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State Budgetary Healthcare Institution of the City of Moscow "City Clinical Hospital No. 31 named after Academician G. M. Savelyeva of the Moscow City Department of Healthcare"

CLINICAL STUDY PROTOCOL **Analysis of the etiopathogenesis of postoperative complications in orthopedic patients in Moscow using the example of knee and hip arthroplasty and the development of an algorithm for diagnosis and prevention of these complications**

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1. Relevance and justification

A significant number of diseases in the practice of a traumatologist
The disease has a progressive course and at the terminal stages the question of reconstructive surgery using various types of implants invariably arises. The scientific novelty of the study is

it in a large prospective study of patients before and after endoprosthetic replacement with endosseous implants, which will include
assessment of mineral homeostasis, somatic status and immune status of the patient, and a morphological characterization of the bone tissue in the implantation zone will also be given, and in patients with periimplantitis, an assessment
microbiota around implants. The clinical problem that the project "Assessment of the Prevalence of Complications after Implantation" aims to solve
endoprosthetics of large joints in the territory of the Russian Federation has a number of limitations, primarily related to the collection and analysis of statistical data.
data, however, according to epidemiological research for
In 2019, 6,606 cases of implant-associated infection after knee or hip arthroplasty were registered in the country, which accounted for 2.91% of primary surgeries [Sereda A.P. et al.
al. Epidemiology of hip and knee arthroplasty and periprosthetic infection in the Russian Federation // Traumatology
and orthopedics of Russia. Vreden Russian Research Institute of Traumatology and Orthopedics, 2021. Vol. 27, No. 3. P. 84–93.]. Description of the problem being solved
1. Increased number of patients with peri-implant infection, aseptic instability, periprosthetic fractures, need for repeated hospitalization and operations, unpredictable outcome of retreatment, additional mortality, high economic burden. 2.

The problem concerns a wide range of age groups of patients who underwent knee and hip arthroplasty, as well as traumatologists and orthopedists working in traumatology departments.
and orthopedic centers of the Moscow Health Department 3. Progressive increase in the incidence of peri-implant infection, aseptic instability, peri-prosthetic fractures, increased financial burden on Moscow health care, increased mortality and mortality associated with
this nosology, an increase in disability

In connection with the widespread development of high-tech medical assistance in the field of traumatology and orthopedics provided to patients with severe forms of osteoarthritis of the hip and knee joints and
aseptic necrosis, an increase in the number of knee and hip joint endoprosthetics, a proportional increase occurs
serious complications after endoprosthetics, and the most formidable of

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and economically costly - this is the development of peri-implant infection.
Today, the scale of peri-implant infection is close to epidemic. It is worth noting that peri-implant infection is not always associated
associated with violation of surgical treatment tactics and quality of prostheses.
Often the reasons for the development of this life-threatening complication are not the ends are clear. At present, in Russia and in the city of Moscow, no large-scale prospective and retrospective study of the causes has been conducted before development of periplantar infection, the pathogenesis links have not been fully studied, and methodological approaches to the prevention and treatment of this group of patients have not been developed, which makes this topic relevant and promising. The main links will be established based on the results of the project
pathogenesis of peri-implant infection, the risk spectrum will be determined development of this complication, individual characteristics of the patient that increase the risk of developing this complication will be identified,
The principles of thanatogenesis of this complication have been determined, and other ways of managing such patients will also be determined. Based on the obtained diagnostic algorithms and recommendations will be generated based on this data on treatment tactics and preoperative preparation of patients with severe forms of osteoarthritis of the hip and knee joints, fractures of the femoral heads and aseptic necrosis, and also developed methodological recommendations for the intravital and postmortem diagnosis of peri-implant infection. The developed recommendations will

are in demand by general practitioners, rheumatologists, traumatologists-orthopedists, pathologists, rheumatologists, general practitioners, and endocrinologists. Implemented

The implementation of the program and its results is aimed at reducing the share peri-implant infection in morbidity and mortality rates.

2. Goal and objectives

The aim of the project is to establish the etiopathogenesis and morphological changes in tissues after complications of endoprosthetics.
large joints (PPI, aseptic instability, etc.) in patients of different age groups with an assessment of somatic, immune status, mineral metabolism of calcium and its metabolism, and also to develop methodological recommendations for preoperative examination

List of tasks to be addressed within the framework of the implementation of Project 1. Development of a clinical research protocol; 2. Recruitment of a cohort of patients within the study of at least 600 people for conducting
comprehensive assessment of the patient's initial status: assessment of mineral volume

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exchange (Total calcium, serum magnesium, inorganic phosphorus, 25OH Vitamin D, osteocalcin, BetaCross laps, Bone formation marker matrix P1NP, Parathyroid hormone); assessment of immune status (Interleukin 10 (IL-10, Interleukin 10, IL-10), Interleukin 1 beta (IL-1beta, IL-1b, Interleukin 1 beta, IL-1b), Interleukin 6 (IL-6, Interleukin 6, IL-6), Interleukin 8 (IL-8), Complement Component C4, Tumor Necrosis Factor (TNF) necrosis factor alpha, TNFalpha, sachectin), lymphocyte phenotyping (main subpopulations) – CD3, CD4, CD8, CD19, CD16, 56 (Lymphocyte phenotyping (main subsets panel): CD3, CD4, CD8, CD19, CD16, 56); microbiological research and PCR research, as well as somatic status (therapist, rheumatologist) and analysis of the results of the conducted instrumental research methods (MRI, CT, densitometry, radiography); 3. The study includes a single, less frequent two-fold examination of each patient from the group of the above-mentioned indicators at the preoperative stage.; 4. Conducting a study each patient with complications of osseointegration of the endoprosthesis from the group the above-mentioned indicators at the postoperative stage.; 5. Endoprosthetics/revision endoprosthetics of the knee and hip joint.; 6. Collection of tissue samples and metal structures (their fragments) from peri-implant areas for intravital pathological examination of the patient, scanning electron microscopy, sonication followed by microbiological examination (at least 5 samples) to form a characteristic of the microbiota in patients with developed complications; 7. Evaluation of the obtained results of the correlation between the somatic, immune, homeostatic (mineral) status of the patient and the development of postoperative complications, statistical analysis of the data, formation of a database data; 8. Implementation of the results of the work into clinical practice of at least the State Budgetary Healthcare Institution “City Clinical Hospital No. 31 named after Academician G.M. Savelyeva of the Moscow Health Department”. 9. Characterize pathomorphological and immunohistochemical changes, including assessment of local immunity (CD3, CD4, CD8, CD20, CD56, CD68) in the peri-implant area.

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Study design

Materials and methods

Sample size of patients participating in the study: 750 patients

Justification for calculating the patient sample size The
power calculation was performed for a minimum of 400-450 patients 1. Power formula For the t-test for the difference between two independent means: Power = 1 ÿ ÿ = P(T > t_{crit} | H_{1}) where T is a non-
central t-distribution with degrees of freedom: df = nÿ +
nÿ ÿ 2 and a non-centrality parameter: ÿ = d ÿ ÿ(nÿ nÿ / (nÿ + nÿ)) t_{crit} = t_{1ÿÿ/2, df} (two-sided
critical t) Total: Power = 1 ÿ F_{nc}(t_{crit}; df, ÿ)

F_{nc} is the distribution function of non-central t. 2. Substitution of
numbers nÿ = nÿ = 200, df = 398 ÿ = 0.05 ÿ t_{crit} ÿ 1.968 Cohen«sd = 0.3

ÿ = 0.3 × ÿ(200 200 / 400) = 0.3 × ÿ100 = 3.0 We calculate
the probability: Power = 1 ÿ
F_{nc}(1.968; 398, 3.0) ÿ 0.70 Answer: power ÿ 70%. 3.
Cohen's effect (Cohen»sd) d =
(ÿÿ ÿ ÿÿ) / ÿ
ÿÿ, ÿÿ – means of two groups ÿ –
"common" standard deviation (pooled SD)
Interpretation (Cohen, 1988): 0.2 – small
effect 0.5 – medium
effect 0.8 – large effect

Description of cohorts/patient groups

Cohort 1: Patients with hip pathology who are indicated for endoprosthetics. Size
of group/cohort 1, people: 300

Inclusion criteria for group/cohort No. 1: Patients
over 45 years of age
Idiopathic coxarthrosis
stage 3 Secondary

coxarthrosis stage 3 (ANFH, post-traumatic coxarthrosis, rheumatoid arthritis, etc.)

Exclusion criteria for group/cohort #1:

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Patients with infection of the area
hip joint Patient's refusal to participate in
the study Inability to follow up

patient for 3 years Psychiatric illnesses in
the anamnesis Somatic diseases in

stages of decompensation

Study Design for Cohort 1:

No.	Name of intervention/ treatment	Description of intervention/treatment
1	Hip arthroplasty with histological sampling	Performed on all patients
2	Revision surgeries with collection of histological material and removal of metal structures	In case of development of postoperative complications

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The indicators that will be assessed in the study of cohort/group No. 1 are:

No.	Performance evaluation indicator research	Description of the indicator	Time/period of evaluation indicator
1	Beta-Cross laps	reagent	before the primary operation and before surgery in case of re-visual intervention state
2	Clinical blood test	blood test	before the primary operation and before surgery in case of re-visual intervention state
3	Bone formation marker P1NP matrix	reagent	before the primary operation and before surgery in case of re-visual intervention state
4	Parathyroid hormone	reagent	before the primary operation and before surgery in case of re-visual intervention state
5	Sowing of wound discharge for microflora	Microbiological analysis Liz	before surgery in case of re-visual intervention state
6	Total calcium	reagent	before the primary operation and before surgery in case of re-visual intervention state
7	25OH vitamin D	reagent	before the primary operation and before surgery in case of re-visual intervention state
8	Serum magnesium	reagent	before the primary operation and before surgery in case of re-visual intervention state
9	Interleukin 10	reagent	before the primary operation and before surgery in case of re-visual intervention state
10	Interleukin 1 beta	reagent	before the primary operation and before surgery in case of re-visual intervention state
11	Interleukin 6	reagent	before the primary operation and before surgery in case

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			audit inter- wanderings
12	Interleukin 8	reagent	before the primary operation and before the operation in case audit intervention statehood
13	Tumor necrosis factor	reagent	before the primary operation and before the operation in case audit intervention statehood
14	Phagocytic activity of leucocytes reagent		before the primary operation and before the operation in case audit intervention statehood
15	Definition of herpes viruses by PCR method	reagent	before the primary operation and before the operation in case audit intervention statehood
16	Immunohistochemistry of six (6) species antibodies (CD3, CD4, CD8, CD20, CD56, CD68)	reagent	before the primary operation and before the operation in case audit intervention statehood
17	Lymphocyte phenotyping (main subpopulations) – CD3, CD4, CD8, CD19, CD16, CD56	reagent	before the primary operation and before the operation in case audit intervention statehood
18	Densitometry	Instrumental research following	before the primary operation and before the operation in case audit intervention statehood
19	Performing an MRI of the hip joint	Instrumental use- following	before the primary operation and before the operation in case audit intervention statehood
20	Performing a CT scan of the hip joint	Instrumental use- following	before the primary operation and before the operation in case audit intervention statehood
21	X-ray of the pelvic bones	Instrumental use- following	before the primary operation and before the operation in case audit

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			interventions
22	Pathomorphological examination of bone section femoral head	Bone marrow examination fabrics	before the primary operation and before the operation in case audit intervention statehood
23	Pathomorphological examination of intra-articular tissues	Soft tissue research fabrics	before the primary operation and before the operation in case audit intervention statehood
24	X-ray of the hip joint	Instrumental research	before the primary operation and before the operation in case audit intervention statehood
25	Sonication of removed implants and further microbiological study	Laboratory research	before surgery in case audit intervention statehood
26	Therapist's conclusion	Consultation with a therapist	before the primary operation
27	Sowing of microflora of discharge pharynx and nose	Instrumental use- following	before the primary operation
28	PCR test for infectious agents (viral, bacterial flora, fungi) with assessment of microbiota in the peri-implant area	Laboratory analysis	before surgery in case audit intervention statehood
29 EGD$		Instrumental use- following	before the primary operation
30	inorganic phosphorus	Reagent	before the primary operation and before the operation in case audit intervention statehood
31 Total	protein	Reagent	before the primary operation and before the operation in case audit intervention statehood
32	Albumen	Reagent	before the primary operation and before the operation in case audit intervention statehood
33 ALT		Reagent	before the primary operation and before the operation in case

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			audit inter- wanderings
34 AST		Reagent	before the primary operation and before the operation in case audit intervention statehood
35	Creatinine	Reagent	before the primary operation and before the operation in case audit intervention statehood
36	Urea	Reagent	before the primary operation and before the operation in case audit intervention statehood
37	Uric acid	Reagent	before the primary operation and before the operation in case audit intervention statehood
38	Glucose	Reagent	before the primary operation and before the operation in case audit intervention statehood
39	Glycated hemoglobin	Reagent	before the primary operation and before the operation in case audit intervention statehood
40	Total bilirubin	Reagent	before the primary operation and before the operation in case audit intervention statehood
41	Direct bilirubin	Reagent	before the primary operation and before the operation in case audit intervention statehood
42 Gamma-GT		Reagent	before the primary operation and before the operation in case audit intervention statehood
43	Iron	Reagent	before the primary operation and before the operation in case audit

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			interventions
44	Cholesterol	Reagent	before the primary operation and before the operation in case audit intervention statehood
45	Triglycerides	Reagent	before the primary operation and before the operation in case audit intervention statehood
46	Potassium	Reagent	before the primary operation and before the operation in case audit intervention statehood
47	Sodium	Reagent	before the primary operation and before the operation in case audit intervention statehood
48	Chlorine	Reagent	before the primary operation and before the operation in case audit intervention statehood
49	C-reactive protein	Reagent	before the primary operation and before the operation in case audit intervention statehood
50 ESR		Reagent	before the primary operation and before the operation in case audit intervention statehood
51	Rheumatoid factor	Reagent	before the primary operation and before the operation in case audit intervention statehood
52 APTT		Reagent	before the primary operation and before the operation in case audit intervention statehood
53 MNO		Reagent	before the primary operation and before the operation in case audit intervention statehood

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54	Fibrinogen	Reagent	before the primary operation and before the operation in case audit intervention statehood
55	Prothrombin index	Reagent	before the primary operation and before the operation in case audit intervention statehood
56	Determination of blood group by ABO system	Reagent	before the primary operation
57	Determination of the Rh factor	Reagent	before the primary operation
58	Definition of Kell	Reagent	before the primary operation
59	Rhesus antigen phenotyping reagent		before the primary operation
60	TSH	Reagent	before the primary operation
61	T3	Reagent	before the primary operation
62	T4	Reagent	before the primary operation
63 NT-proBNP		Reagent	before the primary operation
64	Clinical urine analysis	Reagent	before the primary operation and before the operation in case audit intervention statehood

Cohort 2: Patients with knee joint pathology who are indicated for endoprosthetics

Group/cohort size #2, people: 300

Inclusion criteria for group/cohort #2:

Patients over 45 years old
Idiopathic gonarthrosis stage 3
Secondary gonarthrosis stage 3 (aseptic necrosis, post-traumatic gonarthrosis, rheumatoid arthritis, etc.)

Exclusion criteria for group/cohort No. 2: Patients with knee area infection
joint Patient's refusal to participate in the study
Inability to observe the patient in
for 3 years Psychiatric illnesses in
history of somatic diseases in the stage
decompensation

Study Design for Cohort 2:

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No.	Name of intervention/ treatment	Description of intervention/treatment
1	Knee joint endoprosthetics with collection of histological material	Performed on all patients
2	Revision surgeries with collection of histological material and removed metal structures	In case of development of postoperative complications

The indicators that will be assessed in the study of cohort/group #2:

No.	Performance evaluation indicator research	Description of the indicator	Time/period of evaluation indicator
1	Beta-Cross laps	reagent	before the primary operation and before the operation in case audit intervention statehood
2	Clinical blood test	blood test	before the primary operation and before the operation in case audit intervention statehood
3	Bone formation marker P1NP matrix	reagent	before the primary operation and before the operation in case audit intervention statehood
4	Parathyroid hormone	reagent	before the primary operation and before the operation in case audit intervention statehood
5	Sowing of wound discharge for microflora	Microbiological analysis	before surgery in case audit intervention statehood
6	Total calcium	reagent	before the primary operation and before the operation in case audit intervention statehood
7	25OH vitamin D	reagent	before the primary operation and before the operation in case audit intervention statehood
8	Serum magnesium	reagent	before the primary operation

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			and before the operation in case audit intervention statehood
9	inorganic phosphorus	reagent	before the primary operation and before the operation in case audit intervention statehood
10	Interleukin 10	reagent	before the primary operation and before the operation in case audit intervention statehood
11	Interleukin 1 beta	reagent	before the primary operation and before the operation in case audit intervention statehood
12	Interleukin 6	reagent	before the primary operation and before the operation in case audit intervention statehood
13	Interleukin 8	reagent	before the primary operation and before the operation in case audit intervention statehood
14	Tumor necrosis factor	reagent	before the primary operation and before the operation in case audit intervention statehood
15	Phagocytic activity of leucocytes reagent		before the primary operation and before the operation in case audit intervention statehood
16	Definition of herpes viruses by PCR method	reagent	before the primary operation and before the operation in case audit intervention statehood
17	Immunohistochemistry of six (6) species antibodies (CD3, CD4, CD8, CD20, CD56, CD68)	reagent	before the primary operation and before the operation in case audit intervention statehood
18	Lymphocyte phenotyping (main subpopulations) – CD3,	reagent	before the primary operation and before the operation in case

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	CD4, CD8, CD19, CD16, CD56		audit inter- wanderings
19	Densitometry	Instrumental use- following	before the primary operation and before the operation in case audit intervention statehood
20	Performing an MRI of the knee joint stav	Instrumental use- following	before the primary operation and before the operation in case audit intervention statehood
21	Performing a CT scan of the knee joint	Instrumental use- following	before the primary operation and before the operation in case audit intervention statehood
22	X-ray of the knee joint in two projections	Instrumental use- following	before the primary operation and before the operation in case audit intervention statehood
23	Full-length radiography of the lower limbs (telerentgenograms)	Instrumental use- following	before the primary operation and before the operation in case audit intervention statehood
24	Pathomorphological examination of intra- articular tissues	Soft tissue research fabrics	before the primary operation and before the operation in case audit intervention statehood
25	Pathomorphological examination of a bone section of the tibial plateau	Bone marrow examination fabrics	before the primary operation and before the operation in case audit intervention statehood
26	Sonication of removed implants and further microbiological study	Laboratory research	before the primary operation and before the operation in case audit intervention statehood
27	Therapist's conclusion	Consultation with a therapist	before the primary operation and before the operation in case audit intervention statehood
28	Sowing of microflora of discharge pharynx and nose	Laboratory testing before primary surgery	
29 PCR	test on	reagent	before the primary operation

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	infectious agents (viral, bacterial flora, mushrooms) with an assessment of the microbiota in peri-implant area		and before the operation in case audit intervention statehood
30 EGDS		Instrumental use- following	before the primary operation
31 Total	protein	reagent	before the primary operation and before the operation in case audit intervention statehood
32	Albumen	reagent	before the primary operation and before the operation in case audit intervention statehood
33 ALT		reagent	before the primary operation and before the operation in case audit intervention statehood
34 AST		reagent	before the primary operation and before the operation in case audit intervention statehood
35	Creatinine	reagent	before the primary operation and before the operation in case audit intervention statehood
36	Urea	reagent	before the primary operation and before the operation in case audit intervention statehood
37	Uric acid	reagent	before the primary operation and before the operation in case audit intervention statehood
38	Glucose	reagent	before the primary operation and before the operation in case audit intervention statehood
39	Glycated hemoglobin	reagent	before the primary operation and before the operation in case audit

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			interventions
40	Total bilirubin	reagent	before the primary operation and before the operation in case audit intervention statehood
41	Direct bilirubin	reagent	before the primary operation and before the operation in case audit intervention statehood
42	Gamma-GT	reagent	before the primary operation and before the operation in case audit intervention statehood
43	Iron	reagent	before the primary operation and before the operation in case audit intervention statehood
44	Cholesterol	reagent	before the primary operation and before the operation in case audit intervention statehood
45	Triglycerides	reagent	before the primary operation and before the operation in case audit intervention statehood
46	Potassium	reagent	before the primary operation and before the operation in case audit intervention statehood
47	Sodium	reagent	before the primary operation and before the operation in case audit intervention statehood
48	Chlorine	reagent	before the primary operation and before the operation in case audit intervention statehood
49	C-reactive protein	reagent	before the primary operation and before the operation in case audit intervention statehood

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50 ESR		reagent	before the primary operation and before the operation in case audit intervention statehood
51	Rheumatoid factor	reagent	before the primary operation and before the operation in case audit intervention statehood
52 APTT		reagent	before the primary operation and before the operation in case audit intervention statehood
53 MNO		reagent	before the primary operation and before the operation in case audit intervention statehood
54	Fibrinogen	reagent	before the primary operation and before the operation in case audit intervention statehood
55	Prothrombin index	reagent	before the primary operation and before the operation in case audit intervention statehood
56	Determination of blood group by ABO system	reagent	before the primary operation
57	Determination of the Rh factor	reagent	before the primary operation
58	Definition of Kell	reagent	before the primary operation
59	Rhesus antigen phenotyping reagent		before the primary operation
60	TSH	reagent	before the primary operation
61	T3	reagent	before the primary operation
62	T4	reagent	before the primary operation
63 NT-proBNP		reagent	before the primary operation
64	Clinical urine analysis	laboratory research urine	before the primary operation and before the operation in case audit intervention statehood

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Justification for the absence of a control group
This scientific work is a cohort continuous study, in which a control group is not implied.

It is planned that the patient will sign a written informed consent, participating in the study: Yes

It is planned to obtain permission from the ethics committee to conduct research with patients: Yes

Name of the Ethics Committee: Ethics Committee of the State Budgetary Healthcare Institution City Clinical Hospital No. 31 named after Academician G.M. Save-

left DZM

Conclusion

Reducing the development of postoperative complications, with particular emphasis on

prevention of periprosthetic infection. This is a serious complication not only

causes significant suffering to the patient, but also requires a long, multi-

staged and expensive treatment, including revision surgery.

improving the quality and standardization of medical care in the field of primary

endoprosthetics through the implementation of proven clinical protocols

preoperative diagnostics and patient selection. The most important component

an individualized approach is becoming more common, taking into account the associated

patient's illness, which helps to minimize the risks of perioperative

negative consequences. The logical continuation of this work is

reduction in the number of re-hospitalizations due to complications

such as instability of endoprosthesis components and wound infection.

Achieving this goal directly depends on the effectiveness of the measures taken

previous stages, as well as from establishing a high-quality diagnostic system

ki at the preoperative stage. An integral and extremely significant result

the implementation of all the above measures will result in a significant reduction

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economic burden associated with the treatment of these postoperative

complications. Each complication results in direct costs for repeat surgeries,

expensive antibiotics, long hospital stays and subsequent

rehabilitation, as well as indirect losses due to the extension of the period of non-working

patients' abilities. Thus, investments in prevention, improved

quality improvement and standardization of medical care not only improve clinical

results and patient satisfaction, but also demonstrate high

high economic efficiency, relieving the burden on the healthcare system and

optimizing the distribution of resources.

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