TRICOLOR

The use of TRIple fixed-dose COmbination in the treatment of arteriaL hypertension: opportunity for effective BP control with cOmbined antihypertensive theRapy

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BACKGROUND

Arterial hypertension (HT) is one of the major independent risk factors for cardiovascular events. The HT prevalence in Russia is about 44%, and this figure is expected to continue its growth. The prevalence of uncontrolled HT also remains high [1-2]. The majority of patients require a combination antihypertensive treatment in order to achieve blood pressure control (BP). One of the strategies for increasing the treatment efficacy is prescription of the fixed-dose combinations (FDCs) of antihypertensive drugs [3-5].

This approach based on the use of combinations of ≥2 and often ≥3 agents with different modes of action, aiming at achievement of the target BP, is reflected in the guidelines for the treatment of HT [6-7].

As a result, a new strategy has emerged, with the rapid development of different FDCs containing the renin-angiotensin-aldosterone system (RAAS) blocker (angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), or aliskiren), calcium channel blocker [CCB] (usually amlodipine), and diuretic (hydrochlorothiazide (HCT) or indapamide).

Clinical studies have been published demonstrating that these triple combinations in a single tablet effectively reduce BP in patients with uncontrolled HT on the top of dual therapy with fixed-dose or free combinations [8].

In patients treated with combination antihypertensive therapy, the compliance with treatment is one of the key factors contributing to the non-achievement of BP control. It has been shown that FDCs of several antihypertensive drugs significantly improve the treatment compliance, which in turn may be translated into even greater efficacy [9].

At the same time, there are scarce data on several aspects of the use of triple FDCs. In particular, the advantages of triple FDCs in comparison with traditional approach to the treatment require complex investigation with the use of outpatient methods of BP measurement of. The effect of triple FDCs on the quality of life (QOL) of hypertensive patients is also of interest.

AIM AND OBJECTIVES OF THE PROGRAM:

To assess the antihypertensive effectiveness effect on the 24-hour BP profile, as well as tolerability of and compliance to the treatment with a triple FDC of amlodipine / indapamide / perindopril arginine in hypertensive patients in the real clinical practice.

Primary endpoints:

- The effectiveness of triple FDC of amlodipine / indapamide / perindopril arginine in terms of BP control in hypertensive patients from the real clinical practice.

Secondary endpoints:

- The 24-hour BP profile on the top of FDC of amlodipine / indapamide / perindopril arginine in hypertensive patients from the real clinical practice.
- Tolerability of the triple FDC of amlodipine / indapamide / perindopril arginine in hypertensive patients from the real clinical practice.
- Compliance with the treatment with triple FDC of amlodipine / indapamide / perindopril arginine in hypertensive patients from the real clinical practice.

DESIGN AND METHODOLOGY

Type of program: Multicenter, observational, non-controlled, open-label program.

Investigators: Cardiologists and outpatient (primary care) physicians (general practitioners).

Number of patients: 1,300 hypertensive patients.

The patient is included in the program if prior to the study his/her doctor decided to adjust treatment, targeted at the BP control improvement, by prescription of a triple FDC of amlodipine / indapamide / perindopril arginine. The prescription of the triple FDC of amlodipine / indapamide / perindopril arginine during the program is made by the doctor's decision according to the instructions for medical use of this FDC.

Presumably, each doctor will include 4 patients in average. It is planned to include 1,300 patients.

Time frame of the program

First subject in (FSI):	November, 2018
Last subject last visit (LSLV):	January, 2019
Database lock:	February, 2019
Statistic report:	May, 2019
Clinical study report:	January, 2020.

Inclusion criteria

- Age 18 to 79 years
- Essential hypertension
- Patient's consent to participate in the program
- Doctor's decision to prescribe FDC of amlodipine / indapamide / perindopril arginine, according to the instruction for use, prior to the inclusion in the program.

Non-inclusion criteria

- Symptomatic, or secondary arterial hypertension
- Office BP ≥ 180/110 mm Hg on treatment (at V0 visit)
- History of myocardial infarction, unstable angina, or cerebrovascular accident within the past 1 year
- CHF of class III-IV NYHA
- Type I diabetes or decompensated type 2 diabetes
- Diseases with severe organ dysfunction (hepatic failure, renal failure, etc.)
- Contraindications to or known intolerance of dihydropyridine calcium channel blockers (including amlodipine) and/or indapamide and/or ACE inhibitors (including perindopril) and/or their fixed combination
- Inability to understand the nature of the program and/or to follow the doctor's recommendations, including ones for the BP self-monitoring.

During the program it is planned to perform:

- *Office BP measurements*. Arterial pressure should be measured in accordance with the recommendations of the European Society for Hypertension (ESH) using an auscultatory or oscillometric method and a semi-automatic sphygmomanometer. Before measurements, the patient should be in the sitting position for 3-5 minutes. The BP is measured on each arm, and the arm with the highest BP value is considered as reference one. Three measurements are carried out on the reference arm when patient is in the sitting position, and the average value of the second and third BP measurements with an interval of at least 1-2 minutes is recorded.
- *Pulse rate (HR) measurement*.
- *Ambulatory blood pressure monitoring (ABPM)* (in those patients, in whom it is required, according to the decision of treating physician, based on his/her experience and established practice). The BP will be measured on the non-dominant arm. The measurements will be carried out every 15 minutes in the daytime from 7:00 to 23:00 and every 30 minutes in the nighttime from 23:00 to 7:00.
- *BP self-monitoring*. Throughout the program, with the exception of the days scheduled for ABPM, patients will be keeping diaries of BP self-monitoring. The BP will be measured in a sitting position on the same arm of the working arm after a 5-minute rest with 1-2 minute interval between measurements. It is planned to carry out 3 measurements of BP in the morning after awakening (before breakfast and before taking the study drug) and in the evening before bedtime. In the diary, the average values of the SBP and DBP will be recorded, the BP will be monitored 6 days prior to the visit to doctor.
- *Surveys:*
  - Assessment of the *patient's quality of life (QoL)* will be carried out using the standardized QoL survey SF36 (Appendix 2).
  - Assessment of the *patient's compliance with the treatment* will be carried out using the compliance questionnaire (Appendix 3).
- *Assessment of the treatment tolerability* by completion of the standard pharmacovigilance form.

COURSE OF THE PROGRAM

The program will include hypertensive patients, to whom the doctor prescribed the triple FDC of amlodipine / indapamide / perindopril arginine in the routine clinical practice, based on his/her own experience and in accordance with the instruction for medical use of the drug.

Ambulatory Blood Pressure Monitoring [11]:

The 24-hour BP profiles:

Dipper: nighttime BP reduction >10% from daytime values, or ratio “nighttime/daytime BP» is <0.9 and >0.8 [normal 24-hour BP profile].
Reduced dipper: nighttime BP reduction by 1 to 10% from daytime values, or ratio “nighttime/daytime BP» is <1 and >0.9 [reduced 24-hour BP profile].
Non-dipper: Absence of nighttime BP reduction or its increase, or ratio “nighttime/daytime BP» is ≥1 [this profile is associated with a high cardiovascular risk].
Extreme dipper: The substantial nighttime BP reduction by >20% from daytime values or ratio “nighttime/daytime BP» is <0.8 [questionable cardiovascular risk].
Nocturnal hypertension: increase in the absolute values of nighttime BP.

Target BP level

In accordance with the guidelines of the Russian Hypertension Society (RMOAG)/Russian Society of Cardiology (VNOK) for the treatment of hypertension (2010, version 4), BP control is defined as office BP <140/90 mm Hg.

Duration of the program: 12 weeks.

During this time, the patient's visits to the doctor are scheduled in accordance with the presented flow chart.

Flow chart of the program

Time	Week 0 (V1)	Week 2 (V2)	Week 4 (V3)	Week 12 (V4)
Defining the inclusion/non-inclusion criteria	X			
Patient’s informed consent	X			
Medical history, risk factors and lifestyle	X			
Recording of the current therapy	X	X	X	X
BP and HR measurements	X	X	X	X
Body weight and height	X			
ABPM (in a part of patients)	X			X
Issuing the diaries for BP self-monitoring				
Recoding of the data of BP self-monitoring		X	X	X
Assessment of adverse events		X	X	X
Completion of the QoL questionnaire	X			X
Completion of the Treatment compliance questionnaire	X			X

Visit 1 (inclusion in the program)

- Selection of patients; defining the inclusion/non-inclusion criteria.
- Providing a patient with the Diary for BP self-monitoring and instruction on its completion.
- Carrying out the following examinations:
    - BP and HR measurements;
    - ABPM (in those patients, to whom it was prescribed by the doctor).
- Recoding of the current therapy; completion of the questionnaires:
    - SF36 questionnaire for the QoL assessment (Appendix 2);
    - Patient's treatment compliance questionnaire (Appendix 3).

Visit 2

- Carrying out the following examinations:
    - BP and HR measurements;
    - Control of the completion of BP self-monitoring diary by a patient.
- Antihypertensive treatment at the time of visit.
- Assessment of the adverse events.

Visit 3

- Carrying out the following examinations:
    - BP and HR measurements;
    - Control of the completion of BP self-monitoring diary by a patient.
- Antihypertensive treatment at the time of visit.
- Assessment of the adverse events.

Visit 4. Completion of the program

- Carrying out the following examinations:
    - BP and HR measurements;
    - ABPM (in those patients, to whom it was prescribed by the doctor).
- Antihypertensive treatment at the time of visit.
- Completion of the questionnaires:
    - SF36 questionnaire for the QoL assessment (Appendix 2);
    - Patient's treatment compliance questionnaire (Appendix 3).
- Assessment of the adverse events.

- Collection of the diaries of BP self-monitoring.

CONCOMITANT TREATMENT

The treatment with any drugs, including antiplatelets, statins, nitrates, anti-inflammatory or other drugs, is determined by the treating physician.

Diet and physical activity

During the program there will be no additional restrictions of diet or physical activity.

Collecting and reporting the safety data

1. Definitions

1.1 Pharmacovigilance information

Pharmacovigilance data include any unintended or adverse event associated with the use of a medicinal product in humans, whether or not considered drug related, including the following special situations (situations where no adverse event occurred but information needs to be collected):

- exposure during pregnancy or breastfeeding;

- overdose, abuse, misuse, off-label uses, medication error, occupational exposure (including professional one);

- lack of the treatment efficacy of drug.

1.2. Adverse event (AE)

Adverse event (AE) is any untoward medical occurrence in a patient or clinical-trial participant who received the medicinal product, which does not necessarily have a causal relationship with the use of this medicinal product.

An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered as related to the medicinal product.

1.3. Adverse (drug) reaction (ADR)

Adverse reaction (synonyms: Adverse drug reaction, Suspected adverse (drug) reaction, Adverse effect, Undesirable effect) is a response to a medicinal product which is noxious and unintended.

“Response” in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

1.4. Serious adverse (drug) reaction (SADR)

Serious adverse reaction is an adverse reaction, which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

2. Responsibilities

2.1. Events to be reported

All available information about the following events reported during the study will be recorded:

- All serious adverse drug reactions related to the use of fixed-dose combination of amlodipine/ indapamide/ perindopril arginine
- All non-serious adverse drug reactions related to the use of fixed-dose combination of amlodipine/ indapamide/ perindopril arginine
- All reports about special situations (see 1.1)
- All adverse events.

2.2. Responsibilities of investigator

At medical visits during the program the investigator will ask a patient participating in the program to indicate whether or not an adverse event (serious or not) has occurred.

Investigator has to assess causal relationship between an adverse event and the investigated drug intake, as well as the seriousness criteria and later on the outcome of the event.

In case of Adverse Events, Adverse Drug Reactions or special situations that occurs during the program (both serious and non-serious), the investigator must complete the “Adverse event / Adverse drug reaction / Special Situation Reporting Form” (Appendix 1) without waiting for the clinical outcome or the results of additional investigations.

If the event is serious, it will be notified immediately (in the same or next working day at the latest) to Servier company in Russia via e-mail to address pvmail.rus@servier.com or by fax to number (495) 937-47-66. The anonymized copies of all the available and relevant laboratory findings, hospitalisation reports or other investigation results performed in connection with the adverse event should be attached to the form.

All other events should be reported by investigator within 2 working days.

The same rules apply for the transferring of additional information about the event.

The investigator must ensure the appropriate follow-up of the patient depending on the nature of event, until it resolves. The investigator will continue to notify follow up data according to timeframes defined above.

If investigator does not follow-up a patients anymore (i.e. in case of hospitalisation followed by the treatment by specialist or the participant's general practitioner,…), he/she will do every effort to contact the specialist or department in charge of follow-up of the patient, so as to have additional information and report it to Servier company in Russia.

2.3. Responsibilities of sponsor/marketing authorization holder (MAH)

Independently of the regulatory obligations of investigator, the sponsor/MAH must report the pharmacovigilance data to the appropriate authorities in accordance with the Good Vigilance Practice and local regulations.

Cases are closed when an adverse event has recovered or patient's condition was stabilized and the report is deemed sufficiently detailed for adequate medical analysis of the case.

Ethical considerations

The program will be conducted in accordance with the principles of the Declaration of Helsinki, as amended in Fortaleza, Brasil, in 2013. Protocol of program was checked and approved in accordance with the legislation of the Russian Federation and will be complied with by the sponsor, especially with regard to data protection. Patients will be fully informed, and they will need to provide a written consent before participation in the program. Investigator should confirm in the CRF that the patient has provided an informed consent. The "Informed consent" implies that there was an individual discussion with the participant about the nature of the interview and examinations to be conducted.

The sponsor will not have data that allow identification of participants.

The study documents will be approved by the Ethics Committee.

Organizational structure and responsibilities

Investigators will receive informed consent forms and involve participants, ensure data collection in accordance with the protocol, fill in case report forms (CRFs) and verify the accuracy of the information in these CRFs, as much as possible. The patient will be provided with all information to obtain informed consent. At the same time, participants will be asked to provide their consent to the use of their personal data. The data of the participants will remain completely confidential.

Sponsor

The sponsor will be responsible for all stages of the program, for providing the resources necessary to initiate and perform the program in accordance with local regulations, as well as for the validity of the recorded data.

Statistical center

All data will be transferred and centralized by the sponsor.

Effectiveness and tolerability variables:

- Mean change in the office SBP and DBP (in mm Hg) measured in the sitting position
- Percentage (%) of patients at the target levels of the office BP (SBP <140 mm Hg and DBP <90 mm Hg): in general sample and in subgroups (men, women, patients with IHD, diabetes, metabolic syndrome, ISAH, and patients older than 65 years)
- Change in the proportion of patients with different 24-hour BP profiles (dipper, non-dipper, reduced dipper, extreme dipper, nocturnal hypertension)
- Mean change in the 24-hour SBP and DBP (in mm Hg) in patients who performed ABPM
- Mean change in the daytime SBP and DBP (in mm Hg) in patients who performed ABPM
- Mean change in the nighttime SBP and DBP (in mm Hg) in patients who performed ABPM
- Percentage (%) of patients at the target levels of the office BP (24-hour SBP <135 mm Hg and DBP < 85 mm Hg) in patients who performed ABPM
- Change in the mean score of the SF-36 survey (Appendix 2)
- Changes in the treatment compliance score by the Compliance questionnaire (Appendix 3)
- List of SAEs
- List of AEs
- List of AEs that resulted in the withdrawal of the triple FDC of amlodipine / indapamide / perindopril arginine.
- List of ADR
- List of SADR
- List of special situations

Statistical parameters

All parameters will be analyzed using the methods of descriptive statistics. For each parameter, the number of patients, mean, standard error, minimum and maximum values will be indicated.

Statistical analysis

- The baseline characteristics will be analyzed in all the patients who started the treatment (intention-to-treat [ITT] population). In case of significant differences between two treatment groups, the baseline characteristics will be provided for both of them.
- Changes in the SBP and DBP (with the corresponding confidence intervals) will be assessed in the patients who completed the program without major deviations from protocol (per-protocol population [PPP]).
- The analysis of parameters with normal distribution will be performed using the Student's t-test for paired measurements; otherwise the non-parametric Wilcoxon test will be used. The percentage of patients with normalized BP, as well as the percentage of patients who responded to treatment (with 95% confidence intervals), will be calculated.
- Questionnaires: The score for each scale will be calculated as the sum of scores for questions constituting the scale.
- Assessment of the AEs will be carried out in all the patients who started the treatment (ITT population).

Administrative aspects

The ownership of documentation, data and results of the program.

The sponsor reserves the exclusive right to all materials, information, unpublished documentation, results and information received during the program. The sponsor reserves the right to send data from the program (case report forms, results of analysis, reports) to the health authorities.

No unpublished documentation or information transmitted to investigators can be transferred to unauthorized persons without the prior formal written permission of Sponsor.

Publication and communication

Sponsor is responsible for communication and publication of data on the program. No aspect of the results of this program or other data may be published, submitted or distributed without the expressed written permission of Sponsor. Participants of the program fully transfer to the Sponsor the authority for the first presentation, communication and publication of the results on behalf of all employees. No other communication or publication is permitted before this first publication. Any subsequent communication or publication must first be reviewed and approved by the Sponsor and must refer to the program and the first publication.

APPENDIX 1.

Adverse event / Adverse drug reaction / Special Situation Reporting Form*

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Please send this form immediately by fax (495) 937-47-66 or by email to pvmail.rus@servier.com, or pass it to the associate of the company.

Year of birth or **Age**	**Gender**	**Height**	**Weight**	**Patient's ID:**
____ or ___	M / F	___	___	_____

Description of adverse event/reaction/special situation:	**Date of event onset**	**Date of event termination (in case of recovery)**
	__ __ ____	__ __ ____

Criteria of seriousness: ☐ NO
☐ YES (please, specify from stated below)
- ☐ Death
- ☐ Life threatening
- ☐ Hospitalization or prolongation of existing hospitalisation
- ☐ Persistent or significant disability or incapacity
- ☐ Congenital anomaly/birth defect
- ☐ Medically important event

Outcome:
- ☐ Recovered
- ☐ Recovered with consequences (persistent structural or functional impairment)
- ☐ Not yet recovered
- ☐ No recovery
- ☐ Death
- ☐ Unknown

General disease(s) / Concomitant disease(s) (please indicate year when first diagnosed).

Course adverse event/reaction/special situation (please enclose relevant findings, e.g. laboratory, hospital reports, histology, etc.):

Causal relationship with intake of the studied drug: ☐☐
☐ NO ☐ ☐ YES ☐ NOT APPLICABLE

***If «Yes»**, please indicate dates of the use of investigational drug in the first line of the table below:*

***If «No» or «Not applicable»**, please specify whether the adverse event/special situation is related to the medication of Servier company (which is specified in the table below)*:
☐ NO ☐ YES *Please indicate the name of the medication of Servier company:* ……

List of current medications	**Daily dose / route of administration**	**Dates of intake: from**	**to**	**Indication**
		-		
		-		
		-		

Name (last, first, patronymic) of doctor:
Speciality:
Work address:
Phone number: _____
(city code)

Date:

Stamp
(whenever possible)

Signature:

**Special situations are cases when adverse event was not observed, but the information should be collected: the impact of the drug during pregnancy/breastfeeding, abuse, misuse, medication error, overdose, off-label use, occupational exposure, or treatment failure…*

APPENDIX 2.

The SF-36 health survey questionnaire

(The survey was developed by RAND Health on the basis of Medical Outcomes Study; the Russian version was developed and recommended by the Multinational Center for Quality of Live Research)

Name of patient _____

Date of completion _____

Please circle one number for each statement.

1. In general, would you say your health is?

Excellent 1

Very good.....2

Good 3

Fair.....4

Poor 5

2. *Compared to one year ago*, how would you rate your health in general *now*?

Much better now than one year ago 1

Somewhat better now than one year ago …… 2

About the same.....3

Somewhat worse now than one year ago……..... 4

Much worse now than one year ago ……5

3. The following items are about activities you might do during a typical day. Does *your health now limit you* in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
A. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
B. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	1	2	3
C. Lifting or carrying groceries.	1	2	3
D. Climbing **several** flights of stairs.	1	2	3
E. Climbing **one** flight of stairs.	1	2	3
F. Bending, kneeling, or stooping.	1	2	3
G. Walking **more than a mile**.	1	2	3
H. Walking **several blocks**.	1	2	3
I. Walking **one block**.	1	2	3

J. Bathing or dressing yourself.	1	2	3

4. During the *past 4 weeks*, have you had any of the following problems with your work or other regular daily activities *as a result of your physical health*:

	Yes	No
A. Cut down the **amount of time** you spent on work or other activities.	1	2
B. **Accomplished less** than you would like.	1	2
C. Were limited in the **kind** of work or other activities.	1	2
D. Had **difficulty** performing the work or other activities (for example, it took extra effort).	1	2

5. During the *past 4 weeks*, have you had any of the following problems with your work or other regular daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)?

	Yes	No
A. Cut down the **amount of time** you spent on work or other activities.	1	2
B. **Accomplished less** than you would like.	1	2
C. Didn't do work or other activities as **carefully** as usual.	1	2

6. During the *past 4 weeks*, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all..... 1
Slightly 2
Moderately 3
Quite a bit..... 4
Extremely 5

7. How much *bodily* pain have you had during the *past 4 weeks*?

None 1
Very mild 2
Mild 3
Moderate..... 4
Severe 5
Very severe ……..……6

8. During the *past 4 weeks*, how much did *pain* interfere with your normal work (including both work outside the home and housework)?

Not at all..... 1
A little bit 2
Moderately 3
Quite a bit..... 4
Extremely 5

9. These questions are about how you feel and how things have been with you *during the past 4 weeks*. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the *past 4 weeks*...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
A. Did you feel full of pep?	1	2	3	4	5	6
B. Have you been a very nervous person?	1	2	3	4	5	6
C. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
D. Have you felt calm and peaceful?	1	2	3	4	5	6
E. Did you have a lot of energy?	1	2	3	4	5	6
F. Have you felt downhearted and blue?	1	2	3	4	5	6
G. Did you feel worn out?	1	2	3	4	5	6
H. Have you been a happy person?	1	2	3	4	5	6
I. Did you feel tired?	1	2	3	4	5	6

10. During the *past 4 weeks*, how much of the time has *your physical health or emotional problems* interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time 1
Most of the time.....2
Some of the time.....3
A little of the time …… 4
None of the time.....5

11. How TRUE or FALSE is *each* of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
A. I seem to get sick a little easier than other people	1	2	3	4	5
B. I am as healthy as anybody I know	1	2	3	4	5
C. I expect my health to get worse	1	2	3	4	5
D. My health is excellent	1	2	3	4	5

The survey has the following scales:

1. Physical functioning (PF).
2. Role physical (RP).
3. Bodily pain (BP).
4. General health (GH).
5. Vitality (VT).
6. Social functioning (SF).
7. Role emotional (RE).
8. Mental health (MH).

All the scales of survey constitute two composite measurements: Physical Component Summary (PCS) (scales 1 to 4) and Mental Component Summary (MCS) (scales 5 to 8).

The method for calculating the main parameters of the SF-36 questionnaire

Scale	Questions	Minimal and maximal values	Possible range of values
1. Physical functioning (PF)	3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, and 3J	10 – 30	20
2. Role physical (RP)	4A, 4B, 4C, and 4D	3 – 8	4
3. Bodily pain (BP)	7 and 8	2 – 12	10
4. General health (GH)	1, 11A, 11B, 11C, and 11D	5 – 25	20
5. Vitality (VT)	9A, 9E, 9G, and 9I	4 – 24	20
6. Social functioning (SF)	6 and 10	2 – 10	8
7. Role emotional (RE)	5A, 5B, and 5C.	3 - 6	3
8. Mental health (MH)	9B, 9C, 9D, 9F, 9H.	5 – 30	25

For items 6, 9A, 9E, 9D, 9H, 10, and 11, the count-down is applied.

The formula for calculating the values:
[(actual value of the scale) – (minimal possible value on the scale] : (possible range of values) □ 100.

Requirements for presenting the results:

1. Number of cases per each parameter should be indicated;
2. Descriptive statistics: M ± SD, Me (LQ; UQ), % (n/N);
3. Accuracy of results (estimates, P value); Confidence interval (for main results of the study) and P value;
4. Statistical methods (parametric and non-parametric) and statistical packages should be mentioned.

The recommended statistical packages for the data processing are StatSoft Statistica v.6.0, and SPSS 9.0.

APPENDIX 3.

Assessment of patient's compliance with medical therapy [12].

Question	YES	NO
Did you forget to take your medication this morning?		
Since the last visit to the doctor, have you run out of your medication?		
Have you ever taken your medication later than the usual time?		
Have you ever not taken your medication because, on some days, you forgot about it?		
Have you ever not take your medication because you had the impression that it was doing more harm than good?		
Do you think that you have too many tablets to take?		

Answer "No" to all the questions: good compliance;

Answer "Yes" to 1-2 questions: minor compliance;

Answer "Yes" to 3 or more questions: noncompliance.

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