Clinical investigations

of hardware-software system for bio-resonance

diagnostics “Metatron”

Product:

Model 4025 with “Metapathia GR Hunter” software, version 1.9.3.25.

Serial numbers: 94409413, 94409425, 94409436, 94409441, 94409450, 94409455

“Metatron”-4025 version Clinical with “Metapatia GR Clinical” software, version 1.10.6.6, serial number 944-0678

“Metatron” (prototype model) with “Metapathia GR Clinical” software, version 1.9.6. 30

“Metatron” (prototype model) with “Metapathia GR Clinical” software, version 1.10.6.6

“Metatron”-4021 with “Metapathia GR Professional” software, version 1.8.10.23, serial number 94409446

“Metatron TorDi” (prototype model) with “Metapathia TorDi” software, version 08.12.24.1

“Metatron”-4025 version Clinical (prototype model) with “NutriSoft Diamond” software, version 1.12.01.12

“Metatron”-4017 with “NutriSoft Emerald” software, version 2.09.05.21, serial numbers 92310527, 92310569

“Metatron”-4025 version Clinical (prototype model) with “Red Dragon” software, version 1.12.02.28

Clinical investigations organizer
“The Institute of Practical Psychophysics” Limited Liability Company, address: 2, 1st Proizvodstvennaya str., Omsk, 644031, Russia

Clinical investigations plan No PKI-1-2009

Regulatory source: ISO 14971-2011

Date: 13.03.2013

The report is drawn up by:

Head of clinical investigations department of the IPP – N.L. Ogluzdina

Summary of clinical investigations

Clinical investigations should prove that diagnostic hardware-software system "Metatron" allows the following in non-invasive mode:

- register functional deviations of human organism's systems and organs;

- detect topical foci of functional deviations;

- evaluate possibility of preliminary diagnosis;

- evaluate dynamics of functional changes.

The goal of clinical investigations at verification of developed software – is to confirm a designated purpose of HSS "Metatron", namely – evaluation of psychophysiological condition of a patient on the whole and diagnosing of many diseases and progressing states (at least in 79.8% of cases).

The goal of clinical investigations at verification of changes introduced into a software – is to check functioning of changes introduced into a software. Compliance rate – 79.8% at least.

The goal of clinical investigations at validation of HSS "Metatron" compliance to specifications stated – is to check that a product is operational and functions properly and allows the following in non-invasive mode:

- register functional deviations of human organism's systems and organs;

- detect topical foci of functional deviations;

- evaluate possibility of preliminary diagnosis;

- evaluate dynamics of functional changes.

The goal of clinical investigations at validation of prototype models – is to confirm a designated purpose of HSS, evaluate accuracy of results (79.8% at least) and safety of a model.

Investigation subjects – patients aged 18-45 with clinically proven nosological diagnoses.

Investigation method – confirmation of proven nosological diagnoses of verified patients.

Clinical investigations started on 03.01.2009.

Clinical investigations completed on 25.12.2012.

Results:

Achieved accuracy is 93.9%.

Conclusion:

Designated purpose of hardware-software system of computed non-linear (NLS) diagnostics "Metatron" - evaluation of psychophysiological condition of a patient on the whole and diagnosing of many diseases and progressing states – is confirmed clinically.

Contents:

1. Introduction

Regulatory documents: ISO 14155-2011, MEDDEV 2.7.1. rev.3, QM-01-2012 Quality manual, W-QMS-7-3-2012 Risks management, STO-QMS-7.3.-15-2011 Software of hardware-software system "Metatron" – life cycle processes. Management procedure.

Clinical investigations of HSS "Metatron" are carried out in the Institute of Practical Psychophysics in order to:

- Verify developed software;

- Verify changes introduced into software;

- Validate compliance of HSS “Metatron” (end product) to specifications stated (on sampling basis);

- Validation of prototype models.

2. Materials and methods

2.1 Description of a product

a) manufacturer – the Institute of Practical Psychophysics, Limited Liability Company;

b) model line investigated:

Model 4025 with "Metapathia GR Hunter" software, version 1.9.3.25.

Serial numbers: 94409413, 94409425, 94409436, 94409441, 94409450, 94409455

"Metatron"-4025 version Clinical with "Metapatia GR Clinical" software, version 1.10.6.6, serial number 944-0678

"Metatron" (prototype model) with "Metapathia GR Clinical" software, version 1.9.6. 30

"Metatron" (prototype model) with "Metapathia GR Clinical" software, version 1.10.6.6

“Metatron”-4021 with “Metapathia GR Professional” software, version 1.8.10.23, serial number 94409446

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“Metatron”-4025 version Clinical (prototype model) with “NutriSoft Diamond” software, version 1.12.01.12

“Metatron”-4017 with “NutriSoft Emerald” software, version 2.09.05.21, serial numbers 92310527, 92310569

“Metatron”-4025 version Clinical (prototype model) with “Red Dragon” software, version 1.12.02.28

c) Hardware-software system of bio-resonance diagnostics “Metatron” operates on the basis of approximate screening diagnostics of functional changes in human organism method, which consists in detection of possible location of pathological process and degree of its extent.

Indications:

• Screening-diagnostics of the functional status of human organs and systems;

determining the probabilistic localization of functional changes locuses;

• Approximation of one or few provisional diagnoses;

• Assessing dynamics of dysfunctional changes in a human body.

Contraindications:

• Less than 7 years old;

• Epilepsy, mental disorders;

• Hyperthermia (> 38°C);

• Aftertreatment after a myocardial infarction or a stroke;

• Pregnancy;

• Implanted heart pacemaker;

• Presence of foreign objects in a human body, such as implants, metallic and other

structures, i.e., endoprostheses, etc.).

2.2 Summary of clinical investigations plan

Clinical investigations goals:

The goal of clinical investigations at verification of developed software – is to confirm a designated purpose of HSS "Metatron", namely – evaluation of psychophysiological condition of a patient on the whole and diagnosing of many diseases and progressing states (at least in 79.8% of cases).

The goal of clinical investigations at verification of changes introduced into a software – is to check functioning of changes introduced into a software. Compliance rate – 79.8% at least.

The goal of clinical investigations at validation of HSS "Metatron" compliance to specifications stated – is to check that a product is operational and functions properly and allows the following in non-invasive mode:

- register functional deviations of human organism's systems and organs;

- detect topical foci of functional deviations;

- evaluate possibility of preliminary diagnosis;

- evaluate dynamics of functional changes.

<u>The goal of clinical investigations at validation of prototype models</u> – is to confirm a designated purpose of HSS, evaluate accuracy of results (79.8% at least) and safety of a model.

Clinical investigations design

a) Evaluation of acquired data is carried out by its comparison with clinically proven nosological diagnoses of 1) cardiovascular diseases, 2) gastrointestinal tract diseases, 3) diseases of liver and gall bladder;

b) patients aged 18 – 45 with clinically proven nosological diagnoses of 1) cardiovascular diseases, 2) gastrointestinal tract diseases, 3) diseases of liver and gall bladder;

c) There should be no x-ray or physical therapy devices close to the investigation room.

To stabilize measuring conditions diagnostics should be carried out at relative humidity of 60-85% and temperature of +17°C - +25°C.

Before the investigation a patient should remain in a calm wake condition for at least 15 minutes. It is not recommended to carry out diagnostics after abundant meals, physical and psycho-emotional stresses.

d) Studies carried out using the hardware-software system «Metatron», allow obtaining frequency spectra from the researched structures, which are compared with the available spectral etalons of pathological processes. The obtained coefficient of spectral differences allows evaluating the probability of preliminary diagnoses.

To evaluate results of an examination by means of graphs analysis, both status of input signal – it is depicted by red color (S), and status of output signal depicted by dark blue color (N) have to be observed. Shape of graphs will let you determine to which of etalon processes it is closer and define spectral similarity between etalon process and graph which was obtained from a patient.

These operating rhythms of functional systems of an organism have a low-frequency range (GHz).

- 1.8 – skeletal system;

- 2.6 – coarse connective tissue, joints, and cardiac valves;

- 2.6-3.4 – loose connective tissue, striated muscular, and cardiac muscle;

- 3.4 – unstriated muscular tissue.

- 4.2 – tessellated epithelium of the digestive tract;

- 4.9 – stratifies squamous and columnar epithelia; reproductive organs;

- 4.9-5.8 – lymphoid ring of the pharynx, upper section of the respiratory tract, lymphatic system, spleen, ovaries, and prostrate;

- 6.6 – peripheral nervous system, bronchus epithelium, adrenals, and thyroid;

- 7.4 – central sections of sensory analysers except the optic ones, and sub cortical structures of the brain, pons cerebelli; cerebellum, limbic system and lungs parenchyma;

- 8.2 – retina, optic nerve, cerebral cortex.

This program allows comparing of spectral differences values (D) with present etalon database. Results are displayed on a screen as a table where in upper line etalon with minimal spectral difference is shown. If index of spectral differences is less than 0.425, possibility of pre-diagnosis is more than 90%, these etalons marked with red color. Spectral difference value from 0.450 to 0.750 evidences about possibility of pre-diagnosis from 90% to 50%.

e) criteria for inclusion:

- Age from 18 to 60 years old with clinically proven nosologcial diagnoses of 1) cardiovascular diseases, 2) gastrointestinal tract diseases, 3) diseases of liver and gall bladder.

f) criteria for exclusion:

• Less than 7 years old;

• Epilepsy, mental disorders;

• Hyperthermia (> 38°C);

• Aftertreatment after a myocardial infarction or a stroke;

• Pregnancy;

• Implanted heart pacemaker;

• Presence of foreign objects in a human body, such as implants, metallic and other structures, i.e., endoprostheses, etc.).

g) Before diagnosing a therapist should learn from a patient if there are contraindications for examination. Objectives of examination should be explained to a patient.

1. Patient is seated on a chair near operator therapist. Information about functional condition of organs and tissues is read noninvasevely by magnetic inductors which shall be put on (according to poles) before investigation.

2. Collecting of information about patient and storing it in PC memory (patient's name, date of birth, sex, age, address, phone number, organ resections).

3. Select investigation type:

Express – allows investigation of full topographic pictures without detailed elaboration.

Standard - allows investigation of separate biological structures if some pathological changes are present.

Detailed - allows investigation of all biological formations structure which may be necessary for high quality scientific researches.

4. Investigation form selection:

Software selection allows investigating of polyorgan models in order to reveal functional changes, then analyze them and start automatic research of organs, histological and cytological structures.

Manual selection allows therapist to choose organs for investigation.

5. Investigation – measuring of functional changes degree in control points placed on polyorgan, organ, histological and cytological models, results evaluated according to six grade Flandler's scale (Annex 3): 1 – degree of latent functional activity; 2 – degree of optimal regulation; 3 – shifting of properties to a higher level, stress of regulatory systems; 4 – asthenisation of regulatory mechanisms; 5 – compensated disorders of adaptation mechanisms; 6 – decompensation of adaptation mechanisms, severe functional disorders.

6. Investigation results analysis.

7. Drawing up of a conclusion, advices to a patient.

h) There are no criteria for exclusion or discontinuing of subjects participation in investigations, because initially there are criteria to rule out the possibility to become a subject of investigations (point i).

i) number of subjects necessary for inclusion into clinical investigations:

- cardiovascular diseases – at least 35 subjects;

- gastrointestinal tract diseases – at least 40 subjects;

- diseases of liver and gall bladder – at least 30 subjects.

j) presence of adverse events or effects is ascertained according to complaints of volunteers. They should notify research center about it in written form.

k) period of HSS "Metatron" application in clinical investigations is 120 days. Period of further monitoring of a certain subject during clinical investigations is 3 days.

l) Factors which may question results of clinical investigations:

- inadequate training of researcher for work with HSS "Metatron";

- medicinal treatment of a subject during clinical investigations period;

- any treatment procedures (physiotherapy, massage) of a subject during clinical investigations period;

- when subject does not inform about resections.

m) Statistical analysis

Verification of clinical investigations results is carried out by comparing of obtained data with clinically proven nosological diagnoses, i.e. true-positive results (coincidence of screening diagnostics investigation results with data of functional and laboratory researches).

Altogether 105 subjects with pathological processes from declared nosological groups must be investigated.

Processing of materials must show true-positive results in 78.9% of cases at least.

3. Results

Clinical investigations started on 03.01.2009.

Clinical investigations completed on 25.12.2012.

Investigation summary table: model 4025 “Metatron” with “Metapathia GR Clinical” software.

409 investigations were carried out.

Nosological groups	Pathologies confirmed by clinical methods (number of cases)	Percentage of confirmation
Cardiovascular system pathologies, total	147	140 cases 95,2%
hypertensive disease	55	53
ischemic heart disease	19	18
myocardiodystrophy	19	18
heart rhythm disorder	51	48
aortic valve stenosis	3	3
gastrointestinal tract pathologies, total	169	157 cases 92,9%
catarrhal gastritis	73	71
erosive gastritis	22	20
gastric ulcer	13	11
chronic pancreatitis	21	18
duodenitis	14	14
colitis	16	14
large intestine dyskinesia	8	7
Grohn's disease	1	1
large intestine polyp	1	1
liver and gall bladder pathologies	93	88 cases 94,6%
chronic cholecystitis	42	41
choledocholithiasis	23	23
cholangitis	5	4
liver cirrhosis	7	6
fatty hepatosis	9	8
chronic pancreatitis	7	6

Proven diagnosis of a patient was confirmed after investigation at cardiovascular pathology in 140 cases (95.2%); at gastrointestinal tract pathology – in 157 cases (92.9%), at liver and gall bladder pathology – in 88 cases (94.6%).

Investigation summary table: model 4025 “Metatron” with “Hunter” software.

58 investigations were carried out.

Nosological groups	**Pathologies confirmed by clinical methods (number of cases)**	**Percentage of confirmation**
Cardiovascular system pathologies, total	10	10 cases 100%
hypertensive disease	3	3
ischemic heart disease	1	1
myocardiodystrophy		
heart rhythm disorder	5	5
aortic valve stenosis		
atherosclerosis	1	1

gastrointestinal tract pathologies, total	33	33 cases 100%
catarrhal gastritis	11	11
erosive gastritis	1	1
gastric ulcer	12	12
chronic pancreatitis		
duodenitis	4	4
colitis	4	4
large intestine dyskinesia		
Grohn's disease		
large intestine polyp	1	1
liver and gall bladder pathologies	15	15 cases 100%
chronic cholecystitis	7	7
choledocholithiasis	4	4
cholangitis	1	1
liver cirrhosis	1	1
fatty hepatosis		
chronic pancreatitis	1	1
toxic hepatitis	1	1

In total 58 investigations were carried out, where in all cases (100%) diagnosis set by other methods (ultrasound, endoscopy, tomography) was confirmed.

Investigation summary table: model 4021 “Metatron”, serial number 94409446, with “Metapathia GR Professional” software, version 1.8.10.23.

3 investigations were carried out.

Nosological groups	**Pathologies confirmed by clinical methods (number of cases)**	**Percentage of confirmation**
Cardiovascular system pathologies, total	2	2 cases 100%
hypertensive disease		
ischemic heart disease		
myocardiodystrophy	1	1
heart rhythm disorder	1	1
aortic valve stenosis		
atherosclerosis		
gastrointestinal tract pathologies, total	3	3 cases 100%
catarrhal gastritis		
erosive gastritis	2	2
gastric ulcer		
chronic pancreatitis		
duodenitis		

colitis		
large intestine dyskinesia		
atrophic gastritis	1	1
large intestine polyp		
liver and gall bladder pathologies	2	2 cases 100%
chronic cholecystitis	1	1
choledocholithiasis	1	1
cholangitis		
liver cirrhosis		
fatty hepatosis		
chronic pancreatitis		
toxic hepatitis		

In all 3 cases (100%) diagnosis set by other methods (ultrasound, endoscopy, tomography) was confirmed.

Investigation summary table: model "Metatron TorDi" with "Metapathia TorDi" software, version 08.12.24.1.

78 investigations were carried out (45 women, 33 men).

Nosological groups	**Pathologies confirmed by clinical methods (number of cases)**	**Percentage of confirmation**
Cardiovascular system pathologies, total	32	29 cases 90,6%
hypertensive disease	9	8
ischemic heart disease	4	4
myocardiodystrophy	2	2
heart rhythm disorder	11	10
hypotension	2	2
atherosclerosis	4	3
gastrointestinal tract pathologies, total	51	50 cases 98%
catarrhal gastritis	21	21
erosive gastritis	7	7
gastric ulcer	4	3
chronic pancreatitis	7	7
duodenitis	9	9
enteritis	2	2
nonspecific ulcerative colitis	1	1
atrophic gastritis		
large intestine polyp		
liver and gall bladder pathologies	20	19 cases 95%
chronic cholecystitis	11	11
choledocholithiasis		
calculous cholecystitis	6	5
liver cirrhosis		

cholecystic hepatosis	2	2
chronic pancreatitis		
toxic hepatitis	1	1

Proven diagnosis of a patient was confirmed after investigation at cardiovascular pathology in 29 cases (90.6%); at gastrointestinal tract pathology – in 50 cases (98%), at liver and gall bladder pathology – in 19 cases (95%).

Investigation summary table: model 4025 "Metatron" version Clinical (prototype model) with "NutriSoft Diamond" software, version 1.12.01.12.

35 investigations were carried out (19 women, 16 men).

Nosological groups	Pathologies confirmed by clinical methods (number of cases)	Percentage of confirmation

Cardiovascular system pathologies, total	11	9 cases 81,8%
hypertensive disease	3	2
ischemic heart disease	2	2
myocardiodystrophy	1	1
heart rhythm disorder	5	4
hypotension		
atherosclerosis		
gastrointestinal tract pathologies, total	19	18 cases 94,7 %
catarrhal gastritis	6	6
erosive gastritis		
gastric ulcer	2	2
chronic pancreatitis	2	2
duodenitis	3	3
enterocolitis	3	2
nonspecific ulcerative colitis		
atrophic gastritis		
large intestine polyp	3	3
liver and gall bladder pathologies	10	9 cases 90%
chronic cholecystitis	6	5
choledocholithiasis	3	3
calculous cholecystitis		
liver cirrhosis	1	1
cholecystic hepatosis		
chronic pancreatitis		
toxic hepatitis		

Proven diagnosis of a patient was confirmed after investigation at cardiovascular pathology in 9 cases (81.8%); at gastrointestinal tract pathology – in 18 cases (94.7%), at liver and gall bladder pathology – in 9 cases (90%).

Investigation summary table: model 4017 “Metatron”, serial number 92310527, with “NutriSoft Emerald” software, version 2.09.05.21.

33 investigations were carried out (23 women, 10 men).

Nosological groups	**Pathologies confirmed by clinical methods (number of cases)**	**Percentage of confirmation**
Cardiovascular system pathologies, total	12	10 cases 83,3%
hypertensive disease	6	5
ischemic heart disease	2	2
myocardiodystrophy		
heart rhythm disorder	4	3
hypotension		
atherosclerosis		
gastrointestinal tract pathologies, total	26	24 cases 92,3%
catarrhal gastritis	11	10

erosive gastritis	3	3
gastric ulcer	2	1
chronic pancreatitis	3	3
duodenitis	4	4
enterocolitis		
colitis	2	2
atrophic gastritis	1	1
large intestine polyp		
liver and gall bladder pathologies	16	14 cases 87,5%
chronic cholecystitis	10	10
choledocholithiasis	3	2
calculous cholecystitis		
cholangitis	1	1
fatty hepatosis	2	1
chronic pancreatitis		
toxic hepatitis		

Proven diagnosis of a patient was confirmed after investigation at cardiovascular pathology in 10 cases (83.3%); at gastrointestinal tract pathology – in 24 cases (92.3%), at liver and gall bladder pathology – in 14 cases (87.5%).

Investigation summary table: model 4025 “Metatron” version Clinical with “Red Dragon” software, version 1.12.02.28.

27 investigations were carried out (13 women, 14 men).

Nosological groups	**Pathologies confirmed by clinical methods (number of cases)**	**Percentage of confirmation**
Cardiovascular system pathologies, total	6	5 83,3%
hypertensive disease	3	2
ischemic heart disease	2	2
myocardiodystrophy		
heart rhythm disorder	1	1
hypotension		
atherosclerosis		
gastrointestinal tract pathologies, total	17	16 93,7%
catarrhal gastritis	5	5
erosive gastritis		
gastric ulcer	1	1
chronic pancreatitis		
duodenitis	3	3
enterocolitis	3	3
Grohn's disease	1	1
atrophic gastritis	2	2
large intestine dyskinesia	2	1
liver and gall bladder pathologies	11	9 81,8%

chronic cholecystitis	6	5
choledocholithiasis	3	2
calculous cholecystitis		
cholangitis		
fatty hepatosis	1	1
chronic pancreatitis		
toxic hepatitis	1	1

Proven diagnosis of a patient was confirmed after investigation at cardiovascular pathology in 5 cases (83.3%); at gastrointestinal tract pathology – in 16 cases (93.7%), at liver and gall bladder pathology – in 9 cases (81.8%).

Thus, true-positive results (coincidence of bioresonance diagnostics investigation results with data of functional and laboratory researches) are the following:

Nosological groups	Pathologies confirmed by clinical methods (number of cases)	Percentage of confirmation
cardiovascular system pathologies, total	220	205 cases 93,2%
gastrointestinal tract pathologies, total	318	301 cases 94,6%
liver and gall bladder pathologies	167	156 cases 93,4%
Total:	705	662 cases 93,9%

4. Conclusion

During clinical investigations 643 patients were examined. 705 cases of previously detected by clinical methods pathologies were registered. During clinical investigations with HSS "Metatron" 662 cases were confirmed, which amounts 93.9%.

Consequently, the goal of clinical investigations – to confirm designated purpose of hardware-software system and evaluate results accuracy (79.8% at least) – is achieved.

Designated purpose of hardware-software system of computed non-linear (NLS) diagnostics "Metatron" - evaluation of psychophysiological condition of a patient on the whole and diagnosing of many diseases and progressing states – is confirmed clinically.

Thus, HSS "Metatron" allows the following in non-invasive mode:

- register functional deviations of human organism's systems and organs;

- detect topical foci of functional deviations;

- evaluate possibility of preliminary diagnosis;

- evaluate dynamics of functional changes.

Clinical trials reports are enclosed in the Annex 2.

5. Investigators

N.L. Ogluzdina

Head of clinical trials department

V.I. Nesterova

Director of the IPP

6. Signatures

N.L. Ogluzdina

Head of clinical trials department

V.I. Nesterova

Director of the IPP

13.03.2013

Annex A

Clinical investigations plan

PKL-1-2009

1. Head of clinical investigations

N.L. Ogluzdina

Head of clinical trials department of the Institute of Practical Psychophysics

2. Clinical investigations organizer

"The Institute of Practical Psychophysics" Limited Liability Company, address: 2, 1st Proizvodstvennaya str., Omsk, 644031, Russia

3. Monitoring

Verification of results is carried out by comparing of acquired data with clinically proven nosological diagnoses:

<u>Cardiovascular diseases:</u>

Instrumental diagnostics

1. **Electrocardiography — evaluation of functional activity of metabolic processes in heart.**
2. **Echocardiography — ultrasound evaluation of heart and vessels, diagnosing of congenital and acquired diseases.**
3. **Twenty-four-hour monitoring of ECG and BP — it is a system of constant monitoring of heart activity, blood pressure and pulse.**
4. **Exercise ECG testing (veloergometry).**

Laboratory diagnostics

7. General (clinical) blood test — evaluation of qualitative and quantitative values of peripheral blood, classical approach to primary non-specific diagnostics.

8. General (clinical) urine test — evaluation of physical and chemical properties of urine, microscopy of urinary sediment.

9. Biochemical blood test — qualitative and quantitative values of functional activity of kidneys and liver, levels of lipids and carbohydrates metabolism, diagnosing of latent anemia, risks of cardiovascular diseases (homocysteine level), evaluation of blood coagulation properties and risks of cardiovascular diseases complication (fibrinogen level).

<u>Gastrointestinal diseases:</u>

Instrumental diagnostics

1 Diagnostic esophagogastroduodenoscopy (proctoscopy, rectosigmoidectomy — according to indications) allows therapist to carry out qualitative examination of mucous tunic of various gastrointestinal tract regions.

2 Ultrasound research allows evaluating of structural condition of abdominal cavity organs: liver, bile-excretory system, pancreas, spleen.

3 Contrast radiography of gastrointestinal tract.

Laboratory diagnostics

1 General (clinical) blood test — evaluation of qualitative and quantitative values of peripheral blood, classical approach to primary non-specific diagnostics.

2 General (clinical) urine test — evaluation of physical and chemical properties of urine, microscopy of urinary sediment, classical approach to primary non-specific diagnostics.

3 Biochemical blood test — qualitative and quantitative values of functional activity of kidneys and liver, levels of lipids, proteins and carbohydrates metabolism, evaluation of iron content.

4 Helicobacter pylori markers blood test — evaluation of M and G class antibodies presence in blood in order to reveal causing agent and define stage of infectious process.

5 Evaluation of gastrin amount in blood — gastrin — gastro-intestinal peptide, stimulating secretion of hydrochloric acid in stomach, its quantity plays major role in diagnosing of ulcerous lesions and gastrinomas.

<u>Diseases of liver and gall bladder:</u>

- **General (clinical) blood test — evaluation of qualitative and quantitative values of peripheral blood, classical approach to primary non-specific diagnostics.**

- **General (clinical) urine test — evaluation of physical and chemical properties of urine, microscopy of urinary sediment, classical approach to primary non-specific diagnostics.**
- **Biochemical blood test — qualitative and quantitative values of functional activity of kidneys and liver, levels of lipids and carbohydrates metabolism.**
- **Ultrasound research allows evaluating of structural condition of abdominal cavity organs: liver, bile-excretory system, pancreas, spleen.**
- **Duodenal intubation**
- **Roentgenoscopy**
- **Viral hepatitis markers blood test — detection of old and present infection.**
- **Parasitic invasion markers blood test — detection of old and present invasions.**

4. Quality management and data management

1. Planning

1.1. Clinical investigations plan is developed in order to ensure scientific validity and repeatability of investigations results in accordance with modern scientific knowledge and achievements of clinical practice and objectives of clinical investigations.

1.2. Development of plan is carried out on clinical investigations organizer's initiative.

2. Development

2.1. Organizer (developer) prepares the draft (first edition) and designates the document. Registration of clinical investigations plan is carried out in Quality Management Department of the organizer.

2.2 If necessary the developer sends draft of the document to participants of the procedure and settles contentious issues with them.

2.3. If there are no disagreements, the organizer prepares final version of the document according to received comments.

2.4. Responsibility for contents, regulations, values and requirements set by the document is placed on the developer of the document.

3. Confirmation

3.1. The organizer sends final version of the document to all interested parties for confirmation:

3.2. Parties, participating in confirmation of the document, place their signatures below the document, stating name, position and date.

3.3. Besides (if necessary), the organized agrees the document with all interested departments of the IPP and third parties.

4. Approval and introduction

4.1 The document is introduced by signatures of authorized persons of the organizer and the investigation center. Date of approval must be placed below approving signature.

5. Amendments

5.1. The plan is amended by the organizer if there were replacement, adding or exclusion of certain requirements of the document, introduction of new and more

progressive requirements, alteration of technology, according to audit results, and also on initiative of the investigation center.

If the plan must be amended on initiative of the investigation center, head of the investigation center sends to the organizer suggestions regarding amendment.

6. Revision, cancellation, withdrawal and elimination

6.1. If major correction of the document is necessary, when amending is unacceptable, the organizer (developer) decides about revision of the document.

6.2. New version of the document is subjected to all stages of management in accordance with requirements.

6.3. Number of new version of the document sequentially increases by one. Newly introduced document must have alteration number 0 (zero).

6.4 Cancellation of the document happens when:

- **Terms of clinical investigations agreement are changed;**
- **Investigation center is changed;**

6.5. Cancellation of the document is carried out by authorized person who approved it.

7. Keeping

7.1. Keeping of the document must ensure:

- **availability;**
- **quick access;**
- **safety.**

7.2. Period of clinical investigations documents keeping is 15 years.

5. Brief description of clinical investigations

Clinical investigation should prove that diagnostic hardware-software system "Metatron" allows non-invasive:

- registration of functional changes of systems and organs in human organism;

- detection topical foci of functional changes;

- detection probability of preliminary diagnosis;

- evaluation of functional changes dynamics.

6. Signatures

a) The organizer **V.I. Nesterova**

b) The head of investigations **N.L. Ogluzdina**

7. Identification and description of investigated medical device.

a) Manufacturer - "The Institute of Practical Psychophysics" Limited Liability Company; model number 4025, 4017, identification number _____, manufacturing date _____, software _____, software version number _____.

b) Hardware-software system of bio-resonance diagnostics "Metatron" operates on the basis of approximate screening diagnostics of functional changes in human organism method, which consists in detection of possible location of pathological process and degree of its extent.

Indications:

• Screening-diagnostics of the functional status of human organs and systems;

determining the probabilistic localization of functional changes locuses;

• Approximation of one or few provisional diagnoses;

• Assessing dynamics of dysfunctional changes in a human body.

Contraindications:

• Less than 7 years old;

• Epilepsy, mental disorders;

• Hyperthermia (> 38°C);

• Aftertreatment after a myocardial infarction or a stroke;

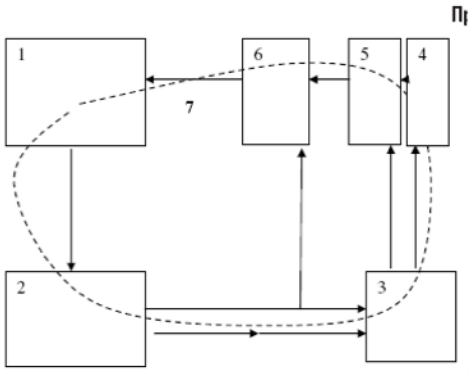
• Pregnancy;

• Implanted heart pacemaker;

• Presence of foreign objects in a human body, such as implants, metallic and other structures, i.e., endoprostheses, etc.).

c) Hardware-software system of bio-resonance diagnostics "Metatron" is a diagnostic system with biological feedback between patient and processor-telemetric unit and it may be used for evaluation of patient functional states.

The system (pic. 1) includes a unit producing series of electromagnetic stimuli, which is controlled by microprocessor and uses certain frequencies.



Pic. 1. Basic scheme of hardware-software system «Metatron» operation.

1 – processor-telemetric unit (microprocessor unit and telemetric module);

2 – unit producing series of stimuli;

3 – patient;

4 – capacity register;

5 – trigger sensor;

6 – timing unit;

7 – patient's biological feedback circuit.

In order to single out the patient's reaction this device uses a unit synchronizing stimuli with the sensor modulated by both the signal from the processor telemetric module, and that from the sensor (maintaining operation of the timing unit), picking data from a particular patient. The sensor element remotely perceives the response of the patient' brain waves to the irritant. The sensor is a broad-frequency noise generator (using the re-designed generating diode 2G401V).

Modulation frequencies: low-frequency – 240Hz; high-frequency – 4.9 GHz

Information signal is taken from the sensor and passed through amplification path. The amplification coefficient of the differential amplifier is at least 60 db. Frequency range for processing of information surges in a sampling noise ranged from 4 to 600 kHz. Clock frequency of the shift register is 1.2 ± 0.03 MHz.

Studies carried out using the hardware-software system «Metatron», allow obtaining frequency spectra from the researched structures, which are compared with the available spectral etalons of pathological processes. The obtained coefficient of spectral differences allows evaluating the probability of preliminary diagnoses.

To evaluate results of an examination by means of graphs analysis, both status of input signal – it is depicted by red color (S), and status of output signal depicted by dark blue color (N) have to be observed. Shape of graphs will let you determine to which of etalon processes it is closer and define spectral similarity between etalon process and graph which was obtained from a patient. These operating rhythms of functional systems of an organism have a low-frequency range.

- 1.8 – skeletal system;

- 2.6 – coarse connective tissue, joints, and cardiac valves;

- 2.6-3.4 – loose connective tissue, striated muscular, and cardiac muscle;

- 3.4 – unstriated muscular tissue.

- 4.2 – tessellated epithelium of the digestive tract;

- 4.9 – stratifies squamous and columnar epithelia; reproductive organs;

- 4.9-5.8 – lymphoid ring of the pharynx, upper section of the respiratory tract, lymphatic system, spleen, ovaries, and prostrate;

- 6.6 – peripheral nervous system, bronchus epithelium, adrenals, and thyroid;

- 7.4 – central sections of sensory analysers except the optic ones, and sub cortical structures of the brain, pons cerebelli; cerebellum, limbic system and lungs parenchyma;

- 8.2 – retina, optic nerve, cerebral cortex.

This program allows comparing of spectral differences values (D) with present etalon database. Results are displayed on a screen as a table where in upper line etalon with minimal spectral difference is shown. If index of spectral differences is less than 0.425, possibility of pre-diagnosis is more than 90%, these etalons marked with red color. Spectral difference value from 0.425 to 0.750 evidences about possibility of pre-diagnosis from 90% to 85%.

d)

Delivery set of HSS "Metatron" is shown in Table 1.

Table 1

No.	Name	Number
1	Main unit	1
2	Main resonator (GR-unit)	1
3	Resonance chamber	1
4	Power adaptor	1
5	USB-2.0 cable	1
6	Suitcase	1
Software and accompanying documents		
7	Technical passport	1
8	User's manual	1
9	Software (CD)	1

Appearance of hardware-software system of bio-resonance diagnostics "Metatron" is shown on pictures 2 and 3.

Main unit has the following control elements, indicators and slots for electrodes, interface and power cables:

1 — indicator of N (L) – main resonator connection.

2 — indicator of S (R) – main resonator connection.

3 — power indicator.

4 — power ON/OFF button.

5 — power adaptor slot.

6 — PC connection slot.

G — magnetic inductors connection slot.

Pic. 2. FRONT PANEL

Pic. 3. BACK PANEL

Setting up and operation procedures

1. Setting up of main unit.

1.1. Power adaptor should be plugged into slot 5 of main unit.

1.2. USB cable should be connected to slot 6 of main unit and then connected to a PC trough USB slot.

1.3. Magnetic inductors should be connected to G slot of main unit.

1.4. Resonance chamber should be connected to R slot of main unit.

1.5. Plug power adaptor to 220-230 power supply.

1.6. Turn on power button 4.

1.7. Place GR-unit on a patient's head in the following manner: headphone with L mark should be placed on left templar region, headphone with R mark should be placed on right templar region.

2. Software set up.

2.1. Software will launch only on PC to which it was installed initially, because it is protected from multiple copying.

2.2. It is recommended to copy software to any place of your hard drive, software allows copying within one PC.

If PC and main unit are turned on simultaneously operation mode turns on automatically.

Transportation and storage

1. Main unit is transported by all vehicles, except non-heated cargo bays of airplanes, in accordance with standards of transportation valid for this type of vehicle.

2. During short-termed storage main unit must be kept in closed room with air temperature of 10 to 35°C and relative humidity of 80 % at 25°C. Air in the room must be free from admixtures causing corrosion.

e) Hardware-software system of bio-resonance diagnostics "Metatron" is intended for therapists, general practitioners (family doctors), therapists of functional diagnostics of medioprophilactic institutions, having official authorization for corresponding type of medical activity.

f) Description of procedures related to use of the system

1. The system (main unit) is sent to a customer thoroughly checked and may operate in no-failure mode for a long time, but user should keep it clean and protect from mechanical damages.

2. Surfaces of the system and main resonator should be disinfected by repeated wiping with cloth wetted in 1% chloramine solution or 70% spirit.

3. During technical maintenance the following aspects should be checked:

— power cord insulation quality;

— absence of dirt on connectors of magnetic inductors, synthesizers and sensors.

If necessary these connectors must be cleaned by soft brush wetted in spirit.

4. Diagnostics must be carried out in a specialized room equipped with table, chairs and PC. There should be no x-ray or physical therapy devices close to the room.

To stabilize measuring conditions diagnostics should be carried out at relative humidity of 60-85% and temperature of +17°C - +25°C. Before investigation patient should remain in calm wake condition for at least 15 minutes. It is not recommended to carry out diagnostics after abundant meals, physical and psycho-emotional stresses.

5. Before diagnosing a therapist should learn from a patient if there are contraindications for examination. Objectives of examination should be explained to a patient.

1. Patient is seated on a chair near operator therapist. Information about functional condition of organs and tissues is read noninvasevely by magnetic inductors which shall be put on (according to poles) before investigation.

2. Collecting of information about patient and storing it in PC memory (patient's name, date of birth, sex, age, address, phone number, organ resections).

3. Select investigation type:

Express – allows investigation of full topographic pictures without detailed elaboration.

Standard - allows investigation of separate biological structures if some pathological changes are present.

Detailed - allows investigation of all biological formations structure which may be necessary for high quality scientific researches.

4. Investigation form selection:

Software selection allows investigating of polyorgan models in order to reveal functional changes, then analyze them and start automatic research of organs, histological and cytological structures.

Manual selection allows therapist to choose organs for investigation.

5. Investigation – measuring of functional changes degree in control points placed on polyorgan, organ, histological and cytological models, results evaluated according to six grade Flandler's scale (Annex 3): 1 – degree of latent functional activity; 2 – degree of optimal regulation; 3 – shifting of properties to a higher level, stress of regulatory systems; 4 – asthenisation of regulatory mechanisms; 5 – compensated disorders of adaptation mechanisms; 6 – decompensation of adaptation mechanisms, severe functional disorders.

6. Investigation results analysis.

7. Drawing up of a conclusion, advices to a patient.

8. Preceding investigations and justification of clinical investigations

8.1. Literature sources analysis

Plan of literature sources analysis

1. Objectives of literature sources analysis
2. Criteria of literature sources selection
3. Evaluation of documents
4. Report of literature sources analysis

1. Objectives of literature sources analysis – to demonstrate compliance with declared diagnostic efficiency of hardware-software system of bio-resonance diagnostics "Metatron", and evaluate if there is sufficient clinical data in literature to demonstrate its safety and clinical efficiency.

2. Criteria of literature sources selection.

Definition of studies: literature regarding NLS-technology, NLS-diagnostics, bio-resonance diagnostics.
Selection of literature: collections of scientific papers, literature in foreign languages, dissertations, non-specialized magazines, Internet.

Comparison of studies with ultrasound study, X-ray, MRI method, biochemical analysis of blood, electrocardiogram, general blood analysis, Doppler sonography, electroencephalogram.
Analysis of studies: generalization; revealing of weak and strong points; risks and benefits of NLS- technology, NLS-diagnostics, bio-resonance diagnostics.

3. Evaluation of documents.

a) To evaluate literature sources we used studies containing results regarding clinical efficiency and safety of non-linear (NLS) diagnostics, based on bio-resonance technology, allowing to acquire maximum information about degree, depth and intensity of changes in human organism. In majority of cases using of this technology has a principal value for proper diagnosing, and thus for proper choosing of treatment. Functioning of hardware-software system of bio-resonance diagnostics "Metatron" is based on NLS-diagnostics technology, described in corresponding studies.
b) 9431 patients (men and women), aged from 7 to 84 years old were examined.
Distribution of examined patients according to nosological forms is shown in table 1.

Table 1

Organs and systems diseases	Patients examined
Respiratory apparatus diseases	1030
Nerve system diseases	188
Endocrine system diseases	997
Cardiovascular system diseases	394
Stomach diseases	792
Pancreas diseases	854
Liver diseases	86
Gall bladder diseases	302
Intestine diseases	87
Urogenital system diseases	4594
Musculoskeletal system diseases	107

During examinations we used: hardware-software system of bio-resonance diagnostics "Metatron", model 4025 and model 4017. These medical devices operate on the basis of NLS-diagnostics, which is one of the methods of bio-resonance diagnostics.

Verification of NLS-examinations results was carried out by comparison of acquired data and with nosological diagnoses clinically proven by means of standard methods of hardware diagnostics and laboratory researches.

Conclusions of authors are proved by available data. Articles sufficiently reflect modern medical practice and level of diagnostic technologies. Also there are references to scientific papers. All scientific principles are followed in clinical examinations, results of which included into published works.

Evidence of equivalence of "Metatron" system's essential characteristics to characteristics of devices in abovementioned literature:

From clinical point of view: Using of medical devices with one and the same goal – diagnostics of functional disorders in human organism.

From technical point of view: Using in the same conditions – non-sterile, noninvasive. Using of the same development methods – information processed by software. Functioning is based on the same principles – reading and processing of information with a view of human health condition diagnostics.

From biological point of view: Using of specified frequency set impulses corresponding to certain human organ.

4. Report of literature sources analysis

a) Hardware-software system “Metatron” allows registering of psychophysical deviations in system and:

- get precise evaluation of functional state in form of topical analysis;
- control effectiveness and results of different therapies;
- analyze organism’s functional condition change dynamics during treatment;
- locate primary nidus of functional deviation;
- evaluate basic parameters of biosystem’s homeostasis;
- evaluate pathology character, using expert systems.

b) Literature review allows recommending this diagnostic method for application at every stage of medical care in clinics, hospitals, sanatoria and rehabilitation centers and other medical institutions.

c) HSS “Metatron” hazards evaluation

- Skin diseases hazard

Safety measures: contact with a patient is fulfilled with use of headphones (magnetic inductors) placed on a patient’s head. Before use inner surface of magnetic inductors must be disinfected by double cleaning with gauze or cotton cloth wetted in 1% solution of chloramine or 70% solution of spirit.

- Electrical shock hazard

Safety measures: design documentation presupposes use of nonconductor materials. Protective and decorative surfaces of the system provide corrosion protection of parts and subassemblies and are designed according to electric safety standards.
Design concept:
- Power adapter socket is placed on the back side of the system.
- Interface port socket, all peripheral devices of the system and indication elements on the panel are powered with low-voltage power (not more than 15 V).
- The system is efficient at power supply through the adapter from a single-phase network of an alternating current with a voltage from 187 V up to 242 V and frequency 49-51 Hz.
- Electric durability of isolation between power adapter wire plug and a metal foil with the size of 10x20 cm, placed on a surface of adapter case or the system, should provide absence of breakdowns and superficial isolation blockings at a test of sine wave voltage not less than 1500 V with frequency of 50 Hz.

- Heat shock hazard at system overheating

Safety measures: power consumption of the system is below 13 VA.
Protective element preventing power override relating to normal figures is used. In case of override the element shuts down the system.

- Electromagnetic signal level override

Safety measures: electromagnetic compatibility tests are carried out in accordance with requirements.

- Incorrect maintenance by operator
Safety measures: The Institute of Practical Psychophysics holds training courses for HSS "Metatron" operators on the base of State Medical Academy of Omsk twice in a year with state diplomas issuing.

- Power supply failure
Safety measures: we recommend to use of uninterruptible power supply unit.

- Disproportionate wear.
Safety measures: operation manual states requirements on capacity and performance of HSS: working cycle – from 3 minutes till 1 hour. Maximum continuous running time is 24 hours. The average time between failures of the system is not less than 2500 hours.
Average service life of the system before write-off is not less than 5 years. Criterion of write-off is inexpediency of the system's efficient condition restoration on technical and economic parameters.

d) All published works are related to practical application of NLS-technology, which underlies HSS "Metatron" functioning. It should be noted that the Institute of Practical Psychophysics is the inventor of the technology and that is why it cannot be compared to other similar technologies.

e) all published works related to this topic are available on: www.metatron-nls.ru.

f) In the end we can say that bio-resonance diagnostics with hardware-software system "Metatron" is safe, highly informative, available and affordable for detecting of various diseases and syndromes. The technology is compatible with all existing diagnostic methods.

Hardware-software system "Metatron" allows registering of psychophysical deviations in system and:

- get precise evaluation of functional state in form of topical analysis;
- control effectiveness and results of different therapies;
- analyze organism's functional condition change dynamics during treatment;
- locate primary nidus of functional deviation;
- evaluate basic parameters of biosystem's homeostasis;

Obtained clinical data allows recommending this diagnostic method for application at every stage of medical care in clinics, hospitals, sanatoria and rehabilitation centers and other medical institutions.

g) 15.12.2010

Professor V.I. Nesterov

8.2. Pre-clinical investigations and previous clinical application.

Clinical investigation were carried out in Russia in the following institutions:

- International Academy of non-linear diagnostic system;
- Moscow institute of medical and social rehabilitation;
- municipal hospital No 40 of Omsk;
- municipal hospital No 20 of Omsk;
- clinic of Ministry of Healthcare of Omsk.

Verification of results is carried out by comparing of received data with clinically specified nosological diagnoses by apprehensibility, specificity and accuracy. Special terms are used:

a) true-positive results (coincidence of bioresonance diagnostics investigation results with data of functional and laboratory researches);
b) false-positive results (results positive according to bioresonance diagnostics by hardware-software system “Metatron” and not revealed by standard modern methods);
c) false-negative results (pathology is revelaed by modern methods and not revealed by bioresonance diagnostics method);
d) true-negative results (absence of pathology is ascertained both by bioresonance diagnostics by hardware-software system “Metatron” and modern methods and clinical trials).

1780 patients with different nosological forms, aged from 7 to 93 years old were examined (table 1).

Distribution of researched patients according to nosological forms.

Table 1

Organs and systems diseases	Patients examined
Respiratory apparatus diseases	455
Nerve system diseases	350
Endocrine system diseases	374
Cardiovascular system diseases	430
Stomach diseases	523
Pancreas diseases	290
Liver diseases	337
Gall bladder diseases	360
Intestine diseases	466
Kidneys diseases	325

Genital system diseases	360

The following data was received after processing:
a) true-positive results – 82.2%;
b) false-positive results – 9.7%;
c) false-negative results – 12.2%;
d) true-negative results – 17.8%.

Acquired parameters are shown in table 2.

Diagnostic parameters of bio-resonance diagnostics

Table 2

Parameter	Definition	%
apprehensibility	Ratio of true-positive results to a sum of true positive and false-negative results (parameter shows percentage of revealing ill patients with bioresonance diagnostics among patients with confirmed by clinical researches illness);	92,7
specificity	Ratio of true-negative results to a sum of true-negative and false-positive results (parameter shows percentage of healthy patients revealing among patients with confirmed by clinical trials healthy state);	37,6
accuracy (coincidence per cent)	Ratio of true-positive and negative results to all variants of results.	85,6

Diagnostic parameters of bioresonance diagnostics apprehensibility at different diseases of organs and systems are the following (Table 3).

Diagnostics apprehensibility with use of bio-resonance diagnostics method.

Table 3.

Diseases of organs and systems	Apprehensibility
Respiratory apparatus diseases	77,2
Nerve system diseases	75,7
Endocrine system diseases	78,8
Cardiovascular system diseases	83,3

Stomach diseases	89,8
Pancreas diseases	85,7
Liver diseases	83,4
Gall bladder diseases	88,0
Intestine diseases	86,6
Kidneys diseases	76,8
Genital system diseases	79,3

Thus HSS “Metatron” allows non-invasively:
- register functional deviations of human organism’s systems and organs;
- detect topical foci of functional deviations;
- set preliminary diagnosis;
- evaluate dynamics of functional changes.

8.3 Analysis and evaluation of risks related to use of investigated device

The Institute of Practical Psychophysics applies the following regulatory documents for risks management:
1. EN 14971
2. EN 60601-1-4
3. EN 60601-1-2
4. EN 60601-1:1990+A1+A11+A12+A2+A13
5. R-QMS-7-3-2012 Risks management

1. Analysis and evaluation of risks

Risks management at manufacturing of the IPP’s product is carried out in the following way: For each stage of product life cycle possible dangers, probable weight, probability, risk level are evaluated. Risk level is evaluated as product of danger realization possibility and weight of consequences:
Risk = probability*potential weight

Weight and probability are evaluated by expertise. Table 1 is used for evaluation.

Risks level evaluation

Table 1

	Potential weight (consequences)			
	No harm 0	**Light 1**	**Medium 2**	**Severe 3**

Probability low 1	0	1	2	3
Probability average 2	0	2	4	6
Probability high 3	0	3	6	9

Severe (3) – serious deterioration of a state of health of a patient, a user or a third person. Serious deterioration of a state of health may include: persistent dysfunction of an organism; a condition requiring treatment or medical interbention.

Medium (2) – any indirect harm caused by medical decision, action or non-action based on information or results acquired with HSS "Metatron".
Examples are:
- misdiagnosis,
- delayed diagnosis,
- delayed treatment,
- inappropriate treatment.

Light (1) – malfunction or deterioration of performance of quality of functioning of HSS "Metatron", and:
- flaws of design or manufacturing of HSS "Metatron";
- flaws in labeling, user's manual and/or advertising materials of HSS "Metatron".

Probability low – unlikely or minor probability of risk occurrence;
Probability average – accidental or single probability of risk occurrence;
Probability high – frequent or multiple probability of risk occurrence.

Risks of 0 and 1 lever are not considered as potentially harmful for customers.

1.2 Risks evaluation

Table 2

Product life cycle stage	**Risk**	**Potential weight**	**Probability**	**Risk rate**

Evaluation results form table 2

At risk level 2 and higher risk management actions are developed.
Actions are approved by the Developer and the Head of QMS department.

9. Objectives of clinical investigations.

Clinical investigations should prove that diagnostic hardware-software system "Metatron" allows the following in non-invasive mode:

- register functional deviations of human organism's systems and organs;

- detect topical foci of functional deviations;

- evaluate possibility of preliminary diagnosis;

- evaluate dynamics of functional changes.

<u>The goal of clinical investigations at verification of developed software</u> – is to confirm a designated purpose of HSS "Metatron", namely – evaluation of psychophysiological condition of a patient on the whole and diagnosing of many diseases and progressing states (at least in 79.8% of cases).

<u>The goal of clinical investigations at verification of changes introduced into a software</u> – is to check functioning of changes introduced into a software. Compliance rate – 79.8% at least.

<u>The goal of clinical investigations at validation of HSS "Metatron" compliance to specifications stated</u> – is to check that a product is operational and functions properly and allows the following in non-invasive mode:

- register functional deviations of human organism's systems and organs;

- detect topical foci of functional deviations;

- evaluate possibility of preliminary diagnosis;

- evaluate dynamics of functional changes.

<u>The goal of clinical investigations at validation of prototype models</u> – is to confirm a designated purpose of HSS, evaluate accuracy of results (79.8% at least) and safety of a model.

Subject of investigations: diagnostics of functional disorders in human organism.
Physical effect

Method of screening diagnostics is based on noninvasive use of electromagnetic signals (1,8 – 8,2 Hz) and biological feedback (BF) among operator, patient and hardware-computing unit. As a result an outline of BF is formed; initiating trigger receives a reaction of patient's brain waves to an irritant and sends digital signal back to hardware unit. Function of initiating sensor is to perceive respond reaction of patient for informational codes sent by central computer-telemetric unit, converting it into digital signal and sending it back to computer-telemetric unit. Sensor is noise generator on the basis of radioelement, remotely subjected to

patient's brain waves effect. Direct current of optimized value within range of a few microamperes (preferably 1-5 mcA) is supplied by power unit for unit powering.

10. Design of clinical investigations

a) Verification of acquired result will be carried out by its comparison with clinically proven nosological diagnoses of 1) cardiovascular diseases, 2) gastrointestinal tract diseases, 3) diseases of liver and gall bladder.

b) Patient aged from 18 to 45 years old with clinically proven nosologcial diagnoses of 1) cardiovascular diseases, 2) gastrointestinal tract diseases, 3) diseases of liver and gall bladder.

c) There should be no x-ray or physical therapy devices close to the room.
To stabilize measuring conditions diagnostics should be carried out at relative humidity of 60-85% and temperature of +17°C - +25°C. Before investigation patient should remain in calm wake condition for at least 15 minutes. It is not recommended to carry out diagnostics after abundant meals, physical and psycho-emotional stresses.

d) Studies carried out using the hardware-software system «Metatron», allow obtaining frequency spectra from the researched structures, which are compared with the available spectral etalons of pathological processes. The obtained coefficient of spectral differences allows evaluating the probability of preliminary diagnoses.

To evaluate results of an examination by means of graphs analysis, both status of input signal – it is depicted by red color (S), and status of output signal depicted by dark blue color (N) have to be observed. Shape of graphs will let you determine to which of etalon processes it is closer and define spectral similarity between etalon process and graph which was obtained from a patient. These operating rhythms of functional systems of an organism have a low-frequency range.
- 1.8 – skeletal system;
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- 6.6 – peripheral nervous system, bronchus epithelium, adrenals, and thyroid;
- 7.4 – central sections of sensory analysers except the optic ones, and sub cortical structures of the brain, pons cerebelli; cerebellum, limbic system and lungs parenchyma;
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This program allows comparing of spectral differences values (D) with present etalon database. Results are displayed on a screen as a table where in upper line etalon with minimal spectral difference is shown. If index of spectral differences is less than 0.425, possibility of

pre-diagnosis is more than 90%, these etalons marked with red color. Spectral difference value from 0.450 to 0.750 evidences about possibility of pre-diagnosis from 90% to 50%.

e) criteria for inclusion:

- Age from 18 to 60 years old with clinically proven nosologcial diagnoses of 1) cardiovascular diseases, 2) gastrointestinal tract diseases, 3) diseases of liver and gall bladder.

f) criteria for exclusion:

• Less than 7 years old;
• Epilepsy, mental disorders;
• Hyperthermia (> 38°C);
• Aftertreatment after a myocardial infarction or a stroke;
• Pregnancy;
• Implanted heart pacemaker;
• Presence of foreign objects in a human body, such as implants, metallic and other structures, i.e., endoprostheses, etc.).

g) Moment of subject inclusion into investigations is considered to the moment when the subject signs informed consent and becomes a participant of clinical investigations.

h) Before diagnosing a therapist should learn from a patient if there are contraindications for examination. Objectives of examination should be explained to a patient.

1. Patient is seated on a chair near operator therapist. Information about functional condition of organs and tissues is read noninvasevely by magnetic inductors which shall be put on (according to poles) before investigation.
2. Collecting of information about patient and storing it in PC memory (patient's name, date of birth, sex, age, address, phone number, organ resections).
3. Select investigation type:
Express – allows investigation of full topographic pictures without detailed elaboration.
Standard - allows investigation of separate biological structures if some pathological changes are present.
Detailed - allows investigation of all biological formations structure which may be necessary for high quality scientific researches.
4. Investigation form selection:
Software selection allows investigating of polyorgan models in order to reveal functional changes, then analyze them and start automatic research of organs, histological and cytological structures.
Manual selection allows therapist to choose organs for investigation.
5. Investigation – measuring of functional changes degree in control points placed on polyorgan, organ, histological and cytological models, results evaluated according to six grade Flandler's scale (Annex 3): 1 – degree of latent functional activity; 2 – degree of optimal regulation; 3 – shifting of properties to a higher level, stress of regulatory systems; 4 – asthenisation of regulatory mechanisms; 5 – compensated disorders of adaptation mechanisms; 6 – decompensation of adaptation mechanisms, severe functional disorders.

6. Investigation results analysis.

7. Drawing up of a conclusion, advices to a patient.

i) There are no criteria for exclusion or discontinuing of subjects participation in investigations, because initially there are criteria to rule out the possibility to become a subject of investigations (point i).

j) number of subjects necessary for inclusion into clinical investigations:
- cardiovascular diseases – at least 35 subjects;
- gastrointestinal tract diseases – at least 40 subjects;
- diseases of liver and gall bladder – at least 30 subjects.

k) presence of adverse events or effects is ascertained according to complaints of volunteers. They should notify research center about it in written form.

l) period of HSS "Metatron" application in clinical investigations is 120 days. Period of further monitoring of a certain subject during clinical investigations is 3 days.

m) Factors which may question results of clinical investigations:
- inadequate training of researcher for work with HSS "Metatron";
- medicinal treatment of a subject during clinical investigations period;
- any treatment procedures (physiotherapy, massage) of a subject during clinical investigations period;
- when subject does not inform about resections.

11. Statistical analysis

Verification of clinical investigations results is carried out by comparing of obtained data with clinically proven nosological diagnoses, i.e. true-positive results (coincidence of screening diagnostics investigation results with data of functional and laboratory researches).

Altogether 105 subjects with pathological processes from declared nosological groups must be investigated.

Processing of materials must show true-positive results in 78.9% of cases at least.

12. Deviations from clinical investigations plan.

All deviations from clinical investigations plan must be registered in written form according to the following template:

Date	Essence of deviation	Reason of deviation (discontinuing) of subject participation	Name of person who made this note	Date of organizer notification	Deviation value

13. Amendment of clinical investigations plan.

The plan is amended by the organizer if there were replacement, adding or exclusion of certain requirements of the document, introduction of new and more progressive requirements, alteration of technology, according to audit results, and also on initiative of the research center.

If the plan must be amended on initiative of the research center, head of the research center sends to the organizer suggestions regarding amendment.

The organizer considers these suggestions and introduces amendments. Amendments and corrections are shown on Page of amendments registration:

Page of amendments registration

Number of amendment	No. of section, point of the plan, related to the amendment	Description	Date of amendment	Signature of person, who introduced the amendment
1	2	3	4	5

Any amendments of the document causing any alterations of other documents must be followed by amendment of all related documents.
Document amendment management procedure is similar to procedure of main document management.

14. Adverse events and adverse device effects

a) Information regarding adverse events and adverse effects of HSS "Metatron" during clinical investigations must be immediately sent to the following addresses:

1. E-mails: ipp.info@bk.ru, doctorVera@inbox.ru, info@nls-metatron.cz

2. Mailing address: The Institute of Practical Psychophysics – 2, 1st Proizvodstvennaya str., Omsk, 644031, Russia

Institute of Practical Psychophysics - Europe s.r.o. ICO 28546156 DIC CZ28546156 Nad Zavodistem 409/8, 159 00 Praha, Czech Republic.

b) Adverse events and adverse effects of HSS "Metatron":
- Harm - physical injury or damage to the health of people, or damage to property or the environment.

- Incident - "Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or

indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health."

- Indirect harm – diagnostic hardware-software system "Metatron" do not act directly on the individual. Harm may occur as a consequence of the medical decision, action taken/not taken on the basis of information or result(s) provided by the device.

Examples include
- misdiagnosis,
- delayed diagnosis,
- delayed treatment,
- inappropriate treatment,
- transfusion of inappropriate materials.

Types of incidents which must be reported to the organizer by investigation center:

An event has occurred

This also includes situations where testing performed on the device, examination of the information supplied with the device or any scientific information indicates some factor that could lead or has led to an event.

Typical events include, but are not limited to:

a) A malfunction or deterioration in the characteristics or performance.

A malfunction or deterioration should be understood as a failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.

b) False positive or false negative test result falling outside the declared performance of the test.

c) Unanticipated adverse reaction or unanticipated side effect

d) Interactions with other substances or products

e) Degradation/destruction of the device (e.g. fire)

f) An inaccuracy in the labelling, instructions for use and/or promotional materials.
Inaccuracies include omissions and deficiencies. Omissions do not include the absence of information that should generally be known by the intended users.

The event led, or might have led, to one of the following outcomes:

- death of a patient, USER or other person
- serious deterioration in state of health of a patient, USER or other person

A serious deterioration in state of health can include:

a) life-threatening illness
b) permanent impairment of a body function or permanent damage to a body structure
c) a condition necessitating medical or surgical intervention to prevent a) or b)
d) any indirect harm as a consequence of an incorrect diagnostic when used within manufacturer´s instructions for use

c) Timescale for adverse events and adverse effects of HSS "Metatron" reporting to the organizer

Upon investigation center became aware that an event has occurred and that one of its devices may have caused or contributed to that event, the following time lines apply in a case of:

- *Serious health threat*: Immediately (without any delay that could not be justified)
but not later than 2 calendar days after awareness by the investigation center of this threat.

- *Unanticipated serious deterioration in state of health*: Immediately (without any delay that could not be justified) but not later than 2 calendar days after awareness by the investigation center of this threat.

- *Others*: Immediately (without any delay that could not be justified) but not later than 7 calendar days after awareness by the investigation center of this threat.

15. Early cessation or suspension of clinical investigations

Early cessation of clinical investigations is possible when expected amount of investigation subjects sampling is completed. Decision on early cessation of clinical investigations is taken the organizer on the basis of preliminary report issued by investigation center.

Besides, cessation (or suspension) of clinical investigations is obligatory when cases describe in p.16 of the plan happen. If such events happen, the organizer decides about cessation (or suspension) of clinical investigations, after notifying by investigation center.

16. Possibility of clinical investigations results publishing

Results of clinical investigations may be published as scientific works and reports at scientific conferences, and also as advertising materials. All publishing is possible after receiving of written consent of the organizer and after the organizer becomes familiar with a document.