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RECOVID study Pharmacoeconomics Analysis

Final Report

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List of abbreviations

AER	Adverse Event Report
ARDS	Acute respiratory distress syndrome
ASPEN	American Society of Parenteral and Enteral Nutrition
CHI	Compulsory health insurance
COPD	Chronic obstructive pulmonary disease
COVID-19	Novel coronavirus infection caused by the SARS-CoV-2 virus
CRF	Case Registration Form
CSG	Clinical and statistical group
ESPEN	European Society for Clinical Nutrition and Metabolism
GI	Gastrointestinal
ICU	Intensive Care Unit
IF	Inpatient Facility
LOCF	(last observation carried forward) – a method of filling in the missing values in the statistical processing of results
MO	Medical organization
OF	Outpatient Facility
ONS	Oral Nutritional Supplement
PD	Patient diary
RRS	Rehabilitation Routing Scale
SIRS	Systemic Inflammatory Response Syndrome

Tables and pictures

Relevance

Nutritional support is the process of providing patients with additional nutrition using special products that are well balanced in quantitative and qualitative proportions [1]. The need for nutritional support is spoken and written by a large number of experts [2] who study not only serious diseases accompanied by protein-energy deficiency (cancer [3], COPD [4]), but also specialists who provide assistance to athletes in the framework of training and recovery cycles [5], which indicates the widespread and high importance of nutritional support as a phenomenon.

Many international and Russian experts note that nutritional support is necessary for patients not only to maintain the metabolic reserves of the body, but also to increase resistance to treatment (surgical, drug, radiation), as well as to increase the rehabilitation potential.

Since the outbreak of the new coronavirus infection COVID-19, the main target organ was initially considered to be lungs with the development of pneumonia and ARDS. A few reports have dealt with extrapulmonary symptoms such as gastrointestinal dysfunction. As the results of treatment of patients with coronavirus infection accumulate, the picture has changed significantly. A group of scientists in a descriptive multicenter crossover study showed that out of 204 patients with COVID-19 who were treated at 3 hospitals in the People's Republic of China from January 18 to March 18, 2020, 47% of lung lesions were combined with gastrointestinal dysfunction (violation taste and appetite, diarrhea, vomiting, abdominal pain, motility disorders), in 41% of cases the lung damage was not accompanied by gastrointestinal dysfunction, in 3% there were only gastrointestinal dysfunctions, in 9% the disease proceeded without lung and gastrointestinal tract damage. A higher level of liver function tests was also revealed in the group of patients with gastrointestinal dysfunction [6].

The manifestation of a systemic inflammatory response syndrome (SIRS) as a result of viral invasion leads to severe metabolic disorders. The main metabolic manifestations of SVR reflect the syndrome of hypermetabolism-hypercatabolism with a complex violation of the metabolism of proteins, lipids, carbohydrates, increased consumption of carbohydrate-lipid reserves and the breakdown of tissue proteins. As a result of severe metabolic disorders and progressive nutritional deficiency, the structure of the pulmonary parenchyma is damaged, the elasticity of the fibers of the lung tissue, the production of surfactant decrease, the permeability of the pulmonary epithelium increases, the atrophy of the alveolar septum, etc. muscles, first reducing their tone, and then the force of contraction, increasing the manifestations of acute respiratory failure, the development of respiratory distress syndrome in an adult. Energy consumption by the lungs reaches 40-50% of the needs of the whole organism. The basis of the developing metabolic dysfunction is hypercatabolism, resistance to exogenous introduction of common nutrients - macro- and micronutrients, as well as an increased need for energy substrates and plastic material. Progressive metabolic disorders and nutritional deficiency lead to the formation of multiple organ failure, which should be considered as the most severe form of manifestation of a systemic inflammatory response. In this regard, adequate correction of metabolic disorders and full provision of energy-plastic needs can improve the results of treatment of the respiratory system (pneumonia, acute pulmonary injury syndrome, adult respiratory distress syndrome) [7].

In this regard, it is obvious that the prevention, diagnosis and correction of nutritional status disorders can be considered as one of the most important methods of treating patients with coronavirus infection COVID-19, aimed at resolving the systemic inflammatory response and correcting the body's metabolic response to viral invasion.

The temporary methodological recommendations of the Ministry of Healthcare of Russia for the prevention, diagnosis and treatment of a new coronavirus infection (version 11 of May 7, 2021) provide for the need to include nutritional support in medical rehabilitation measures

already at the 1st stage when providing medical care in intensive care units and infectious diseases therapeutic departments [8].

ASPEN (American Society for Parenteral and Enteral Nutrition) and ESPEN (European Association for Clinical Nutrition and Metabolism) in their recommendations note the need for nutritional therapy in patients with COVID-19. ESPEN believes that support should be provided as early as possible. On admission, the nutritional status of each infected patient should be assessed. The importance of oral food intake is noted as long as possible. It is necessary to provide a sufficient amount of calories: enteral: 27–30 kcal / kg / day; parenteral (ICU): <70% of energy costs at an early stage, 80-100% after the third day. Provide adequate amounts of protein and amino acids: enterally: ≥1 g / kg / day; parenteral (ICU): 1.3 g of protein / day [9]. The ASPEN guidelines are similar.

Thus, it becomes obvious that the component of nutritional support should be involved in the therapeutic process, and the adequate nutritional support for patients with COVID-19 is an urgent and relevant topic.

RECOVID Study

The Final Report of a prospective, open-label, two-arm comparative, investigator-initiated, low-interventional, observational, randomized study evaluating the effect of NUTRIDRINK®® 200ml Specialty Nutritional Formula (ONS) on the recovery ability of COVID-19 patients was presented for analysis. (RECOVID Study (Recovery in COVID-19))

The Study was organized by the NATIONAL ASSOCIATION OF CLINICAL NUTRITION AND METABOLISM (OGRN 1177700022170), headed by Doctor of Medical Sciences, Professor Sergei Viktorovich Sviridov, the research was carried out using digital CTMS and EDS managed by Enrollme.ru JSC (OGRN 118774645724).

Data collection was carried out in the following scientific medical centers:

1. City clinical hospital # 4 (Moscow)
2. Pirogov Medical university (Moscow)
3. City clinical hospital by Saint George the Great Martyr (St. Petersburg)
4. Pokrovskaya hospital (St. Petersburg)
5. City clinical hospital # 11 (Omsk)
6. Central city clinical hospital # 24 (Ekaterinburg)

The main objectives of the study were:

1. To examine the effect of the additional nutrition support on recovery of physical health in patients with COVID-19;
2. To examine the effect of additional nutrition support on quality of life of patients with COVID-19.

Secondary study objectives were:

3. To examine the effect of the additional nutrition support on hospitalization period of patients with COVID-19.

Study design and research methodology:

The study enrolled 205 patients infected with the novel coronavirus infection COVID-19 admitted to the intensive care units of the Research Centers according to the inclusion/non-inclusion criteria. According to the results of the analysis of the Study documentation, the statistical analysis included data on 185 patients randomized into two groups: 95 subjects in the research group and 90 subjects in the control group.

Patients randomized to the research group received oral nutritional supplement (ONS) NUTRIDRINK® 200 ml in amount of 2 bottles (400 ml) daily for 28 days from the date of inclusion. In the hospital setting, additional nutritional support was added to the patient's standard hospital diet. After discharge from the hospital, the patient received at his disposal the necessary amount of ONS NUTRIDRINK® 200 ml in amount of 400 ml per day and took it in addition to his/her usual diet. ONS NUTRIDRINK® 200 ml was recommended to be taken between the main meals.

In another group, patients received a standard hospital diet, and when discharged from the hospital - their usual diet.

The study had 4 visits:

- Screening and 1 visit upon admission of the patient to the hospital and switch to the respiratory support, after obtaining the informed consent of the patient, respectively, and after confirming the patient's ability to eat independently (in person);

- 2nd visit after the patient was transferred from the intensive care unit to the regular ward or after cancelation of the respiratory support (approximately 7-14 days after 1 visit) (in person)
- 3rd visit on the day of discharge of the patient from the medical institution (approximately 14 – 21 days after 1 visit) (in person)
- 4th visit on the 28th day after the first visit (by phone or e-mail)

The total duration of the observations was 28 days from the date of the 1st visit.

During each visit, the investigator filled out the patient's Case Report Forms (CRF). Throughout the duration of the study, the doctor and patient kept a Patient Diary (DP) and filled out Patient Survey (OP) forms. If adverse events were detected during the study, the doctor filled out an Adverse Events Report (AER).

Criteria for inclusion, non-inclusion and deletion

Inclusion criteria

The study included patients who simultaneously met all the inclusion criteria listed below:

- Age 18-69 years;
- Confirmed new coronavirus infection COVID-19 (based on laboratory and/or computerized tomography data);
- Necessity of respiratory support (oxygen insufflation, non-invasive lung ventilation, artificial lung ventilation, as well in a prone position);
- Ability to take food spontaneously in the amount of 60% and more of energy and protein needs (possibility of spontaneous food intake will be determined with the three-swallow test; consumed food will be controlled with the “quarter of a plate” method);
- Presence of the informed consent signed by a patient for the study enrollment and processing of personal data.

Non-inclusion criteria

If the patient met at least one of the non-inclusion criteria listed below, he/she was NOT included in the study:

- Diabetes mellitus;
- Renal failure;
- Hepatic insufficiency;
- Systemic disease;
- Oncological disease in the active phase;
- Poor survival prognosis.

Exclusion criteria

If the patient met at least one of the following exclusion criteria, he/she was excluded from the study:

- Aggravation of a patient’s condition requiring his transfer to enteral feeding and/or parenteral nutrition;
- Occurrence of complications requiring surgical interventions;
- Patient’s transfer for treatment to another inpatient unit;

- Complications induced by the product for additional nutrition support (diarrhea, nausea, vomiting);
- Patient’s withdrawal of the informed consent for the study enrollment and processing of personal data.

Statistical analysis plan

The statistical analysis included data from all patients for whom there is an estimate of the intervention effects for at least one visit. The missing data were filled by the method of separate substitutions using the LOCF (last observation carried forward) approach, on the assumption that positive dynamics of changes is expected for the indicators.

Descriptive statistics are provided to describe the effects of the intervention:

- Mean,
- Standard deviation,
- Median,
- 25 and 75 quantiles,
- Minimum,
- Maximum.

As parameters of the effectiveness of the intervention were used:

- indicator of quality of life "physical component of health" according to the SF-36 questionnaire;
- indicator of quality of life "mental component of health" according to the SF-36 questionnaire;
- total score according to the SF-36 questionnaire;
- indicator "handgrip strength" (in decanewtons);
- the length of time the patient is on respiratory support (in days);
- duration of hospitalization (in days);
- assessment of changes in the severity of the patient's condition according to Post-COVID19 Functional Status (PCFS) Scale;
- changing of the index of the Nutritional Impact Symptom (NIS) Check-list scale.

Non-specific SF-36 questionnaire (Medical Outcome Study Short Form Health Survey) contains 36 questions covering 8 scales including physical and social activity, limitations in physical activities because of health problems, mental health, vitality, bodily pan, general health perceptions.

The questionnaire scales are grouped into two measures: “physical health” and “mental health”:

Physical health (PH)

Scale components:

- Physical functioning,
- Physical role
- Pain intensity

- General health

Mental Health (MH)

Scale components:

- Mental health
- Emotional role
- Social functioning
- Vitality

The data interpretation and calculation of physical health and mental health indexes were performed in accordance with http://therapy.irkutsk.ru/doc/sf36a.pdf .

The physical health and mental health indexes, as well as total quality of life score representing the sum of physical and mental components were analyzed for the study and control groups

Safety parameters were not analyzed due to the absence of any reports or complaints about adverse events caused by the investigational product.

The null hypothesis reflects the absence of differences between the groups, the alternative - the presence of differences in the indicator between the groups of the tested intervention and the control.

To analyze the data on the SF-36 questionnaire and its components, a two-way ANOVA was carried out. In addition, it is additionally provided for pairwise comparisons of visits in groups using the corresponding variant of the Student's t-test.

For the remaining variables, the data of which are not considered continuous, nonparametric tests were used (Wilcoxon test for comparing dynamics of changes within groups and Mann-Whitney for analyzing values between groups at visits). In addition, a Mann-Whitney analysis was performed using the Mann-Whitney test for deltas at visits 1 and 4 to assess the change in the severity of the patient's condition on the Post-COVID19 Functional Status (PCFS) Scale and the changes in the index of the Nutritional Impact Symptom (NIS) Check-list for patients with malnutrition.

For each variable, a gender and age subgroup analysis (<55 and> = 55) is provided. Subgroup analyzes were performed using the same method as in the main population.

The study used a two-tailed significance level of 0.05.

Justification of the study and the results obtained

As noted above, the problem of nutritional support is very relevant. The authors in the framework of the report confirm this fact with literary data and note the following:

Nutrition plays an important role in maintaining health and preventing disease. Amid the coronavirus (COVID-19) pandemic, nutritional status has been noted as a risk factor for serious illnesses, including obesity and malnutrition.

The continuous spread of COVID-19 has led to a global pandemic, with the number of infections exceeding 216 million cases and the death toll reaching 4.5 million (at the time of this report). Due to the novelty of this pandemic, the scientific community is looking for effective vaccines as well as drugs to treat pathology. One of the biggest challenges is to reduce inflammation without compromising the patient's proper immune response. In this case, science should focus not only on effective drugs, but also on nutrition. Thus/ during the COVID-19

pandemic, the importance of proper nutritional status and dietary habits was widely emphasized, not only as a matter of preventing the occurrence of noncommunicable diseases that can lead to more serious infections, but also as a way to regulate the inflammatory status of patients. Indeed, underestimating the importance of nutrition for COVID-19 patients can have a significant impact on the outcome of these patients.

SARS-CoV-2 respiratory syndrome is often accompanied by prolonged immobilization, which can cause a decrease in muscle function up to sarcopenia. Sarcopenia is associated with an increased risk of malnutrition, disability and, more generally, a deterioration in quality of life. The risk of malnutrition in patients with COVID-19 is associated with chronic pathologies and reduced food intake caused by nausea, diarrhea and loss of appetite.

It has already been demonstrated that malnutrition slows recovery time and increases hospitalization times. Consequently, prevention, diagnosis and compensation for nutritional deficiencies should be carried out regularly for hospitalized patients with COVID-19 in the rehabilitation unit to improve both short-term and long-term prognosis. During hospitalization, oral nutritional supplements (ONS) are useful in case of malnutrition or in cases where the common intake is only 50-60% of the planned. In the case of dysphagia, it is necessary to change the composition of the diet in addition to ONS supplements. The European Society for Clinical Nutrition and Metabolism (ESPEN) recently published some recommendations for improving the nutrition of patients withCOVID-19 infection. This guide includes specific recommendations for patients hospitalized in intensive care units, including early enteral nutrition (where possible), the use of age restrictions that promote emptying the onset of parenteral nutrition in situations where enteral nutrition is impossible/un tolerated, and the use of enteral nutrition after extubation in case of oral feeding intolerance. According to these ESPEN recommendations, enteral nutrition is preferred for patients in the intensive care unit.

A recent study found that three-quarters of COVID-19 patients admitted to non-ICU units had nutritional deficiencies and sarcopenia when assessing hand strength. Screening for malnutrition and muscle failure should be started immediately at the start of treatment to improve nutritional status, as well as maintain muscle mass and physical performance. During hospitalization, the hand grip measured by a hand dynamometer is an inexpensive and easy monitoring tool even in conventional departments.

Thus, the authors convincingly substantiate the feasibility of nutritional support for patients with novel coronavirus infection COVID-19.

Investigational product

The RECOVID study evaluated the feasibility of using 200 ml of the ONS NUTRIDRINK® twice a day for nutritional support of patients with a new coronavirus infection.

Composition per 100 ml NUTRIDRINK® 200 ml:

Energy value	(kJ)	625
	(kcal)	150
Protein (15.8% energy)	(d)	5,9
Fats (35.3% energy)	(d)	5,8
Saturated k-ty	(d)	0,6
Omega-6: Omega-3 k-you	(ω6:ω3)	5,1 : 1
Carbohydrates (49% energy)	(d)	18,4
Sahara	(d)	6,7
Lactose	(d)	< 0,025
Fibre		0

Osmolarity	(mosm/l)	455

Recommendations for use

High-protein, high-calorie mixture for specialized nutrition of patients with malnutrition or risk of its development. The product can be used as an additional or single nutritional source. It is used only orally, through a tube or in small sips for 20-30 minutes. Fluid intake should be monitored to ensure an adequate level of hydration of the body.

Frequency of administration: 1-3 bottles per day as an addition to the diet, 5-7 bottles per day as the only source of nutrition, unless otherwise prescribed by a doctor. The dosage is calculated depending on the protein and energy requirements. A clinically significant effect occurs when taken for at least 14 days.

Duration of use is not limited

Contraindications

- Age up to 18 years.
- Galactosemia.
- Complete mechanical obstruction of the intestine.
- Individual intolerance to any component of the mixture.

An important positive property of NUTRIDRINK® 200 ml product, in our opinion, is the ability to stored it in a dry place at a temperature of 5-25 ° C. Thus, the need for a medical organization in refrigeration equipment, which is necessary, as a rule, for storing most food products, is reduced.

RECOVID study results

Summary for the efficacy assessment

The Quality of Life score was measured at each visit using a standard non-specific questionnaire SF36. Overall quality of life and, in particular, the physical and mental components of quality of life were assessed according to a standard scoring protocol. A statistically significant improvement was found in the research group for the physical component of the scale on the 4th visit in the general population (The "All Patients" parameter). Further analysis of the subgroups showed that this effect was mostly pronounced in subjects younger than 55 years of age, who showed a reliable response at the 3rd and 4th visits of the study, while in women and patients aged > = 55 there were no significant differences in the endpoint.

Performing a hand grip test showed a statistically significant improvement in the research group and in all of its subgroups.

A statistically significant level of reduction in the duration of respiratory support and the total duration of hospitalization in the research group and all its subgroups was also found.

Summary for the safety assessment

The investigational product NUTRIDRINK® 200 ml was expected to show its safety when used in patients infected with COVID-19. Undesirable reactions when using the product in patients were not detected.

Pharmacoeconomic analysis of the RECOVID study results

As follows from the above data, the use of NUTRIDRINK® 200 ml is claimed as an effective and safe tool improving prognosis of the course of the new coronavirus infection COVID-19.

Further, an economic assessment of the results was carried out.

The analysis of the economic feasibility of using NUTRIDRINK® on the basis of the RECOVID study data was performed by Enrollme.ru LLC with a team of authors: **M.U.Frolov**, PhD, Associate Professor of the Department of Pharmacology and Pharmacy, Volgograd State Medical University, Ministry of Healthcare of Russia, Head of the Department of Pharmacology, Volgograd Medical Research Center, and **V.A.Rogov**, PhD, Associate Professor of the Department of Management and Economics of Pharmacy, Volgograd State Medical University, Ministry of Healthcare of Russia.

The purpose of this study was to determine the economic feasibility of using the ONS NUTRIDRINK® 200 ml to provide a required nutritional support for patients with moderate-to-severe COVID-19.

To achieve this goal, the following tasks have been completed:

1. Search for suitable methodological approache to perform the analysis, taking into account the specifics of the selected product group;
2. Determination of efficiency criteria reflecting the potential positive economic effect of the use of new medical technology;
3. Calculation of the economic effect of the application of the new technology.

Selection of the method of pharmacoeconomic analysis

Existing methods of pharmacoeconomic analysis are usually divided into basic and additional. This separation is due to the fact that the use of the main method allows to solve the problem of choosing an economically feasible alternative to treatment, while additional methods serve to solve narrower and more specific tasks [22].

The main methods of clinical and economic analysis are:

1) **Cost - effectiveness analysis**, which allows to assess an economic value of using a drug or other mean / technology that offers a therapeutic or restorative effect, based on a comparison of its cost and health effects (or its individual indicators). In the cost-effectiveness analysis, costs are divided into a non-price efficiency indicator, expressed, for example, in units of lowering blood pressure, reducing mortality, increasing the number of cured patients, etc. The purpose of the analysis is to choose the intervention with the lowest price-to-efficiency ratio.

This method allows to choose a product that would meet a number of requirements: a) it is cheaper, but at least as effective; b) is more effective, but more expensive, and additional benefits justify additional costs; c) is less effective, but less expensive, while the additional advantages of the compared technology do not justify additional costs. Since it is possible to use performance indicators obtained within a relatively short period of time (observation period) in this analysis, this is one of the most frequent methods used in pharmacoeconomic analysis.

The cost-to-efficiency ratio is determined by the formula:

$$CEA=(DC+AC)/Ef,$$

where DC is direct cost, AC is indirect costs, Ef is the performance indicator.

A comparison of the cost-effectiveness ratio of one product to another will show the cost of an additional unit of the final result of treatment. When analyzing the increment of cost effectiveness, the difference between the costs of the two alternative treatment options is divided by the difference in their efficacy indicators:

$$CEAincr=((DC1+AC1) — (DC2+AC2)) / (Ef1-Ef2)$$

CEAincr is a cost-effectiveness measure that demonstrates how much additional investment requires one additional efficacy unit when using more efficient technology.

2) **Cost - utility analysis** allows an economic assessment of a product's performance based on indicators that combine data on life expectancy and quality of life. In this analysis, several performance indicators (criteria) are used. The most commonly used indicator is the saved years of quality of life (QALY), reflecting the change in life expectancy and its quality, which can be achieved with the help of the evaluated intervention. The result of the cost-benefit analysis is expressed in the cost of intervention for 1 acquired year of quality life with the amount spent on intervention. One of the advantages of the technique is the ability to compare using a universal indicator of the economic efficiency of different medical technologies, for example, drug treatment and organizational approaches, etc. However, this is one of the most time-consuming methods of assessment, requiring reliable evidence on the effect of the drug on life expectancy and its quality. The calculation of the cost-utility ratio is carried out according to the formula:

$$CUR=(DC+AC)/Ut$$

where CUR is a measure of cost per unit of utility (the cost of a unit of utility, for example, 1 year of quality life), Ut is a measure of utilitarianism

or

$$CURincr=((DC1+AC1) — (DC2+IC2)) / (Ut1-Ut2)$$

CURincr is an indicator of the increment of costs per unit of utility when comparing two technologies (i.e. added value, for example, 1 year of quality life)

Numerous studies have accepted that treatment (prevention) technologies are cost-effective (cost-effective) at costs of less than $ 20,000 /QALY acceptable (most treatments have just such a cost) - at costs from $ 20,000 /QALY to $ 40,000 /QALY,borderline - at costs from $ 40,000 /QALY to $ 60,000 /QALY and expensive - at costs from $ 60,000 /QALY to $ 100,000 /QALY.The cost of treatment (prevention) technologies of more than $ 100,000 /QALY is considered unacceptable. In Russia, such a gradation of costs does not exist, which makes it difficult both to assess economic feasibility (there are no thresholds, it is necessary to compare the drug under study with an alternative), and comparison with foreign data.

3) **Cost minimization analysis** is a special case of cost-effectiveness analysis, in which two or more interventions characterized by identical efficacy and safety, but of different costs, are compared. Cost minimization analysis is recommended for use in a comparative study of different forms or different conditions for the use of one drug or one medical technology.

In practice, the analysis of "cost minimization" is used extremely rarely, so interventions and medications characterized by the same effectiveness are not frequent. For example, the effectiveness of generics of the same drug can vary significantly, therefore, when analyzing the economic feasibility of their use, a cost-effectiveness analysis is used [23].

4) **Cost-benefit analysis** is a type of clinical and economic analysis in which both costs and results are presented in monetary terms. In this analysis, the clinical effects must be expressed in monetary form, which is not always possible, so this analysis has limited use and is not recommended as the main research method.

Auxiliary types of clinical and economic analysis include:

5) **Analysis of the "cost of the disease"** is a method of studying all the costs associated with the management of patients with a certain disease both at a certain stage (period of time) and at all stages of medical care, as well as with disability and premature mortality. This analysis does not involve comparing the effectiveness of medical interventions, can be used to study the typical practice of managing patients with a specific disease and is used to achieve certain tasks, such as cost planning, determining tariffs in the health care system and health insurance, etc., as well as one of the stages of cost-utility or cost-effectiveness analyses.

6) **ABC analysis** is a controlling method, most often used to analyze the cost structure of medications in a medical institution, region, etc. When conducting an ABC analysis, the share of costs for each used drug for the study period of time (for example, 1 year) is determined, all medications are ranked in descending order of costs for them, and are divided into three groups: "A" - the most expensive, which in total took 80% of the costs, "B" - less expensive, which in total took 10% of the cost, and "C" - the least expensive, which took the remaining 5%. In group A should be drugs with efficacy, confirmed in accordance with the principles of evidence-based medicine, if group A includes drugs with unproven effectiveness, then this indicates an inappropriate expenditure of funds.

Several directions of ABC analysis are applicable [22]:

- Analysis of purchases of various drugs at the level of a medical institution, region;
- Analysis of drugs used in a certain pathology;
- Analysis of the use of certain drugs within one pharmacotherapeutic group (for example, antihypertensive agents);
- ABC analysis is often supplemented by VEN and frequency analysis;

7) **VEN-analysis** - the distribution of medicines by degree of importance: V (vital)-vital, E (essential) - important, N (non-essential) -secondary, unimportant, insignificant drugs. This type of analysis was proposed by WHO more than 20 years ago [23]. The distribution of drugs in these categories is possible using two approaches - formal (checking for compliance with regulatory documents) and expert (assessment of significance from the standpoint of a particular disease). The formal approach is to assign the drug to the appropriate group based on the presence of this drug in lists and lists regulating drug provision (for example, the List of vital and essential medicines). At the same time, drugs available in the lists receive an index V, and those not specified in documents - index N. the method is much simpler, but the list may not include some really important drugs due to the high cost and other reasons. With an expert approach, highly qualified experts evaluate drugs in terms of their importance for the diagnosis and treatment of a particular pathology.

8) **Frequency analysis** is a retrospective assessment of the frequency of application of a particular technology [22].

All types of analysis complement each other and allow to assess the structure of expenses and identify cases of irrational distribution of finances. For example, the predominance of secondary drugs (N) in category A is considered irrational. Based on the results of ABC and VEN analysis, recommendations can be developed to improve approaches to drug therapy. These types of analysis are also useful in studying the typical practice of managing patients with specific nosology, as they allow identifying inefficient and excessively expensive technologies. ABC-, VEN-and frequency analyses should be carried out regularly in order to systematically assess the rationality of resource use.

Based on the data presented in the RECOVID report, we were not able to find a criterion for comparing the effectiveness that would allow to fully apply one of the described methods of pharmacoeconomic analysis. As part of our research, we used mathematical methods of analysis directly based on the results of the RECOVID study.

Calculation of direct medical costs for nutritional support NUTRIDRINK® 200 ml in the treatment of COVID-19 patients in a hospital setting.

Based on open sources, we determined that the cost of 1 bottle of NUTRIDRINK® 200 ml is an average of 235 rubles [10,11] Based on this, the cost of courses of different durations was calculated (Table 1):

Table 1. The cost of a nutritional support with NUTRIDRINK® 200 ml in different time intervals.

base cost NUTRIDRINK® 200 ml. No1, rubles.	235 ₽
the cost for 1 day, rubles.	470 ₽
the cost for 14 days, rubles.	6 580 ₽
the cost for 30 days, rubles.	14 100 ₽
the cost for 365 days, rubles.	171 550 ₽

Calculation of direct medical costs of COVID-19 care

Direct medical costs of the medical care provided to the patients with COVID-19 were calculated in accordance with the Decree of the Government of the Russian Federation of December 28, 2020 No. 2299 "On the program of state guarantees of free medical care for citizens for 2021 and for the planning period of 2022 and 2023" and the Tariff Agreement for payment of medical care provided under the territorial program of compulsory medical insurance of the city of Moscow for 2021 of 30.12.2010 [12]. According to this, the accounting of the first bed-day is allowed when the patient is in the department for 12 hours or more.

In accordance with the above, for 1 case, the cost of treatment in an outpatient facility at the expense of the relevant budgets - 14042.2 rubles, at the expense of compulsory medical insurance - 22261.5 rubles, including federal medical organizations - 25617.3 rubles, in medical organizations (with the exception of federal medical organizations) - 22141.7 rubles, for 1 case of treatment in the profile of "oncology" at the expense of compulsory medical insurance - 83365.5 rubles, including in federal medical organizations -50752,1 rubles, in medical organizations (with the exception of federal medical organizations) - 84701,1 rubles;

When a patient is admitted to the hospital for 1 case of hospitalization in medical organizations (their structural units) providing medical care in stationary conditions, at the expense of the relevant budgets - 81334.1 rubles, at the expense of compulsory medical insurance - 37382.3 rubles, including federal medical organizations - 56680.9 rubles, in medical organizations (with the exception of federal medical organizations) - 36086.5 rubles.

The correction coefficients for calculating the cost of the completed case of hospitalization were for OF (outpatient facility) and IF (inpatient facility/hospital) are 0.65 for a planned visit, 0.6 for an emergency visit with deterioration.

Cost factors for varying degrees of severity of the disease (novel coronavirus infection COVID-19) are presented in Table 2:

Table 2. Reimbursement cost of COVID-19 treatment in hospitals based on case severity.

	Cost factors	The price of the completed case
COVID-19 coronavirus infection (Level 1)	2,87	69 737 ₽
COVID-19 coronavirus infection (Level 2)	4,96	120 521 ₽
COVID-19 coronavirus infection (Level 3)	7,4	179 809 ₽
COVID-19 coronavirus infection (Level 4)	12,07	293 283 ₽
CORONAVIRUS INFECTION COVID-19 (after-treatment)	2,07	50 298 ₽
Medical rehabilitation after COVID-19 coronavirus infection (3 points for RRS)	1,08	26 242 ₽
Medical rehabilitation after COVID-19 coronavirus infection (4 points for RRS)	1,61	39 121 ₽
Medical rehabilitation after COVID-19 coronavirus infection (5 points for RRS)	2,15	52 242 ₽
Medical rehabilitation after COVID-19 coronavirus infection (2 points for RRS)	1	24 298 ₽
Medical rehabilitation after COVID-19 coronavirus infection (3 points for RRS)	1,4	34 018 ₽

From a clinical point of view, level 1 corresponds to a mild form of the disease, level 2 – to a moderate severity, level 3 – to severe and level 4 – to extremely severe course of COVID-19. Accordingly, the tariffs of compulsory medical insurance reflect the ratio of treatment costs taking into account the severity of the course.

Table 2 notes some inconsistency in the classification of the cost of medical rehabilitation, due to various classification features of admission of patients in the mode of rehabilitation therapy in the conditions of OF and IF in various categories of MO. However, given the impossibility of determining which MO potential patients will fall into, it is advisable to use average cost values when calculating the cost of a completed case of medical rehabilitation after the CORONAVIRUS infection COVID-19, which is the assumption of this study.

The cost of providing care to severe patients in intensive care is calculated as follows:

Accounting of medical care provided to the patient in the ICU [12]:

- from 12 hours to 48 hours inclusive - is carried out using the code 83010;
- over 48 hours up to 96 hours inclusive - carried out using the code 83020;
- over 96 hours up to 144 hours inclusive - using code 83030;
- over 144 hours up to 192 hours inclusive - using code 83040;
- over 192 hours - using code 83050.

The total costs associated with finding a patient in the ICU in the treatment of COVID-19 are presented in Table 3.

Table 3. Expenses of the compulsory medical insurance system for the provision of patient care in the ICU

code	Category	Amount, RUB
83010	Intensive care, 1st category of complexity	17047,26
83020	Intensive care, 2nd category of complexity	97193,09
83030	Intensive care, 3rd category of complexity	139188,75
83040	Intensive care, 4th category of complexity	178017,75
83050	Intensive care, 5th category of complexity	221825,88

It is worth noting the fact that the payment for being in the ICU for such patients is very specific for the regions. Thus, when paying under the CSG system (clinical and statistical groups), the subject of the Russian Federation has the right to additionally allocate subgroups for cases of organ dysfunction within the framework of the CSG approved at the federal level, taking into account the established criteria (assessment on the SOFA scale of at least 5 points and continuous ventilation for 72 hours or more). When analyzing the current situation in the regions, a pronounced heterogeneity of approaches to payment was noted - for example, the allocation of subgroups of CSG st12.013 in the Chelyabinsk region:

- CSG st12.013.1 "Influenza and pneumonia with organ dysfunction syndrome (severe COVID-19)" (code 930) provided continuous mechanical ventilation for 120-240 hours (it5);
- CSG st12.013.4 "Influenza and pneumonia with organ dysfunction syndrome (extremely severe COVID-19)" (code 938) provided that mechanical ventilation is performed continuously for more than 240 hours (it6).

In St. Petersburg, separate tariffs have been allocated for resuscitation benefits for the provision of medical care in stationary conditions to the adult population with COVID-19 (Table 4).

Table 4. Tariffs for resuscitation benefits in the provision of medical care in stationary conditions to the adult population

Tariff code for CSG	Name of CSG adult	Tariff, rub.

261344	Resuscitation manual with differential diagnosis of critical conditions	**59 827,10**
431010	Resuscitation of the 1st category of complexity (up to 24 hours inclusive)	**15 117,20**
431020	Resuscitation of the 2nd category of complexity (from 25 to 72 hours inclusive)	**32 842,50**
431030	Resuscitation of the 3rd category of complexity (from 4 to 5 days inclusive)	**55 285,40**
431040	Resuscitation of the 4th category of complexity (from 6 to 9 days inclusive)	**80 711,50**
431050	Resuscitation of the 5th category of complexity (from 10 days)	**138 187,60**
431060	Resuscitation for patients with severe complicated forms of influenza (from 14 days)	**193 461,80**

Attention is drawn to the fact that this method of calculation allows you to associate the duration of stay in the hospital not only with the severity of the process, but also with additional costs.

The RECOVID study included patients on different types of respiratory support, both in intensive care and in the general ward. Taking into account the fact that respiratory support does not directly correlate with being in the ICU, and the corresponding endpoint referred only to the duration of the respiratory support itself, we did not consider it possible to allocate a separate calculation of economic efficiency for resuscitation rates and limited ourselves to the chimkoy rates of the completed case for the treatment of moderate (level 2-3) COVID-19. The results obtained are presented with the next chapter.

Evaluation of the cost-effectiveness of NUTRIDRINK® in the treatment of Covid-19 patients.

As noted earlier, a number of intermediate endpoints were achieved in the study, which made it possible to evaluate the use of NUTRIDRINK® 200 ml as effective.

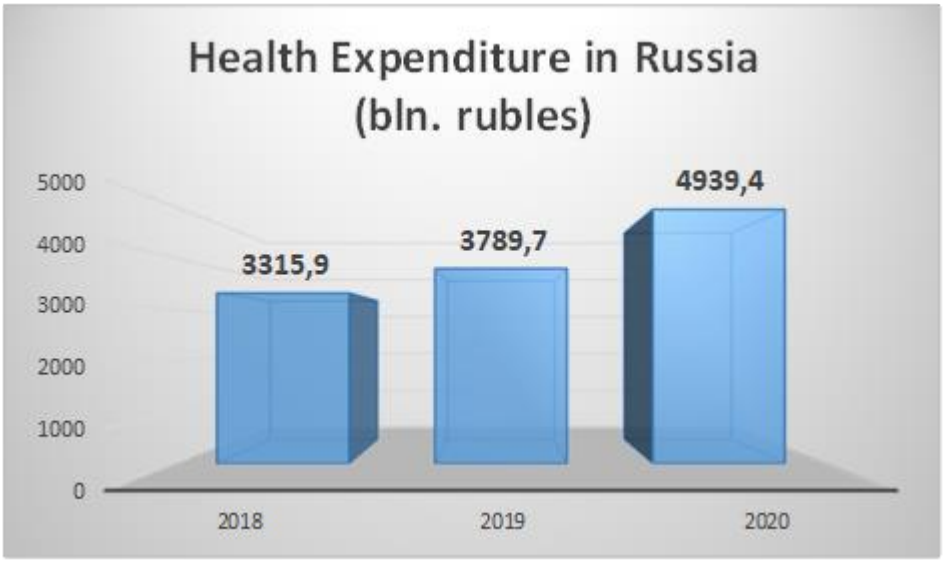
In 2020, a huge burden fell on the health care system due to the need to rapidly deploy new capacities to treat patients with a new coronavirus infection. So, in 2020, the number of infectious beds for adult patients and children increased from 51.9 thousand in 2019 to 278 thousand in total, 223.1 thousand "COVID" beds were deployed in Russia, of which 123 thousand were equipped with an oxygen supply system and 28.4 thousand with ventilators. That is, the new coronavirus infection forced a fourfold increase in the bed capacity of the infectious disease service.

The federal budget allocated 95.6 billion rubles (95,689,879.3 thousand rubles) for equipping and re-equipping the bed fund for patients with coronavirus infection, including the construction of specialized hospitals (the amount was obtained as a result of an analysis of all government orders for 2020). Most of the funds, 68.18 billion rubles, were allocated within the

framework of the state program "Development of federal relations and creation of conditions for effective and responsible management of regional and municipal finances".

The total expenditures of regional and federal budgets on health care in 2020, according to the Ministry of Finance (Official Statistics of the Ministry of Finance of the Russian Federation "Consolidated Budget of the Russian Federation") on the execution of the consolidated budget, amounted to more than 4.9 trillion rubles. (4,939.4 billion). This is 30.3% higher than the financing of 2019 (3,789.7 billion rubles) and by 48.9% - the expenses of 2018 (3,315.9 billion rubles). Thus, we can conclude that the average cost of creating one new "COVID" bed could be several million rubles in 2020.

Figure 1. Indicators of consolidated expenditures of all budgets for health care in the Russian Federation in 2018-2020



At the beginning of 2021, the repurposing and equipment of one COVID bed was estimated by the Minister of Health of Russia Mikhail Murashko at 800 thousand rubles [24]. It is obvious that after the extraordinary efforts and costs that have been undertaken by the federal government and regional authorities, the need for new beds today is not so acute. However, as a significant cost indicator, the efficiency of using a single bed continues to matter.

The statistically significant reduction in the duration of respiratory support and especially the total duration of hospitalization, which were observed during the RECOVID study and had statistical significance both in the general population and in all subpopulations of patients - the parameters are easily digitizing and obviously have a direct impact on the speed of bed turnover, and this indicator is very important, especially in the context of the deployment of a set of anti-epidemic measures to combat the new coronavirus infection. Increasing the speed of turnover of the bed fund not only allows for providing high-quality and timely care to a larger number of patients, but also allows the medical organization to receive a greater amount of funding from the Compulsory Medical Insurance Fund.

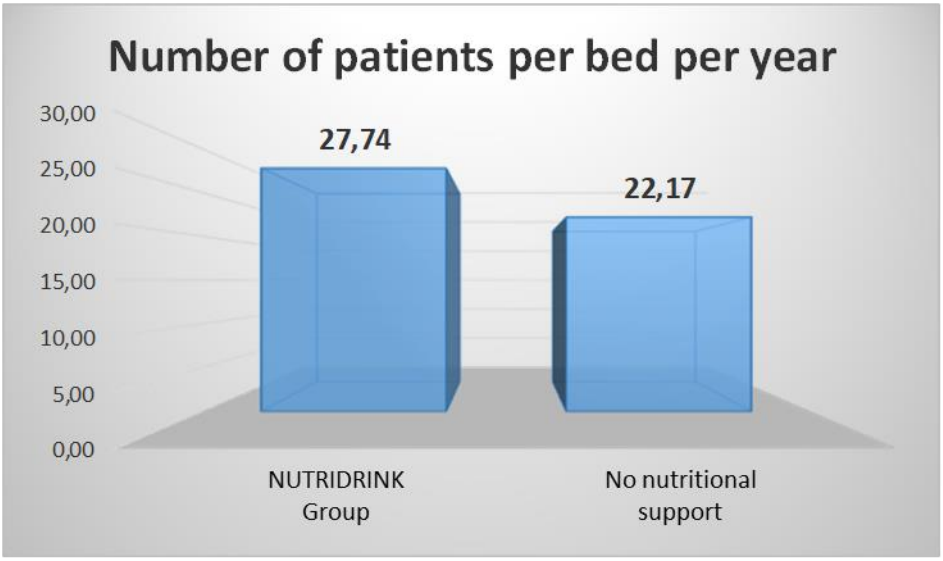
The efficiency calculation showed the following results (table 5):

Table 5. Median values of the indicator "Total period of hospitalization", RECOVID, 2020

Median	Research Group	Control group	Change
Hospitalization: All patients	13,16	16,47	3,31
Hospitalization: Women	13,22	16,31	3,08
Hospitalization: Men	13,11	16,58	3,47
Hospitalization: age < 55	13,33	16,80	3,47
Hospitalization: age >= 55	12,98	16,17	3,20
median	**13,16**	**16,47**	**3,31**
Number of patients per 1 bed per year	27,74	22,17	**5,57**

Thus, nutritional support for patients with COVID-19 with NUTRIDRINK® 200 ml in the proposed scheme (2 bottles of 200 ml per day) allows for an additional 5.57 patients per 1 bed of a COVID hospital during the year, increasing the turnover of the bed fund by a quarter (25.1%) (Figure 2).

Figure 2. Change in bed turnover for patients receiving additional nutritional support with NUTRIDRINK® and patients receiving a normal hospital diet, based on 1 year.



Assessing the direct economic effect of using NUTRIDRINK® 200 ml, it should be noted that the average cost of treatment of one completed case of COVID-19 of moderate severety (level 2-3) in the conditions of MO is 150165 rubles. Thus, an additional 5.57 beds per year allow the MO to additionally earn 836419 rubles. Recall that the nutritional support with NUTRIDRINK® 200 ml per 1 bed-year costs 171 550 rubles (table 1). Thus, the gross additional income of a medical organization from 1 bed to treat patients with COVID-19 per year, minus the additional cost of providing nutritional support, is:

664869 ₽ per year **(1 bed)**

Based on the results of improving the efficiency of existing beds, it can be also hypothetically assumed that increasing their turnover through systematic nutritional support for all patients with COVID-19 can significantly reduce the burden on the health system in terms of repurposing and maintaining the reserve of beds. For example, in June 2021, due to a new

increase in the number of COVID-19 cases, 35,000 beds from the reserve were deployed until the required number of 154,000 beds is reached. Given the 25% increase in bed turnover as a result of patients receiving additional nutritional support, significantly less effort may have been required. But it should be noted that accurate quantification of this indicator, however, is not assessable in this study.

Also, taking into account the fact that in the Russian Federation the reimbursement rates are set for 1 completed case of COVID-19, and not for 1 day of treatment of such patients, it is impossible to determine the effectiveness of the proposed nutritional support per 1 patient.

In addition, we consider it necessary to note another important result of the study - a comparative change in the parameter of the increase of the hand grip as the patient recovers.

Loss of muscle strength by patients in the ICU is associated with an increased risk of disability [13, 14], mortality [15], and is also a criterion for reducing life expectancy [14,16,17]. Regardless of clinical differences, patients in the ICU exhibit similar forms of skeletal muscle dysfunction, including impaired contractility, decreased synthesis, and increased degradation of muscle proteins.

Thus, the quantitative measurement of contractile functions, including muscle strength, can be used for diagnostic and prognostic purposes for critically ill patients. Variables of peripheral motor nerve and muscle function are of interest, as muscle weakness (loss of arm strength leading to decreased motor function) and fatigue (exercise-induced decrease in the ability to generate and maintain strength or power output) can compromise the quality of life of patients who survive critical illnesses [18-20].

According to the latest data, the hand muscle strength can be used to predict morbidity and mortality associated with ICU [21]. The researchers studied 12 muscle groups in patients who had spent at least 5 days on respiratory support and had no previous signs of neuromuscular disease. According to the report, weakness was observed in all muscle groups tested. However, the hand grip effort had better test results compared to measuring function in the 12 muscle groups studied. Based on this, the researchers hypothesized that critical disease does not have a selective effect on a particular skeletal muscle, but weakens the strength of all major muscle groups, including arm muscles. Thus, it seems rational to quantify the strength of readily available reference muscles, such as arm muscles, to predict the incidence of muscle weakness caused by ICU.

In the work, the authors note that the results of the hand grip test may correlate with the need for rehabilitation measures in patients after the ICU, however, this relationship is not obvious and the significance of this criterion requires further study.

According to this indicator, the results of patients in the research group exceeded those of patients in the control group by 7.86%. The indicator of change in carseed effort is one of the significant in assessing the general physical condition of the patient and can, according to some authors, significantly affect the need for rehabilitation. Direct linear extrapolation of these benefits to the costs of rehabilitation of patients is, of course, incorrect. However, it can be hypothetically assumed that if such linear extrapolation was available, then nutritional support with NUTRIDRINK® could lead to a reduction in medical costs for the rehabilitation of each patient with RRS 2-4 points per:

2 000 – 3 000 ₽

At the same time, additional costs for the purchase of the product do not arise, since this indicator is secondary to the efficiency associated with the turnover of beds.

Conclusion

In conclusion, it should be noted that the presented multicenter randomized study RECOVID was performed at a high scientific level, effective and suitable for the selected populations statistical methods of data processing were applied.

As for the results of the pharmacoeconomic evaluation of the results of the RECOVID study, we note the following:

1. the proposed method of nutritional support allows for 1 year to treat an additional 5.57 patients in 1 bed of a COVID hospital, thus increasing the turnover of the bed fund by almost a quarter (25.1%). This is an important indicator for health care providers and stakeholders and can be used to planning the bed reserve to combat the pandemic of novel coronavirus infection;
2. with the average cost of treatment of one completed moderate-to-severe case of COVID-19 (level 2-3) in a medical organization is - 150165 rubles. Thus, an additional 5.57 beds per year allow a medical organization on the basis of current tariffs to receive additional income in the amount of 664869 rubles from one bed per year, given the extra costs of nutritional support accounted.

Thus, the application of the method of nutritional support described in the final report of the RECOVID study is economically justified.

In addition, a literature search showed that the indicator of increase in hand grip studied during the study may correlate with the volume of subsequent rehabilitation of patients who have had a new coronavirus infectionCOVID-19, but this issue requires further investigation.

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