cardiology, rheumatology, therapy	Kemerovo
37	Nina Alekseevna Karaseva	**92**	58	oncology	St. Petersburg
38	Veronika Borisovna Popova	**90**	20	pulmonology, therapy	St. Petersburg
39	Petr Aleksandrovich Chizhov	**89**	20	cardiology, pulmonology, rheumatology, clinical pharmacology, therapy	Yaroslavl
40	Ivan Surenovich Sardanyan	**89**	20	clinical pharmacology, pediatry	St. Petersburg
41	Arkady Lyvovich Vertkin	**89**	6	clinical pharmacology, therapy	Moscow
42	Marina Nikolaevna Nechaeva	**88**	73	oncology	Arkhangelsk
43	Elena Alekseevna Shumetova	**88**	15	cardiology	Ivanovo
44	Sergey Stepanovich Yakushin	**87**	32	cardiology, pulmonology, rheumatology, nephrology, therapy	Ryazan
45	Andrey Petrovich Rebrov	**85**	37	cardiology, rheumatology, therapy	Saratov
46	Sergey Alekseevich Tyulyandin	**84**	32	oncology	Moscow
47	Elena Valentinovna Borodulina	**82**	17	clinical pharmacology, therapy	Tomsk
48	Olga Petrovna Ukhanova	**81**	39	allergology and immunology, otorhinolaryngology, pulmonology, therapy	Stavropol
49	Sergey Valentinovich Cheporov	**81**	14	oncology	Yaroslavl
50	Vladimir Vitalyevich Rafalsky	**80**	38	cardiology, clinical pharmacology, therapy	Kaliningrad
51	Zhanna Davidovna Kobalava	**80**	22	cardiology, endocrinology, therapy	Moscow
52	Nadezhda Vitalyevna Kovalenko	**79**	45	oncology	Volgograd
53	Viktor Borisovich Shunkov	**78**	28	cardiology, clinical pharmacology, therapy	St. Petersburg
54	Natalya Petrovna Shilkina	**78**	21	gastroenterology, rheumatology, cardiology, therapy	Yaroslavl
55	Boris Yakovlevich Alekseev	**76**	54	oncology, urology	Moscow
56	Olga Sergeevna Samoylova	**76**	52	hematology, oncology	Nizhny Novgorod
57	Evgeny Arsenyevich Gotovkin	**76**	35	oncology	Ivanovo
58	Evgeniya Isaakovna Shmidt	**76**	33	rheumatology	Moscow
59	Aleksey Georgievich Manikhas	**76**	30	oncology	St. Petersburg
60	Galina Lyvovna Ignatova	**75**	17	pulmonology, therapy	Chelyabinsk

61	Olga Viktorovna Bugrova	**71**	39	nephrology, rheumatology, therapy	Orenburg
62	Oleg Nikolaevich Lipatov	**71**	36	oncology	Ufa
63	Galina Aleksandrovna Chumakova	**71**	31	gastroenterology, cardiology, therapy	Barnaul
64	Mikhail Yurievich Byakhov	**71**	24	oncology	Moscow
65	Natalya Nikolaevna Maslova	**71**	21	neurology	Smolensk
66	Vadim Borisovich Shirinkin	**70**	44	oncology	Orenburg
67	Dina Damirovna Sakaeva	**69**	42	oncology	Ufa
68	Georgy Moiseevich Manikhas	**69**	30	hematology, oncology	St. Petersburg
69	Nadezhda Vladimirovna Izmozherova	**69**	25	cardiology, clinical pharmacology, therapy	Ekaterinburg
70	Irina Valentinovna Sidorenko	**69**	11	allergology and immunology, pulmonology	Moscow
71	Boris Vladimirovich Afanasyev	**68**	37	hematology, oncology	St. Petersburg
72	Aleksandr Voleslavovich Gordienko	**68**	35	gastroenterology, cardiology, therapy	St. Petersburg
73	Leysan Ildarovna Myasoutova	**68**	23	rheumatology	Kazan
74	Gadel Maratovich Kamalov	**68**	14	cardiology, therapy	Kazan
75	Grigory Pavlovich Arutyunov	**68**	12	aviation and space medicine, cardiology, rheumatology, therapy	Moscow
76	Svetlana Anatolyevna Protsenko	**67**	41	oncology	St. Petersburg
77	Natalya Evgenyevna Nikulenkova	**67**	29	rheumatology	Vladimir
78	Lyudmila Gennadyevna Lenskaya	**67**	10	pulmonology, surgery, clinical pharmacology, therapy	Tomsk
79	Mikhail Valeryevich Kopp	**66**	29	oncology	Samara
80	Natalya Nikolaevna Vezikova	**66**	20	rheumatology, therapy	Petrozavodsk
81	Natalya Aleksandrovna Yeremina	**66**	14	Ophthalmology, clinical pharmacology, therapy	Nizhny Novgorod
82	Natalya Grigoryevna Astafyeva	**66**	8	allergology and immunology, pulmonology	Saratov
83	Elena Pavlovna Ilivanova	**65**	31	rheumatology	St. Petersburg
84	Ekaterina Yurievna Valuiskikh	**64**	45	gastroenterology, therapy	Novosibirsk
85	Aleksandr Valerievich Luft	**64**	43	oncology, surgery	St. Petersburg
86	Yuri Pavlovich Uspensky	**64**	35	gastroenterology, therapy, infectious diseases	St. Petersburg
87	Anton Sergeevich Povzun	**64**	29	nephrology, rheumatology, pulmonology, therapy	St. Petersburg
88	Lyubov Anatolyevna Shpagina	**64**	20	hematology, cardiology, pulmonology, clinical pharmacology, therapy	Novosibirsk
89	Aleksey Vladimirovich Smolin	**63**	50	oncology	Moscow
90	Valery Mikhailovich Chistyakov	**63**	39	oncology, clinical pharmacology, therapy	Pyatigorsk
91	Anna Valerievna Alyasova	**63**	36	oncology	Nizhny Novgorod
92	Olga Polikarpovna Alekseeva	**63**	33	gastroenterology, therapy	Nizhny Novgorod
93	Aleksandr Yurievich Vishnevsky	**63**	26	anesthesiology, intensive-care medicine, cardiology	St. Petersburg

94	Viktor Avenirovich Kostenko	**62**	22	cardiology, therapy	St. Petersburg
95	Vsevolod Borisovich Matveev	**61**	41	oncology, urology	Moscow
96	Diana Nodarievna Alpenidze	**61**	25	endocrinology, therapy	St. Petersburg
97	Konstantin Nikolaevich Zrazhevsky	**61**	23	cardiology, therapy	St. Petersburg
98	Farit Akhatovich Khabirov	**60**	27	neurology	Kazan
99	Anastasia Aleksandrovna Bagretsova	**60**	15	therapy	Arkhangelsk
100	Svetlana Borisovna Yerofeeva	**60**	15	cardiology, therapy, clinical pharmacology	Moscow

**The data are given as of July 2019*
Data from www.grls.rosminzdrav.ru

Diagram 31



**The data are given as of July 2019*
Data from www.grls.rosminzdrav.ru

Table 22

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**
1	Mikhail Vladimirovich Dvorkin	**90**	112	oncology	Omsk
2	Daniil Lyvovich Stroyakovsky	**86**	118	oncology, neurology	Moscow
3	Konstantin Konstantinovich Laktionov	**81**	148	oncology, surgery	Moscow
4	Vladimir Ivanovich Vladimirov	**76**	161	oncology, urology	Pyatigorsk
5	Vladimir Mikhailovich Moiseenko	**76**	121	oncology	St. Petersburg
6	Marina Nikolaevna Nechaeva	**73**	88	oncology	Arkhangelsk
7	Dmitry Petrovich Udovitsa	**68**	117	hematology, oncology	Krasnodar
8	Igor Dmitrievich Lifirenko	**68**	99	oncology	Kursk
9	Natalya Vladimirovna Fadeeva	**64**	110	oncology	Chelyabinsk

10	Guzel Zinnurovna Mukhametshina	**61**	120	oncology	Kazan
11	Oleg Aleksandrovich Gladkov	**59**	104	oncology	Chelyabinsk
12	Nina Alekseevna Karaseva	**58**	92	oncology	St. Petersburg
13	Sergey Vladimirovich Orlov	**54**	124	oncology	St. Petersburg
14	Boris Yakovlevich Alekseev	**54**	76	oncology, urology	Moscow
15	Olga Sergeevna Samoylova	**52**	76	hematology, oncology	Nizhny Novgorod
16	Kislov Nikolay Victorovich	**52**	59	oncology	Yaroslavl
17	Aleksey Vladimirovich Smolin	**50**	63	oncology	Moscow
18	Nadezhda Vitalyevna Kovalenko	**45**	79	oncology	Volgograd
19	Vadim Borisovich Shirinkin	**44**	70	oncology	Orenburg
20	Aleksandr Valerievich Luft	**43**	64	oncology, surgery	St. Petersburg

**The data are given as of July 2019*
Data from www.grls.rosminzdrav.ru

Table 23

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
1	Aleksandr Leonidovich Khokhlov	**85**	473	cardiology, clinical pharmacology, pulmonology, therapy	Yaroslavl
2	Alina Sergeevna Agafyina	**71**	169	aviation and space medicine, clinical pharmacology, neurology, therapy	St. Petersburg
3	Konstantin Anatolyevich Zakharov	**56**	97	infectious diseases, clinical pharmacology, therapy	St. Petersburg
4	Olga Vilorovna Reshetko	**53**	143	rheumatology, clinical pharmacology, therapy	Saratov
5	Sergey Mikhailovich Noskov	**51**	227	rheumatology, clinical pharmacology, therapy	Yaroslavl
6	Anna Nikolaevna Galustyan	**49**	176	allergology and immunology, infectious diseases, clinical pharmacology, oncology, pediatrics, pulmonology, therapy	St. Petersburg
7	Elena Anatolyevna Smolyarchuk	**41**	139	rheumatology, clinical pharmacology, therapy, ophthalmology	Moscow
8	Valery Mikhailovich Chistyakov	**39**	63	oncology, clinical pharmacology, therapy	Pyatigorsk
9	Vladimir Vitalyevich Rafalsky	**38**	80	cardiology, clinical pharmacology, therapy	Kaliningrad
10	Grigory Vladimirovich Rodoman	**35**	99	clinical pharmacology, surgery	Moscow
11	Anton Sergeevich Yedin	**33**	104	dermatovenerology, clinical pharmacology, therapy	St. Petersburg
12	Vladimir Valentinovich Yakusevich	**28**	100	clinical pharmacology, therapy	Yaroslavl
13	Viktor Borisovich Shunkov	**28**	78	cardiology, clinical pharmacology, therapy	St. Petersburg
14	Nadezhda Vladimirovna Izmozherova	**25**	69	cardiology, clinical pharmacology, therapy	Ekaterinburg
15	Vasily Bogdanovich Vasiluk	**23**	58	clinical pharmacology, therapy	St. Petersburg
16	Evgeniya Vladimirovna Akatova	**22**	53	cardiology, rheumatology, clinical pharmacology, therapy	Moscow

17	Aleksandr Yurievich Malygin	**21**	104	anesthesiology-intensive care medicine, clinical pharmacology	Yaroslavl
18	Petr Aleksandrovich Chizhov	**20**	89	cardiology, pulmonology, rheumatology, clinical pharmacology, therapy	Yaroslavl
19	Ivan Surenovich Sardanyan	**20**	89	clinical pharmacology, pediatry	St. Petersburg
20	Lyubov Anatolyevna Shpagina	**20**	64	hematology, cardiology, pulmonology, clinical pharmacology, therapy	Novosibirsk

**The data are given as of July 2019*
Data from www.grls.rosminzdrav.ru

Table 24

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

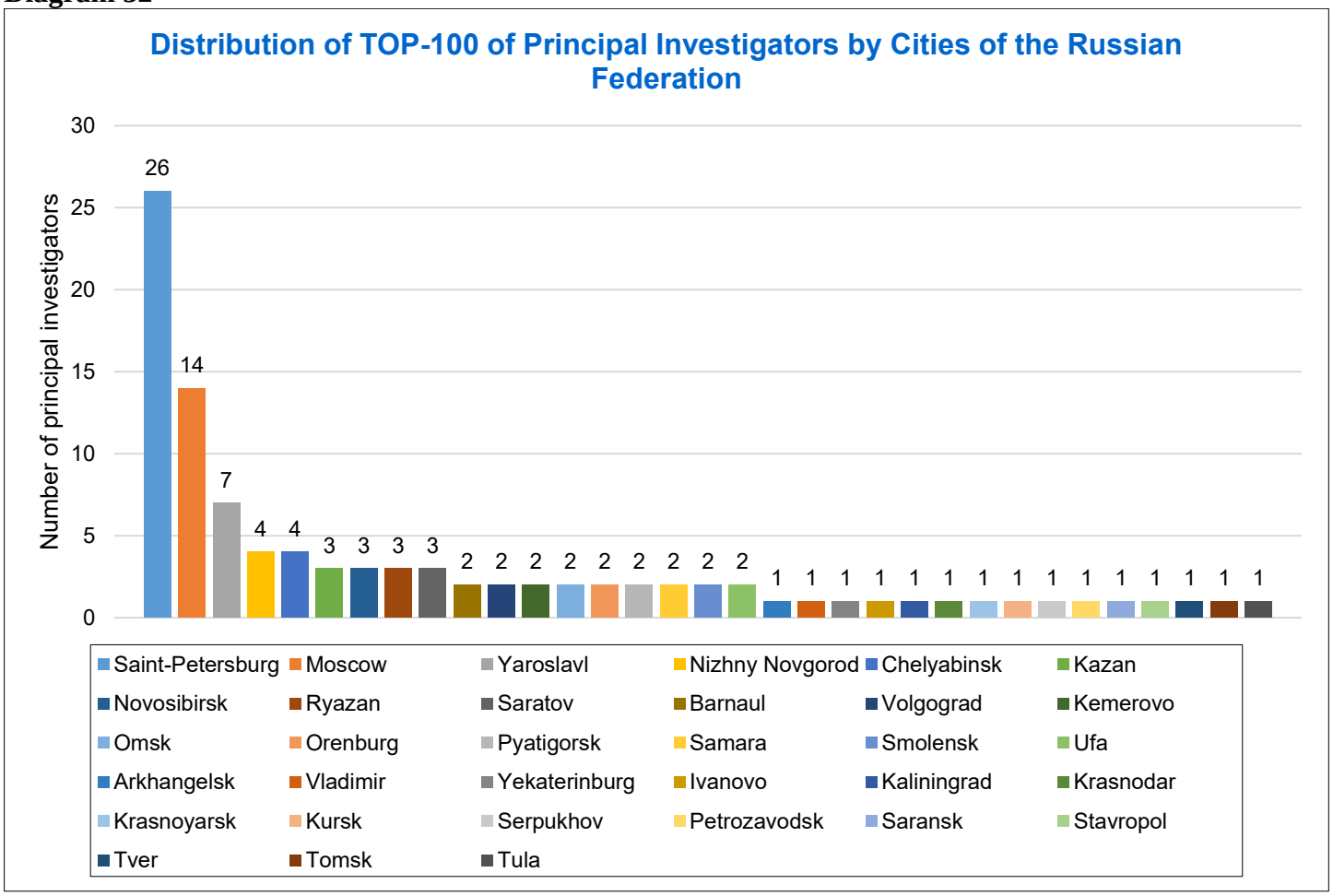
Reference number	Principal investigator's full name	Number of ongoing CTs	Total number of CTs	Specialization	City
1	Marina Leonidovna Stanislav	**66**	167	rheumatology	Moscow
2	Olga Leonidovna Barbarash	**57**	150	cardiology, endocrinology	Kemerovo
3	Olga Borisovna Yershova	**56**	179	rheumatology, cardiology, therapy	Yaroslavl
4	Yuri Grigoryevich Shvarts	**49**	133	cardiology, nephrology, rheumatology, therapy	Saratov
5	Ekaterina Yurievna Valuiskikh	**45**	64	gastroenterology, therapy	Novosibirsk
6	Marina Fedorovna Osipenko	**44**	97	gastroenterology, pulmonology, clinical pharmacology, therapy	Novosibirsk
7	Vladimir Ilyich Simanenkov	**41**	115	gastroenterology, clinical pharmacology, therapy	St. Petersburg
8	Ivan Gennadyevich Gordeev	**40**	156	cardiology, therapy	Moscow
9	Artyom Yurievich Vorobyov	**39**	100	neurology	MR, Serpukhov
10	Olga Petrovna Ukhanova	**39**	81	allergology and immunology, otorhinolaryngology, pulmonology, therapy	Stavropol
11	Olga Viktorovna Bugrova	**39**	71	nephrology, rheumatology, therapy	Orenburg
12	Andrey Petrovich Rebrov	**37**	85	cardiology, rheumatology, therapy	Saratov
13	Olga Borisovna Nesmeyanova	**36**	53	rheumatology, therapy	Chelyabinsk
14	Aleksandr Voleslavovich Gordienko	**35**	68	gastroenterology, cardiology, therapy	St. Petersburg
15	Yuri Pavlovich Uspensky	**35**	64	gastroenterology, therapy, infectious diseases	St. Petersburg
16	Elena Vladimirovna Zonova	**35**	59	hematology, rheumatology, therapy	Novosibirsk
17	Tatyana Alekseevna Raskina	**34**	94	cardiology, rheumatology, therapy	Kemerovo
18	Vasily Ivanovich Trofimov	**33**	127	gastroenterology, pulmonology, cardiology, therapy	St. Petersburg
19	Evgeniya Isaakovna Shmidt	**33**	76	rheumatology	Moscow
20	Olga Polikarpovna Alekseeva	**33**	63	gastroenterology, therapy	Nizhny Novgorod

21	Igor Gennadyevich Bakulin	**33**	59	gastroenterology, infectious diseases, therapy	St. Petersburg
22	Sergey Stepanovich Yakushin	**32**	87	cardiology, pulmonology, rheumatology, nephrology, therapy	Ryazan
23	Galina Aleksandrovna Chumakova	**31**	71	gastroenterology, cardiology, therapy	Barnaul
24	Elena Pavlovna Ilivanova	**31**	65	rheumatology	St. Petersburg
25	Natalya Evgenyevna Nikulenkova	**29**	67	rheumatology	Vladimir
26	Anton Sergeevich Povzun	**29**	64	nephrology, rheumatology, pulmonology, therapy	St. Petersburg
27	Dmitry Borisovich Sonin	**28**	55	dermatovenerology	Ryazan
28	Oleg Raisovich Ziganshin	**28**	53	dermatovenerology, urology	Chelyabinsk
29	Kamil Daniyalovich Kaplanov	**28**	50	hematology	Volgograd
30	Farit Akhatovich Khabirov	**27**	60	neurology	Kazan
31	Aleksandr Yurievich Vishnevsky	**26**	63	anesthesiology, intensive-care medicine, cardiology	St. Petersburg
32	Dmitry Yurievich Platonov	**26**	53	gastroenterology, cardiology, rheumatology, therapy	Tver
33	Diana Nodarievna Alpenidze	**25**	61	endocrinology, therapy	St. Petersburg
34	Diana Grigoryevna Krechikova	**25**	54	rheumatology	Smolensk
35	Elena Mikhailovna Volodicheva	**25**	51	hematology	Tula
36	Dmitry Vladimirovich Pokhabov	**24**	53	neurology	Krasnoyarsk
37	Natalya Nikolaevna Varnakova	**23**	106	therapy	Nizhny Novgorod
38	Leysan Ildarovna Myasoutova	**23**	68	rheumatology	Kazan
39	Konstantin Nikolaevich Zrazhevsky	**23**	61	cardiology, therapy	St. Petersburg
40	Zhanna Davidovna Kobalava	**22**	80	cardiology, endocrinology, therapy	Moscow
41	Viktor Avenirovich Kostenko	**22**	62	cardiology, therapy	St. Petersburg
42	Yulia Gennadyevna Samoylova	**22**	53	endocrinology	Tomsk
43	Natalya Petrovna Shilkina	**21**	78	gastroenterology, cardiology, rheumatology, therapy	Yaroslavl
44	Natalya Nikolaevna Maslova	**21**	71	neurology	Smolensk
45	Veronika Borisovna Popova	**20**	90	pulmonology, therapy	St. Petersburg
46	Natalya Nikolaevna Vezikova	**20**	66	rheumatology, therapy	Petrozavodsk
47	Galina Korneevna Matzievskaya	**20**	57	rheumatology	St. Petersburg
48	Svetlana Anatolyevna Smakotina	**20**	56	cardiology, rheumatology, therapy	Kemerovo
49	Irina Evgenyevna Poverennova	**20**	55	neurology, oncology	Samara
50	Aleksey Nikolaevich Boyko	**20**	52	neurology	Moscow

**The data are given as of July 2019*

Data from www.grls.rosminzdrav.ru

Diagram 32



**The data are given as of July 2019*

Data from www.grls.rosminzdrav.ru

IMCT STATISTICS FOR ONCOLOGY AND ONCOHAEMATOLOGY, 2018

Table 25

Distribution of IMCTs by Therapeutic Areas, 2018			
Therapeutic area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**
Oncology and oncohaematology	97	33.8%	6 681
Gastroenterology	37	12.9%	2 346
Cardiology and CVD	21	7.3%	5 161
Neurology	18	6.3%	1 288
Dermatology	17	5.9%	996
Rheumatology	13	4.5%	922
Pulmonology	13	4.5%	894
Infectious Diseases (except HIV/HCV/tuberculosis)	11	3.8%	1 644
Haematology	10	3.5%	262
Endocrinology	7	2.4%	584
Nephrology	6	2.1%	525
Ophthalmology	6	2.1%	616
Psychiatry	5	1.7%	576
Obstetrics/Gynaecology	5	1.7%	295
Urology	4	1.4%	647
Allergology	4	1.4%	314
Otorhinolaryngology	3	1.0%	62
Immunology	3	1.0%	31
Hepatology	2	0.7%	155
Phlebology	2	0.7%	448
Tuberculosis	1	0.3%	64
Narcology	1	0.3%	80
Other	1	0.3%	6
TOTAL	287	100.0%	24 597

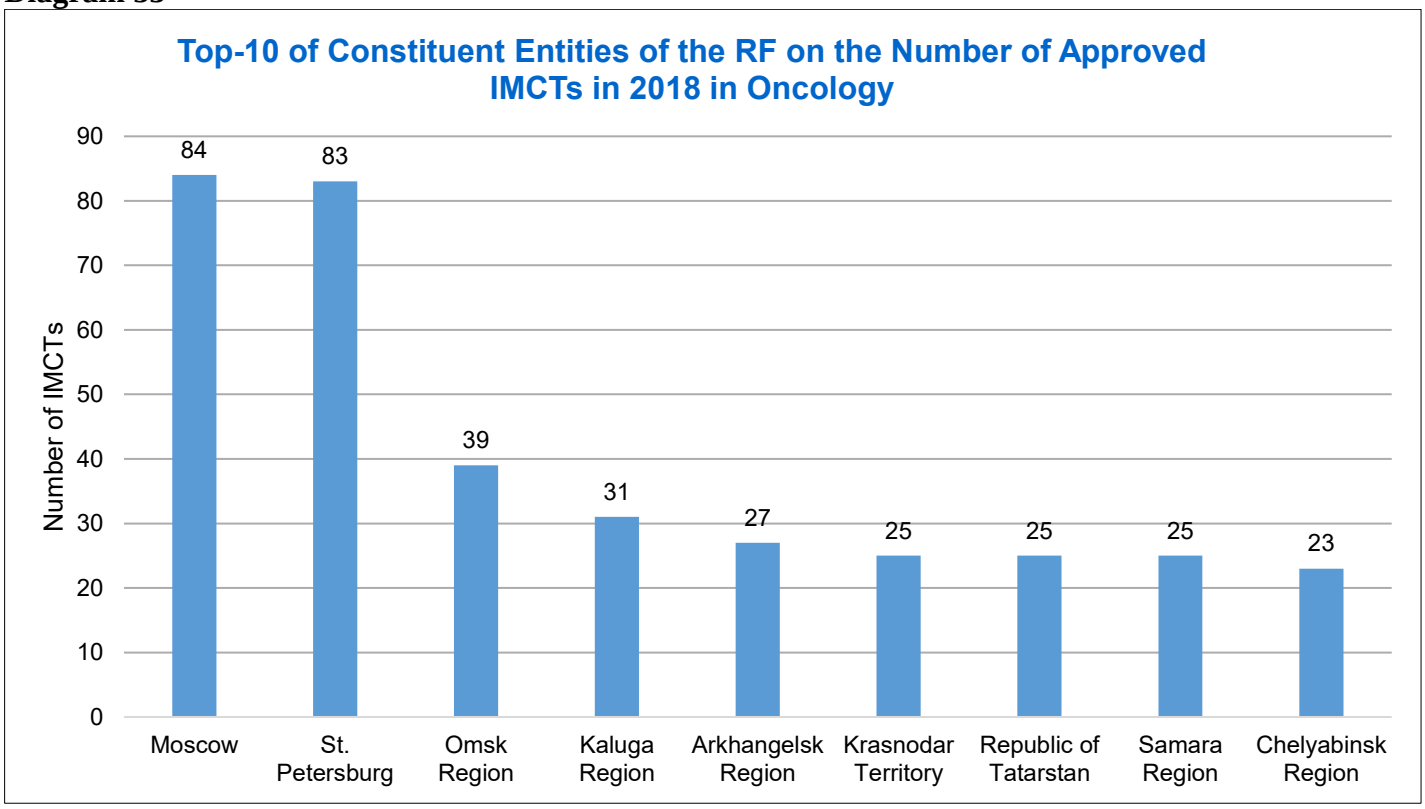
Data from www.grls.rosminzdrav.ru

Table 26

IMCT Distribution in Oncology and Oncohaematology, 2018			
No.	**Disease type**	**Number of IMCTs**	**Claimed number of subjects**
1	Lung and pleural cavity tumours	19	1 462
2	Breast tumour	12	1 935
3	Leukemia	11	282
4	Genitourinary system tumours	10	1 112
5	Tumours without known localisation	8	447
6	Gastrointestinal tumours	7	676
7	Female reproductive system tumours	7	599
8	Multiple myeloma	6	347
9	Melanoma	6	148
10	Liver tumours	4	161
11	Head and neck tumours	4	141
12	Lymphoma	3	335
	TOTAL	97	7 645

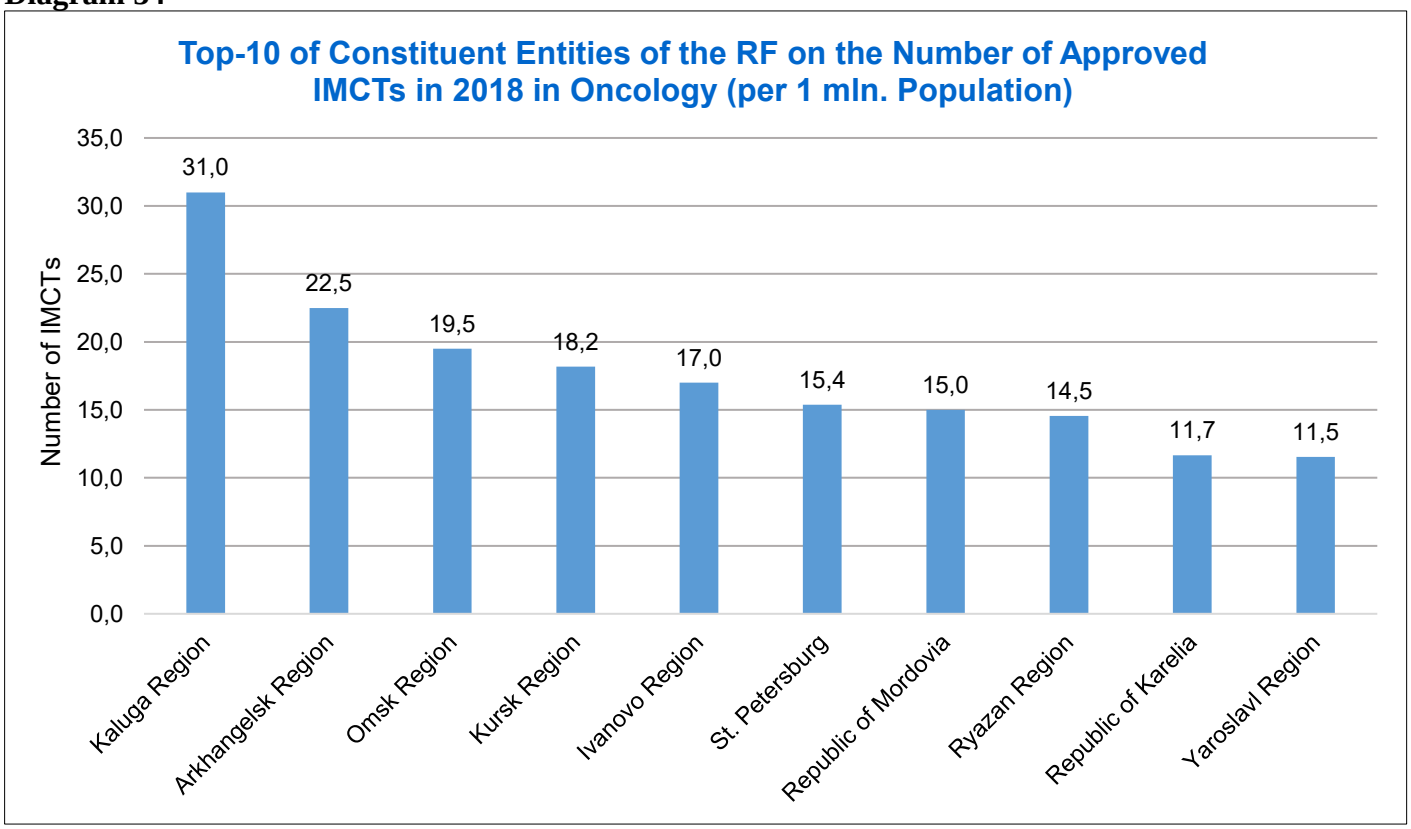
Data from www.grls.rosminzdrav.ru

Diagram 33



Data from www.grls.rosminzdrav.ru

Diagram 34



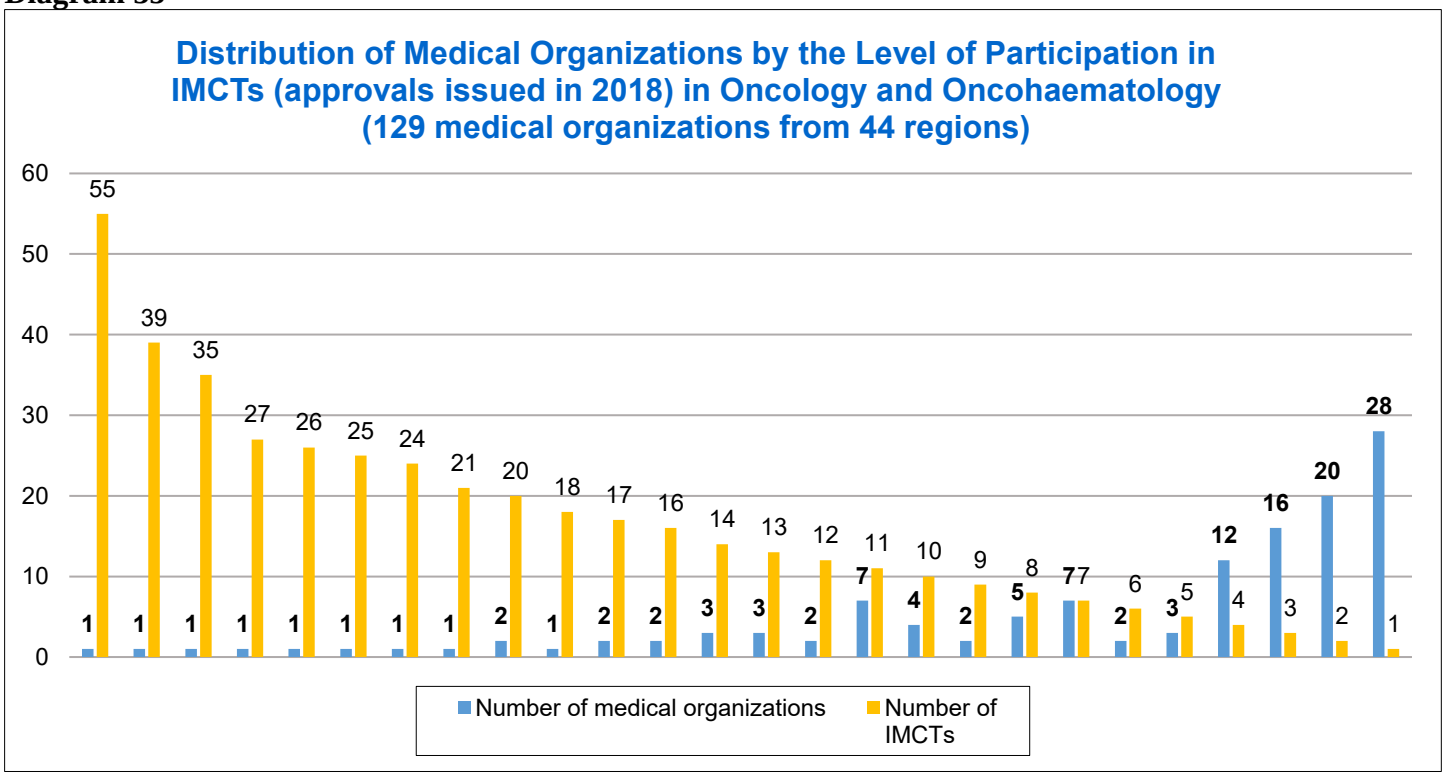
Data from www.grls.rosminzdrav.ru

Table 27

Top-10 of Medical Organizations on the Activity of Participation in IMCTs in Oncology and Oncohaemotology Approved in 2018			
Place in ranking	**Name of medical organization**	**Number of IMCTs approved in 2018 with participation of this medical organization**	**Number of centres approved in 2018 for conducting IMCTs**
1	N.N. Blokhin Russian Cancer Research Centre, Russian Ministry of Health, Moscow	55	58
2	Clinical Oncological Dispensary, Omsk	39	46
3	N.N. Petrov Research Institute of Oncology, Russian Ministry of Health, St. Petersburg	35	35
4	Arkhangelsk Clinical Oncological Dispensary, Arkhangelsk	27	27
5	St. Petersburg Clinical Practical Research Centre for Specialised Types of Medical Aid (Oncological), St. Petersburg	26	28
6	Republican Clinical Oncology Dispensary of the Ministry of Healthcare of Tatarstan Republic, Kazan	25	25
7	National Medical Research Radiology Centre, Russian Ministry of Health, Obninsk	24	31
8	St. Petersburg City Clinical Oncological Dispensary, St. Petersburg	21	21
9-10	Leningrad Regional Oncology Center, St. Petersburg	20	22
9-10	Kursk Regional Clinical Oncology Center, Kursk	20	20

Data from www.grls.rosminzdrav.ru

Diagram 35



Data from www.grls.rosminzdrav.ru