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# METHODOLOGICAL ASPECTS IN CONDUCTING PHARMACOECONOMIC STUDIES OF THERAPY OF SPASTIC CEREBRAL PALSY

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**Abstract:**

This article touches upon the main methodological aspects of conducting pharmacoeconomic analysis of treatment of spasticity in patients with cerebral palsy. The authors evaluated the relevance of conduct of such studies basing on epidemiological and social and economic data. The stages of information retrieval and inclusion criteria in the effectiveness analysis are covered in detail. Special attention is paid to assessing the methodological quality of the studies. The authors highlighted the components of the cost analysis and assessment of the economic burden of this disease and describes the features of assessing the quality of life in children with cerebral palsy using a variety of methods.

**Key words:** pharmacoeconomics, methodology of pharmacoeconomic researches, cerebral palsy, spasticity, botulinum toxin type A, baclofen, efficiency analysis, cost analysis, information retrieval, criteria of effectiveness.

**Introduction**

Cerebral palsy (CP) is one of the most widespread and socially significant neurological diseases that affect as various aspects of physical and psychoverbal development of children from birth and the as stages of their personal development and adaptation in society. In the last years there is a clear trend in the increasing of number of children with disabilities in Russia and it should be noted that CP takes first place in the structure of infant neurological disability [5]. It should be noted that the number of patients with a diagnosis of cerebral palsy established for the first time in life, has significantly increased in 2014 in comparison with indicators of previous years (Fig.1) from 7.1 thousand people in 2005 to 7.7 thousand in 2014 among patients aged 0 to 14 years [1].

According to the latest available data on 20.02.2017 on the general prevalence of CP in child population from 0 to 14 years, at the end of 2014 in the Russian Federation lived 80 690 patients with cerebral palsy [2]. In 75% of patients with CP spastic form of the disease (spastic diplegia and spastic tetraplegia) were diagnosed [3,5]. The dynamics of CP prevalence and spastic CP prevalence are presented in figure 2.

In addition to the severe medical and social importance of the treatment of disabling childhood diseases of the nervous system, chronic disease and the epidemiological situation, it is necessary to consider economic losses for the society as a whole, expressed as the cost of providing medical care and expenses for pension and social security.

It should be noted that more innovative technologies being implemented in the field of therapy of children’s neurological diseases, in particular, botulinum toxin type A was included in the standard of specialized care for children with cerebral palsy [10]. Given the need for lifelong therapy of spasticity in children with cerebral palsy and high cost of this category of drugs is the reason for conducting pharmacoeconomic evaluation and analysis of the burden of spastic forms of CP in the Russian Federation. The objective of this article is the adaptation of modern methods of pharmacoeconomic analysis and information retrieval to the peculiarities of the nosology of “cerebral palsy”.

It is necessary to consider many aspects in the treatment of a specific disease for rational decision-making during introduction new medical technologies and assess the adequacy of the use of health services: the effectiveness of selected types of treatment, financial and organizational capacities of the health system at all levels.

In such circumstances, the decisions on the implementation of medical technologies should include comprehensive and evidence-based assessment.

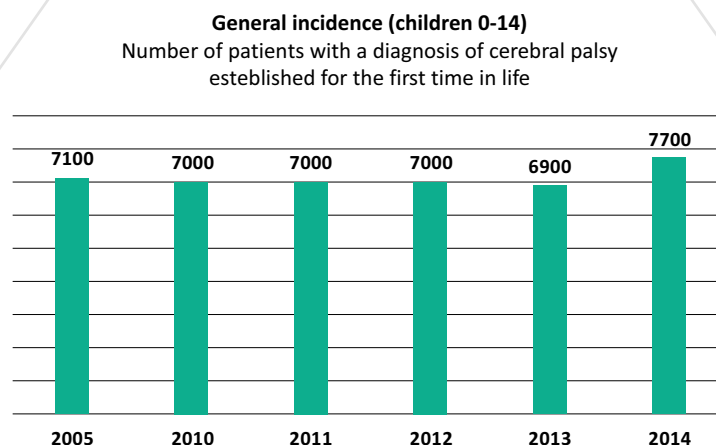
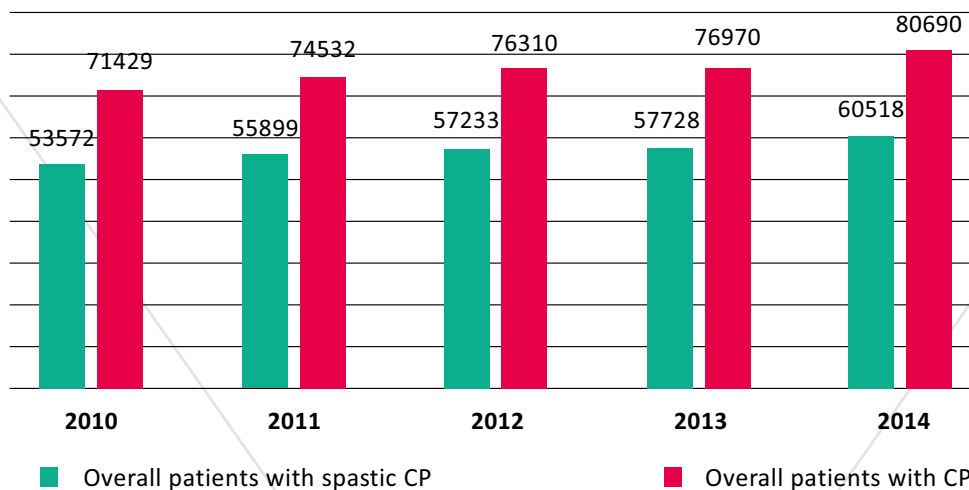


Figure 1. Number of patients with a diagnosis of cerebral palsy established for the first time in life

## Prevalence of cerebral palsy (patients of 0-14 years)

### Overall patients



**Figure 2.** Dynamics of general prevalence of CP since 2010 to 2014 год in child population 0-14 years old.

In this way, the pharmacoeconomics are able to give evidence-informed decisions in the field of CP, as it is the science that studies in comparative terms the relationship between cost and efficiency, safety and quality of life when alternative treatment is [6]. Broad methodological apparatus of pharmacoeconomics includes analysis of the methods applied at all levels of the health system and is able to take into account the specifics of the treatment of patients with CP.

#### Information retrieval

Information retrieval for the pharmacoeconomic analysis includes the formulation of questions using the PICO method (patient/intervention/comparator/outcome), which is determined by the population under study patients, evaluated health technology and therapy comparison of clinical outcomes. This method of identifying the most important issues in this medical problem is widely used for developing clinical guidelines and in the preparation of systematic reviews. In the preparation of clinical guidelines is also necessary to identify the most critical outcomes. PICO's example for information retrieval of studies on spastic CP of lower limbs is presented in Table 1.

**Table 1.** PICO for information retrieval of studies on spastic CP of lower limbs

<b>Population</b>	Children (in this review defined as individuals between 2 and 14 years of age) requiring treatment for equinus or equinovarus foot deformity associated with cerebral palsy
<b>Intervention</b>	Intra-muscular injections of BtA in dosage into calf muscles (the soleus muscle and/or gastrocnemius muscle) in combination with physiotherapy
<b>Comparator</b>	Placebo, no treatment and standard treatment
<b>Outcome</b>	See Table 2
<b>Study design</b>	RCT

During standardization of studies, the authors made the criteria of RCT in efficacy analysis [4].

#### Inclusion criteria:

- Absence of contractures in spastic muscles of the lower limbs
- Patients not previously endured surgery on the studied muscles
- Patients were not taking the centrally acting muscle relaxant during the BTA treatment and did not receive the blockade with phenol and ethanol
- BTA was injected in the same muscle
- Equinus gait: m.Gastrocnemius, m. Soleus
- Equinovarus gait: m.Gastrocnemius, m. Soleus, posterior Tibialis
- All patients are able to walk by themselves or using walking aids

#### Clinical outcomes

Preferably, the criteria of effectiveness used in the pharmacoeconomic study, therapy of spastic forms of cerebral palsy, consistent with the International Classification of Functioning, Disability and Health (ICF), a part of the WHO classifications [7]. In this classification, the various domains of an individual with a specific change in health are systematically grouped.

**Table 2.** Effectiveness criteria for pharmacoeconomic assessment of treatment of spastic CP of lower limbs

<p><b>Body functions and body structures</b> (changes in physiological systems or in anatomical structures)</p> <p>The measure of disability is assessed</p> <ul style="list-style-type: none"> <li>• Spasticity (Tardieu scale)</li> <li>• Muscle tone (Ashworth scale or modified Ashworth scale)</li> </ul>
<p><b>Activity (execution of a task or action by an individual)</b></p> <p>The level of activity limitation is assessed</p> <ul style="list-style-type: none"> <li>• Individual goal identification, rating and scaling (Goal Attainment Scaling (GAS), Gross Motor Function Measure (GMFM))</li> <li>• Activities of daily living skills (Pediatric Evaluation of Disability Inventory (PEDI), (Functional Independence Measure for Children (WeeFIM))</li> </ul>
<p><b>Participation (involvement in a life situation)</b></p> <p>The level of limitation of participation is assessed</p> <ul style="list-style-type: none"> <li>• None</li> </ul>
<p><b>Criteria of effectiveness, not suiting to The International Classification of Functioning, Disability and Health</b></p> <p>Health-related quality of life</p> <ul style="list-style-type: none"> <li>• Child Health Questionnaire (CHQ)</li> <li>• Pediatric Quality of Life Inventory</li> <li>• Utility obtained with questionnaires and standard gamble, time trade-off visual analog scale</li> <li>• Safety</li> <li>• The frequency of orthopedic surgery in pediatric patients</li> </ul>

To conduct pharmacoeconomic studies in accordance with the above criteria, it is necessary to conduct information search in the database Pub-Med, Medline, Medscape, PubMed, Cochrane Library, database "Russian Medicine" of the Central Scientific Medical Library at I.M. Sechenov First Moscow State Medical University, scientific electronic library "elibrary.ru", free search engines such as Yandex, Google.

The next step of analysis is to evaluate the quality of scientific data on the critical outcomes. Currently there are many tools that determine the reliability of scientific data, but the most widely used technique is the one developed by a group of foreign scientists specializing in evidence-based medicine from McMaster University, Harvard University, Cochrane centres of Norway and Germany. The four-point system is used in this system, in which 4 points are for evidence with a high level of quality and 1 point – for evidence with low quality. Initial scores are determined by the study design, RCT are estimated as ones with a high level of accuracy, observational studies, by contrast,



have a low level of quality. Then five factors that can lower the total score and three factors that increase scores are taken into account. The GRADE system focuses on the assessment of each important clinical outcome, and the quality of the assessment of different clinical outcomes in the same study or group of studies (meta-analysis) may vary. Then five factors (risk of bias, inconsistency, indirectness, imprecision, publication bias), which can lower the total score and three factors, rising the score (large effect, dose response, all plausible residual confounding reduce a demonstrated effect. GRADE pays attention to the assessment of each critical outcome and reliability of the assessment of different clinical outcomes in the same study or group of studies (meta-analysis) may vary [8].

An important stage of GRADE is assessment of risk of bias or methodological quality of the study. For this assessment GRADE system uses Cochrane Risk of Bias tool. Indicators of risk are: lack of allocation concealment, lack of blinding (especially when the outcomes are subjective), incomplete accounting of patients and outcome events, selective outcome reporting bias, stopping early for benefit.

Special attention should be given to this clinical result as the quality of life associated with health, expressed as QALY. This index is a widely used aggregate measure of efficiency that takes into account both qualitative and quantitative assessment of life. To calculate QALY it is necessary to determine the utility of treatment of the patient with some form of the disease.

To determine the preferences of patients and evaluation of utility of the most commonly used questionnaires since they are the most intuitive and comfortable for the patient and the researcher way of getting information. Questionnaires allow the patient to assess the health status, relative to each other or the extreme condition (death). Among the most common questionnaires can highlight the EuroQoL Index (EQ-5D), 36-item Short Form Health Survey (SF-36) and Health Utility Index (HUI) [19]. These questionnaires have been translated into most European languages and is suitable for international use. An alternative approach to the assessment of patient's preferences is the use of methods of direct assessment such as standard gamble, time trade-off methods, visual analog scale [22].

The results of evaluation of usefulness from the point of view of parents of patients with different forms of cerebral palsy from foreign study by Finnell and co-authors are shown in Table 4 [21].

**Table 4.** Utility from parents of children with CP of different severity.

Severity of disease	Utility (Standard gamble method)	Utility (Time trade-off method)
Mild	0,83	0,87
Moderate	0,73	0,78
Severe	0,56	0,58

The definition of the QALY is an important part of pharmacoeconomic analysis because the definition of the efficiency criterion, the ratio of this index with data on cumulative annual cost of therapy per patient, allows to make a conclusion on the acceptability of the studied health technology in the analysis of "willingness-to-pay threshold".

Willingness-to-pay analysis is a universal tool for decision making in the healthcare. The peculiarity of this method is providing the results of the use of certain medical technologies in monetary terms. Willingness-to-pay threshold shows the amount (in national currency units of the country) that society is willing to spend to achieve a certain therapeutic effect or a surrogate endpoints for this category of patients., i.e. for 1 additional QALY [20].

**Cost analysis**

An integral part of any pharmacoeconomic study is cost analysis. When conducting a pharmacoeconomic analysis of the treatment of spasticity in patients with cerebral palsy should consider the direct and indirect costs [4]:

Direct costs:

- Cost of BTA therapy
- The cost of correction of side effects of therapy BTA
- Costs for inpatient and outpatient medical care
- Costs for sanatorium-resort medical care
- Costs for orthopedic interventions

The cost of medical care consisted of expenditures on primary health care on an outpatient basis and expenses on specialized medical care in a hospital environment [4]. The cost of sanatorium care should also be included. Medical services for disease diagnosis, treatment of disease, condition and

treatment control, and also the list of medicinal products for medical use for the treatment of this disease indicating the average daily and course doses were taken from the two projects of standards of the Ministry of Health: "The standard for primary health care in children with cerebral palsy" [9] and "The standard of specialized medical care in children with cerebral palsy" [10]. These standards are the most modern ones of medical aid to children with cerebral palsy on 20.02.2017. The cost of sanatorium care was calculated on the basis of the Order of the health Ministry of the Russian Federation No. 213, dated 22.11.2004 g "On approval of the standard sanatorium-resort care for cerebral palsy patients"[11].

The costs of diagnostic and therapeutic procedures have been calculated on the basis of prices provided in the tariffs of the Federal mandatory health insurance Fund of Moscow [12].

The cost of correction of side effects was calculated as follows: the frequency and pattern of side effects were determined based on data from randomized clinical trials and guidelines regarding the use of drugs BTA and the muscle relaxant Baclofen [13-15], as well as standards of medical care, and the cost of therapy was derived from the rates of the Federal mandatory health insurance Fund Moscow, the category of "Cost per completed case." [12].

The cost of orthopedic operations was calculated on the basis of the Decree of the RF Government dated December 19<sup>th</sup> 2016 r № 1403 " On the programme of state guarantees of free rendering to citizens of medical care for 2017 and on planning period 2018 and 2019" [16].

Indirect costs:

- Disability pensions
- Disable child care benefit

During calculation of indirect costs information retrieval of main legislative acts relating to social welfare payments for patients with cerebral palsy and their families was conducted. Consequently, in accordance with article 18 of the Federal law of 15 December 2001 No. 166-FZ "On state pensions in the Russian Federation" pensions for disabled children in 2015 are 13 391 ruble for a month [17]. The amount of care allowance for disabled children in 5500 rubles was determined according to the presidential Decree of 26 February 2013 № 175 "On monthly cash payments to unemployed able-bodied persons caring for a disabled child under the age of 18 or a disabled person since the childhood of I group" [18].

**Conclusion**

The main methodological aspects of conducting pharmacoeconomic analysis of treatment of spasticity in patients with cerebral palsy are covered. The authors evaluated the relevance of conduct of such studies basing on epidemiological and social and economic data. The stages of information retrieval and inclusion criteria in the effectiveness analysis are covered in detail. Special attention is paid to assessing the methodological quality of the studies. The authors highlighted the components of the cost analysis and assessment of the economic burden of this disease and describes the features of assessing the quality of life in children with cerebral palsy using a variety of methods.

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