ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER № 11

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CONTENTS

SUMMARY

As usual, we begin this newsletter with statistics. In the first six months of 2015, the Ministry of Health issued 347 approvals to conduct clinical trials. This is down 4.4% compared to the same period of the previous year. The number of approvals for international multi-centre clinical trials (IMCTs) is down 3.7% (131 compared to 136). The number of bioequivalence studies with foreign sponsors is down notably, by 23.3% (46 compared to 60). In contrast, the number of bioequivalence studies with Russian sponsors is up slightly, by 5% (63 compared to 60). Local trials of efficacy and safety showed a similar picture. For foreign drugs, these type of trials are down 12.5% (23 approvals compared to 32), while for Russian drugs they are slightly up (79 compared to 75).

In the overall structure of the market for the first half of this year, the share of IMCTs has not changed compared to 2014, amounting to 37.7%. 31.4% of the total market share accounted for bioequivalence studies. For local trials of efficacy and safety - 30.9%. Anticipated changes to the local trials sector have not come about so far, but from January 1, 2016, new requirements will come into force concerning the registration of separate medicinal forms of generics. It is possible that we are seeing a picture, which will begin to change at the beginning of the coming year. But let's not get ahead of ourselves.

In the rating of activity of medical organisations specialising in bioequivalence studies, it seems that the main players in the top positions remain the same as last year although in a slightly different order. There are also some new organisations in Top-10 list, which were not reflected in the previous newsletters.

An analysis of the practice of the FGBU Research Centre for Expertise of Medicinal Products (further – FGBU) and the Ethics Council reviews, as well as the complicated situation connected with the approval of clinical trials, has been conducted in this issue. The share of cases approved by the Ethics Council is up slightly from last year (66% compared to 62.6%), although there is a significant drop in the share of cases passing FGBU review on the first go (58% compared to 71.8%). As a result, just 42.6% of applications made it through without notes from one or the other expert group (the figure for the previous year was 43.7%). We must also note that this year there is a significant increase in the number of non-critical notes from FGBU – 11.7% compared to 1.5% last year. This is probably the consequence of the implementation of the practice of questions from the expert panel. This factor could end up having a positive influence. Admittedly, there is nothing positive to say about critical notes. In this issue of the newsletter we will further describe the very complicated and ever-worsening stalemate with FGBU.

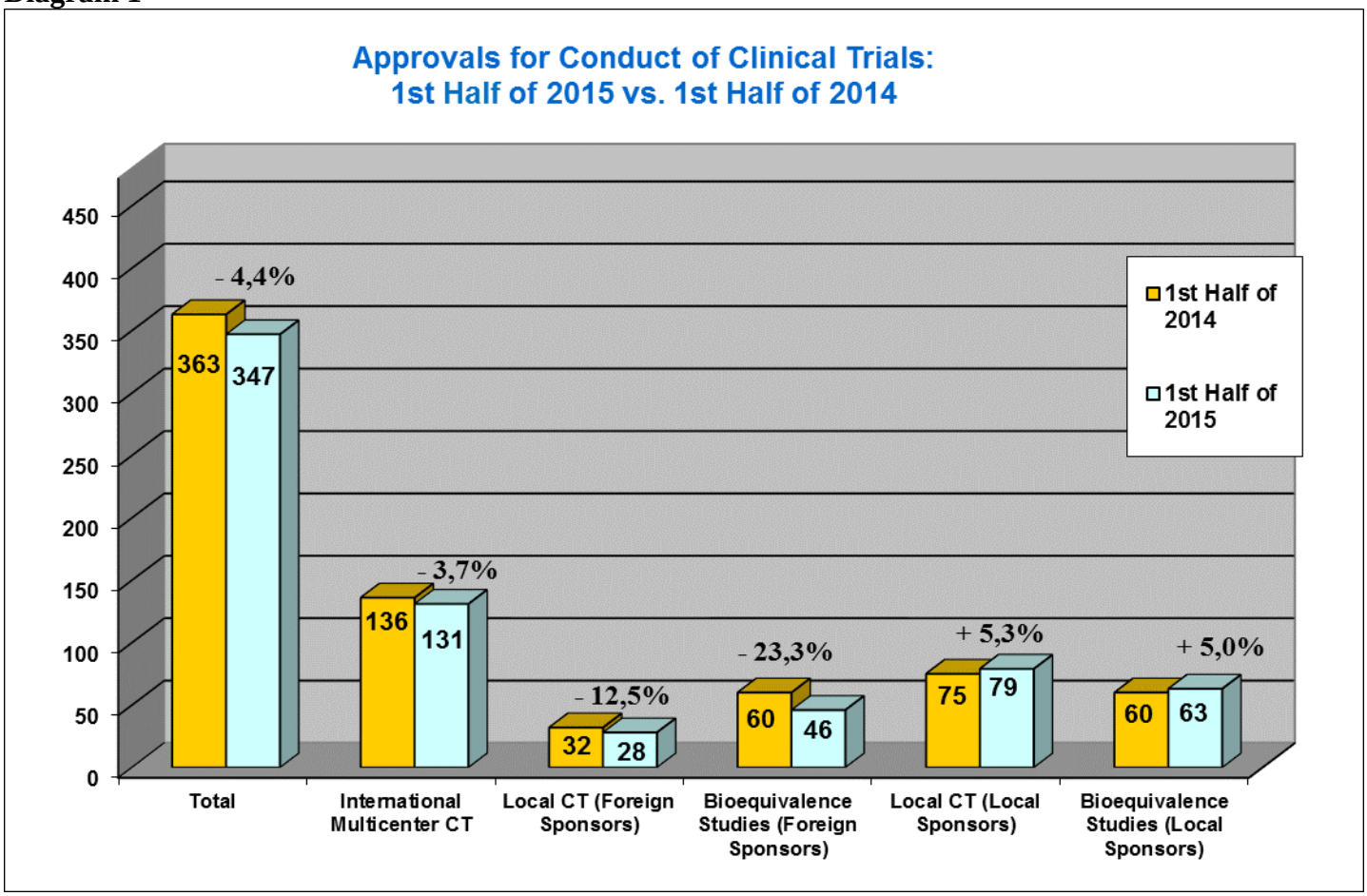
The next subject of this issue is the quality of clinical trials. In the newsletter we cite data from a comparative analysis of results of inspections by the FDA in Russia and in other countries, as well as the results of checks by Roszdravnadzor. As before, there is a difference in the nature of the discovered findings between international and local clinical trials.

In the last section of this newsletter we present the results of a poll on the subject of the future for clinical trials in Russia.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In the first six months of 2015, the Ministry of Health of the Russian Federation issued 347 approvals to conduct clinical trials. This was down 4.4% compared to the same period of the previous year, when they issued 363 approvals (Diagram 1). The number of approvals for international multi-centre clinical trials (IMCTs) remained almost unchanged, a difference of just five trials (3.7%) from last year (131 compared to 136).

Diagram 1



Data from www.grls.rosminzdrav.ru

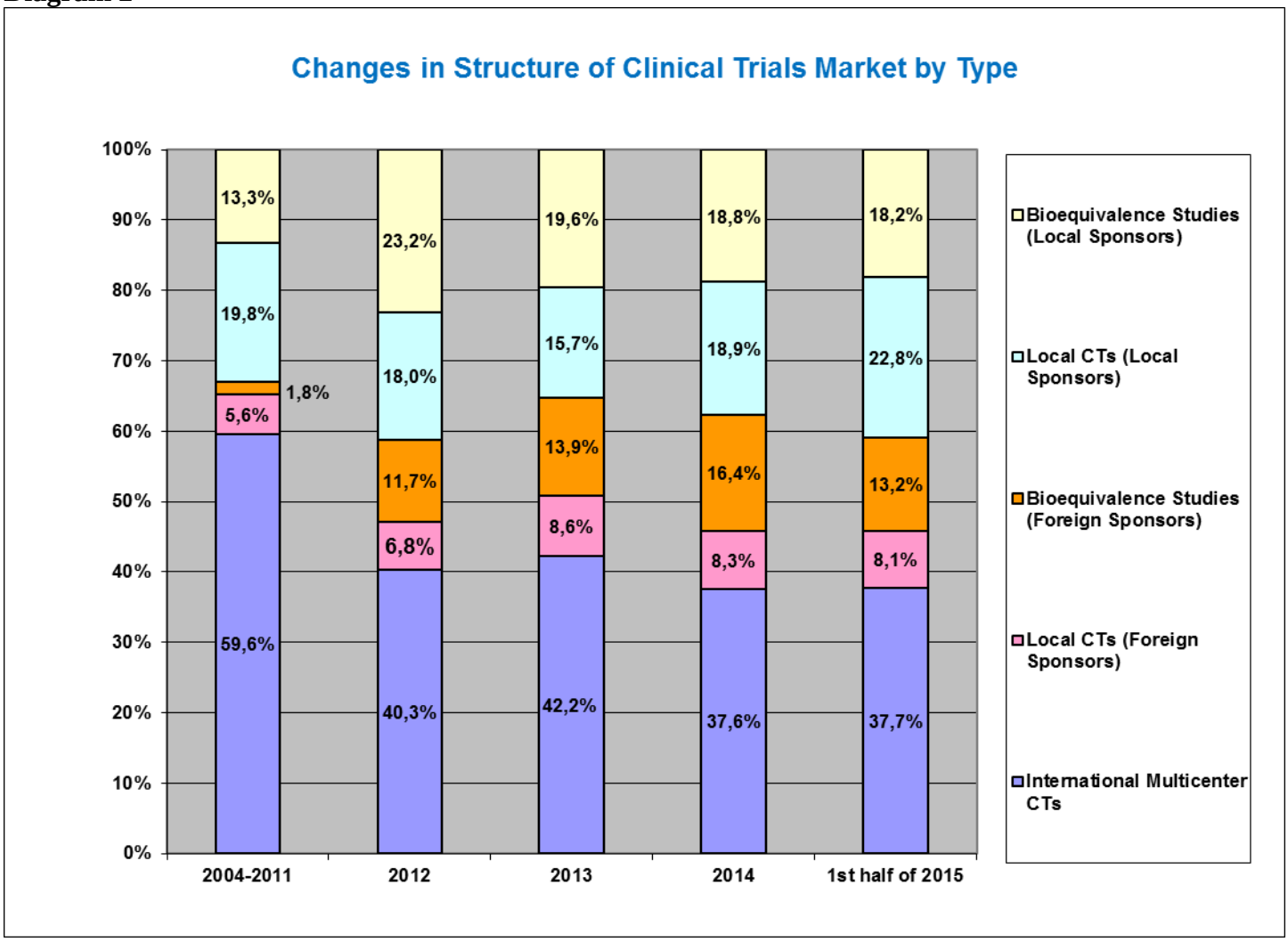
There is a bigger drop, of 23.3%, in the sector of bioequivalence studies of foreign medicines (46 approvals compared to 60 in the first half of 2014). There is a slightly less dramatic decline, of 12.5%, in the number of approvals for local trials of efficacy and safety of foreign medicines (28 approvals compared to 32). The number of approvals for local trials by Russian sponsors, on the other hand, increased by 5.3% (79 compared to 75). There is also an insignificant increase in the number of bioequivalence studies by Russian sponsors – by 5% (63 compared to 60).

In Diagram 2 we show the changes in the structure of the market by types of trials. It is clear that in the first half of this year the picture is not drastically different from the previous three years. Significant changes, as we remember, came in from 2012 as a result of the adoption of the law “On the Circulation of Medicines”, leading to significant growth in the number of local trials, first and foremost for foreign manufacturers.

As you may recall, in the previous issue of the newsletter we made a prognosis on the changing market structure, which, as we can see from the diagram, has not happened yet. And so, in connection with the implementation of the new rules on registering generics as of January 1, 2016, we expect significant contraction of the sector for local trials due to manufacturers’ refusal from trials for so-called ‘therapeutic equivalency’ for those pharmaceutical forms of generics for which it is not possible to conduct bioequivalence studies. We suggested that some changes would be noticeable already in early 2015, but that has yet to happen. It is possible

that the reason is in market inertia, as well as exhaustion and lack of trust from market players as a result of such frequent changes in legislation. Since the rules will change as of January 1 of the coming year, and the market has seen many examples of rules being brought in and then changed with others implemented, it is entirely possible that many manufacturers are waiting to see what will happen. And not wanting to waste time, they are continuing to put in applications for trials, the need for which we expect to evaporate in the coming year. Only time will tell if we are right in our predictions.

Diagram 2

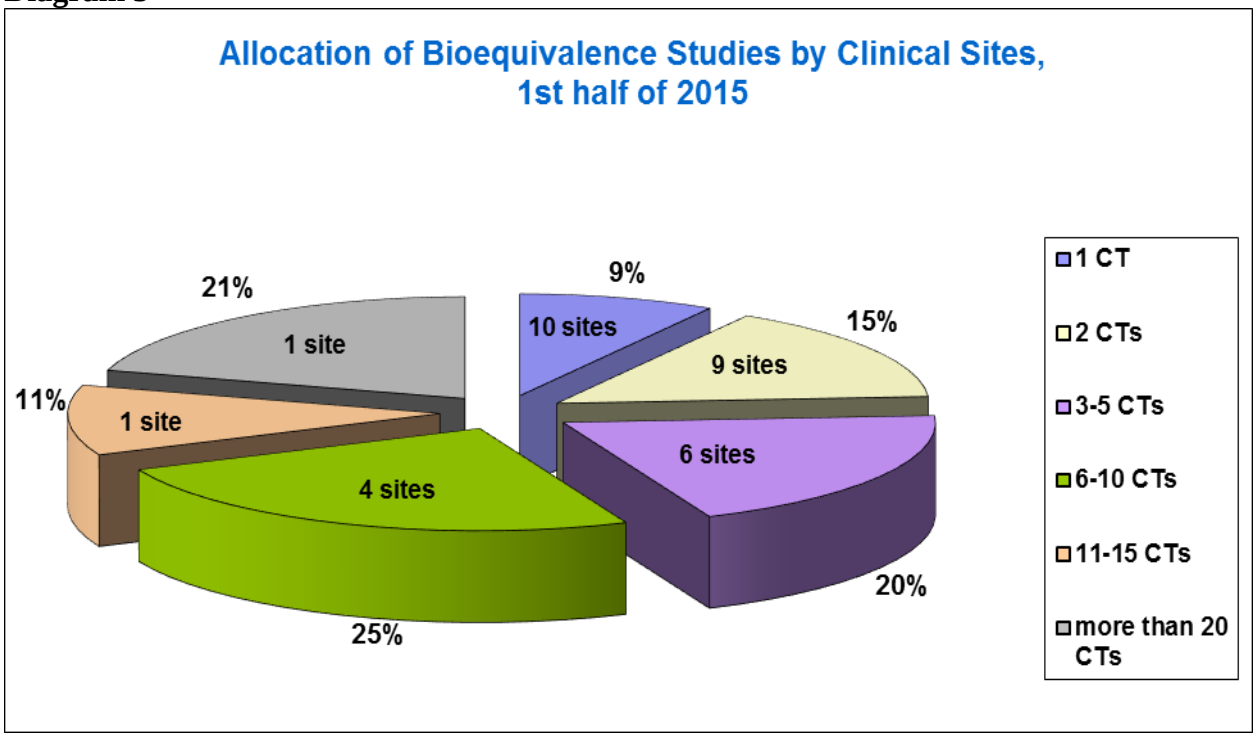


Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

For now the dominant share of the Russian market of clinical trials remains with generics. And almost a third (31.4%) are for bioequivalence studies. In the first half of 2015 109 approvals were issued for this type of trial (63 for domestic and 46 for foreign medicines), with planned participation of 4,156 volunteers.

Compared with 2014, the number of active clinical sites conducting bioequivalence studies changed insignificantly – 31 centres compared to 30 a year ago. In Diagram 3 we can see the breakdown of trials by centre. And so, more than 20 bioequivalence studies (21% of the total of this type) were conducted in just one centre.

Diagram 3



Data from www.grls.rosminzdrav.ru

In Table 1 we see a list of the most active centres by the number of bioequivalence studies conducted. Compared with the previous year, this list has changed slightly. Yaroslavl Clinical Hospital No.3, which was in the fourth place a year ago, this year is at the top of the list and has bumped the previous year's leader, Yaroslavl Clinical Hospital No.2, into second place. Similarly with a loss of one position in the ranking was the North-West Research Centre for Hygiene and Public Health in St. Petersburg (from the second to the third place) and Klinika Semeinogo Vracha+ in Nizhny Novgorod (from the third to the fourth place). Republic Clinical Hospital No.2 in Kazan, which was not on the list last year, shared the 5-6 place with the Medical Centre Probiotek (8th place last year). BioEk in St. Petersburg, also not in the list last year, was in 7th place.

Positions 8-10 were shared between three organizations, two of which also were not on the list last year.

The First Moscow State Medical University named after I.M. Sechenov, which in pursuit of modern trends even closed its clinic for early-phase trials, freeing beds for the needs of bioequivalence studies, and which in 2012 was in the fifth place, in 2014 slipped to the ninth place, and this year is not even in the top 10.

Table 1

TOP 10 Clinical Centres by Number of Bioequivalence Studies, 1st Half of 2015						
№	Clinical Centre	Total number of bioequivalence studies in the centre	Number of bioequivalence studies (foreign sponsors)	Number of bioequivalence studies (local sponsors)	Place in the ranking, 1st half of 2015	Place in the ranking, 1st half of 2014
1	The State Health Institution of the Yaroslavl Region "Clinical Hospital №3", Yaroslavl	24	12	12	1	4
2	The State Health Institution of the Yaroslavl Region "Clinical Hospital №2", Yaroslavl	13	6	7	2	1
3	The Federal State Institution of Science "The North-west Research Center of Hygien and Public Health", St. Petersburg	9	3	6	3	2
4	LLC "The Family Doctor + Clinic", Nizhny Novgorod	8	0	8	4	3
5	LLC "The Medical Centre "Probiotech", Serpuhov, Moscow Region	6	1	5	5-6	8
6	The State Autonomous Health Care Institution "Republic Clinical Hospital №2", Kazan	6	3	3	5-6	n/a
7	LLC "BioEq", St. Petersburg	5	0	5	7	n/a
8	The Federal State Institution of the Siberian Branch of Russian Academy of Medical Science (RAMN) "The Scientific-Research Institute of Pharmacology named after E.D. Goldberg" , Tomsk	4	4	0	8-10	9-12
9	The State Health Institution of Moscow Municipal Hospital № 1 named after N.I. Pirogov of the Moscow Department of Healthcare, Moscow	4	0	4	8-10	n/a
10	The Federal State Institution "The Nikiforov Russian Center of Emergency and Radiation Medicine', The Ministry for Civil Defence, Emergencies and Elimination of Consequences of Natural Disasters, St-Petersburg	4	4	0	8-10	n/a

Data from www.grls.rosminzdrav.ru

EXPERTISE OF PLANNED TRIALS: THE PRACTISE OF DISAPPROVALS

This summer we again conducted an analysis of the practice of expert review of planned trials. The bulk of the analysis was, as usual, a poll of ACTO members on the results of going through two review processes – the Ethics Council and the FGBU Research Centre for Expertise of Medicinal Products (further – FGBU). Twenty-five companies took part in the poll. We analyzed the results of the review of initial submissions to conduct clinical trials, made between July 1, 2014 and June 30, 2015. The analysis covered a total of 205 applications, all for international trials.

This time we again had to slightly adjust the parameters of the poll compared to the two previous years (see ACTO Newsletter No.7 and No.9). This was caused by the changes in the process of the expert review. New changes to the law "On Circulation of Medicines" gave expert organizations the right to request additional documents if, in their opinion, the ones submitted were insufficient for experts to make a decision. Implementing this new rule is without a doubt the responsibility of the Russian Ministry of Health, allowing some kind of feedback from the 'black box' of expertise, which the expert review has constituted in some cases. Before this novelty there was only one option – after the expert review the applicant received either approval or refusal. To find out what the experts did not like in the documents submitted the applicant could only ascertain once the final decision by the Ministry of Health was received. Then, having corrected the errors, added further information or answered various questions, the applicant had to resubmit the application to a whole new round of review.

Now there is an opportunity to elaborate and explain during the course of the review, which allows applicants to save precious time. Unfortunately, this new rule applies only to the FGBU review. The Ethics Council does not use the 'questions' practice, and limits itself strictly to the final verdict. Which, by the way, also allows for several options – a negative, a positive, and a positive with conditions. The conditions mean that in general the Council approves the trial, but suggests that the applicant make some changes in the work (most often this refers to small editing corrections or making small changes to the informed consent form). This allows for a certain flexibility. But if the Ethics Council took on board the 'questions' practice, and the FGBU on the other hand took up the practice of approval under conditions for insignificant editing corrections, efficiency of the systems would only increase. Applicants would be very grateful, if the Ministry of Health and the expert organizations would create such an opportunity.

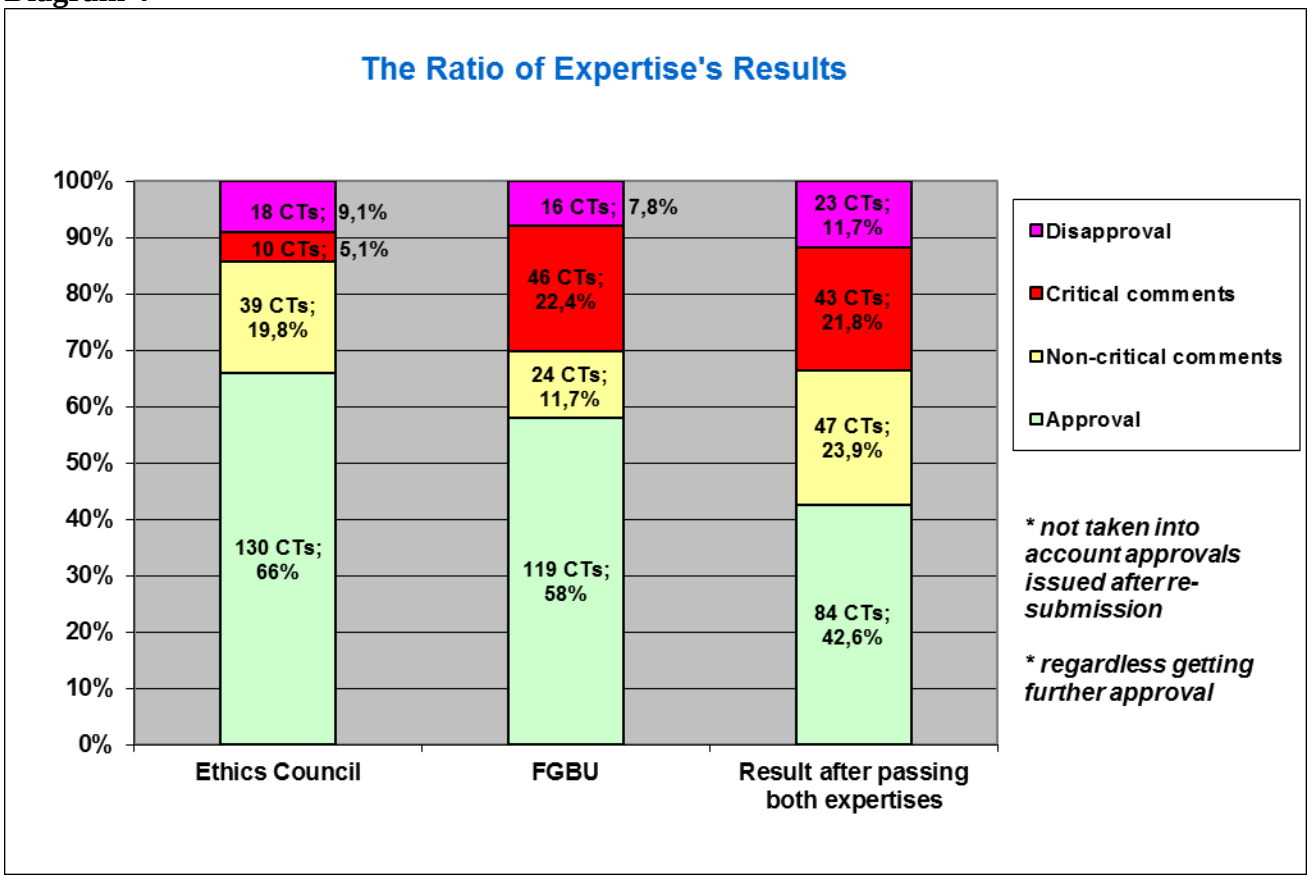
Returning to the analysis in hand, we will touch briefly on the classification used. As we have already mentioned, the result of an expert review can be either an approval, or a disapproval to conduct a trial. As in previous cases, we have broken down the questions from FGBU as well as notes from the Ethics Council on correcting working materials into 'critical' and 'non-critical' comments. By 'critical', we mean those which require changes to be made to the trial protocol, which relate to the design and similar aspects. By 'non-critical', we mean notes on translation, insignificant corrections to various formulations, clarification in patient information (if the latter does not require making changes to the trial protocol) and so on.

The results of the first review of materials by both expert organizations are shown in Diagram 4. The share of the cases approved by the Ethics Council is slightly up compared to last year (66% compared to 62.6%). Although there is a significant decline in the share of the cases approved in the first hearing by the FGBU (58% compared to 71.8%). As a result, just 42.6% of applications passed without notes from either panel. Last year this figure was a bit higher at 43.7%. There is a notable increase this year in non-critical notes from FGBU – 11.7% compared to 1.5% last year. It seems that this is a consequence of implementing the already-discussed practice of questions from the expert panel. Which, generally, can be seen as a positive factor. Unfortunately, same cannot be said for the share of critical comments.

For an objective comparison of this parameter with the previous year's data (when the practice of questions was only just beginning to be implemented, and we did not break down disapprovals and comments, since nearly all negative decisions were made into refusals), it is necessary to collate critical notes and disapprovals in this poll. So, for the Ethics Council review this figure is 14.2% (5.1% + 9.1%). A year ago the share of such refusals was 12.6%.

This figure for the FGBU this year was 30.2% (22.4% + 7.8%) compared to 26.7% last year. The total, based on the results of both review processes, of critical notes and disapprovals was 33.5% compared to 35% last year. This figure was a bit higher than the data for FGBU. This means that in general the main driver of negative statistics are the results of the FGBU review. At the same time, negative results from both expert organizations on the same protocols are much more frequent this year than the last year.

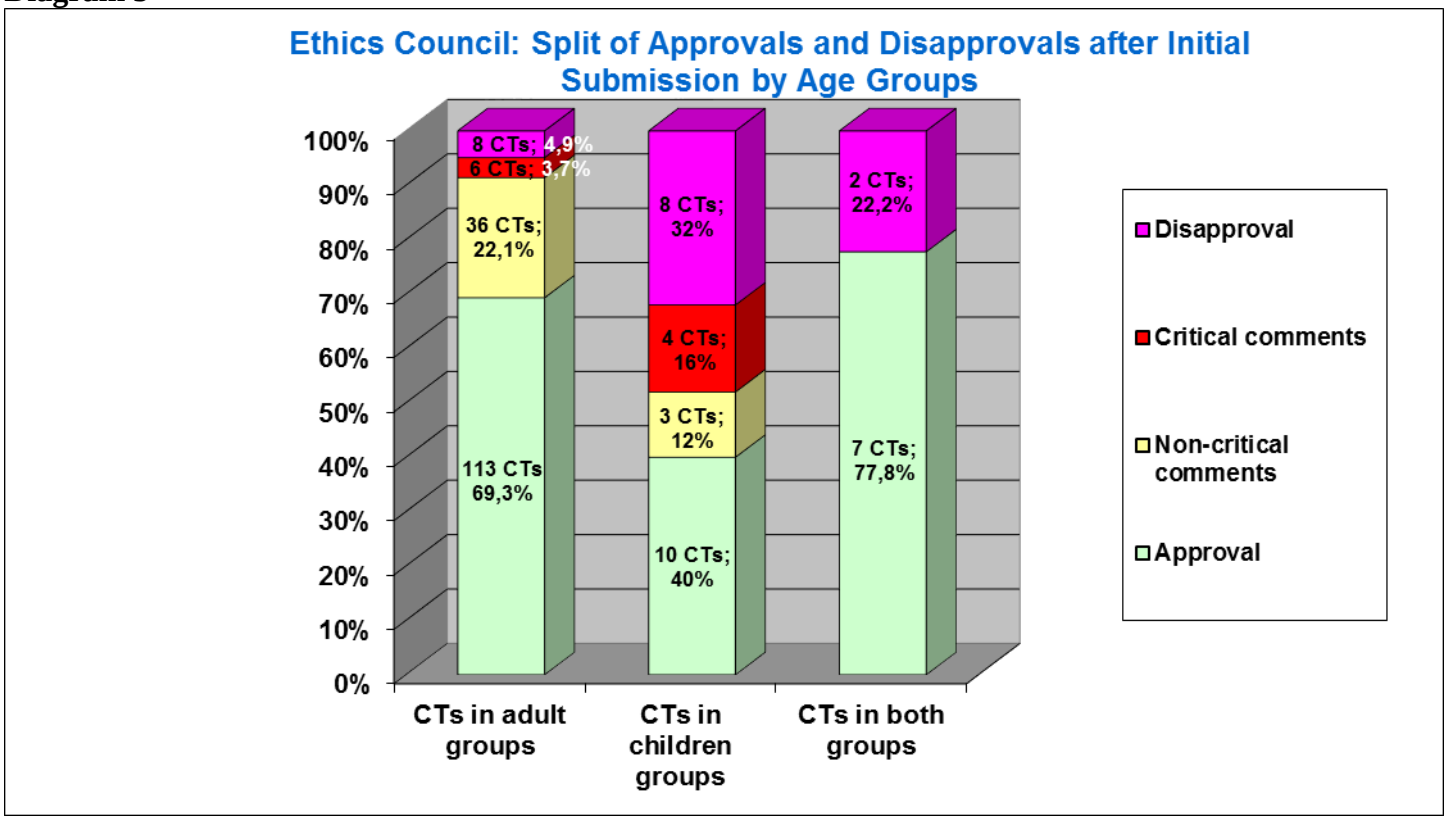
Diagram 4



Data from poll of ACTO members

In diagrams 5 and 6 we present data which allows us to determine how the age of potential trial participants affects the decisions of expert organizations. As usual, all applications to conduct clinical trials were broken down into three groups – protocols with adults, protocols with children, and protocols including both age groups.

Diagram 5

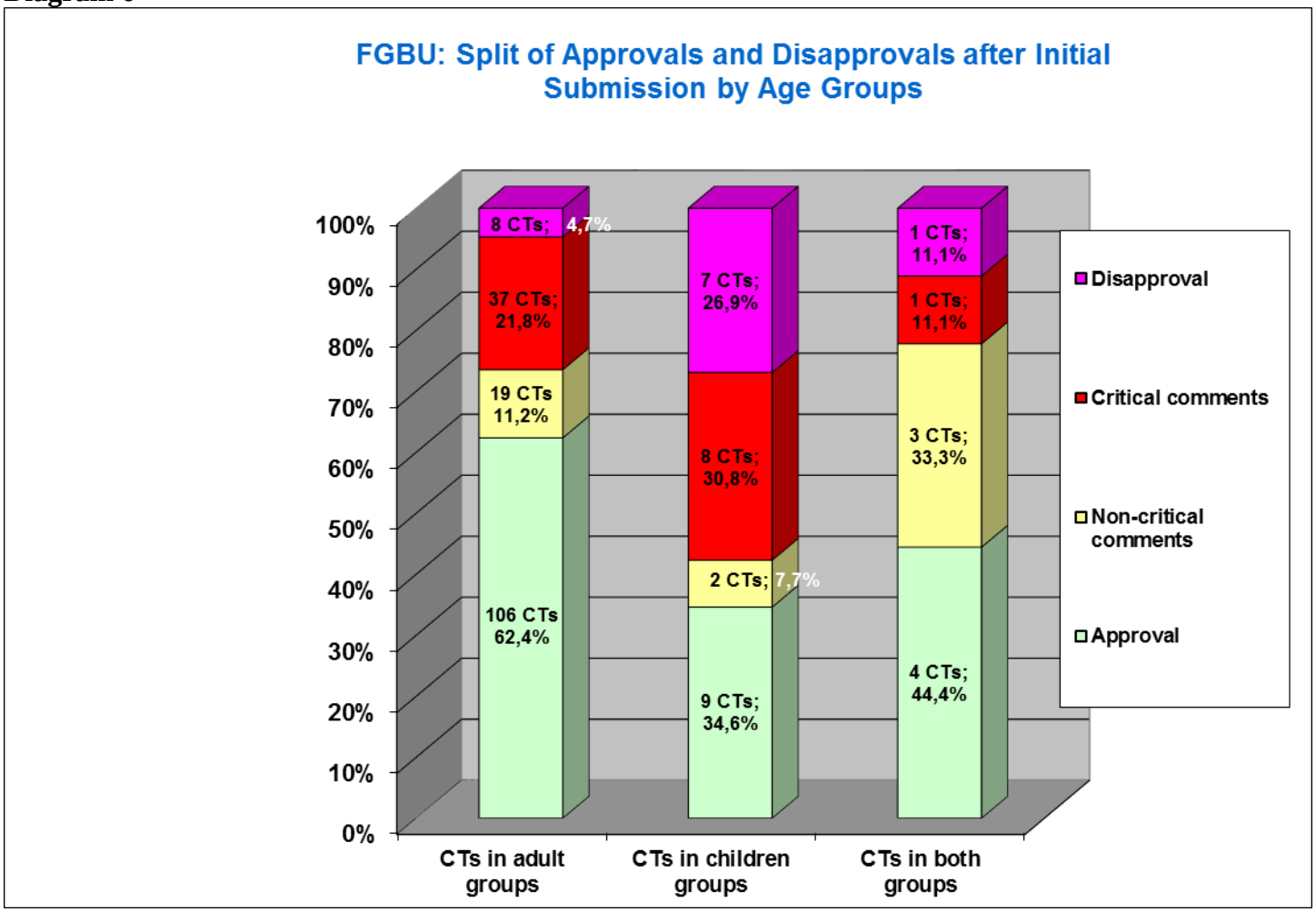


Data from poll of ACTO members

Diagram 5 demonstrates the Ethics Council's preconceived ideas in relation to paediatric protocols. Only 40% of such trials were passed without comments. In two years this figure has dropped by almost 30%. At the same time, if a year ago the majority of comments were of a non-critical nature (the share of cases with this result was 42.9%), now these notes are just 12% of the total number of the protocols reviewed. Such changes are, apparently, the result of the long-term Chairperson, a specialist neonatologist, leaving the Council. With the loss of such an authoritative expert, the Ethics Council has embarked upon the unworthy path of the FGBU. Same conclusion can also be made from the latest content of the Council's comments to paediatric protocols, which are practically copied from the comments of the second expert organization. Although it does not lead to a complete ban on conducting trials with children, it raises significantly an age threshold for the population of children included into the planned group by excluding younger groups from the protocol.

The situation with FGBU review is even worse (Diagram 6). Just 34.6% of paediatric protocols passed this review body without comments (a year ago this figure was 42.9%). The comments, as we mentioned above, are of a traditional nature. In the opinion of the experts, the data presented for review allows conclusions to be drawn about the possibility of conducting trials with the older of the age groups, but not with the younger one. For example, if the application is for ages 6-18, the trial may be granted only for children 12 years and older, but not approved for ages 6-12 years. We could not work out the reasons for such approach. We also could not understand where the threshold lies. Not in one international document were we able to find any strict grading of planned trials for separate age groups of the studied population and requirements for subsequent investigation of medicines first with one and then with another and then with a third and so on, with younger trial participants.

Diagram 6



Data from poll of ACTO members

We looked at the breakdown of the trials approved and not approved at the first attempt by therapeutic field. The results of the review by the Ethics Council are presented in Table 2 and in Diagram 7. Due to the obvious influence of the age criteria on the conclusions of the review in the table we present the data simultaneously in two ways – general, including all cases without regard for the participant age (first figure), and then again, this time not including the paediatric protocols (the second figure, in brackets). The diagram presents the general figures, including paediatric protocols.

The lowest percentage of the cases approved at the first attempt was in psychiatry, with 33.3%. This figure was exactly the same in 2014 and 2013. At the same time, psychiatry saw the highest percentage of the Ethics Council refusals, a double digit number of 55.6%.

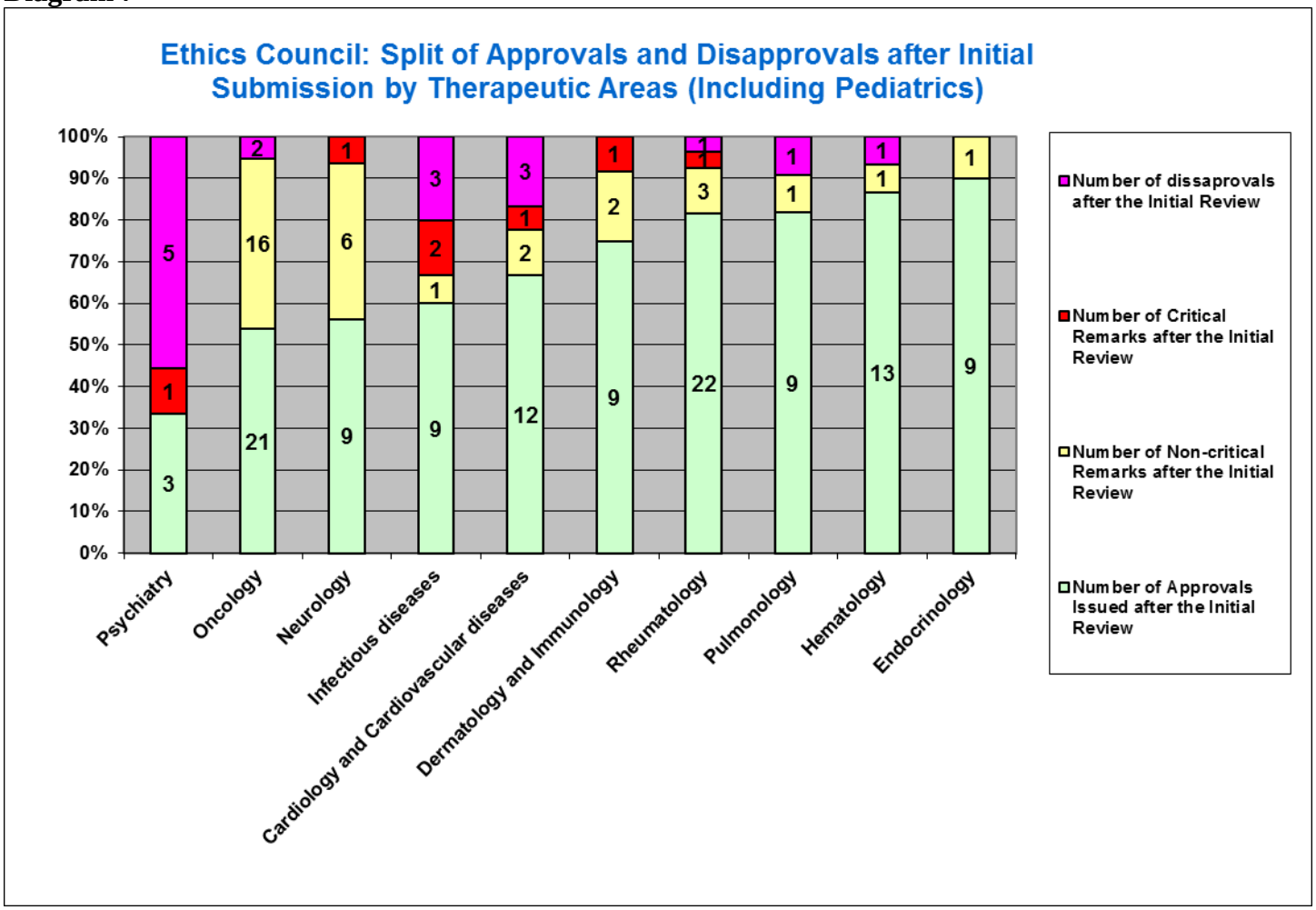
After psychiatry the lowest percentage of approved protocols is in oncology (53.8%). However, the overwhelming majority of comments on these protocols were of a non-critical nature (41%), therefore the situation with cases in this field can be assessed as reasonably tolerable. The same can be said of neurology – 56.3% of cases approved with no notes, and most of the notes (37.5%) were non-critical.

The situation is worse with infectious diseases. On the one hand, the share of protocols approved on the first try is relatively alright at 60%. However, there was a relatively high percentage of disapprovals in this field (20%) and also of critical comments (13.3%). The percentage of disapprovals in cardiology and cardio-vascular diseases can hardly be called low, at 16.7%.

Table 2

Ethics Council: Split of Approvals and Disapprovals by Therapeutic Areas (in Brackets Data Excluding Pediatric Protocols)									
Therapeutic Areas	**Total Number of Initial Submissions**	**Number of Approvals Issued after the Initial Review**	**Approvals Issued after the Initial Review, % of Total**	**Number of Non-critical Remarks after the Initial Review**	**Non-critical Remarks after the Initial Review, % of Total**	**Number of Critical Remarks after the Initial Review**	**Critical Remarks after the Initial Review, % of Total**	**Number of disapprovals after the Initial Review**	**Number of disapprovals after the Initial Review, % of Total**
Oncology	39 (38)	21 (20)	53,8% (52,6%)	16 (16)	41% (42,1%)	0 (0)	0% (0%)	2 (2)	5,1% (5,3%)
Rheumatology	27 (26)	22 (22)	81,5% (84,6%)	3 (2)	11,1% (7,7%)	1 (1)	3,7% (3,8%)	1 (1)	3,7% (3,8%)
Cardiology and Cardiovascular diseases	18 (15)	12 (12)	66,7% (80%)	2 (2)	11,1% (13,3%)	1 (0)	5,6% (0%)	3 (1)	16,7% (6,7%)
Neurology	16 (12)	9 (6)	56,3% (50%)	6 (5)	37,5% (41,7%)	1 (1)	6,3% (8,3%)	0 (0)	0% (0%)
Infectious diseases	15 (12)	9 (9)	60% (75%)	1 (1)	6,7% (8,3%)	2 (1)	13,3% (8,3%)	3 (1)	20% (8,3%)
Hematology	15 (10)	13 (10)	86,7% (100%)	1 (0)	6,7% (0%)	0 (0)	0% (0%)	1 (0)	6,7% (0%)
Dermatology and Immunology	12 (11)	9 (9)	75% (81,8%)	2 (2)	16,7% (18,2%)	1 (0)	8,3% (0%)	0 (0)	0% (0%)
Pulmonology	11 (11)	9 (9)	81,8% (81,8%)	1 (1)	9,1% (9,1%)	0 (0)	0% (0%)	1 (1)	9,1% (9,1%)
Endocrinology	10 (9)	9 (8)	90% (88,9%)	1 (1)	10% (11,1%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Psychiatry	9 (5)	3 (2)	33,3% (40%)	0 (0)	0% (0%)	1 (1)	11,1% (20%)	5 (2)	55,5% (40%)
Urology and Nephrology	6 (6)	3 (3)	50% (50%)	3 (3)	50% (50%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Gastroenterology	6 (6)	5 (5)	83,3% (83,3%)	1 (1)	16,7% (16,7%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Ophthalmology	5 (4)	3 (2)	60% (50%)	1 (1)	20% (25%)	0 (0)	0% (0%)	1 (1)	20% (25%)
Hepatology	3 (3)	2 (2)	66,7% (66,7%)	0 (0)	0% (0%)	1 (1)	33,3% (33,3%)	0 (0)	0% (0%)
Other	5 (4)	1 (1)	20% (25%)	1 (1)	20% (25%)	2 (1)	40% (25%)	1 (1)	20% (25%)
Total	197 (172)	130 (120)	66% (69,8%)	39 (36)	19,8% (20,9%)	10 (6)	5,1% (3,5%)	18 (10)	9,1% (5,8%)

Diagram 7



Data from poll of ACTO members

The data on the breakdown by therapeutic field of the approved and not approved cases by the results of the first review by FGBU is presented in Table 3 and in Diagram 8.

None of the protocols related to ophthalmological diseases had been approved at the first attempt. Five such protocols were submitted for review, three of them (60%) received insignificant comments and two of them (40%) received critical comments. But due to the small total number, ophthalmology was not reflected in the diagram below.

Further, the lowest percentage of trials approved at the first attempt is in psychiatry – just 11.1%. This figure is even worse than the results from the Ethics Council review. This has been totally unexpected to us. For the past several years a strict position of the Ethics Council has been balanced by rather positive position of FGBU. For example, based on the data for the first half of 2013, 77.8% of psychiatry cases were approved by the FGBU at the first attempt. In 2014, 83.3% were approved at the first attempt. But now we observe this sharp decline. This is an example of how infectious the expert behavior could be, with FGBU specialists surpassing in the strictness of the approach even the constant hero of our newsletter, the therapeutic field specialist on the Ethics Council.

As in the previous year, the percentage of the trials in neurology approved at the first attempt is similarly low – 27.8%. In 2014 this figure was 33.3% and it was the lowest for FGBU review. Another therapeutic field in which the share of first-time approved protocols was also low (29.4%) was infectious diseases. Last year the percentage of approved cases was 50%.

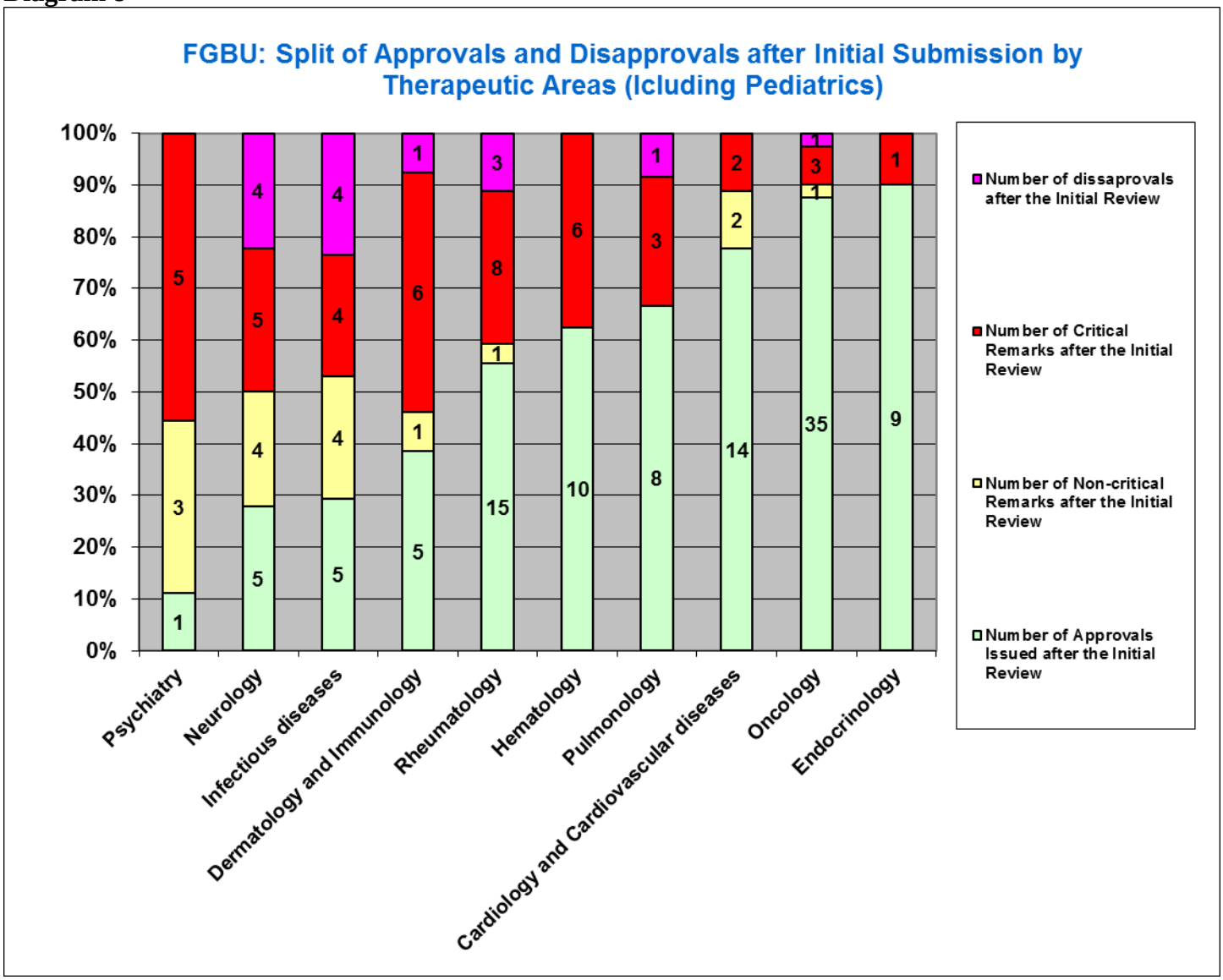
The situation with dermatology and immunology is a bit better, with 38.5% of cases approved without comments. However, the total share of critical comments and disapprovals in this field – 53.9% - exceeded that for neurology (50%) and also for infectious diseases (47%).

Table 3

FGBU: Split of Approvals and Disapprovals by Therapeutic Areas (in Brackets Data Excluding Pediatric Protocols)									
Therapeutic Areas	Total Number of Initial Submissions	Number of Approvals Issued after the Initial Review	Approvals Issued after the Initial Review, % of Total	Number of Non-critical Remarks after the Initial Review	Non-critical Remarks after the Initial Review, % of Total	Number of Critical Remarks after the Initial Review	Critical Remarks after the Initial Review, % of Total	Number of disapprovals after the Initial Review	Number of disapprovals after the Initial Review, % of Total
Oncology	40 (39)	35 (34)	87,5% (87,2%)	1 (1)	2,5% (2,6%)	3 (3)	7,5% (7,7%)	1 (1)	2,5% (2,6%)
Rheumatology	27 (26)	15 (14)	55,6% (53,8%)	1 (1)	3,7% (3,8%)	8 (8)	29,6% (30,8%)	3 (3)	11,1% (11,5%)
Cardiology and Cardiovascular diseases	18 (15)	14 (13)	77,8% (86,7%)	2 (1)	11,1% (6,7%)	2 (1)	11,1% (6,7%)	0 (0)	0% (0%)
Neurology	18 (14)	5 (5)	27,8% (35,7%)	4 (4)	22,2% (28,6%)	5 (5)	27,8% (35,7%)	4 (0)	22,2% (0%)
Infectious diseases	17 (14)	5 (5)	29,4% (35,7%)	4 (4)	23,5% (28,6%)	4 (4)	23,5% (28,6%)	4 (1)	23,5% (7,1%)
Hematology	16 (11)	10 (8)	62,5% (72,7%)	0 (0)	0% (0%)	6 (3)	37,5% (27,3%)	0 (0)	0% (0%)
Dermatology and Immunology	13 (12)	5 (4)	38,5% (33,3%)	1 (1)	7,7% (8,3%)	6 (6)	46,2% (50%)	1 (1)	7,7% (8,3%)
Pulmonology	12 (11)	8 (8)	66,7% (72,7%)	0 (0)	0% (0%)	3 (2)	25% (18,2%)	1 (1)	8,3% (9,1%)
Endocrinology	10 (9)	9 (8)	90% (88,9%)	0 (0)	0% (0%)	1 (1)	10% (11,1%)	0 (0)	0% (0%)
Psychiatry	9 (5)	1 (0)	11,1% (0%)	3 (3)	33,3% (60%)	5 (2)	55,6% (40%)	0 (0)	0% (0%)
Urology and Nephrology	6 (6)	5 (5)	83,3% (83,3%)	0 (0)	0% (0%)	1 (1)	16,7% (16,7%)	0 (0)	0% (0%)
Gastroenterology	6 (6)	4 (4)	66,7% (66,7%)	2 (2)	33,3% (33,3%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Hepatology	3 (3)	1 (1)	33,3% (33,3%)	1 (1)	33,3% (33,3%)	0 (0)	0% (0%)	1 (1)	33,3% (33,3%)
Ophthalmology	5 (4)	0 (0)	0% (0%)	3 (2)	60% (50%)	2 (2)	40% (50%)	0 (0)	0% (0%)
Other	5 (4)	2 (1)	40% (25%)	2 (2)	40% (50%)	0 (0)	0% (0%)	1 (1)	20% (25%)
Total	205 (179)	119 (110)	58% (61,5%)	24 (22)	11,7% (12,4%)	46 (38)	22,4% (21,2%)	16 (9)	7,8% (5%)

Data from poll of ACTO members

Diagram 8



Data from poll of ACTO members

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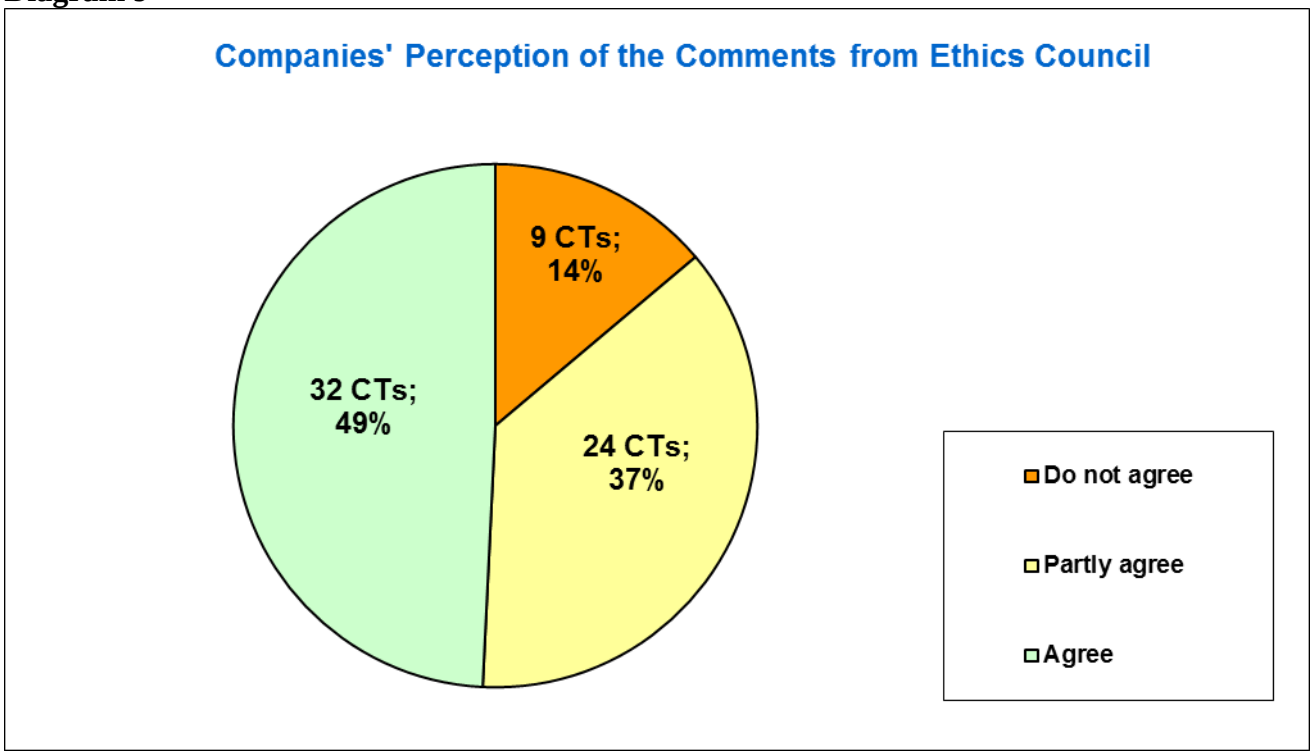
The next parameter that we asked companies to evaluate in the poll was the fairness, in their opinion, of the comments they received from expert organisations. The evaluation was based on three criteria: 'agree', 'partially agree' and 'disagree'. In cases where one protocol received several comments, some of which the company agreed with and some they disagreed with, it was classified as 'partially agree'. But if the company did not agree with the main or most important comment, and all the others were of a secondary nature, then it was classified as 'disagree'.

Results of the poll are presented in Diagram 9 (Ethics Council) and Diagram 10 (FGBU).

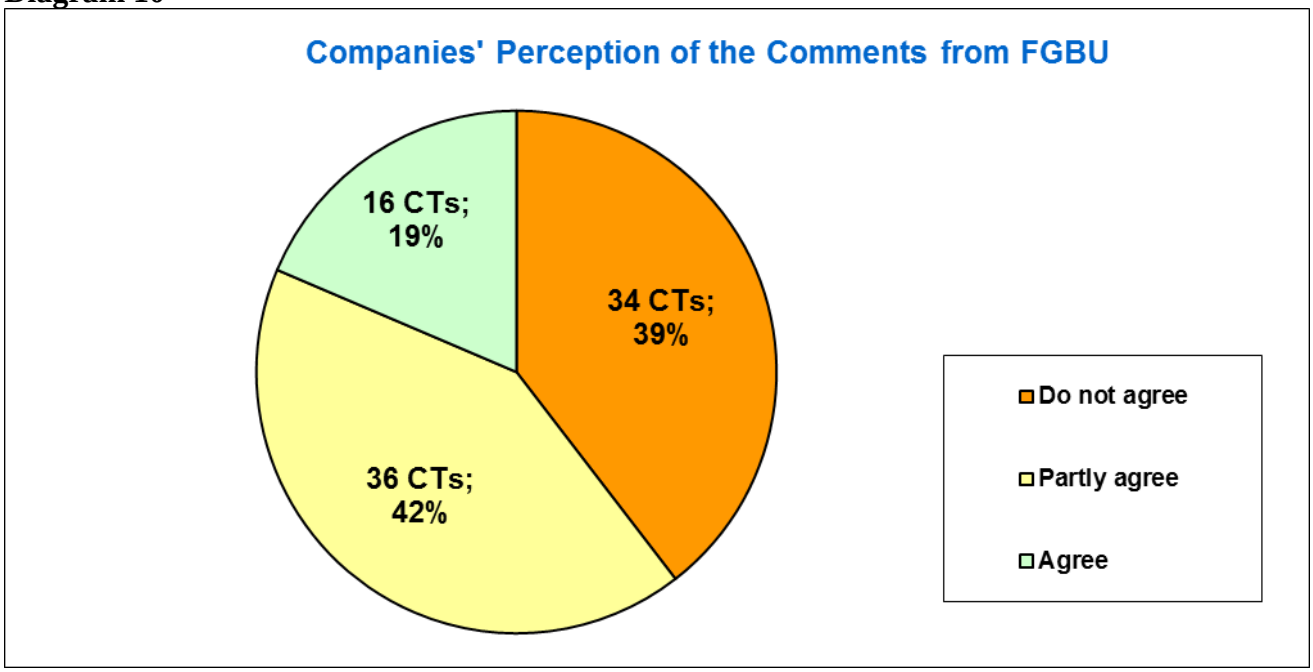
The reviews conducted by the Ethics Council, as we can see from the data, are generally received by the companies as more objective than the reviews by FGBU. Companies agreed with 49% of conclusions by the Ethics Council, whereas respondents fully agreed with the conclusions of FGBU in just 19% of cases. They partly agreed with 37% of conclusions by the Ethics Council, whereas for FGBU this figure was 42%. But finally, they disagreed with conclusions by the Ethics Council in 9% of cases, but with FGBU conclusions in 39% of cases.

Diagram 9



Data from poll of ACTO members

Diagram 10



Data from poll of ACTO members

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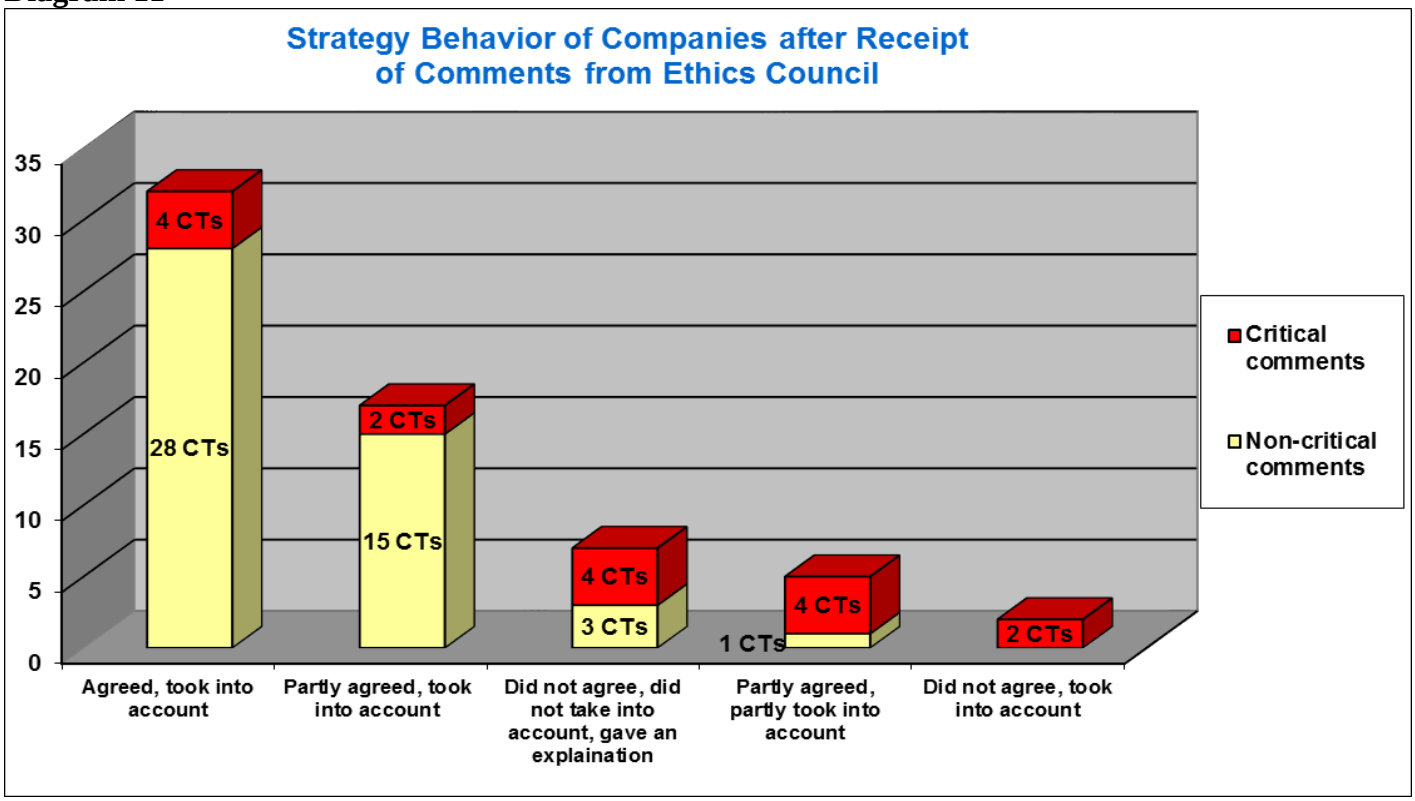
Further, we looked at what strategies the companies more frequently employed once they received comments and in repeat submissions for review.

The strategies were broken down as follows:

- agreed with the comments, fully took them into account;
- partly agreed with the comments, but fully took them into account;
- did not agree with the comments, did not take them into account, but tried to explain their position;
- partly agreed with the comments, and partly took them into account;
- did not agree with the comments, but were forced to take them into account;
- did not agree with the comments, but partly took them into account.

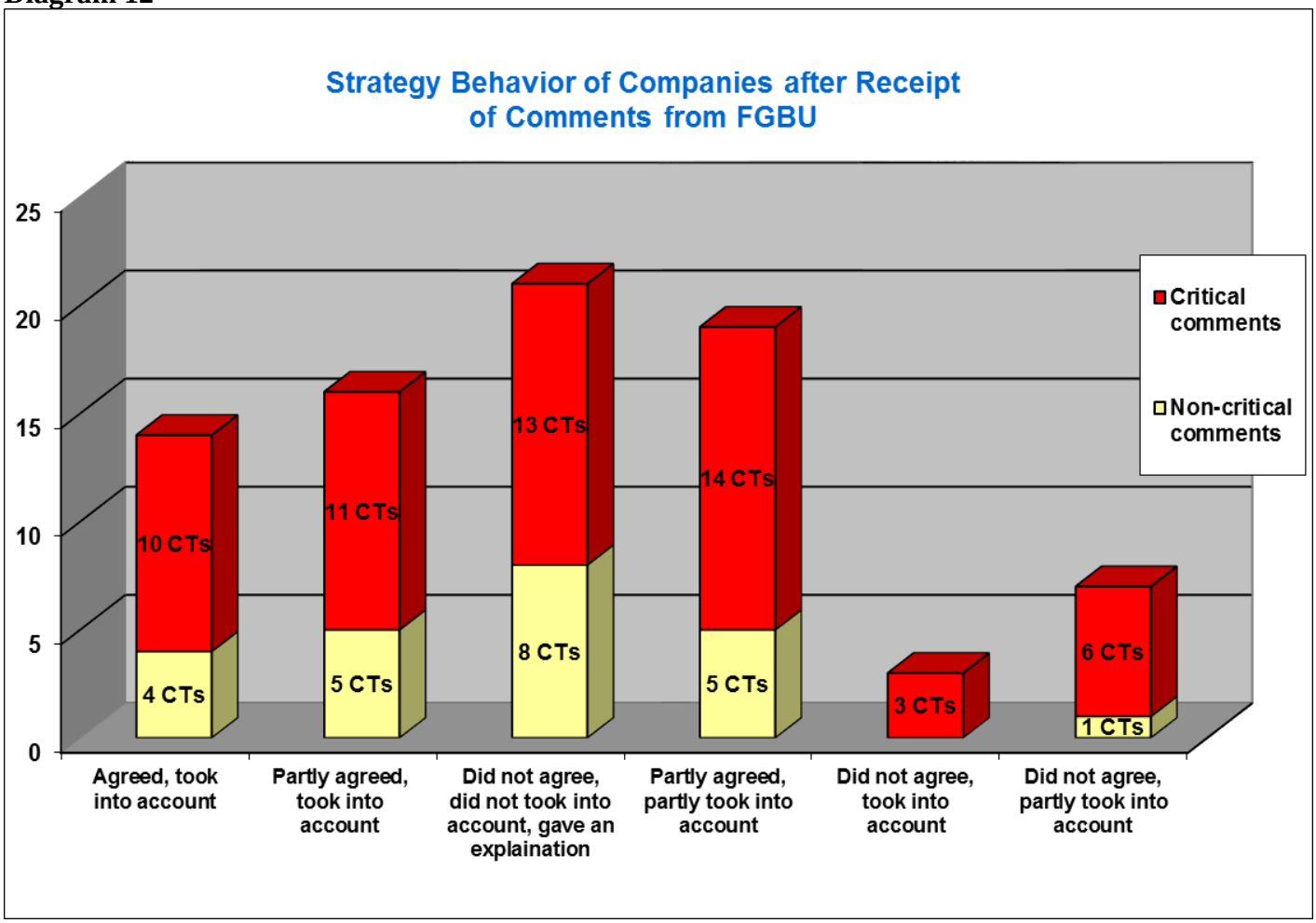
In Diagrams 11 (Ethics Council) and 12 (FGBU) we present the breakdown of these strategies.

Diagram 11



Data from poll of ACTO members

Diagram 12



Data from poll of ACTO members

The data show that with regard to the review by the Ethics Council, companies most frequently agreed with the comments they received, and took them into account (50.8% of cases). The second most common strategy was partial agreement with full compliance (27% of cases). To be clear, these mostly referred to cases with non-critical comments. Often the comments were related to unclear translations, clarification and addition to the informed consent form, and sometimes corrections in terminology. In these cases it is not difficult to comply with the recommendations of the experts.

The picture with FGBU review is completely different. Here the most frequently employed strategies were 'did not agree with the comments, did not take them into account, gave explanations' (26.3%) and 'partly agreed, partly took into account' (23.8%). We will also note that the high share of disagreement with FGBU comments is mostly connected with the practical impossibility of carrying out the experts' recommendations. A bit later we will look at what these recommendations were.

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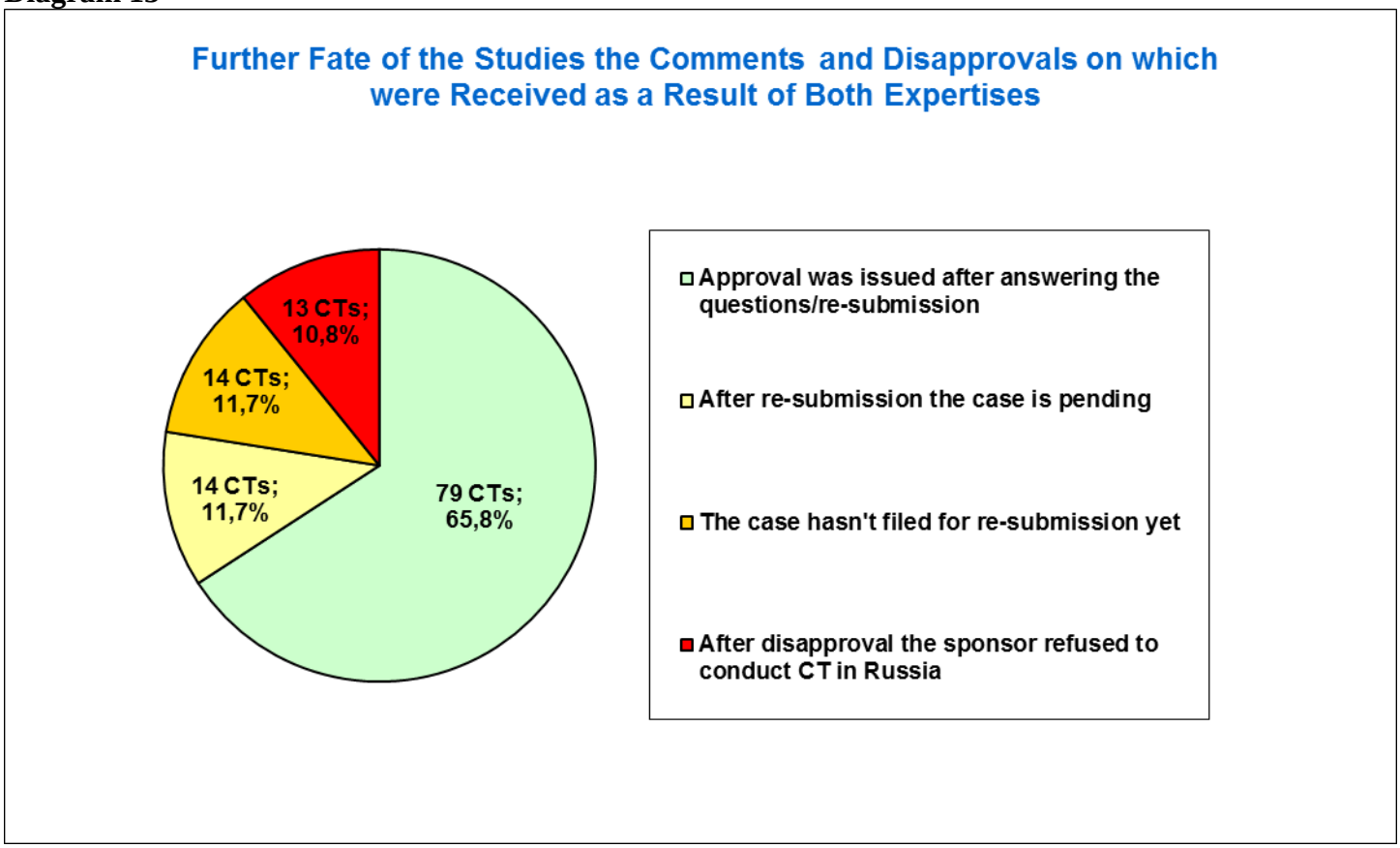
The last but perhaps the most important piece of data for the sponsors is the further fate of the cases on which they received comments in their first round of review. This data on results of review by both bodies is presented in Diagram 13.

Diagram 13



Data from poll of ACTO members

Most trials (65.8%) were approved after a repeat (or sometimes several repeated) submission. The fate of further 23.4% of cases was still unclear as of the time of the poll, some of them were being prepared for a re-submission, and some had already been submitted again and were awaiting a decision. In 13 cases (10.8%) the sponsor had decided not to conduct the clinical trial in Russia.

In the following diagrams (14 and 15) we also present the data on the further fate of trials in which comments were initially received, but now separated by types of review. Here in addition to the further outcome of the case you can see the strategy the company employed having received the comments.

Diagram 14

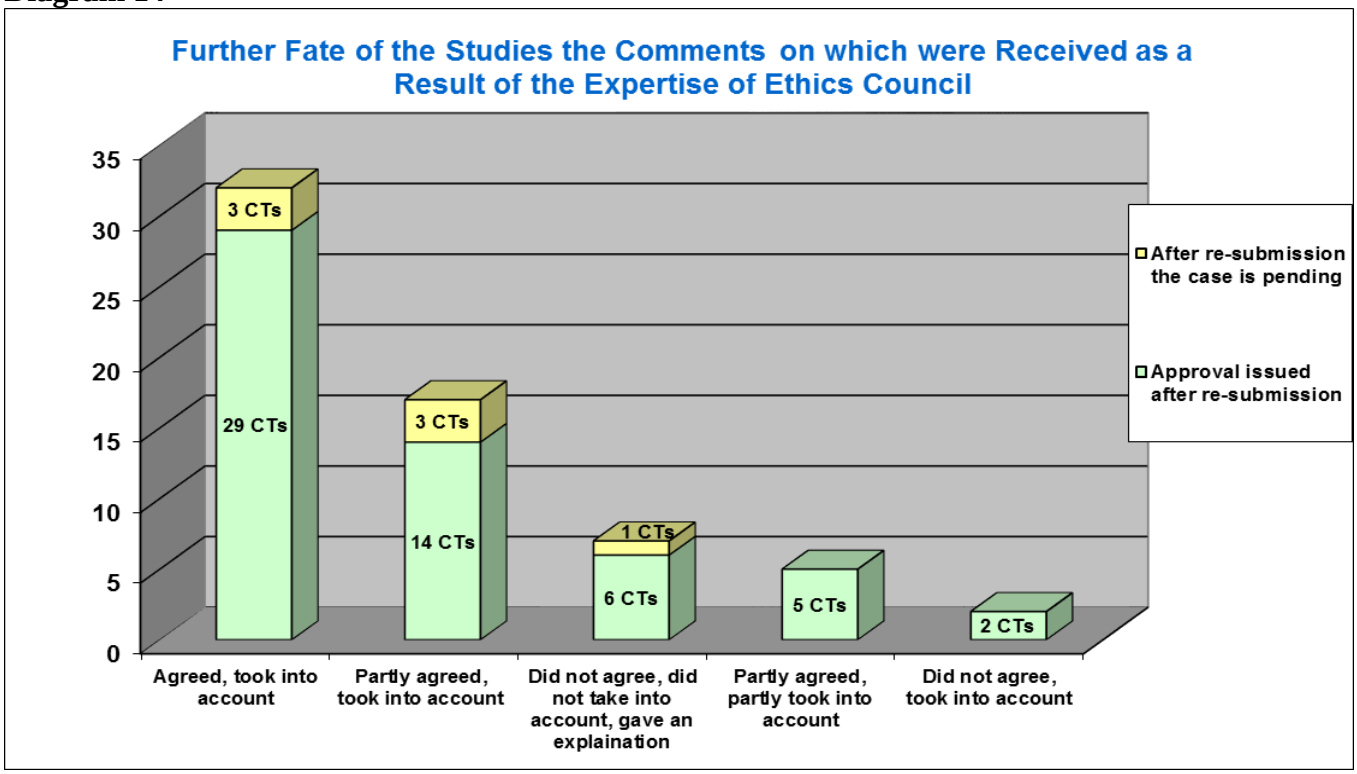
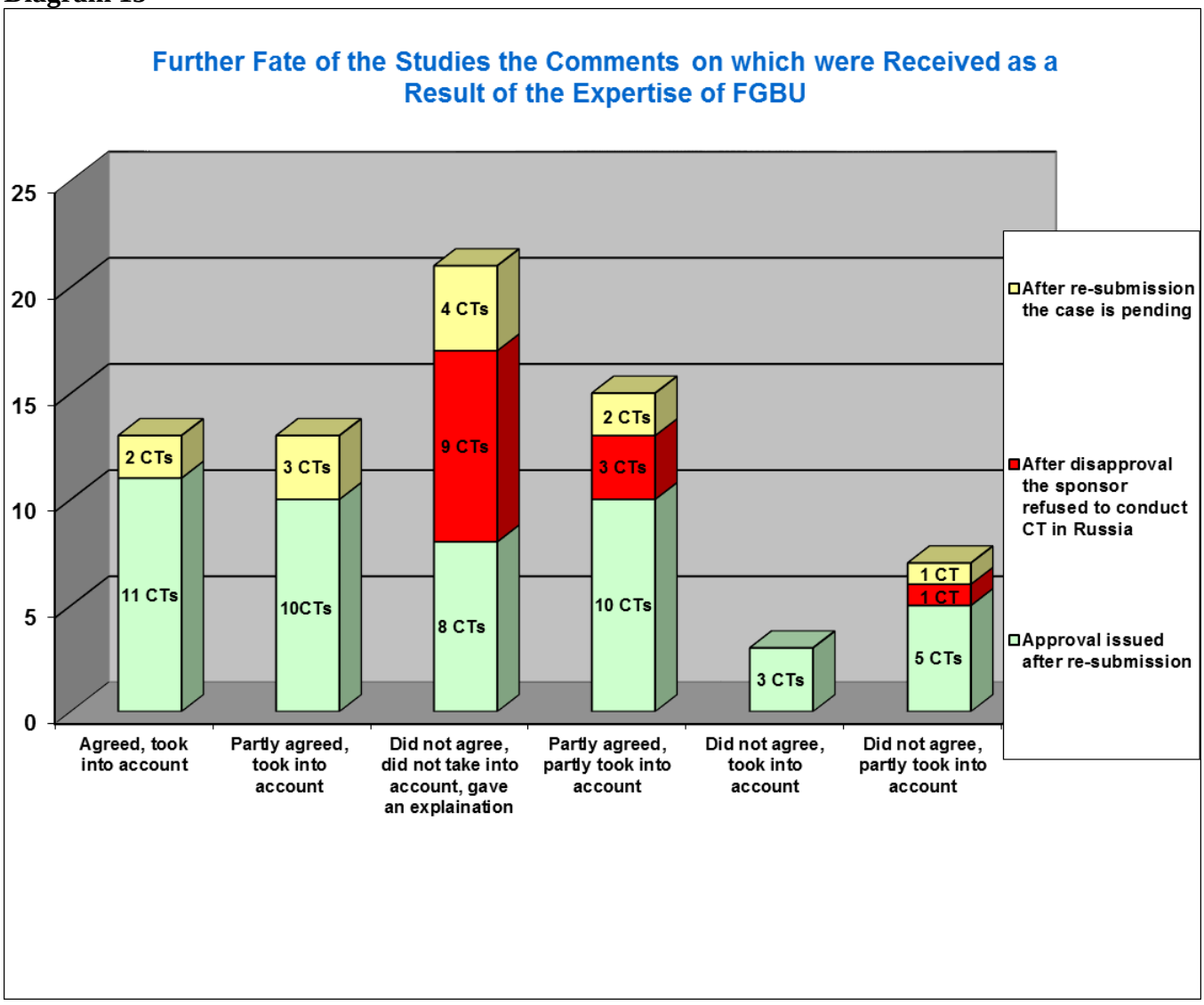


Diagram 15



Data from poll of ACTO members

The necessary but risky strategy of 'did not agree, did not take comments into account, tried to explain position' did, as earlier, yield positive results in some cases. In 8 out of 17 cases (47%), this strategy with the FGBU brought success (if we discount those four trials which are still in the review process). The Ethics Council did not have any such reapplications – all six cases were approved after clarification from the companies (in addition to these six, one trial is still under review).

From the graphics it is also clearly obvious that in all cases of the loss of a trial the fault lies with the FGBU, as the Ethics Council has not once caused such a result.

What were these trials, that in the end the sponsors have decided not to run in this country? Three of them were in oncology and rheumatology, and two were in neurology (both paediatric). One protocol was in each of the following spheres: dermatology, hepatology, ophthalmology, endocrinology, and infectious diseases (the final one was also a paediatric protocol).

The statistics of refusals reflected in the graphics did not reflect one additional protocol in which the sponsor was compelled to walk away from the chance to conduct an IMCT at Russian centres. This was for an anti-tumor medication created on the basis of stem cell technology. It was turned back at the document stage and didn't even make it to review. The reason is that the Russian Ministry of Health flat out refuses to consider such substances as medicinal, though for the past five years they've been promising to pass special legislation on them. As a result, oncology patients have no access to these new treatment opportunities.

Bureaucrat logic

For quite a while already there is a difficult situation connected with the review by FGBU and the Ethics Council. In addition to all the other obstacles on the path to clinical trial approval, there is one additional difficulty, related to obtaining a timely decision from the Ethics Council.

The applicant, submitting the packet of documents to the Ministry of Health, finds himself/herself in the role of a candidate who has taken university entrance exams. He can only wait, without any possibility of communication. The problem is that if the applicant gets a question after the FGBU review has been conducted, and the Ethics Council refuses to approve the trial, then the Ministry of Health does not inform the applicant of the reason for the refusal. In order to find out, the applicant must first send a full and comprehensive answer to the question and wait for the end of the FGBU review process. This is at the same time as they have already understood that the clinical trial cannot be conducted due to a refusal by the Ethics Council. Imagine, that the candidate has already failed one exam (either for an objective or a not entirely objective reason), but he still has to go through a different exam.

The law "On Circulation of Medicines" clearly establishes that the decision by the Ministry of Health on whether to allow or to refuse permission is based on the results of the reviews. Formally, the bureaucrat can refer to the fact that he/she does not have the second decision and therefore can refuse to give the applicant the refusal that he/she holds. This is the formal bureaucratic approach to the matter.

As a result we have a senseless waste of time, energy, and resources. If the applicant had in its hands the reasons for the refusal then in answering FGBU questions it could already begin to prepare its arguments for resubmission. At the same time it could oppose the negative conclusion. Or it could completely give up on the trial at an earlier stage without getting involved in a lengthy correspondence. The Ministry of Health really doesn't lose anything in the event of the refusal and the questions being presented simultaneously.

It has not yet been possible to make a breakthrough in the state of things. The bureaucrats insist that there are rules to managing the paperwork which, essentially, are more important than common sense. An astonishing and logically inexplicable position. But as Russian writer Saltykov-Shchedrin said, "Once in Russia

a man begins to be surprised, he will be paralyzed by surprise and will stand like a stone until death." It seems to be really true.

The Review Panel Museum of Oddities

It is with regret that we must observe that each year the number of complaints about the quality of the review by FGBU only increases. We have already touched on this topic numerous times, sorting out the institutional reasons for this state of affairs (*see ACTO Newsletter No.7).* The main one is the lack of accountability on the part of the review body with regard to the quality of its work. The process prescribed by legislation, when the applicant has no right to contact the experts who are tasked with conducting the review (paid for by the applicant) and given only to the Ministry of Health, and meanwhile, with no interest at all and no responsibility for the final result, has turned the system into a 'black box', the products of which are becoming more and more surreal.

Of course, the law does mention FGBU accountability and that of the experts for the quality of the review. Moreover, it gives the Ministry of Health a mechanism under which the authorities as the client can, if they are dissatisfied with the quality of the work, request a repeat of the expert review (Article 25 of the law "On Circulation of Medicines"). But in the five years since this law came into force, we have never heard of such an example. Although ACTO has submitted inquiries to the Ministry many times over the years. Our official request has not received any response. At the meeting, discussing this issue, the leadership of the department for state regulation of medicines assuredly said that they really do not want to put this into practice. Although they admit that often the conclusions and questions from the experts are quite strange in nature. In such circumstances the companies were recommended to write a letter and ask questions from the experts. And then looking at these, the experts will realize that they asked the wrong thing.

In this issue we decided to present several real life examples of expert questions to their anonymous authors. We should specify that all of these examples are taken from practice, from real submissions for international clinical trials.

Case 1. In reviewing the materials for one planned trial, FGBU, in addition to other additional information, asked for **"a description of changes made to the manufacturing process, the results of evaluation of critical points in the technological process**".

The company had to provide the requested materials, although they were very surprised at the question.

Comments:

The law "On Circulation of Medicines" contains a closed list of documents which must be provided in order to obtain approval for clinical trials. A description of the manufacturing process is not included in this list. Details about the production are included in the registration dossier, but certainly not in the set of documents to obtain approval for the clinical trial. Order of the Russian Ministry of Health and Social Development of 26.08.2010, No. 750н, confirms the "Rules for conducting review of medicines for medical application and the forms of conclusions by the expert committee". The details of these rules also say nothing about the need to evaluate the manufacturing process when preparing the expert conclusion about the possibility of conducting a clinical trial.

In article 14 of the law "On Circulation of Medicines", the principles of the review are listed. The first principle is that of lawfulness.

Leading question to FGBU experts:

Which normative legislative act envisages the provision of data on the manufacturing process at this stage of the review process for approval to conduct clinical trials?

Case 2. The company received a request related to the insufficiency of the materials presented, and one of the points of this request mentioned the need to present "**the draft protocol for the clinical trial containing edited and (or) clarifying information:**

- **present a list of foreign clinical trial centres taking part in the clinical trial, and explain the lack of this trial in international databases (for example: Clinical Trials)"**

Comments:

In the case of an international clinical trial (that is, a trial which is conducted under a single protocol in several countries simultaneously), submission to the various approval bodies in all the participating countries is also done simultaneously. Therefore it would be impossible to present information about where precisely (and not as per the plan) the trial will be approved and conducted. For the same reason, it is not possible for information about the trial to be on the resource ClinicalTrials.gov (which, by the way, is completed by the applicants themselves), at the time that the Russian regulator makes a decision about approval, since the other regulators may still be pondering on the same decision.

According to part 6 article 16 of the law "On Circulation of Medicines", the expert does not have the right to independently collect materials to conduct the review of the medicine. And this also means that the expert cannot know whether 'a protocol for this trial is in the international database'. However, it must know that such presence or absence cannot in any way influence the matter of approval of the clinical trial, since such information is not on the legislated list of required documents.

Despite the groundlessness of FGBU's request, the company presented the experts with the information requested, which had by that time been posted on ClinicalTrials.gov. Admittedly, they did not present it in the protocol as the experts had requested.

Leading question to FGBU experts:

On what basis, in the experts' opinion, should the international protocol contain information which a) has nothing whatsoever to do with the document entitled 'protocol of the clinical trial', b) is available only after such time as the protocol has been drafted and c) is not required under Russian law?

Case 3. Several companies received the requirement from the FGBU described below. The story is as follows. A certain bio-similar, we'll call it X, is put forward for an IMCT (not a registration trial, but an actual IMCT). The original medicine is registered in a number of countries, including Russia, but under various trade names. So in the USA it is called 'A', in Russia, 'B'. The IMCT is planned to be a comparative trial of 'X' with 'A'.

FGBU's notes were as follows:

"Medicine 'A' is not registered in the Russian Federation. The analogousness of the medicine on the market in the Russian Federation as 'B', is not supported by the data supplied. The medicines are manufactured in different facilities. The choice to compare to medicine 'A' is without basis. Therefore in the protocol for the trial it must be shown that in the clinical trial within the Russian Federation the only medicine that will be used for comparison is the one registered in Russia, that is, 'B'."

Comments:

It is not clear where the FGBU experts got such an idea. Probably, they got mixed up on the idea of the comparator medicine used in the practice of clinical trials, and the reference product used for registration.

According to ICH GCP, either the investigational or the marketed product or even the placebo can act as a comparator. In other words, it states that it is not necessary for a comparator to be registered in a specific country or indeed anywhere in the world.

And the concept of the reference product does indeed suppose that we're talking about a fully registered medicine. However the question of reference medicines arises only in a very specific situation – when registering generics.

In this case, that question was not posed. The issue was of conducting an IMCT, where the comparator medicine was selected specifically as medicine 'A', the one that the sponsor needed for the purposes of the trials.

Leading question to FGBU experts:

Do the experts that it is impossible to require a change of the comparator for a particular given country, within the framework of the IMCT? Within the framework of a particular clinical trial it is impossible to use different comparators. Are the experts aware that, in giving this advice, they are by definition excluding Russian centres from this IMCT? Bearing in mind that Russian legislation in no way limits the use unregistered medicines and even placebos as comparators, with the exception of cases in which the aim of the trial is the registration of a generic or bio-similar in Russia? (To emphasise, that was not the case in these instances.)

Case 4. The sponsor plans to conduct two trials on one medicine. One trial includes two stages – a blind stage (comparing two doses of the medicine and a placebo) and an open stage (all participants receive the same dose of the medicine). The second trial is the open one and fully repeats the second stage of the first trial – the participants all receive the same dose of the medicine. The number of patients in the first and the second trial is the same. The company has agreed such a trial's design with FDA. FGBU approves the first trial, but refuses to approve the second trial. The refusal is motivated by the fact that the sponsor failed to present the results of the first trial: "**clinical trial protocol Y can be approved after the completion of clinical trial protocol X with subsequent presentation of full results and report**".

Comments:

The investigational product has marketing authorization in a number of countries around the world. Based on the results of these trials, the company plans to authorize it for a new application. It is obvious that if the Russian regulator wants to wait for the results of the first trial, and the sponsor complete the enrolment in the second trial earlier, then Russia will lose this IMCT.

Leading question to the FGBU experts:

If the first trial was approved, it means that the experts accepted the level of risk of using the medicine. The design of the second trial is exactly the same as that of the second part of the first trial. Therefore, it would be logical to assume that if the experts had looked only at the second trial and had followed the same evaluation criteria but had not known of the existence of the first trial, they would have approved it. In the worst case they would have to admit that approval of the first trial was unwarranted. What would the experts prefer – to be suspected of total lack of logic or of mistakenly approving the first trial? Tertium non datur.

Case 5. The company applied to conduct a clinical trial within the frame of which in Russia they proposed to select 36 patients. Then, because the inclusion criteria were quite strict, the company applied for approval for 13 trial sites. After the review by FGBU the company received the following question:

"1. It is recommended to reduce the number of trial sites in the Russian Federation (13 sites) since only 36 patients are planned for this clinical trial;

2. Increase the number of patients in each trial site taking into account randomization in three treatment groups with no fewer than 3 people in each group;

3. Correct the timeframe for conducting the clinical trial shown in the protocol."

Comments:

It would appear that the number of trial sites opened should be the decision of the clinical trial sponsor. Opening a site does not necessarily mean patients enrolment. Increasing the number of open sites increases the likelihood of finding the necessary number of participants quickly. This is like fishing – you have a higher chance of catching something with 10 hooks than with two. And the law places no limit on the number of trial sites that can be opened, provided that all sites are accredited, and the candidates for principal investigator all meet the required qualifications. Moreover, the law does not instruct the FGBU to exercise oversight over the number of active trial sites.

The suggestion to correct the number of patients per site "taking into account randomization in three treatment groups with no fewer than three people in each group" leads to a single possible conclusion – the expert doesn't have the faintest idea how the randomization is achieved, or how statistics are managed in multicentre trials. To clarify – a multicentre trial envisages that data are collected from separate trial sites and then analyzed collectively. Randomization can be blind to the investigator, and he cannot know what treatment group his/her patients are in. This is how clinical trials are usually conducted in the developed world. Enrolment in the trial can be very complicated, and there are often cases when there is only one patient randomized in a centre. But that does not mean that he cannot be included in the trial until a 'companion' is found (or according to the author of the comments, a further eight people).

Leading question to FGBU experts:

Since everything is clear with the first two comments, the only question is about the last. Since foreign sponsors may not entirely understand what is being requested from them, it would be good to clarify, in which direction precisely should the timeframe of the trial be corrected?

And the final question, to the leadership of the Ministry of Health now. How long are they planning to completely ignore the quality of the expert review, which is headed further and further away not only from the principle of lawfulness, on which the analysis is supposed to be based, but also from the rules of elementary logic? They can hide behind their role as an observer for a long time. However the instances described are of an outrageous nature. And they are only the tip of the iceberg. Clinical trials are just a tiny fragment. Perhaps it's time to look at registration system. We are left to face the question of why no one has yet worked out a system to register orphan drugs, which they so often mention from their lofty podiums. Perhaps we are wrong. But we suggest that for the bureaucrats of the Ministry of Health the time has come to start actually doing something, the time has come to take some kind of responsibility. No matter how much they may wish to avoid doing so.

QUALITY OF CLINICAL TRIALS: RESULTS OF INSPECTIONS BY REGULATORY BODIES

Results of FDA Inspections

In Table 4 we present the data from the FDA website on inspections since 1995[1] up to the first half of 2015. In the year since the last review, the picture in Russia has not changed (*see ACTO Newsletter No.9).* There has only been one additional inspection, and that was actually within the scope of our previous period of evaluation. This is because the data are usually included in the FDA register with a slight delay. Therefore, in the past year there have not actually been any FDA inspections. What's more, the last inspection was dated December 2013. The exact reasons are not known to us, but we can infer that this is connected with the worsening geopolitical situation.

However the number of inspections carried out in other countries has changed, and we were as ever keen to compare the data. For a better understanding of the parameters in the table, we remind you of the FDA's classifications:

NAI (No Action Indicated) – no objectionable conditions or practices were found during the inspection;

VAI (Voluntary Action Indicated) – objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntary. The FDA uses several categories within this class (VAI1, VAI2, VAI2C, etc.[2]) but for simplicity we have compiled them all into one;

OAI (Official Action Indicated) – objectionable conditions were found and regulatory and/or administrative sanctions by FDA are indicated. Such inspection results also have further separate categories under the FDA system (OAIC, OAIR, OAIRR, OAIW), and we have also compiled all such results into one group.

We remind that for a more precise evaluation with the specific data it is necessary to look at the total number of inspections carried out in a given country. The greater the number of inspections, the more accurate the picture is at reflecting the quality of the trials being conducted.

Table 4

Comparative Table of the Results of US FDA Inspections, 1995 – 1st Half of 2015							
Country	**Total number of FDA Inspections with results 1995 - 1st half of 2015**	**NAI**	**NAI, % of Total**	**VAI**	**VAI, % of Total**	**OAI**	**OAI, % of Total**
North America							
USA	**7057**	**3218**	**45,6%**	**3555**	**50,4%**	**284**	**4,0%**
Canada	**167**	**75**	**44,9%**	**91**	**54,5%**	**1**	**0,6%**
Mexico	**24**	**7**	**29,2%**	**17**	**70,8%**	**0**	**0,0%**

1 Beginning from 1994 the FDA started inspecting Russian researchers

2 For more information on the classification of infractions, see

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/ucm073059.htm

South America							
Argentina	56	35	62,5%	20	35,7%	1	1,8%
Brazil	49	25	51,0%	24	49,0%	0	0,0%
Peru	11	5	45,5%	4	36,4%	2	18,2%
Chile	12	7	58,3%	5	41,7%	0	0,0%
Australia	17	10	58,8%	7	41,2%	0	0,0%
Africa							
South Africa	52	26	50,0%	25	48,1%	1	1,9%
Asia							
Japan	13	10	76,9%	3	23,1%	0	0,0%
Thailand	13	5	38,5%	8	61,5%	0	0,0%
China	26	9	34,6%	16	61,5%	1	3,8%
India	54	34	63,0%	20	37,0%	0	0,0%
Turkey	8	2	25,0%	5	62,5%	1	12,5%
Israel	6	5	83,3%	1	16,7%	0	0,0%
South Korea	20	11	55,0%	9	45,0%	0	0,0%
Taiwan	9	7	77,8%	2	22,2%	0	0,0%
Europe							
Austria	16	5	31,3%	11	68,8%	0	0,0%
Denmark	17	9	52,9%	8	47,1%	0	0,0%
Sweden	22	9	40,9%	13	59,1%	0	0,0%
Germany	108	48	44,4%	59	54,6%	1	0,9%
France	84	31	36,9%	52	61,9%	1	1,2%
United Kingdom	99	33	33,3%	64	64,6%	2	2,0%
Spain	37	22	59,5%	13	35,1%	2	5,4%
Italy	57	33	57,9%	21	36,8%	3	5,3%
Finland	15	10	66,7%	4	26,7%	1	6,7%
Netherlands	30	11	36,7%	17	56,7%	2	6,7%
Belgium	32	15	46,9%	14	43,8%	3	9,4%
Poland	101	61	60,4%	40	39,6%	0	0,0%
Hungary	34	18	52,9%	16	47,1%	0	0,0%
Czech Republic	31	16	51,6%	15	48,4%	0	0,0%
Ukraine	26	16	61,5%	10	38,5%	0	0,0%
Russia	100	66	66,0%	33	33,0%	1	1,0%

Data from www.fda.gov

Results of Roszdravnadzor Inspections

This year we decided to repeat our experience of last year and analyse the results of inspections of clinical trials carried out by the Russian regulatory body, Roszdravnadzor. We remind that this gives us information about inspections which have been uploaded to the authority's website. This includes data from the year elapsed, that is, for the second half of 2014 and the first half of 2015. This time we will not linger long on the methodology used for our analysis and the peculiarities of the Russian system of compliance measures (*for more details about this, see ACTO Newsletter No.9).* We will just comment of a few of them in the course of our analysis.

So, in Table 5 we present the data on the total number of inspections carried out, as well as the subjects of the inspections.

Table 5

Statistics on inspections by Roszdravnadzor of the activities of conducting clinical trials, 2nd half of 2014 – 1st half 2015						
Type of inspection	**Number of medical centers inspected**	**The number of principal investigators whose work was inspected**	**The number of inspected clinical trials**		**The number of clinical trial sponsors inspected/The number of inspected clinical trials**	**The number of contract research organizations inspected/The number of inspected clinical trials**
Planned on-site inspections	**48**	**89**	**147**		**1/1**	**2/3**
Unplanned documentary inspection to ensure compliance with previously issued orders	**14**	**14**	**15**		**–**	**–**
Unplanned on-site (complaint-based inspection)	**1**	**1**	**1**		**1/1**	**–**
Unplanned documentary (complaint-based inspection)	**1**	**1**	**3**		**–**	**–**

Source: www.roszdravnadzor.ru

Last year, Roszdravnadzor carried out 48 planned on-site inspections of medical organizations, in the course of which it audited 147 clinical trials being conducted under the leadership of 89 principal investigators. We remind that one of the differences between inspections by Roszdravnadzor and, say, the FDA, is the subject of the inspection. In the USA, the subject of the inspection is a specific trial while in Russia it is the activity of the medical organization conducting the trial, regardless of how many trials the site may be running at any given time.

In addition to medical organizations, in the framework of planned on-site measures two sponsors were also inspected. Based on the results of the checks of one of them, Retinoidy CJSC, there were no infractions found. The second inspection was conducted at AVVA RUS, JSC, where the subject of the inspection was a

bioequivalence study. There was a whole list of infractions, the most serious of which included the sponsor lacking a number of SOPs and not following proper monitoring procedures. There was also a planned, on-site inspection of one of the contract research organizations – Ligand Research. This inspection checked the conduct of two trials, sponsored by Teva and R-Pharm. There were no comments on compliance here.

Unplanned inspections were most commonly documentary and were made with the aim of ensuring that previously uncovered violations had been rectified. In the period under review, Roszdravnadzor conducted 14 such inspections on 15 protocols of clinical trials. In 14 cases the previous infractions had been rectified. In one (a local trial by a domestic manufacturer), the inspection ended with a negative result, the violations were classes as not rectified, and the culprit was fined.

Another reason for unplanned inspections in addition to checking on prior violations were complaints. There were two such complaints filed against medical organisations in the period under review. One, detailed in the Roszdravnadzor report as 'receipt of information about the emergence of threatened risk of harm to life and health' was investigated as part of an on-site inspection. Several violations were indeed uncovered, but they probably would not have satisfied the complainants: Roszdravnadzor determined that the institution 'did not have sufficient measures to guard against accidental or early destruction of documents on clinical trials'. Another inspection, this time documentary, was initiated 'in connection with receipt of information from a concerned citizen'. In the course of this inspection they looked at documents on three clinical trials, conducted under the leadership of one principal investigator. The sponsors and the CRO in the trials were different; therefore the complaint was most likely aimed at the particular investigator. In two of the three trials inspected, no violations were found, and in one of them the violation consisted of 'failure to maintain proper paperwork process'.

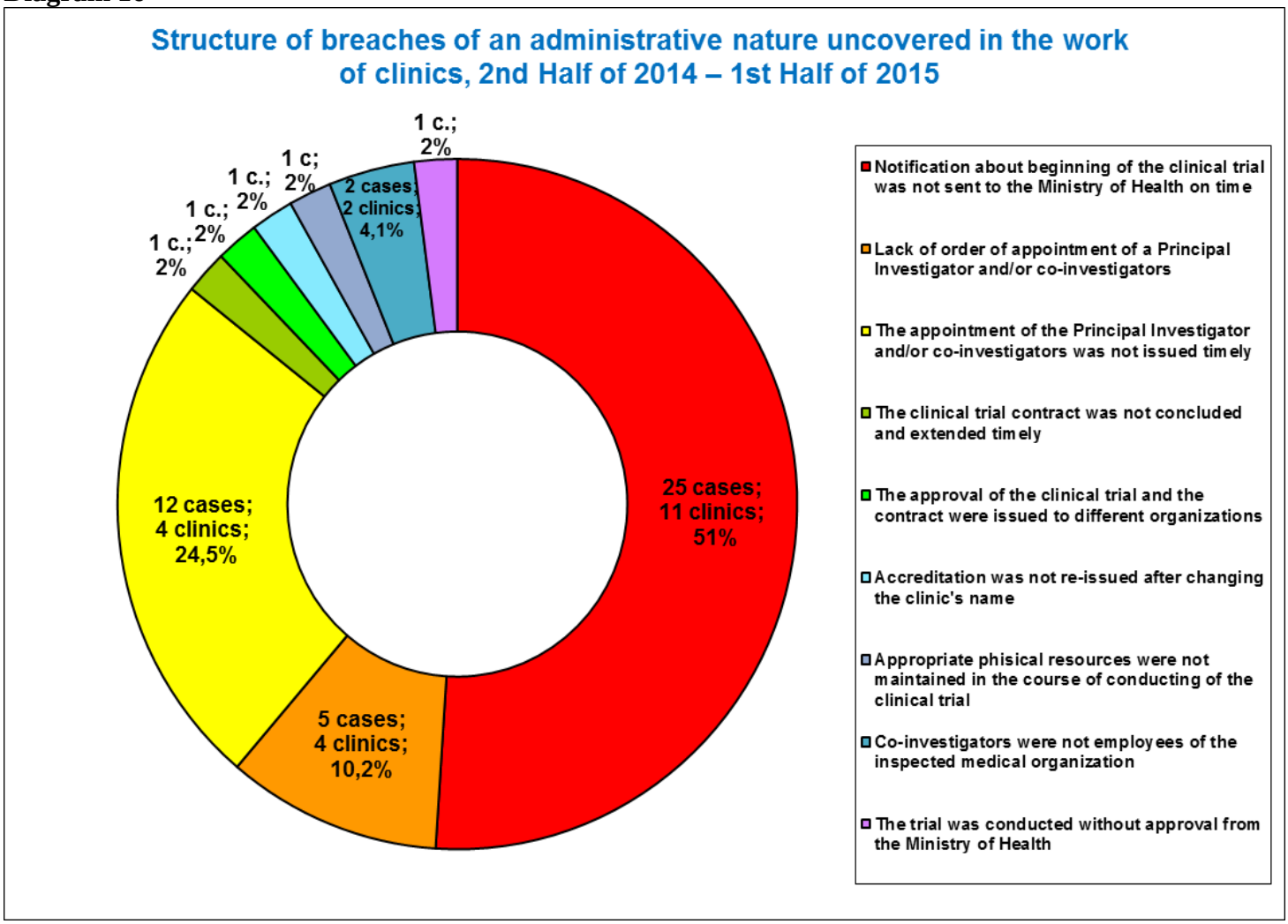
Finally, one more unplanned on-site inspection, also conducted 'in connection with receipt of information from a concerned citizen about the emergence of threats to life and health', involved an inspection not of a medical organisation, but of the sponsor, Biocad, CJSC, specifically, the local trial it was conducting. In the course of the inspection, a violation was discovered: "non-compliance with documentation for the medicine being studied at the trial centre". As a result of the inspection, they were ordered to fix the problem.

But, as the reader will understand, unplanned inspections are still exceptional events, so we will return to the more usual routine work of the regulatory authorities, that of planned clinic inspections. As last time, we broke the violations discovered down into three groups – those which under Russian law relate to the work of the clinic itself, violations in the work of local ethics committees, and violations for which the responsibility lies, according to GCP, with the principal investigator. We repeat that our classification is quite subjective. But we had to come up with something, since Russian legislation relating to clinical trials is quite fragmented and contradictory, it does not entirely specify who has responsibility for a given problem. And the role of the principal investigator, the main party who, according to GCP, holds responsibility for conducting the trial in the centre, in Russian law is undeservingly belittled.

And so, we begin with violations that we assigned to the responsibility of the clinics. These were mostly violations of an administrative nature and relating more to the formal legislative requirements. Although there were also some really serious violations among them.

As we remember from Table 5, throughout the period under review, 48 clinics were inspected. Violations of an administrative nature were uncovered at 15 of them (31.3% of the total number of organisations inspected). These violations are reflected in detail in diagram 16.

Diagram 16



Data from www.roszdravnadzor.ru

The more common violations found by Roszdravnadzor in the work of clinics were, the same as the year earlier, untimely notification of the beginning of clinical trial sent (51% compared to 55% last year). This violation we considered to be strictly formal, it is difficult to take it very seriously. Really, Russian law requires the head of the medical organisation to send notification to the Ministry of Health about the beginning of the trial "within a period not to exceed three working days from the day of the beginning of the clinical trial" (which has already been approved by that same Ministry of Health). This requirement cannot possibly have any effect on patient safety or on the reliability of the data from the trial.

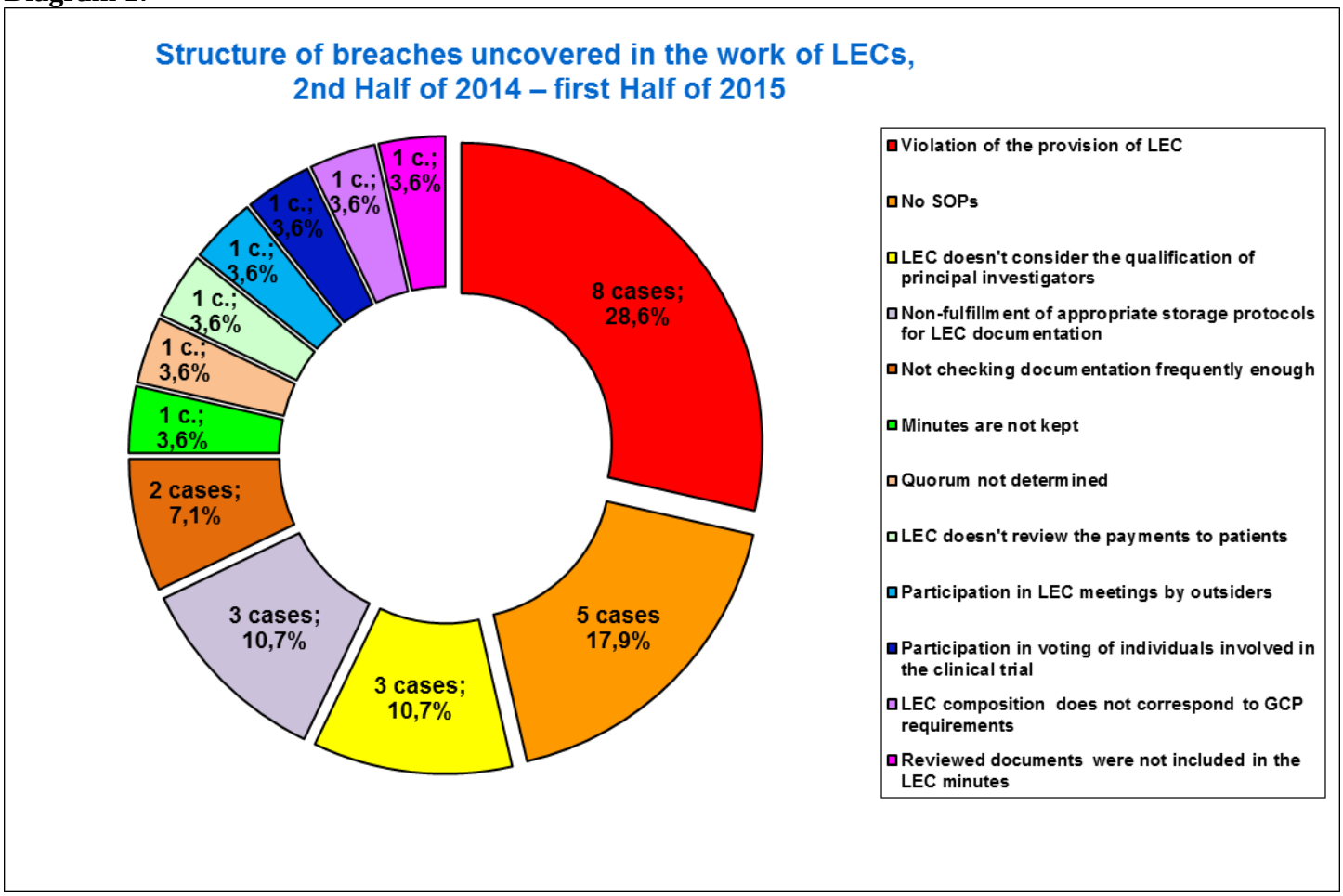
Further there are violations connected with the appointment of principal investigator or co-investigators. Last year this group also took second place (27.8%). In truth, in contrast to this year, at that time all the violations were 'absence of an order of appointment'. This time in a number of cases the issue was about the lack of the order of appointment (10.2% of cases), and in a number of cases it was about such appointment being made late (most likely, the order or trial materials was filed, but the date didn't match that recorded). The share of 'late issued' orders was a further 24.5%. So, if you take both violations together, this category accounts for 34.7% of all violations. Naturally, such discoveries we also did not view as serious from the point of view of clinical trials. The law "On Circulation of Medicines" indeed does fix standards according to which the principal investigator and co-investigators are appointed by the leadership of the medical organisation. The standard is absolutely absurd and illogical once you take into account that the selection of the investigator is left to the sponsor (without the sponsor's approval, no clinical trial will take place at medical institution), and his 'legitimacy' in this position is decided at the level of issuing approval to conduct the clinical trial by the Ministry of Health, as well as the local ethics committee. But the order from the head doctor – that is already the icing on the cake. Although it does not, in fact, make the cake any sweeter.

All other violations that we have classified as the clinics' responsibility were not uniform, they were one-offs. So we will not go into them individually, with the exception of one really serious case. The issue was in conducting a clinical trial without approval. Seeing such an infraction in the Roszdravnadzor report, we thought long and hard about whether this was the responsibility of the clinic, or of the principal investigator. And we decided to put it in both categories.

The next thing we looked at in our analysis was violations by local ethics committees. Altogether, according to the Roszdravnadzor report, there were problems with 11 local ethics committees from 48 clinics inspected. However, determining the share of violations was not possible, because according to Russian legislation it is not required for ever hospital taking part in running trials to have its own local ethics committee. So, leading medical research institutions usually have one 'umbrella' ethics committee for their entire operation. There is also an Interdisciplinary Committee, to which either the sponsor or the principal investigator can turn in the absence of an in-house local ethics committee.

We will not look further into these violations, they are all fairly self-explanatory and are presented in Diagram 17.

Diagram 17



Data from www.roszdravnadzor.ru

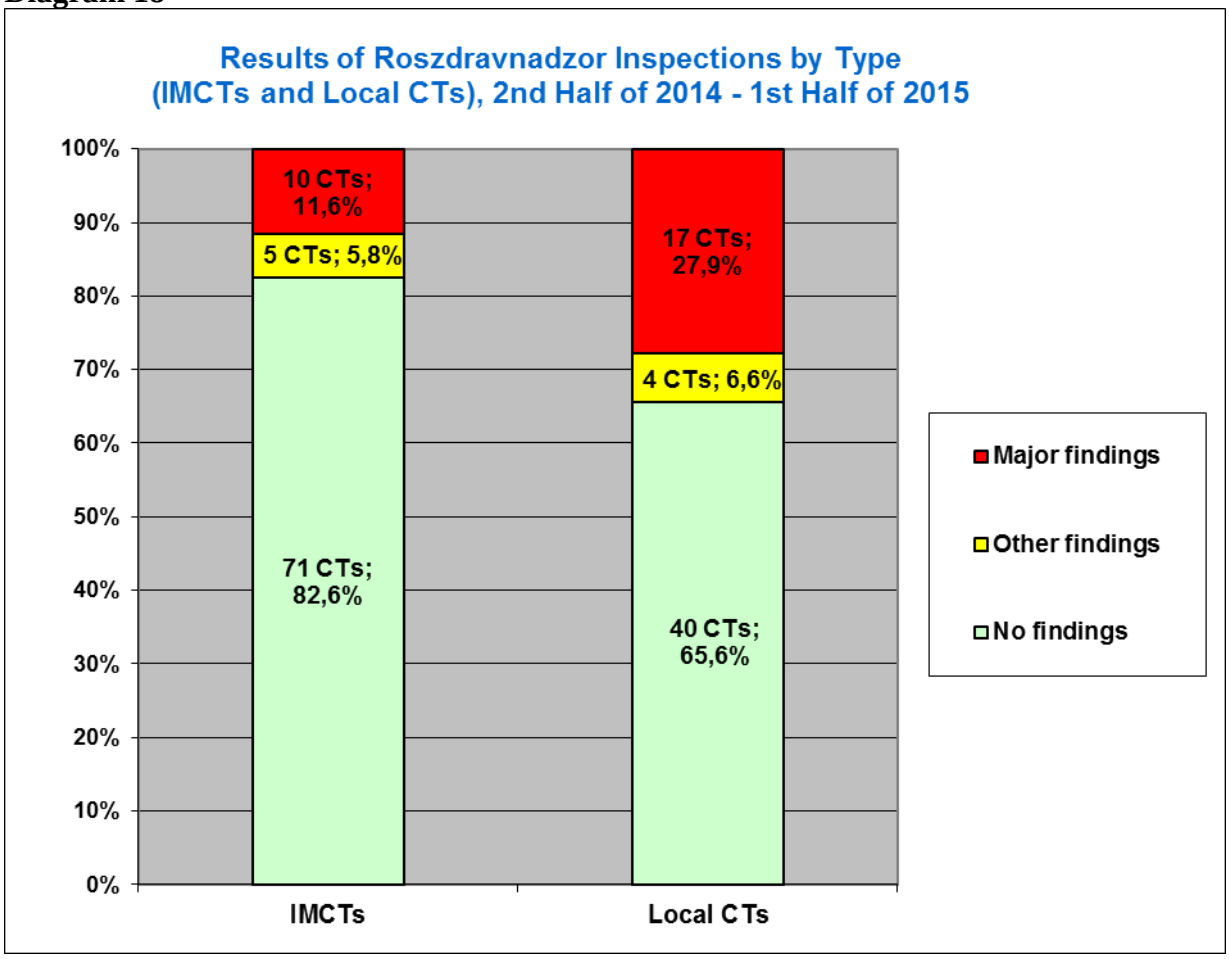
Now we would like to address the main violations that could really affect the quality of the clinical trials and the rights of trial subjects. These are the violations that we classified as the responsibilities of the principal investigators and investigators' teams. As in the previous year, we broke all the inspected trials down into international and local groups. In the IMCT category there were 86 trials, with 61 in the local (including bioequivalence studies).

All violations were further classified as major or minor. Major findings were those which could affect the reliability of the results of the trial or affect the rights and interests of the trial subjects. Minor ones were those which had no such effect. Clearly, such classification is quite subjective, and attempts to reference

particular GCP standards and professional circles can cause serious disagreement. But here the reader can only trust or not trust us, in this classification we were quite strict, choosing to be overly cautious in our evaluations and putting cases of disagreement under the major findings category. In cases where in a single trial there were both minor and major findings, the trial as a whole was placed in the major findings category regardless of how many of each have been found.

The results are presented in Diagram 18. As we can see, the share of trials without findings is higher among IMCTs than in the local trials sector (82.6% compared to 65.6%). In turn, the share of trials, inspection of which helped discover major violations, was 27.9% for local trials and 11.6% for IMCTs.

Diagram 18



Data from www.roszdravnadzor.ru

In contrast to the overall picture, Table 6 gives a better representation of specific violations found by Roszdravnadzor in the course of compliance measures. For convenience, we have broken these down into sub-groups, and also explained them by type of trial – IMCT or local.

Table 6

Infractions discovered in the course of inspections of clinical trials second half of 2014 – first half of 2015		
Type of finding	**IMCTs**	**Local clinical trials**
Conducting the clinical trial as a whole		
Running a clinical trial without approval	**-**	**1**
Obtaining informed consent, patients' rights		
Absence of insurance policy for trial participants	**-**	**1**

	Trial included patients not included on the ICF	-	1
	Patient not given copy of the new issue of the ICF	1	-
	Established procedure for obtaining informed consent not followed	-	1
	When obtaining informed consent, not enough time given to make the decision about participating in the trial	-	1
	Patients not dating the ICF	-	2
	Patients not familiarized with current version of the ICF as approved by the local ethics committee	1	-
	ICF not signed by the person who held the explanatory meeting with the patient	-	2
	Checks to ensure subjects' compliance with medicine administration not carried out	-	1
Clinical Trial paperwork			
	Non-compliance with rules for the data on individual registration cards issued with the medical documentation	1	1
	Not making the correct changes to the patients' individual registration cards	-	3
	Patient IRC lacks information about procedures	-	1
	Primary medical documentation not correctly maintained	-	1
	Primary medical documentation not complying with current standards	4	5
	Lack of appropriate storage for clinical trial documents to guard against accidental destruction	2	4
	Subject not identified on the ICF	-	1
	Non-compliance with precise clinical trial paperwork	6	7
Deviation from protocol			
	Violations of patient inclusion criteria	-	1
	Deviations from protocol without reason	1	6
	Sponsor and local ethics committee not informed of deviations from protocol	-	1
Inventory, storage, and use of medicines			
	Proper inventory of medicine not observed	1	1
	Proper storage of medicine not observed	1	1
	Conditions of medicine storage not conforming to inventory tools in proper order	-	1
Approval by local ethics committee (LEC)			
	Qualifications of responsible researcher not evaluated by the organisation's LEC	-	1
	ICF not approved by LEC	-	1
	Reports on the progress of the clinical trial not presented to LEC	1	-
Administrative matters			
	Qualifications of employee do not correspond with employee's role	1	-
	Personnel's familiarization with their roles and responsibilities within the clinical trial not documented	1	5
	Absence of confirmation of familiarization of PI and co-researchers with the protocol	-	1
	Unaccredited persons not listed in the documentation with a specified responsibility used to perform procedures within the clinical trial	4	4
Total		25	56

Data from www.roszdravnadzor.ru

It would seem that the table gives a fairly vivid depiction of the uncovered violations. All that remains is to single out the particularly noteworthy violations. Really just one, because the most serious issues were found in one trial, which we have already mentioned above, when a trial has been conducted without an approval from the Ministry of Health. This was a trial by the company Unipharm Inc. under the protocol "Trial of Efficacy and Safety of the medicine Vitrum Vision Forte in patients with age-related macular degeneration." The trial was conducted at the N.I. Pirogov Russian National Research Medical University of the Russian Ministry of Health, under the leadership of principal investigator Evgeny Alekseevich Egorov, Professor, President of the Russian Glaucoma Society, member of the Russian Academy of Natural Sciences, RAMTN, and RAEN, holder of the Nesterov Chair of Ophthalmology. Below we list the violations reported in Roszdravnadzor's report on this trial:

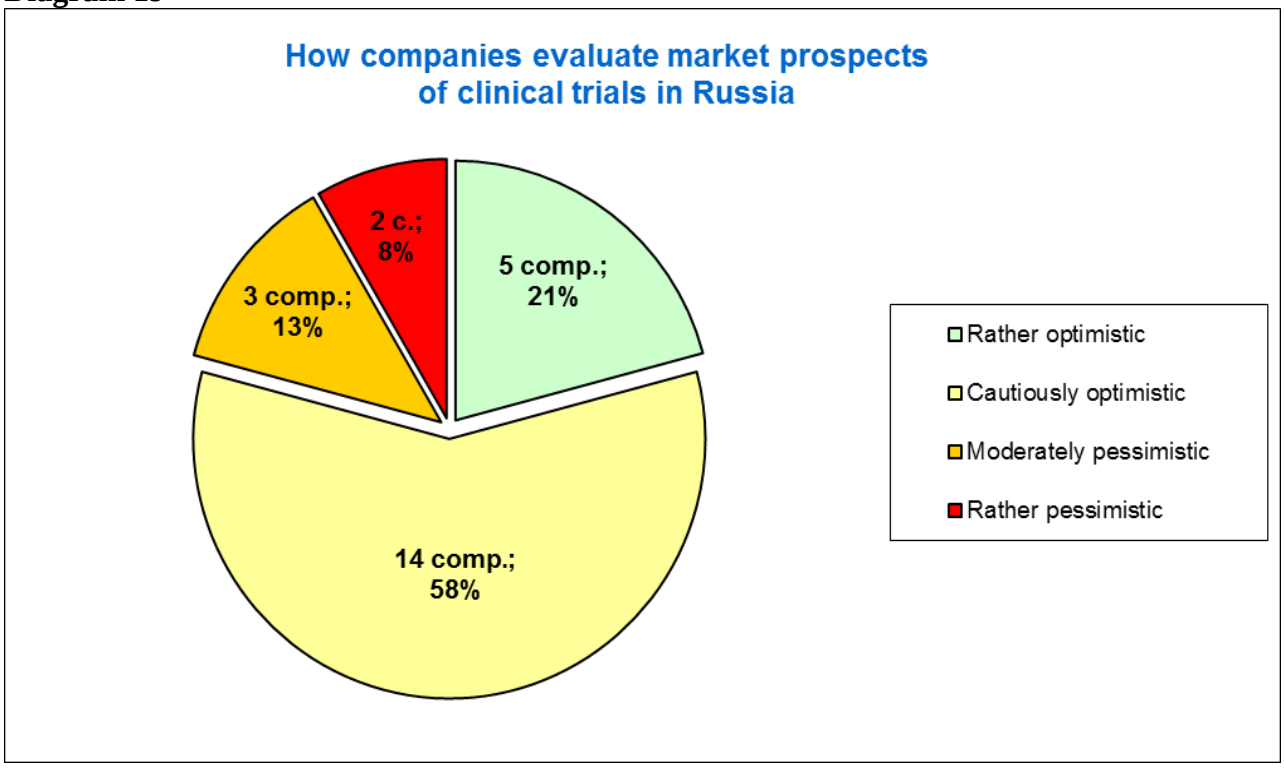
- the clinical trial was conducted at the institution without an approval from the Russian Ministry of Health;
- there was no insurance policy for trial participants;
- the trial included people who had not signed the informed consent forms;
- there were unexplained deviations from the clinical trial protocol;
- the informed consent form has not been approved by the ethics committee;
- lack of confirmation that the principal investigator and co-investigators had been familiarized with the protocol and their responsibilities;
- non-compliance with primary trial documentation.

FUTURE PROSPECTS OF CLINICAL TRIALS IN RUSSIA

This summer ACTO conducted a poll of its members with the goal of getting some prognoses on the Russian clinical trial market. Twenty-four companies took part in the poll. We decided to share the results in our newsletter.

The data can be summarized as follows: 21% of companies polled are rather optimistic about the fate of the Russian clinical trials market, 58% are cautiously optimistic, 13% are moderately pessimistic, and only 8% were rather pessimistic in their assessment of the future of the clinical trials market in Russia. The results are presented in Diagram 19.

Diagram 19



Data from poll of ACTO members

Several respondents noted that to evaluate the near future they would need a longer-term look, because the industry reaction to political and economic changes does not happen right away but rather gradually.

For a better picture we provided several comments received with the poll:

"To assess future prospects, we do not see any country-specific discrimination. Russia remains an attractive country for clinical trials. However, there is a risk that new laws may make the processes more complicated.";

"We do not see any drop of interest in Russia. Talking of the future, the much bigger influence is not the political events, but the bureaucratic system. The big companies take it easier, but the small and medium sized companies with 1-4 products are worried that they might lose money and time in Russia and end up with no results. Russia was a first-choice country before, but this is no longer the case. We have to prove again that we are a leader, we have to work on that. We don't think that Russia will completely exit the IMCT market; we have a huge territory, highly qualified doctors, traditionally high patient enrollment rates (when we start enrollment). But if the bureaucratic situation remains the same, Russia could drop to the bottom of the list";

"We don't have a lot of optimism about the future for the Russian market for CTs, let's just hope it doesn't get any worse";

"The unsystematic and feverish work of the Russian regulatory bodies is worrisome. Altogether it is not clear which way the wind is blowing. It could lead to dramatic declines in the number of trials in the country";

"Neither a crisis nor a political situation will overweight the advantages that Russia has, such as qualified doctors, a centralised healthcare system, relatively quick patient enrollment, the size of the country which provides an opportunity to find patients with rare diseases";

"On one hand, there is a good argument that the country is large, the potential patient base is significant, there are many research centers, the forecast is good. But Russia may be less attractive because of the lengthy approval process and the rather high customs duties";

"The situation with trials is normal, there is no discrimination towards Russia";

"Situations come up when it's hard to get trials for Russia. Western partners don't always include Russia in their country-selection list (partially because of the political situation that affects decision-making). But the number of clinical trials has not dropped significantly, because this is the only way to continue doing business here. We're not pessimistic, but the political situation is having an impact. "Fortunately, we have not felt any change of attitude towards Russia so far";

"Russia is a country with a potential for holding clinical trials – it has a huge patient population, a large number of centres, motivated and qualified investigators, fast enrolment that meets projections, and also adequate quality of the studies. The period of time to obtain approval and licenses to import/export make Russia less competitive with other countries. In addition, we can't rule out the political and economic factors, which have certain negative impacts on all types of businesses."

It is possible that this poll could become a standard feature for the newsletter. In the future it would be possible to compare which trends and feelings are most common among companies, and how their opinions of the future for clinical trials in Russia change across time.