

Original article

Reproducibility of retinal nerve fiber layer and macular volume measurements in patients receiving retinal protection pharmacotherapy

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Abstract: *Background* — High-quality monitoring of the glaucoma plays an important role in the early diagnosis and treatment of glaucoma, for which structural optical coherence tomography (OCT) is used. Technology that increases the repeatability and reproducibility of OCT may differ in different devices, thereby yielding different results.

Objective — To assess the effect of the frequency of retinal protection pharmacotherapy courses on quantitative data regarding the macular volume and the thickness of the retinal nerve fiber layer (RNFL) measured by two instruments, SPECTRALIS and OPTOPOL, and also to evaluate the agreement between the data collected by these devices.

Material and Methods — We monitored 17 patients (34 eyes) diagnosed with primary open-angle glaucoma in the advanced stage from 2019 to 2023. Group 1 including 9 patients (18 eyes) received a course of retinal protection pharmacotherapy with Retinalamin® at an interval of 3 months, while Group 2 comprising 8 patients (16 eyes) received similar treatment at an interval of 6 months. All observed patients underwent structural OCT on REVO NX (OPTOPOL Technology) and SPECTRALIS devices at the onset of the study, as well as after 3 and 6 months.

Results — The agreement between the two devices in measuring RNFL thickness was estimated by the Lin's concordance correlation coefficient (LCCC): in manual mode, $LCCC_{start}=0.69$ (95% CI: 0.51-0.81); while in automatic mode, $LCCC_{start}=0.73$ (95% CI: 0.57-0.84). The agreement between the macular volume measurements was as follows: in manual mode, $LCCC_{start}=0.21$ (95% CI: 0.21-0.29); while in automatic mode, $LCCC_{start}=0.21$ (95% CI: 0.21-0.29).

Conclusion — The agreement between the SPECTRALIS and OPTOPOL devices in terms of RNFL thickness should be considered substantial, while in terms of macular volume, it should be classified as fair. As measured in the manual mode, the RNFL thickness in both groups receiving Retinalamin increased, which can be interpreted as a favorable effect of retinal protection pharmacotherapy.

Keywords: optical coherence tomography (OCT), SPECTRALIS, OPTOPOL, Retinalamin®, retinal protection pharmacotherapy.

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Introduction

After cataracts, glaucoma is the second most common cause of vision impairment. It is the leading etiologic factor of irreversible blindness. [1, 2]. In the Russian Federation, there are over 1 million patients with diagnosed glaucoma, and nearly as many people are unaware of their diagnosis [3].

In recent years, the availability of high technology computer methods for evaluating the state of the visual fields, along with ganglion cells and their axons that form the optic disc (OD), has increased. These methods are based on preliminary diagnostics and dynamic monitoring of the state of visual perception in patients with glaucoma [4, 5]. A major role is given to a detailed

eye examination, taking into account the results of static computer perimetry, optical coherence tomography (OCT) of the optic nerve and retina, biomicroscopy of the eyeball, assessment of the eye hydrodynamics, load ocular tonometry, functional tests with a study of tolerance and intolerance of the optic nerve to intraocular pressure (IOP), and biometry [6].

Despite the variety of novel diagnostic methods, there are still many cases of terminal stage glaucoma diagnosed for the first time [7].

The relevance of early detection and monitoring of glaucoma is obvious, since its incidence rate steadily increases due to the growing proportion of elderly people in the population. The risk of

developing glaucoma increases with age [4]. It has been established that early diagnosis and timely treatment of glaucoma reduces the risk of irreversible blindness, and also improves the quality of life in patients [8-12].

In glaucoma monitoring, the only modifiable risk factor is IOP. Its measurement remains the basis for early detection of glaucoma [13]. Reducing IOP is the only therapeutic measure in the treatment of glaucoma [14]. However, at present, despite achieving target IOP levels, it is possible to stop the progression of the glaucoma only in 50% of cases [7]. Retinal protection therapy aimed at preserving visual functions against the background of IOP stabilization may increase this share. Currently, ophthalmologists prescribe medicines representing many pharmacological groups for the purpose of retinal protection pharmacotherapy in conditions of various diseases, while the choice of drug is determined by the experience of a particular doctor [15].

OCT allows objective and reproducible measurement of the retinal nerve fiber layer (RNFL) thickness, the macular volume, and the parameters of the neuroretinal rim of the OD with high repeatability and reproducibility, at any rate, among the healthy population [16, 17]. However, technologies improving the repeatability and reproducibility of OCT may differ in different measuring devices.

For instance, SPECTRALIS SD-OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) includes a real-time eye gaze tracking system (TruTrack™), which combines confocal scanning laser ophthalmoscopy (cSLO) and spectral domain optical coherence tomography (SD-OCT) to correct eye movements. This allows nearly complete elimination of artifacts associated with involuntary oscillatory movements of the eyeball during the examination. Sequential scanning reduces the variability of longitudinal measurements used to monitor glaucoma progression [18]. To increase the accuracy of retinal layer segmentation, it is possible to analyze the RNFL and macular thickness after manual and automatic segmentation [9, 19].

As for the REVO NX device (OPTOPOL Technology SA, Zawiercie, Poland), it lacks the control over the position of an eyeball. This key point was the goal of our study.

Objective: To assess the effect of the frequency of retinal protection pharmacotherapy courses on quantitative data regarding the macular volume and the RNFL thickness measured by two instruments, SPECTRALIS and OPTOPOL, and also to evaluate the agreement between the data collected by these devices.

Material and Methods

Study sample

This study was conducted from 2019 to 2023 at one of the sites (Public Clinical Hospital No. 2, Chelyabinsk, Russia) of a multicenter prospective randomized controlled trial on the effectiveness of retinal protection pharmacotherapy with Retinalamin®. The study included 17 patients (34 eyes) diagnosed with advanced stage of the primary open-angle glaucoma (POAG). The study was approved by the Ethics Committee and was conducted in accordance with the ethical standards set out in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients were distributed among two groups: Group 1 included 9 women (18 eyes) who received a course of retinal protection pharmacotherapy with Retinalamin intramuscularly at intervals of 3 months (i.e., 4 times a year). Group 2 included 8 study subjects (16 eyes), two of whom were men, who underwent a course of retinal protection pharmacotherapy with Retinalamin intramuscularly 2 times a year.

Clinical and demographic characteristics in the patient groups did not statistically significantly differ in age, gender composition of the groups, visual acuity, central corneal thickness (CCT), IOP, optic disc size, or cup-to-disc ratio (C/D), which compares the diameter of the cup portion of the OD with the total diameter of the OD (Table 1). Data on retinal light sensitivity were published in our previous study [20].

Table 1. Clinical and demographic parameters of study groups

Parameter	Group 1 (n=9 patients; 18 eyes)		Group 2 (n=8 patients; 16 eyes)		<i>P</i> _{3 vs. 6 mos.}
	Me (Q25%; Q75%)	Range	Me (Q25%; Q75%)	Range	
Age, years	72 (68; 69)	from 64 to 83	70 (69; 80)	from 67 to 83	W=133.5; p=0.767
Gender, male female	0/9		2/6		X ² =3.0; p=0.084
BCVA	1.0 (1.0; 1.0)	from 1.0 to 1.0	0.8 (0.7; 1.0)	from 0.5 to 1.0	W=196; p=0.041
CCT, μm	508 (499; 514)	from 476 to 530	524 (512; 536)	from 441 to 536	W=119; p=0.397
IOP, mm Hg	13 (11.2; 15.0)	from 9 to 18	12.5 (9.8; 16.0)	from 6 to 16	W=159; p=0.6146
C/D	0.6 (0.6; 0.7)	from 0.3 to 0.9	0.6 (0.4; 0.7)	from 0.2 to 0.9	W=183.5; p=0.1779
OD, mm ²	1.8 (1.4; 2.1)	from 1.3 to 3.5	2.0 (1.9; 2.1)	from 1.6 to 3.4	W=91.5; p=0.072

BCVA, best corrected visual acuity; CCT, central corneal thickness; IOP, true intraocular pressure; C/D, cup-to-disc ratio, which compares the diameter of the cup portion of the optic disc with the total diameter of the optic disc; OD, optic disc; *P*_{3 vs. 6 mos.}, statistical significance of intergroup differences in the treatment groups every 3 mos. (Group 1) and every 6 mos. (Group 2).

Table 2. Changes in RNFL thickness and macular volume according to structural OCT data after six months of retinal protection pharmacotherapy

Group	At the study onset		After 6 months		Statistical significance based on Wilcoxon test: onset vs. 6 mos.
	RNFL_1	Vol_1	RNFL_2	Vol_2	
Group 1 OPTOPOL	76.0 (70.0; 82.8)	7.4 (7.3; 7.7)	74.0 (71.0; 83.8)	7.3 (7.2; 7.5)	W _{rnfl} =-1.3; p _{rnfl} =0.203; W _{vol} =-0.5; p _{vol} =0.632
Group 2 OPTOTOL	75.5 (70.8; 83.5)	7.5 (7.4; 7.7)	76.0 (68.8; 84.5)	7.4 (7.3; 7.6)	W _{rnfl} =-1.2; p _{rnfl} =0.223; W _{vol} =-1.0; p _{vol} =0.337
Group 1 SPECTRALIS automatic mode	72.0 (64.3; 80.5)	8.0 (7.9; 8.2)	72.0 (64.3; 77.5)	8.0 (7.9; 8.2)	W _{rnfl} =0.9; p _{rnfl} =0.393; W _{vol} =1.0; p _{vol} =0.312
Group 2 SPECTRALIS automatic mode	70.0 (64.5; 80.0)	8.1 (7.9; 8.3)	70.0 (64.8; 81.3)	8.1 (8.0; 8.3)	W _{rnfl} =0.6; p _{rnfl} =0.547; W _{vol} =0.4; p _{vol} =0.704
Group 1 SPECTRALIS manual mode	72.65 (65.0; 80.75)	8.0 (7.9; 8.2)	73.3 (65.0; 84.8)	8.0 (7.9; 8.2)	W _{rnfl} =0.3; p _{rnfl} =0.731; W _{vol} =1.0; p _{vol} =0.312

RNFL, retinal nerve fiber layer; OCT, optical coherence tomography. Data are presented as median with lower and upper quartiles –Me (Q25%; Q75%).

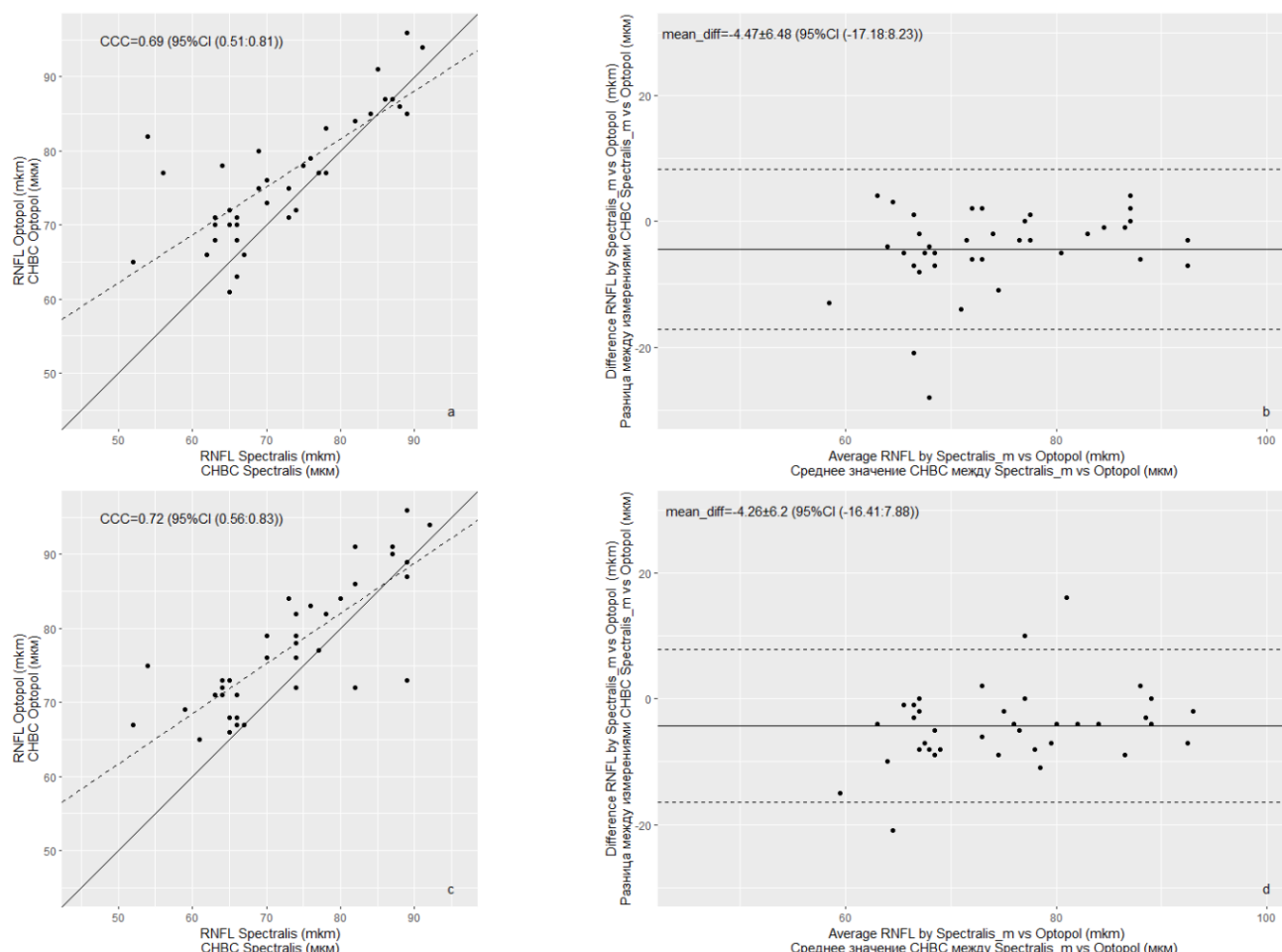


Figure 1. Dot-plot chart showing dependency of RNFL thickness according to Optopol and Spectralis (manual) at baseline (a) and 6 months later (c). Altman-Blunt plot comparing RNFL thickness measured by Optopol and Spectralis (manual) at baseline (b) and 6 months later (d).

Optical coherence tomography

All subjects underwent basic ophthalmological examinations and structural OCT on REVO NX (OPTOPOL Technology SA, Zawiercie, Poland) and SPECTRALIS OCT (SPECTRALIS; Heidelberg Engineering, Heidelberg, Germany) devices in both eyes, as well as standard automated perimetry (SAP) on Octopus 900 instrument (HaaG-Streit International, Koeniz, Switzerland). In both groups, the first measurements were taken before inclusion in the study, and then after 3 and 6 months after the onset of the study. The patients of Group 1 underwent measurements after two courses of retinal protection pharmacotherapy (after 6 mos.), while Group 2 patients were examined after one course (after 6 mos.).

SPECTRALIS OCT (Heidelberg Engineering) with Glaucoma Module Premium Edition (with a scan rate of 40 thousand A-scans/s, axial resolution of 7 μ m and wavelength of 870 nm) generates 24 equally spaced radial B-scans, each consisting of 768 A-scans covering a 15° area centered on the OD, aimed at measuring Bruch's membrane opening minimum rim width (BMO-MRW). The module also produces a 3.5 mm diameter circular scan to measure circumpapillary RNFL obtained by averaging 100 scans. To obtain each of the 24 radial scans, 25 B-scans were recorded and automatically averaged [21]. Measurements of macular thickness were performed using the posterior pole asymmetry scanning protocol. This protocol involves 61 linear scans obtained

from 16 averages; it uses image segmentation algorithm that automatically identifies the Bruch's membrane and the internal limiting membrane, and thickness data are obtained by calculating the distance between these membranes. Segmentation of the internal limiting membrane, as well as of the RNFL border of the circular scan and the macular area, was performed using software in automatic and manual modes. One of the objectives of our study was to determine whether the analysis can be improved by manual correction of software-based errors in segmentation, since the principal factor affecting the frequency of artifacts is inaccuracy of segmentation.

REVO NX (OPTOPOL Technology SA, Zawiercie, Poland) is a device with a speed of 110 thousand A-scans/s, a central wavelength of 830 nm, and an axial resolution of 5 μ m. The default scanning area is 8×8 mm for the macular region and 6×6 mm for the OD, the number of scans is 1,024×140 (A×B scan), and the scanning time is 1.5 s. The RNFL thickness was measured based on the results of averaging the scanning data of the peripapillary zone with a diameter of 3.4 mm and a thickness of 0.1 mm concentrically to the circumference from the center of the OD. The volumetric characteristics of the macular region were calculated using the Early Treatment Diabetic Retinopathy Study (ETDRS) circular diagram. The obtained measurements of morphometric parameters were automatically compared with the standard

database available in the device. This database takes into account the patient's gender and age. The analysis was based on the mean RNFL thickness in the OCT image obtained by averaging the reconstructed image from linear A-scans.

Comparison of data from two OCT devices

The agreement between the data on the RNFL thickness and the macular volume (Table 2) obtained by SPECTRALIS and OPTOPOL was evaluated using the Bland-Altman plot analysis and Lin's concordance correlation coefficient (LCCC). According to the scale for assessing the value of LCCC proposed by Landis J, Koch G [22], the agreement of data with a LCCC value of less than 0.8 and in the range of 0.81-1.0 is considered significant and almost perfect, respectively, while the LCCC level of 0.21-0.4 is considered satisfactory. However, it is helpful to bear in mind that this classification is conditional, since it was adopted for a specific study of the agreement of data regarding the diagnosis of multiple sclerosis.

Therefore, two datasets were available for the analysis of the obtained quantitative characteristics measured by the SPECTRALIS OCT device (Heidelberg Engineering). For comparison with the OPTOPOL device, a dataset obtained both in the automatic segmentation mode and after manual correction was used. In addition, we compared the data on the RNFL and the macular volume collected in the manual and automatic modes of

segmentation using the SPECTRALIS OCT instrument (Heidelberg Engineering).

Inclusion and exclusion criteria

Inclusion criteria for study participants were as follows: residence in the city of Chelyabinsk, advanced POAG subject to compensation of the IOP level, age at inclusion in the study from 45 to 89 years (i.e., middle, elderly and senile ages *sensu* the 2012 classification by the World Health Organization, www.who.int/ru), clinical refraction in the range of ± 6.0 D, astigmatism in the magnitude of ± 1.5 D, any CCT value, and any local hypotensive therapy regimen.

Exclusion criteria for our study were as follows: any other form of primary glaucoma, except for the one specified above; the IOP level beyond the compensation limits according to the Nesterov-Bunin classification [23]; opacities of the ocular optic media that prevent perimetric studies via SAP; other retinal diseases (such as any form of age-related macular degeneration, conditions after retinal vascular occlusions, diabetic retinopathy and its complications), as conventionally recognized according to the methodology of clinical trials (<https://clinicaltrials.gov>); history of ophthalmic surgery; injury and diseases of the eye and ocular adnexa in the anamnesis; diabetes mellitus and other common diseases requiring hormone therapy.

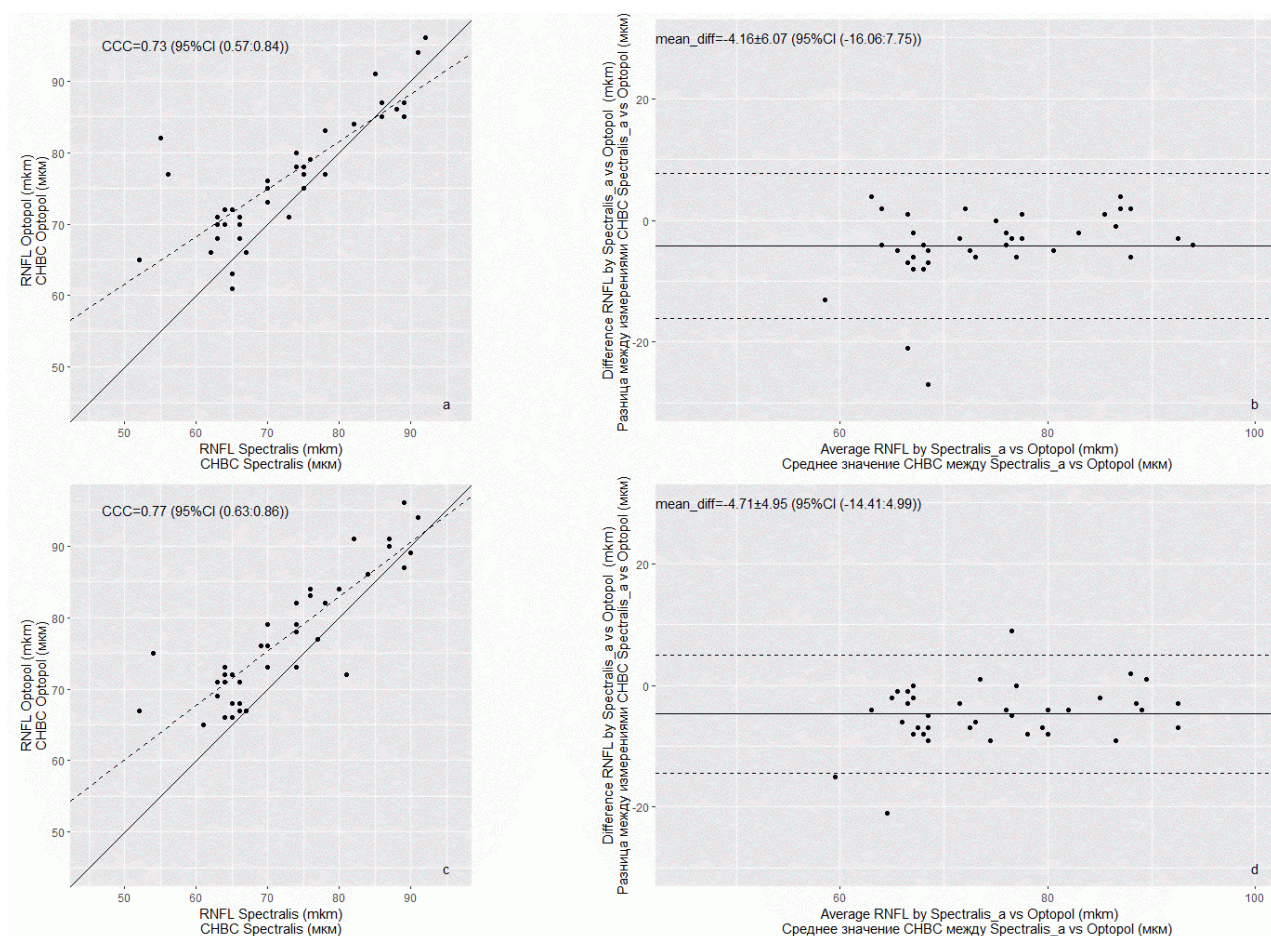


Figure 2. Dot-plot chart showing dependency of RNFL thickness according to Optopol and Spectralis (automatic) at baseline (a) and 6 months later (c). Altman-Blunt plot comparing RNFL thickness measured by Optopol and Spectralis (automatic) at baseline (b) and 6 months later (d).

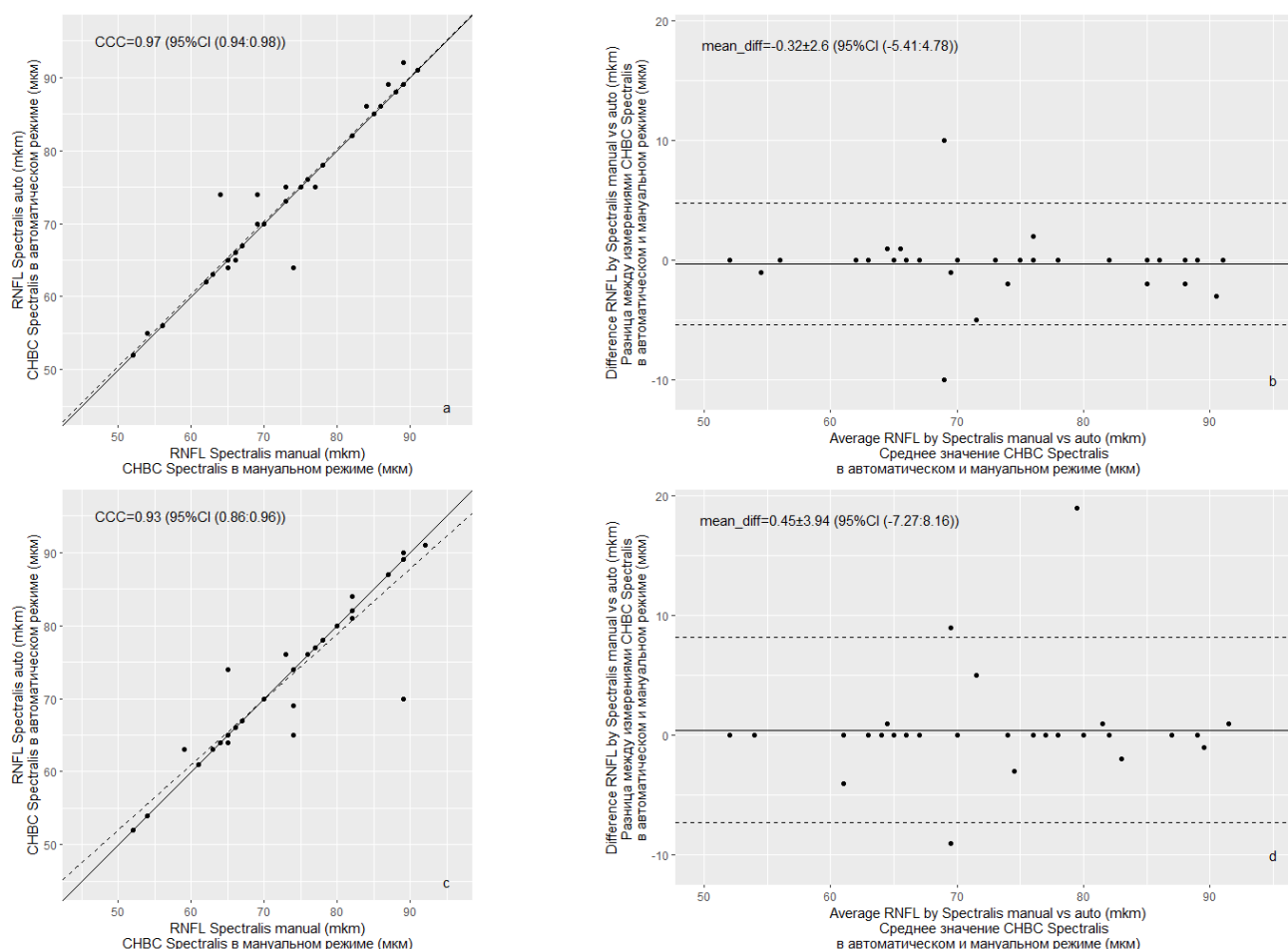


Figure 3. Dot-plot chart of RNFL thickness according to Spectralis (automatic) and Spectralis (manual) data at baseline (a) and 6 months later (c). Altman-Blunt plot comparing RNFL thickness measured by Spectralis (automatic) and Spectralis (manual) at baseline (b) and 6 months later (d).

In all cases, the diagnosis was established in accordance with the system of differential diagnosis of diseases and confirmed by specific research methods according to medical records.

Statistical analyses

Statistical data processing was performed in the R environment (version 4.2.2) [24]. Exploratory data analysis included analysis of outliers (Grubbs test, the *Outliers* package in R), normality of distribution test (Shapiro-Wilk test), and homoscedasticity test in subgroups of the study sample (Levene's test, the *Car* package in R). The parameters are presented in the Me (Q25%; Q75%) format, where Me is the median, while Q25% and Q75% are quartiles. For pairwise comparisons between groups, the Wilcoxon T-test was employed. The analysis of the agreement of the RNFL thickness and macular volume measurements was performed using the Bland-Altman method (the *epiR* package in R) [25], and the LCCC was calculated as well (the *epiR* package in R) [26]. The results were visualized by using the *ggplot2* package in R. The critical significance level was set at 0.05.

Results

The agreement between the measurements of RNFL thickness by the two devices should be considered substantial both at the

onset of the study and after 6 months. In the former case, LCCC_{start} value was 0.69 (95% CI: 0.51-0.81) in the manual mode and 0.73 (95% CI: 0.57-0.84) in the automatic mode. In the latter case, LCCC_{6mos} value was 0.72 (95% CI: 0.56-0.83) in the manual mode and 0.77 (95% CI: 0.63-0.86) in the automatic mode (Figure 1a,c; Figure 2a,c).

Moreover, in absolute values, the differences in RNFL thickness measured by the OPTOPOL device compared with the SPECTRALIS device at the onset of the study (in manual mode, -4.47±6.48, 95% CI: -17.18-8.23; in automatic mode, -4.16±6.07, 95% CI: -16.06-7.75) and after 6 months (in manual mode, -4.26±6.2, 95% CI: -16.41-7.88; in automatic mode, -4.71±4.95, 95% CI: -14.41-4.99) differed from each other by slightly less than 4 μm, and these differences were statistically significant neither at the beginning of the study nor after 6 months in both groups, for both measuring instruments, and both in manual and in automatic modes ($p>0.05$; exact values for all groups are presented in Table 2).

During the observation period, against the background of retinal protection pharmacotherapy, these differences were not statistically significant despite the fact that there were small differences in absolute values between all measurements for the initial data vs. measurements after retinal protection pharmacotherapy, ($p<0.05$, exact values for all groups are shown in Table 2).

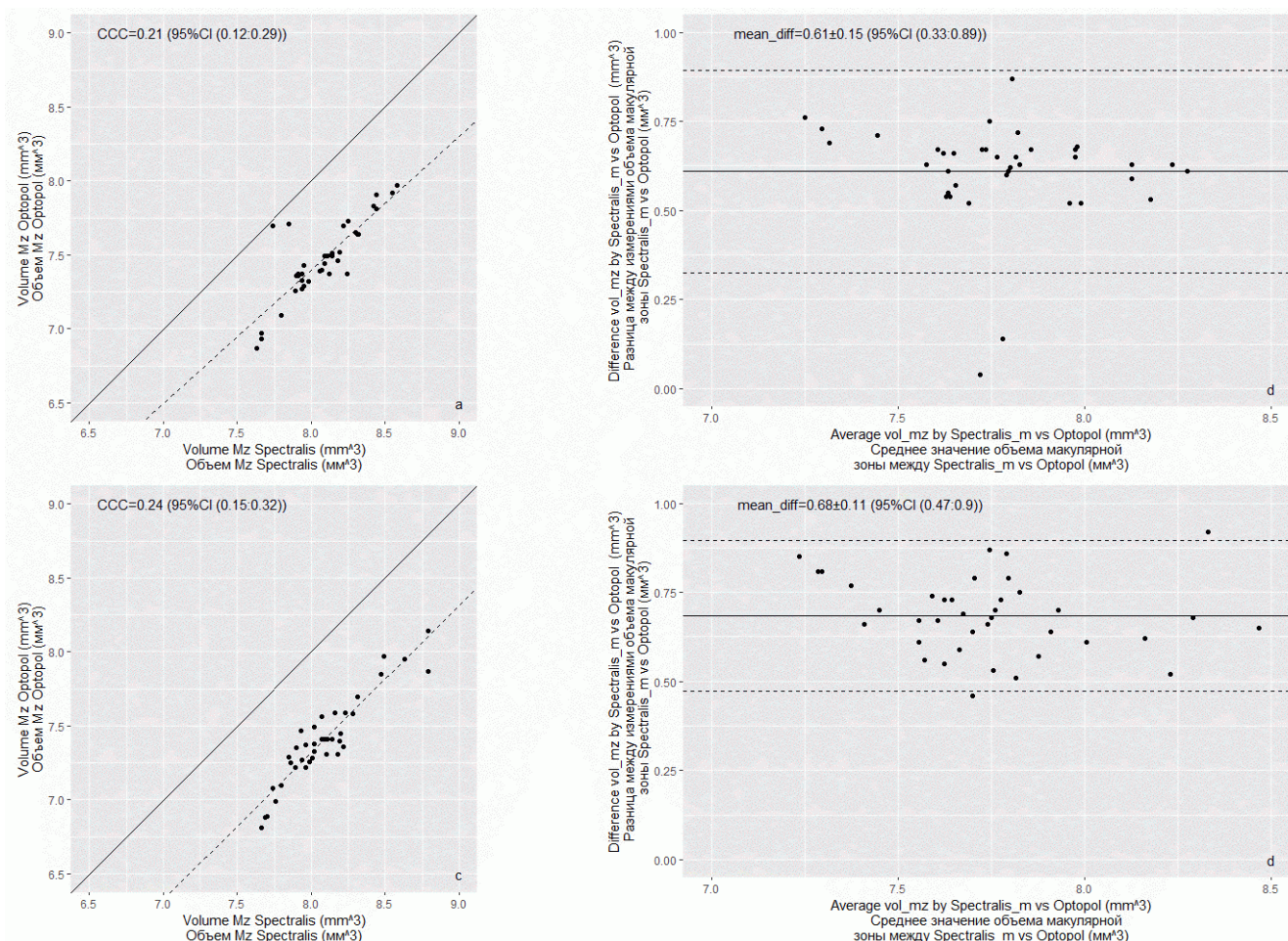


Figure 4. Dot-plot chart of macular volume thickness according to Optopol and Spectralis data (manual) at baseline (a) and 6 months later (c). Altman-Blunt plot comparing the volume of the macular area measured by Optopol and Spectralis (manual) at the beginning of the study (b) and after 6 months (d).

Manual correction of automatic RNFL segmentation at the beginning of the study yielded statistically insignificant increase in the differences between the devices in automatic mode from -4.16 ± 6.07 (95% CI: $-16.06-7.75$) to -4.47 ± 6.48 (95% CI: $-17.18-8.23$) (Figure 3b). However, after 6 months of retinal protection pharmacotherapy, manual correction of automatic RNFL segmentation led to the reverse outcome, viz.: the RNFL thickness was -4.71 ± 4.95 (95% CI: $14.41-4.99$) in the automatic mode vs. -4.26 ± 6.2 (95% CI: $-16.41-7.88$) in the manual mode (Figure 3d).

The agreement between the data obtained in the automatic and manual modes, both the RNFL thickness (Figure 3) and the macular volume (Figure 6), according to the SPECTRALIS device, is early perfect; however, this could have been caused by a small number of observations, and, as a consequence, a small number of manual corrections.

The agreement between the measurements of the macular volume was fair at the onset of the study (in the manual mode, $LCCC_{start}$ was 0.21, 95% CI: 0.21-0.29; in the automatic mode, $LCCC_{start}$ was 0.21, 95% CI: 0.21-0.29), as well as after 6 months of observation (in the manual mode, $LCCC_{6mos}$ was 0.24, 95% CI: 0.15-0.32; in the automatic mode, $LCCC_{6mos}$ was 0.23, 95% CI: 0.14-0.32) (Figures 4 and 5).

Six months after the start of retinal protection pharmacotherapy, the macular volume measurements (in absolute numbers) changed less, compared with the RNFL thickness values, and these changes were not statistically significant as well for the same expected reason: only patients with a stabilized IOP level were included in the study (Figure 5).

Manual correction of macular volume measurements was required in only three observations, both at the onset of the study and after 6 months of retinal protection pharmacotherapy (Figure 6).

Discussion

The absence of statistically significant differences in the studied parameters before and after retinal protection pharmacotherapy is quite anticipated, since we do not expect negative dynamics of the glaucoma in patients with compensated IOP. The judgement about the therapy effectiveness is based on long-term monitoring and the dynamics trend in the RNFL thickness over the entire observation period, as confirmed in our previous study [27].

An inconsistent effect of manual correction on the assessment of structural parameters implied that the small number of cases

requiring manual correction of RNFL measurements in our study probably did not lead to statistically significant differences in RNFL values. However, manual correction can be important for the observation of a specific patient in terms of making a decision on the tactics of further observation. Furthermore, according to the automatic segmentation data at the onset and at the end of the study, according to both devices, we observed a thinning of the RNFL in absolute values of measurements. Contrariwise, after manual adjustment on the SPECTRALIS device in both groups receiving retinal protection pharmacotherapy with Retinalamin, an increase in the thickness of the RNFL was established. However, considering that there is no reason to believe that the use of retinal protection pharmacotherapy leads to an increase in the thickness of the RNFL, the most likely explanation of the observed trend is the stabilization of the glaucoma process rather than an improvement in this parameter. As already mentioned above, in conditions of a long-term monitoring, we may observe a slower progression of the glaucoma process, as shown in our previous studies [20, 27, 28].

The difference between the measurements by different devices is probably of a systemic nature due to different

algorithms for measuring the macular volume (as described above), since on average, there is a shift in measurements by the OPTOPOL instrument relative to the SPECTRALIS device by approximately -0.6 mm^3 in all observations, and these differences are statistically significant ($p < 0.05$; for exact values for all groups, see [Table 2](#)). Besides that, both in the manual and automatic modes, two outliers were observed at the beginning of the study and were still present after manual adjustment. Accordingly, they were generated by the OPTOPOL device readings. However, after 6 months of observation, these outliers were not observed; hence, it can be assumed that an error could be made during automatic segmentation by this device, and manual adjustment may be required for a more accurate assessment of the data ([Figure 4](#)).

The need for manual adjustment in only three cases can be interpreted as a reproducible result. However, the need for manual correction of both RNFL and macular volume data should be interpreted by future researchers as an indication for exclusion from the study. On the other hand, the likelihood of such changes steadily increases in long-term studies.

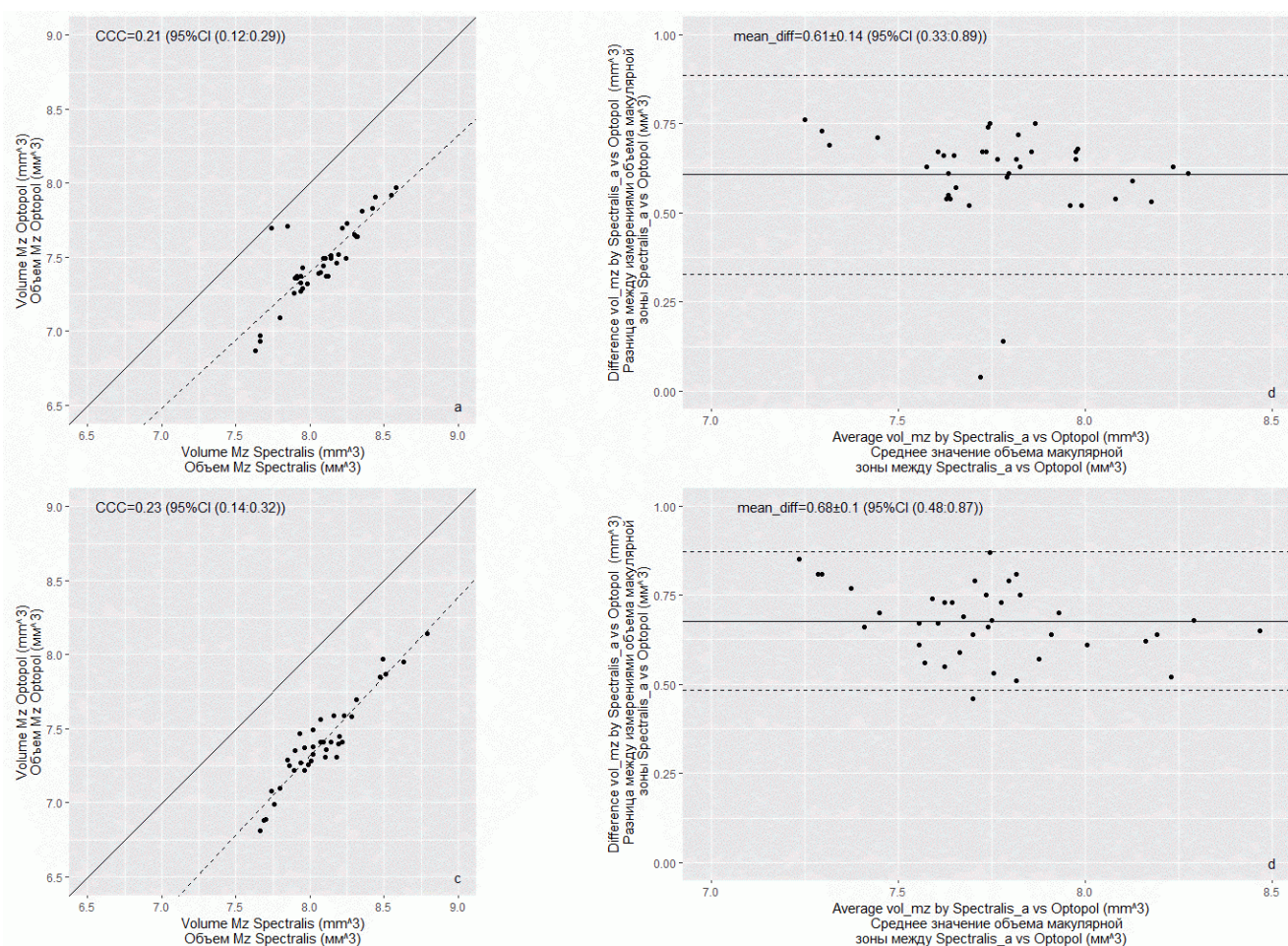


Figure 5. Dot-plot chart of macular volume thickness according to Optopol and Spectralis data (automatic) at baseline (a) and 6 months later (c). Altman-Blunt plot comparing macular volume measured by Optopol and Spectralis (automatic) at baseline (b) and 6 months later (d).

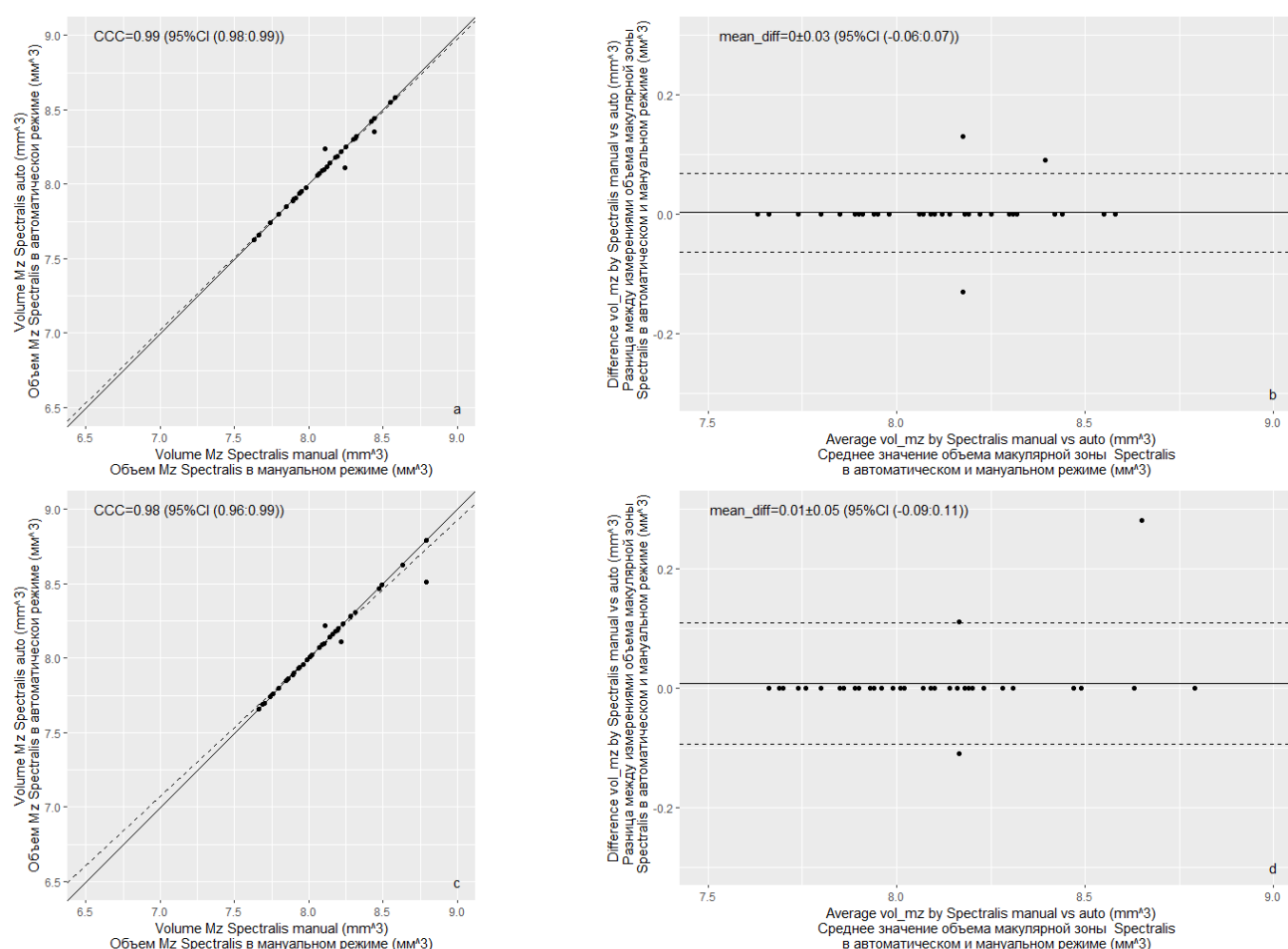


Figure 6. Dot-plot chart of macular volume according to Spectralis (automatic) and Spectralis (manual) data at baseline (a) and 6 months later (c). Altman-Bland plot comparing the volume of the macular area measured by Spectralis (automatic) and Spectralis (manual) at the baseline (b) and after 6 months (d).

Study limitations

The limitations of the study on the effectiveness of retinal protection therapy include a relatively short observation period, during which we observed no statistically significant changes in the structural OCT parameters both in patients receiving retinal protection pharmacotherapy with Retinalamin and in the control group. This was probably due to the compensated IOP level, against which no significant changes in structural parameters are expected in patients with glaucoma. To identify such differences, there are potentially three strategies: increasing the sample size of the treatment group, increasing the duration of the observation period, or a combination of both. Another limitation of this study on the agreement between measurements obtained via two OCT devices is related to the use of OCT data obtained at intervals of just several days, while no significant structural changes in conditions of compensated IOP are expected in such a short period of time.

Conclusion

The results of our study demonstrated that the agreement between the SPECTRALIS and OPTOPOL devices in terms of RNFL thickness was substantial. Regarding macular volume, it was fair. According to the automatic segmentation data presented in

absolute values, at the onset and in the end of the study, according to both devices, we observed a thinning of the RNFL. After manual adjustment on the SPECTRALIS instrument, in both groups receiving retinal protection pharmacotherapy with Retinalamin, we observed an increase in the RNFL thickness, which should probably be interpreted as a favorable effect of retinal protection pharmacotherapy.

Author contributions

All authors contributed equally to the study.

Funding

No external funding was available for the study.

Conflict of interest

None declared by the authors.

Ethical approval

All procedures performed in our study that involved human participants were in accordance with the ethical standards of the institutional Research Ethics Committee and with 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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