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ASSESSMENT OF MEDICAL TECHNOLOGIES IN THE FORMATION OF GOVERNMENT PROGRAMS TO ASSIST PATIENTS WITH RARE METABOLIC DISEASES

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The aim: *carrying out an assessment of the technologies of nutritional and pharmacological therapy of phenylketonuria (PKU) to justify a set of measures for the implementation of the government program to support patients with rare diseases (RD).*

Materials and methods: *scientific publications, regulatory acts, treatment protocols, statistical data, epidemiological indicators, results of patient questionnaires, marketing information, data from the electronic procurement system "ProZorro" were used in the research process. The research was conducted using the methodology of health technology assessment (HTA), methods of marketing analysis, questionnaire survey, document analysis, comparison, systematization and generalization of data.*

Research results. *An analysis of the evaluation of modern approaches to the treatment of hereditary rare metabolic disease (PKU) was carried out. According to clinical protocols, the main technology for the treatment of PKU is nutritional therapy – a diet (diet-for-life) with restriction of the use of phenylalanine (Phe) and the use of food products for special medical purposes (Special low protein foods for phenylketonuria – SLPF-PKU). Innovative drugs "Kuvan" and "Palynziq" are recommended in the case of atypical PKU.*

For RD, specific and innovative cost-effective medical technologies (MT) are usually used, which have insufficient evidence due to limited experience, low availability, and small patient populations. Centralized procurement and managed entry agreements (MEA) make it possible to expand the availability of MT to patients and obtain real data on their safety and effectiveness. Integration into the global information space, participation in international projects, joint clinical assessment (JCA) in accordance with Regulation (EU) 2021/2282 on HTA, cooperation with Orphanet, EURORDIS, other professional and patient organizations are extremely important.

The key components of HTA for RD are socio-economic and organizational and legal aspects, in particular the special status of MT, which provides certain preferences. The foreign experience of providing orphan patients (in particular, reimbursement) is summarized. The legal framework for RD is systematized.

Based on the results of the analysis of PKU prevalence indicators, modelling and budget impact calculations were carried out, considering that SLPF-PKU products are purchased from local budgets.

An analysis of prescriptions, assortment, and prices of SLPF-PKU was carried out using data from the ProZorro procurement system. A survey of 156 patients with PKU made it possible to identify unmet needs and formulate recommendations for expanding the SLPF-PKU food basket.

Conclusions*: Conducting the HTA made it possible to identify key problems, as well as to justify a set of measures for the development and implementation of the government program to support patients with rare diseases, based on the obtained results*

Keywords: *health technology assessment (HTA), government programs, phenylketonuria (PKU), rare (orphan) diseases, food products for special medical purposes; special low protein foods for phenylketonuria – SLPF-PKU; medical technologies (MT), nutritional therapy (diet-for-life)*

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1. Introduction

Rare diseases are a new global priority, given the significant medical needs and the relatively large impact of these diseases and their treatment on the health care budgets of almost all countries. In the conditions of growing needs of health care against the background of limited resources, the problem of ensuring proper (continuous) treatment of orphan patients, which in turn depends on the availability of effective and safe MT, becomes more relevant. To create a general EU strategy for effective and efficient recognition, prevention, diagnosis, and treatment of RD to prolong the duration and improve the quality of life of patients, the EUROPLAN project was introduced by the EU Council in 2009 and recommended to all EU member states to develop a national plan or program/strategy regarding RD [1, 2]. In Ukraine, in 2014–2015, a regulatory basis was created for improving the pharmaceutical provision of orphan patients – relevant changes were made to the Fundamentals of Health Care Legislation, the list of RDs and the procedure for providing patients with medicines, medical devices (MD) and

food products for special dietary consumption. The concept of the development of the system of providing medical care to patients suffering from rare (orphan) diseases for 2021–2026, approved by the order of the CMU of April 28, 2021 No. 377, aims to reduce mortality from RD, improve the quality of life of patients through ensuring fair and equal access to quality medical care for such patients, in particular to quality, effective and safe medicines, MD and SLPF-PKU products. However, due to the imperfection of the legislation, the lack of effective mechanisms for the implementation of the established norms, and the lack of funding, problems arise in providing vital MT, which can cause serious consequences. In the EU countries, the availability of MT for the treatment of RD and the policy of ensuring patient access differ significantly depending on the socio-economic level and the organization of the health care system [3–5]. Thus, from 2000 to 2022, the European Commission granted the status of "orphan medicines" to 2,734 drugs, however, during this period, the EMA approved only 231 applications for the marketing of orphan drugs [6]. In the Netherlands, almost all orphan drugs registered in the EU are subject to reimbursement, in France – 116 orphan drugs, in Latvia – 25, in Romania – 70 [2]. For Ukrainian patients, most of these drugs are unavailable. In Ukraine, based on the established criteria for inclusion in the national program of 12 diseases in children and adults, managed entry agreements (MEA) are being implemented.

Phenylketonuria (PKU) refers to rare inborn metabolic diseases associated with a violation of amino acid metabolism, has a code according to the International Classification of Diseases (ICD-11) 5C50.0, ORPHA code: 716. PKU is characterized by a severe progressive course and requires constant high-cost treatment. According to the American non-profit organization National Organization for Rare Disorders (NORD), the reported incidence of PKU in the United States through newborn screening (NBS) programs ranges from 1:13,500 to 1:19,000. According to the Rare Disease and Orphan Drug Portal (Orphanet), the prevalence PKU in the world is 1–9:100,000 population. In Ukraine, this indicator ranges from 1:6,000 to 1:10,000. The classic form of PKU is most common (98 % of registered cases) [7].

According to the current legislation of Ukraine, children with PKU under the age of 3 receive SLPF-PKU free of charge at the expense of the state budget, children from 3 to 18 years old, adults and pregnant women – according to regional target programs in accordance with the financial support of territorial communities. Difficulties in meeting the needs of orphaned patients are due to the lack of effective and affordable MT, as well as approved standards of treatment. In addition, Ukraine is the only country in Europe that does not have a mandatory health insurance system.

HTA is used in most states for the rational use of limited health care resources and the adoption of appropriate decisions regarding the financing of certain MT. RD populations are small, making it difficult to obtain (high-quality) evidence of clinical and cost-effectiveness. HTA processes are usually not adapted to deal with RDs and orphan drugs, so often countries reimburse costs for these drugs, despite lower quality evidence and higher prices, driven by social motives. In Ukraine, HTA is currently being actively implemented in the context of reforming the healthcare sector, the procurement system, expanding the medical guarantee program, and improving care for orphan patients. Therefore, research aimed at determining the main problems of providing orphan patients with specific MT and substantiating ways to solve them is relevant and timely.

Therefore, **the aim of the study** was to evaluate the technologies of nutritional and pharmacological therapy of PKU to justify a set of measures for the implementation of the program of support for patients with rare metabolic diseases.

2. Research planning (methodology)

To conduct the research and achieve the set goal, the following stages were performed (Fig. 1).

3. Materials and methods

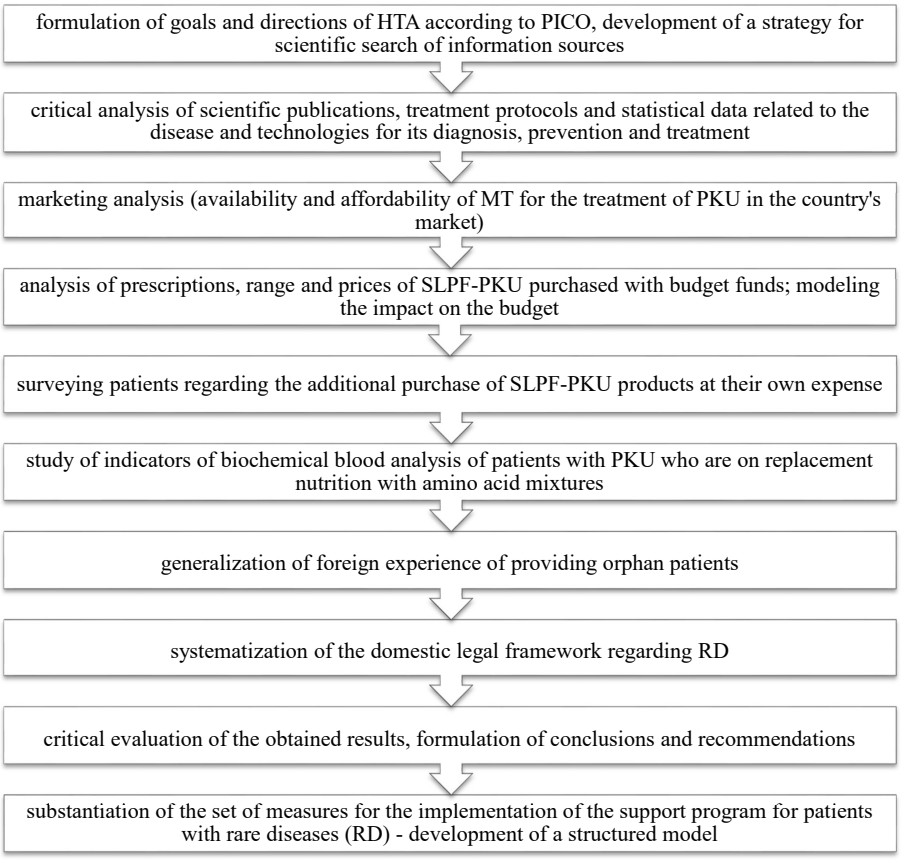

Fig. 1. Research design

Validity, objectivity, and reliability were used to conduct the study, relying on the HTA methodology described in the State HTA Guidelines for Medicines, as there are currently no approved standards for conducting assessments for other types of medical technology (MT).

To ensure a proper evaluation, it is important to clearly formulate the purpose and objectives of the PICO research. *Clinical question:* to examine the clinical effectiveness and safety of MT in the treatment of PKU/HPA compared with placebo; *population*: patients with PKU; *intervention*: diet therapy (diet-for-life) using SLPF-PKU; c*omparator*: placebo; *outcomes*: achievement of the target level of Phe in the blood, indicators of neurocognitive development.

To investigate the question of comparing the clinical effectiveness of MT treatment of PKU, a search was conducted for sources of information on evidence data in the PubMed, Cochrane databases, clinical guidelines, on the websites of international specialized organizations in accordance with the developed search strategy.

Key search terms: PKU diet, phenylalanine-free amino acid. Free full-text, meta-analysis, systematic review as filters were applied, the period 2013–2023 was selected for the search. The literature search was limited to English-language articles and full-text publications in free access.

According to the search results compliance to the specified criteria, 147 publications were found in the PubMed and The Cochrane Library database. 3 publications were selected for further analysis [8–10]. The healthcare system standards of Ukraine [11, 12] and international clinical guidelines and recommendations of scientific societies of other countries [13–17] were considered.

Epidemiological indicators were studied based on statistical data of the Orphanet network [18], the Public Health Center of the Ministry of Health [19] and the results of neonatal screening for 2005–2022 (data provided by the Interregional Specialized Medical Genetic Center – Center of Rare (Orphan) Diseases).

In 2019–2020, on the basis of the Kharkiv Interregional Specialized Medical Genetic Center for Rare (Orphan) Diseases,a study of blood biochemical indicators was conducted in four groups of patients aged 4 to 29 years who used different amino acid mixtures. The composition and technology of SLPF-PKU products were also developed. The results were published earlier [19].

An analysis of medical prescriptions, assortment and prices of SLPF-PKU was carried out using the data of the ProZorro procurement system according to the code of the Unified Procurement Dictionary SC 021:2015:15880000-0 “Special food products enriched with nutrients” (concluded contracts and specifications for them). In order to assess the affordability of SLPF-PKU products, Solvency adequacy ratios ($C_{a.s.}$) were calculated by the formula:

$$C_{a.s.} = \frac{\overline{P}_r}{W_{a.w.}} \times 100\ \%,$$

where C_{as} – solvency adequacy ratio;

P_r – average retail price of MT for a certain period (month, quarter, year);

W_{aw} – average salary for a certain period (month, quarter, year) [20].

When modelling and calculating the impact on the budget, PKU prevalence indicators by region were used, considering that SLPF-PKU products are purchased from local budgets. The need of protein for special therapeutic purposes is determined according to a standardized method (considering the approved norms for patients of various ages who are registered). The cost forecast is based on the current prices of distributors’ price lists and data from the ProZorro electronic procurement system.

In order to implement a patient-centered approach and involve patients in conducting HTA, a questionnaire was developed, and a survey was conducted using Google forms. 156 respondents (adult patients with PKU and parents of patients under the age of 18) took part in the survey, which is 11 % of the total number of patients with PKU living in Ukraine). The survey concerned the specifics of the nutrition of patients with PKU. When conducting the research, the requirements of the ICC/ESOMAR International Code on Market, Opinion and Social Research and Data Analytics were observed. Informed consent was obtained from the study participants.

To study the social and organizational aspects of HTA, the foreign experience of providing orphan patients was summarized. An analysis of the policy on rare diseases in Great Britain was performed – a detailed review of scientific publications and regulatory documents was carried out (in particular, BNF, List of Special Low Protein/ Low Phenylalanine Foods on Prescription NSPKU, Prescription Guideline of NSPKU) [21–23].

In view of the importance of legal aspects of the application of MT, a generalization and systematization of the legal framework was carried out, which regulates the issue of pharmaceutical support for patients with RD, conducting HTA and increasing the availability of MT. A content analysis of regional programs for providing assistance to patients with orphan diseases was carried out.

4. Research results

Analysis of international and national treatment standards shows that approaches to the management of PKU differ significantly in different countries (in particular, diagnostic and treatment technologies, target Phe levels, classification of the disease depending on the severity of the course, duration of treatment).

According to the consensus document of the European Society for Phenylketonuria and allied disorders (ESPKU), the key factor is dietary therapy aimed at preventing negative neurocognitive and psychological consequences by limiting the consumption of Phe in natural products and using protein substitutes to achieve normal nutritional status and optimal blood biochemical parameters [13]. According to modern scientific ideas, there are three main types of amino acid metabolism disorders, which have different severity of the course and, accordingly, different approaches to correcting the condition of patients (Fig. 2).

Treatment of patients with PKU is continuous, it consists in following a strict diet from the moment of diagnosis (diet for life). Numerous studies, including our own [19], have confirmed the effectiveness of following a diet and compensation of the condition due to the use of SLPF-PKU [9–14]. At the same time, the late start of treatment and non-compliance with recommendations lead to disability with the impossibility of further medical and social rehabilitation.

The basis of PKU treatment is an individual approach considering the patient's age, residual activity of the PAH enzyme, tolerance to Phe, etc. In patients with a mild form of PKU, pharmacotherapy is used. To reduce the level of Phe in the blood, BioMarin Pharmaceutical (USA) has developed innovative preparations Palynziq™ (pegvaliase-pqpz) in the form of injections and Kuvan® (sapropterin) in the form of tablets and powder for oral solution. The generic version of sapropterin Javygtor™ is more affordable [15]. These medicines are approved by FDA and EMA, but due to their high cost, they have low affordability. Thus, the price of one dose of Palynziq™ is 394 euros, Kuvan tablet packaging No. 30 – $1,027, packaging of Javygtor™, No. 30 from $1,294.70 USA ($43.16 per dose). In Ukraine, these preparations are available through online ordering. Kuvan was registered in 2022, but it is not included in the National list of essential medicines and the nomenclature of public procurement.

It is worth noting that medicines for the treatment of RD, including PKU, is currently being actively developed. For this purpose, advanced therapy medicinal products (ATMP) can be used innovative MTs of enzyme replacement therapy (enzyme analogs) and genetic engineering ("correction" of the gene responsible for PAH synthesis). It is known about the effectiveness of using large neutral amino acids (LNAA) in the form of microtablets PreKUnil and NeoPhe (PreKUlab, Denmark) [24–28].

To compensate for amino acid deficiency in PKU and to diversify the diet (which is especially relevant for pediatric patients), not only basic products (bread, rice, pasta, classic amino acid mixtures (AAMix)), but also confectionery, ice cream, chocolate, etc. are used. The range, prices, and reimbursement mechanisms of SLPF-PKU vary significantly between countries. Thus, in Portugal, the range of products is 73 names, in Belgium – 92, in Germany – 94, in Italy – 256. Average annual costs per patient vary widely: in the Netherlands – 680 euros, in the Czech Republic – 1,560, in the Great Britain – 962 pounds (according to some estimates – up to 4,000), in the USA for children under 17 years – 1,615 dollars, and for adults – 967 dollars [26, 29, 30].

As part of the study, an analysis of international experience was carried out, namely the peculiarities of the organization of providing "borderline substances" to PKU patients in Great Britain, which includes SLPF-PKU products. Following the HTA of these products by the Advisory Committee on Borderline Substances (ACBS), they have been included in the British National Formulary (BNF) and are currently available on prescription from pharmacies and online stores. The current list contains 146 names [21], the structure of the list of SLPF-PKU available by prescription is presented in Fig. 3.

General practitioners prescribe monthly SLPF-PKU according to the Prescribing Guidelines and dispensing standards of the National Society for Phenylketonuria (NSPKU) [22].

In Ukraine, products for patients with PKU and other metabolic diseases (PKU, HPA, tyrosinemia) can be purchased in online stores, pharmacies and regular supermarkets. Pasta, bread, rolls, pizza base, soups and broths, cookies, waffles, jellies, chips, baking mixes, as well as special baby food are not officially included in SLPF-PKU and their issue is not regulated by law purchases for budget funds. In addition, a preferential VAT rate cannot be applied to these goods, which affects the affordability of these products.

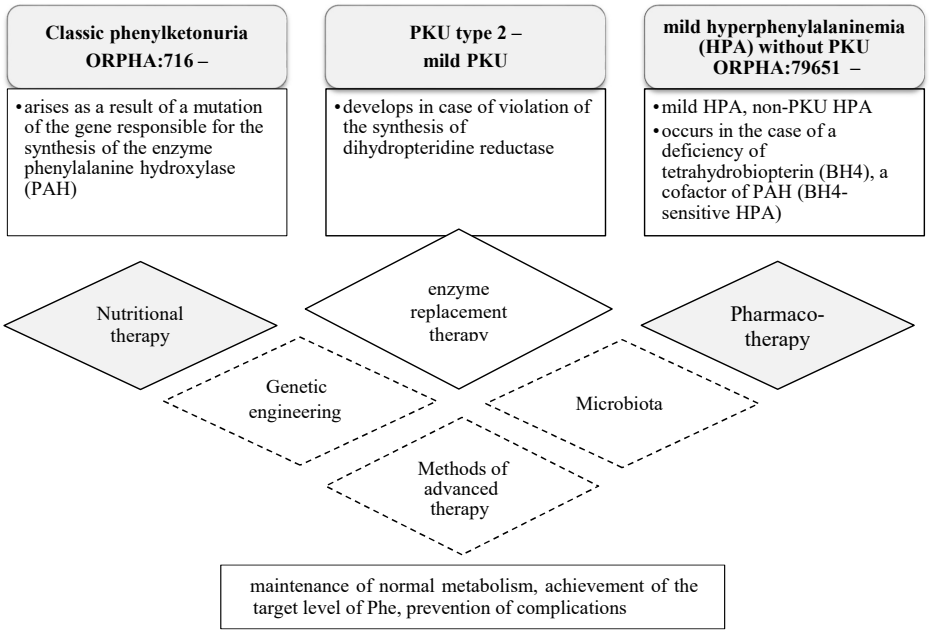

Fig. 2. Medical technologies for the treatment of PKU according to the type and severity of the course

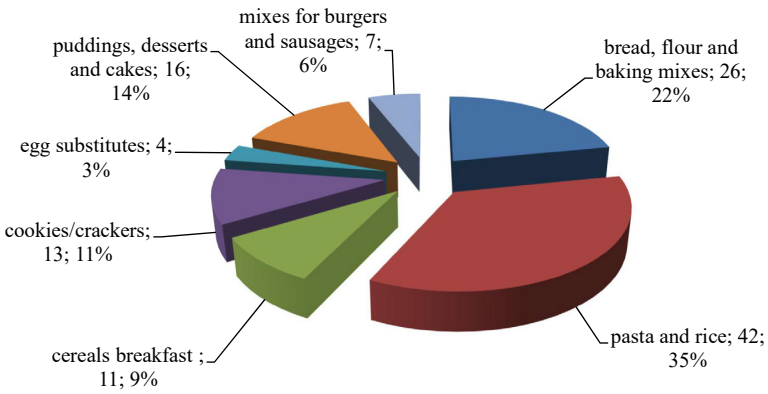

Fig. 3. Structure of the list of SLPF-PKU available by prescription

Regulation and control of the circulation of these goods is carried out by the State Service of Ukraine Food Safety and Consumer Protection. According to the current legislation, from 2022, the basis for placing such products on the market is an official notification of the intention to introduce SLPF-PKU products into circulation. Currently, most of these goods are not put into circulation according to the official procedure [31].

We conducted an analysis of the Ukrainian SLPF-PKU market based on information from the official websites of suppliers, the ProZorro procurement system, and the "E Liki" information system, which allows to check the presence of medicines in specific healthcare facilities.

The results of the analysis of SLPF-PKU prescribed by doctors, which are purchased with the funds of local budgets, are shown in the Table 1.

As a result of the study of medical prescriptions [32], it can be concluded that for patients with PKU, doctors prescribe mainly AAMix in the form of powder (73 %), drinks (13 %), ready-made mixtures (6.7 %) and long acting microtablets (6.7 %). In total, in 2022–2023, about 30 names of SLPF-PKU were purchased by health centers, almost half (47 %) of them are functional baby food products (5 of them are intended for children from birth to 1 year).

Analysis of SLPF-PKU product range by manufacturers and countries of origin showed that imported products are subject to purchase. The largest market share (62 %) belongs to the Nutricia brand (SHS International, Great Britain), second place is occupied by Comida (Vitaflo, Great Britain) – 24 %.

The availability of these vital products for the population could be improved by the establishment of domestic production, as well as legal regulation – giving products for the treatment of rare metabolic diseases, which are prescribed by doctors and purchased with budget funds, the status of "food products for special medical purposes" and the introduction of preferential taxation of 7 % instead of 20 %.

In PKU, the effectiveness of the SLPF-PKU product is determined by its nutritional profile, amino acid composition, dose, distribution and adequate energy consumption, and the rate of absorption by the body. Therefore, the main criteria for the selection of SLPF-PKU by doctors are the optimal protein content in a product unit for a certain age group, a balanced amount of nutrients (amino acids, carbohydrates, fats, vitamins, trace elements) and the lowest conditional value of 1.0 g of protein. The amount of protein can range from 2.0 to 83.3 per 100 g of product. Since the price for a package of SLPF-PKU mixtures ranges from UAH 1,000 to UAH 7,000 (i.e., from EUR 24.81 to EUR 173.70), the price of a conventional gram of protein can vary from UAH 13.50 to UAH 109.00 (from 0.33 to 2.7 euros). In the process of procurement through the electronic procurement system, this indicator is the main criterion for determining the winner. Therefore, if it is necessary to consider other important characteristics of the products, the requirements must be clearly stated in the tender documentation.

A study of indicators of the price affordability of MT for the treatment of PKU was conducted. Calculated solvency adequacy ratios $C_{a.s}$. for SLPF-PKU products ranged from 7.4 to 52.1 %, for PreKUnil microtablets – 220.4 %, NeoPhe – 204.9 %, which indicates extremely low availability of these MTs. According to the data of the State Statistics Service of Ukraine, the average salary in 2023 is UAH 13,423 (approximately EUR 333).

An analysis of the impact on local budget indicators (on the example of the Kharkiv region) was carried out in the part of calculating costs for MT with a time horizon of one year based on direct medical costs. Objective: to estimate the model impact on the MT budget of nutritional therapy of patients with PKU. The results are presented in the Table 2.

The number of PKU patients of the appropriate age categories who are registered in a certain territorial community was determined based on statistical data of the Public Health Center of the MoH and the results of neonatal screening for 2005–2022. Therefore, in 2022, in Ukraine, pediatric PKU patients (up to 16 years) – 825, of which 77 – under 3 years. For the first time in 2022, 29 patients were diagnosed [18]. Unfortunately, there is currently no registry of patients with RD. Analysis of the prevalence of PKU shows that the most patients with PKU are registered in the city of Kyiv (97), as well as Dnipropetrovsk (124 patients, of which 80 are children), Zhytomyr (110, of which 56 are children), Kharkiv (84, including 35 – children), Odesa (83, including 53 children) regions [18].

Next, considering the determined average annual need for special protein therapeutic nutrition for children with PKU (order of the Ministry of Health of Ukraine dated 03.09.2017 No. 1073) and the calculated price per gram of protein, the estimated costs for each age category of patients are determined.

According to the results of the calculations, the projected costs for covering the annual need for SLPF-PKU patients of all age categories in the Kharkiv region is from UAH 27.1 million (EUR 672.500), provided that the winner of the procurement is the product with the minimum price. In this case, about UAH 196.000 (EUR 4.900) per year for one patient will be allocated from the budget for

the purchase of SLPF-PKU for younger children (up to 3 years old), which is UAH 16,300 (EUR 404.5) per month; for children over 11 years old, adults and pregnant women with PKU, this amount is almost twice as much and will be UAH 358.000 (EUR 8.900) per year or UAH 29.800 (EUR 739.5) per month. According to calculations, the introduction of preferential taxation (a rate of 7 % instead of 20 %) would save more than UAH 4.5 million (EUR 111.7) on the purchase of SLPF-PKU products in the Kharkiv region alone.

The simulated impact budget impact was compared with the recommended values of the budget impact scale in Ukraine, in accordance with the updated values of the recommended budget impact assessment scale in Ukraine based on the data of state expenditures on medical equipment in 2021. It was established that, the impact for the budget for 1 year will be large (more than UAH 100 million, i.e. EUR 2.48 million) when purchasing SLPF-PKU.

The analysis of legal aspects is an important component of HTA, which considers the national features of the organization of the health care system and pharmaceutical provision and allows identifying problematic issues in the application of MT.

In Ukraine, according to clause 5 of Article 3 of the Law of Ukraine "On State Financial Guarantees of Medical Services of the Population" and in accordance with the Resolution of the Cabinet of Ministers of Ukraine dated 31.03.2015 No. 160 "On Approval of the Procedure for Providing Citizens Suffering from Rare (Orphan) Diseases with Medicines and Appropriate Food Products for Special Dietary Consumption", the state entrusts the purchase of SLPF-PKU to local budgets.

The conducted content analysis of regional programs shows significant differences in approaches to providing orphan patients with medical care, MD and SLPF-PKU products. Decentralized procurement is carried out at the regional and local level by health departments of regional state administrations and medical institutions. According to the results of a comparative analysis of the prices of the signed contracts, significant price fluctuations (up to 25 %) are observed, which indicates the inefficient use of limited budget funds.

Table 1

Products of special medical nutrition, prescribed by doctors and purchased by medical institutions at the expense of local budgets

Product name	Manufacturer, country	Age of the patient	Price per package, including VAT		Price per 1.0 g of protein	
			UAH	euro*	UAH	euro*
PKU Nutri 1 Concentrated 500 g SHS,	SHS, Great Britain	0–12 months	3,362.17	83.43	13.45	0.33
PKU Anamix Infant 400 g			1,651.85	40.99	31.52	0.78
PKU Nutri 1 Energy 400 g			1,365.84	33.89	28.69	0.71
PKU Anamix Junior 36 g		from 1 year	473.40	11.75	47.34	1.17
PKU Nutri 2 Energy 454 g			2,358.95	58.53	19.24	0.48
PKU Nutri 2 Concentr. 500 g			4,699.36	116.61	15.66	0.39
PKU Lophlex LQ Juicy Berries/Tropical 125 ml		from 4 years	731.80	18.16	36.59	0.91
PKU Nutri 3 Concentr. 500 g		from 8 years	5,380.11	133.50	15.37	0.38
PKU Nutri 3 Energy 454 g		from 9 years	3,088.70	76.64	19.22	0.48
Afenil 1 500 ml	PIAM Farmaceuici, Italy	0–12 months	1,046.00	25.96	104.60	2.60
Afenil 1 200 ml No. 6			2,615.00	64.89	108.96	2.70
Afenil Gel 720 g (24×30)		from 6 months	5,230.00	129.78	17.42	0.43
Afenil 2 500 g		From 1 year	6,276.00	155.73	15.07	0.37
Afenil Medi 15 neutral 750 g (25×30)			7,322.00	181.69	16.27	0.40
Afenil Medi 15 orange			7,322.00	181.69	16.27	0.40
Afenil Micro3H microtabs 4×110 g		from 3 years	6,276.00	155.73	20.17	0.50
Afenil Squash citrus/wild berry 130 ml No. 30			14,121.00	350.40	31.43	0.78
Neutrafenil/(LNAA) microtabs 4×110 g			9,414.00	233.60	30.22	0.75
Afenil Express Neutral 750 g			4,539.60	112.65	10.08	0.25
Comida PKU B formula 500 g	Vitaflo, Great Britain	1–14 years	2,808.00	69.68	18.05	0.45
Comida PKU B 500 g			4,500.00	111.66	12.32	0.31
Comida PKU B Pina Colada 500 g		3–14 years	3,843.00	95.36	10.98	0.27
Comida PKU C 500 g		from 15 years	4,608.00	114.34	12.29	0.30
Comida PKU C Formula 500 g		from 15 years	2,664.00	66.10	11.84	0.29
XPhe Smart K 500 g	Metax, Germany	3–6 years	6,590.00	163.52	20.92	0.52
XPhe Energy K 500 g			3,138.00	77.87	20.92	0.52
XPhe Energy J 660 g		7–14 years	4,557.00	113.08	23.02	0.57
XPhe Smart J 500 g			6,956.00	172.61	19.87	0.49
XPhe Energy A 660 g		from 15 years	4,557.00	113.08	23.02	0.57
XPhe Smart A 500 g			6,956.00	172.61	19.87	0.49
PreKUnil tab. 750 mg No. 550	PreKUlab, Denmark	from 7 years	29,590.00	734.24	–	–
NeoPhe tab. 685 mg No. 550		from 7 years	27,500.00	682.38	–	–

*Note: * prices according to the NBU exchange rate as of July 13, 2023, 1 euro=40.3 UAH*

Table 2

Calculations of forecast indicators of impact on the local budget of the Kharkiv region in 2023 to provide for patients with PKU/PHA

Categories of patients with PKU	Average annual need of special protein for patients with PKU[1]	The number of patients registered at the MGC [2]	Forecast of SLPF procurement costs. The horizon is 1 year							
			per 1 patient				for all patients of the age category			
			Amount, UAH[3]		Amount, euro[4]		Amount, UAH[3]		Amount, euro[4]	
			min	max	min	max	min	max	min	max
adults	26 500 g	49	357,750	2,888,500	8,877	71,675	17,529,750	141,536,500	434,981	3,512,072
children										
0 to 1 year	5500 g	–	74,250	599,500	1,842	14,876	–	–	–	–
1–3 years	14 500 g	4	195,750	1,580,500	4,857	39,218	783,000	6,322,000	19,429	156,873
4–6 years	17 500 g	10	236,250	1,907,500	5,862	47,333	2,362,500	19,075,000	58,623	473,325
7–10 years	19 500 g	11	263,250	2,125,500	6,532	52,742	2,895,750	23,380,500	71,855	580,161
Older than 11 years	26 500 g	10	357,750	2,888,500	8,877	71,675	3,577,500	28,885,000	88,772	716,749
Total	–	–	–	–	–	–	27,148,500	219,199,000	673,660	5,439,181

Note: [1] – order of the Ministry of Health from 03.09.2017, No. 1073; [2] – according to the report on the provision of medical and genetic assistance for 2022 (form No. 49) of the Public Health Center of the MoH of Ukraine http://medstat.gov.ua/ukr/statdanMMXIX.html and taking into account the results of newborn screening (NBS) dynamics for 2005–2022; [3] – according to the minimum and maximum value of a conventional gram of protein (according to the Prozorro electronic system – 13.50 and 109.00 UAH, respectively), i.e., 0.33 and 2.7 euros; [4] – according to the rate of the NBU

An important role in HTA is assigned to the patient, allowing feedback, and adjusting therapy, measuring quality of life and identifying unmet needs that require immediate action. As part of the study, we surveyed 156 PKU patients (or their family caregivers), identifying an unmet need for SLPF-PKU products.

As a result of the survey, it was established that patients will additionally purchase various functional products at their own expense: pasta, bread, rolls, soups and broths, cookies, waffles, jelly, chips, baking mixes, etc. Patients buy 2–3 packs of special low-protein pasta every month (63 %), 16 % – use one pack, the rest – four or more. The most popular pasta brands are "Bezgluten" (Poland) – 61 %, "Mevalia" (Great Britain) – 54 %, "Balviten" (Poland) – 24 %, "Loprofin" (Italy) – 23 %. It was also found out that most respondents (64 %) bake bread themselves, 47 % – buy TM "Bezgluten" bread (Poland), 18 % – "Mevalia" (Great Britain), only 2 % of patients do not use bread and rolls. A third of respondents (31 %) use 1 kg of flour every month, 41 % – 2 kg, the remaining 28 % – more. To compensate for the need for protein in children with PKU, confectionery products are widely used: cookies (78 % of respondents), straws (55 %), waffles (41 %), sticks (30 %), chocolate (24 %), gingerbread (22 %), jelly (9 %), homemade pastries (4 %). To enrich the diet, patients also use porridge: 31 % of respondents use one packet of porridge per month, 30 % – two, 23 % – three. The grocery basket of patients with PKU may include cheese, 38 % buy one pack of cheese per month, 25 % – two, 15 % – three, 11 % – do not use this product. The market offers a limited range of cheese and dairy products. 42 % of respondents said that they use one pack of milk per month, 26 % – two, 14 % – three, 3% – five, the rest – do not use. Most respondents (44 %) use "Milupa" milk (Nutricia), 9 % – "Glutenex" (Poland), 8 % – "Bezgluten" (Poland). Regarding meat substitutes, 35 % of patients buy one package of sausages/pates per month, 18 % – two, 10 % – three, the rest do not use them. Almost half of the respondents (45 %) buy sausages or pâtés of TM "Walter Schot", 29 % – "Loprofin", 3 % – "Metax", 3 % – "Hame", while 22 % of the respondents have never bought pates and sausages.

The conducted survey made it possible to investigate the peculiarities of the diet of patients with PKU, to determine consumer preferences and unsatisfied needs.

At the current stage, the system of providing medical care to patients with RD is being reformed in accordance with the adopted Concept and EU recommendations. That is, we can talk about increasing the availability of modern MT for the diagnosis and treatment of PKU (implemented reference centers, neonatal screening), which will allow timely detection of the disease and thereby influence the quality and results of treatment (diet therapy). Treatment of PKU requires high-cost SLPF-PKU, which patients cannot afford to purchase on their own. According to current legislation, the state provides food for children with PKU up to 18 years of age (up to 3–s – at the expense of the state budget, up to 18 years – at the expense of local programs), adults provide themselves with the necessary products at their own expense or do not follow a special diet at all. There are ongoing discussions on this issue, and approaches to providing for patients with PKU differ in each country. Some scientists expressed the opinion that strict adherence to a diet is mandatory only during the active development of a child (up to 12–14 years). Recent studies confirm the importance of diet adherence in adulthood as well.

To make informed decisions regarding the provision of MT to patients, the guidelines of the International Society for Pharmacoeconomic Research ISPOR recommend the use of multi-criteria decision-making analysis (MCDA), which allows taking into account a number of criteria (indicators of morbidity and mortality, needs

for medicines, MD and medical services; clinical effectiveness and safety, socio-economic consequences, economic feasibility, impact on the budget) and evaluate according to their values and importance. Such an analysis makes it possible to determine the treatment strategy and establish the level of financial impact in the conditions of a limited budget, which should not be transferred to the patient.

Based on the results of the comprehensive evaluation of MT, it is possible to formulate a set of measures for the implementation of the program of support for patients with RD and develop a structured model (Fig. 4).

In order to increase the duration and quality of life of patients suffering from rare metabolic diseases and requiring specific life-long expensive treatment, the main regulatory influences should be focused on the maximum provision of unmet needs with rational use of resources, which is possible under the conditions of conducting the HTA and adopting appropriate policy decisions regarding the financing of innovative MT for diagnostics (screening), prevention and treatment.

In order to expand access to MT (in particular, SLPF-PKU products), the state policy should be aimed at creating favourable conditions for scientific development and implementation of innovations, stimulating the development of local production as an alternative to high-value imported products, and public-pivate partnerships.

The development of a network of reference centers and a well-thought-out information and educational policy, integration into global networks (Orphanet) and cooperation in the field of MTA will contribute to the improvement of medical care for orphan patients.

5. Discussion

The analysis shows that both in the world and in Ukrainian practice, there is no single classification of SLPF-PKU products that would consider all the specifics of its production and consumption (use). The experience of many countries of the world shows that a consistent comprehensive state policy in the field of providing for patients suffering from orphan metabolic diseases, aimed at providing them with safe and affordable products, allows to increase the life expectancy and quality of such patients.

For example, the UK NHS fully reimburses SLPF-PKU prescriptions for children with PKU; adult patients over 60 years old and pregnant women. Other categories of patients must pay £1.29 (€1.5) per unit or, if they purchase a pre-paid certificate, be covered for all prescriptions. However, access to SLPF-PKU may be limited due to the refusal of doctors to issue prescriptions for certain types of products; appointment of a smaller amount [16]. As the analysis showed, doctors prescribe an average of 93 units per year (8 per month), which is 2.5–6.3 times less than officially allowed [8].

According to the results of the study of medicinal prescriptions and purchases of SLPF-PKU, powdered amino acid mixtures, which are presented on the Ukrainian market by foreign companies in a limited assortment and due to high prices, are not available to most of the target group of consumers.

In the context of the implementation of the strategic plan for the development of the domestic health care, the establishment of the domestic production of SLPF-PKU products and the settlement of regulatory issues regarding the special status of such products and the provision of benefits for manufacturers.

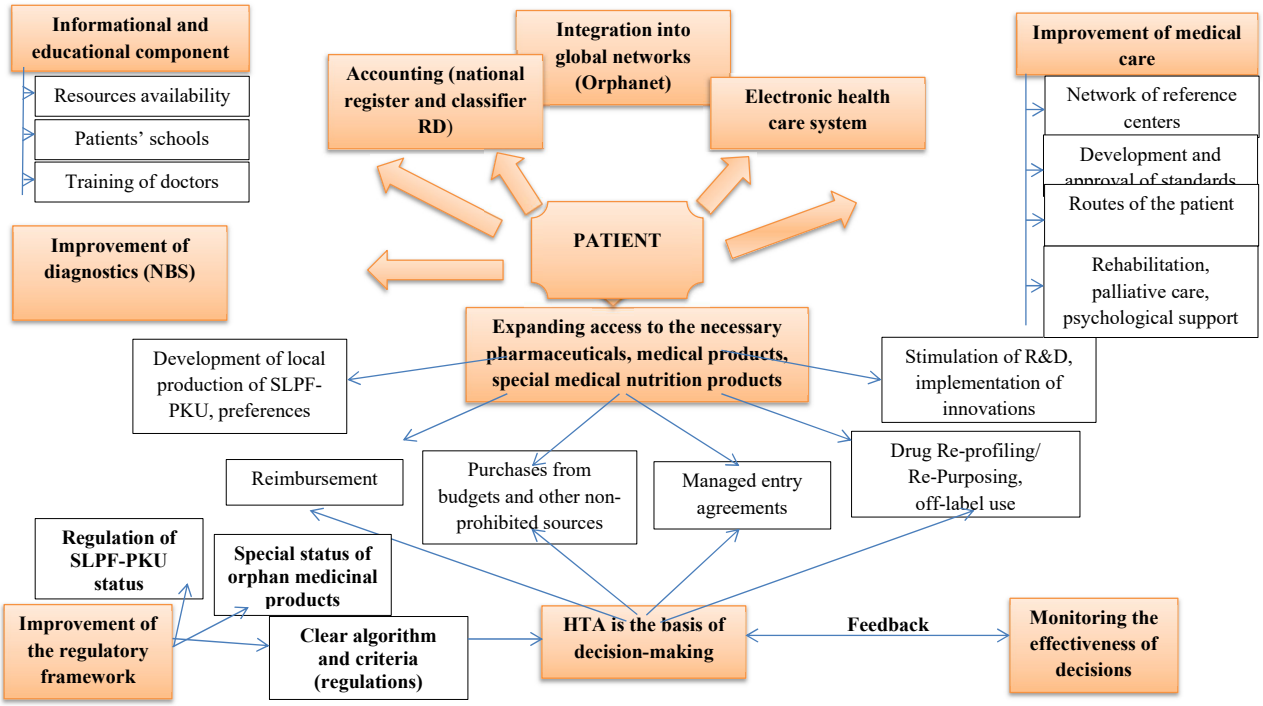

Fig. 4. A structured model for the formation and implementation of a program to support patients with rare diseases

According to calculations, the introduction of preferential VAT taxation at the rate of 7 % for food products for special medical purposes will significantly reduce the prices of these products and reduce the burden on the budget.

Study limitations. Due to the relatively small number of patients, the possibility of conducting full-fledged clinical studies is limited, which affects the level of evidence of the data.

The article presents only a part of the results of a complex study related to the problems of ensuring the availability of MT for the treatment of patients with rare metabolic diseases (PKU) and determining the priority directions for the implementation of RD programs at the national and regional levels of health management.

Prospects for further research. A promising direction of research can be the substantiation of directions for improving the policy of ensuring access and availability of MT for patients with rare metabolic diseases.

6. Conclusions

A comprehensive study made it possible to substantiate the main directions of the formation and implementation of the program of support for patients with RD based on a patient-oriented approach. The key areas include the improvement of diagnostics (expanded neonatal screening, which makes it possible to detect diseases in a timely manner) and medical care (ensuring the operation of reference centers). An important role is given to the informational component, proper patient registration and integration into leading global networks (Orphanet). Expanding access to necessary MT for RD is possible due to stimulation of innovations, repurposing of medicines, development of local production. The status of special medical nutrition products needs to be regulated. Orphan preparations, MDs, and special medical nutrition products require a special approach in conducting HTA, which should be a transparent basis for making decisions regarding MT market admission (feasibility of its use), reimbursement, and purchases with budget funds, in particular, under managed entry agreements.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, including financial, personal, authorship or other nature, which could affect the research and its results presented in this article.

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Data availability

Data will be provided upon reasonable request.

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