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ECONOMIC FACTORS OF CLINICAL TRIALS OF MEDICINES IN SMALL POPULATION COUNTRIES: CASE STUDY OF LATVIA

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Abstract. *The clinical trial process has become a significant type of services that provides huge added value to any national economy. Undoubtedly, the primary group of stakeholders in clinical trials of medicines is pharmaceutical companies that obtain a product as a result of successful clinical trials. However, other groups involved will also obtain materials and intangible benefits from the process of clinical trials of medicines. In this context, the authors tended to find out: What are considered to be the primary economic benefits of clinical trials of medicines in a society with small population? Aim of the research is to analyse economic factors of clinical trials of medicines in countries with small population, taking Latvia as an example. Object of the research: economic factors of clinical trials of medicines. The principle of snowball has been used to make the selection of the participants' survey. The empirical analysis and evaluation of economic factors in unique clinical trials of medicines are based on the qualitative research method of semi-structured individual (in-depth) interviews. According to the survey, the most important economic type of clinical trials of medicinal products in Latvia is "socioeconomic factors", the average index of the factor being 0.82. The most significant three categories of the socioeconomic factors are "Access to the latest treatment methods and preparations" (Index max 1), "Improved patient care (time used per patient)" (Index 0.87) and "Exchange of experience, transfer of knowledge on the most innovative treatment methods" (Index 0.86). Society with small population values the primary economic benefits from clinical trials of medicines. It can be concluded that the socioeconomic factor is the most significant, compared to the direct economic factor and the alternative cost savings factor.*
Keywords: *clinical trials; economic factors of clinical trials; small population countries.*
JEL classification: I19; M29.

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Introduction

Clinical trials of medicinal products are one of the most important parts in developing of new medicines. Clinical trials of medicines are research conducted with humans for the purpose of developing or testing clinical, pharmacological and other pharmacodynamic effects of medicines, identifying side effects caused by their use, examining their pharmacokinetics, in order to determine the safety and efficacy of medicines(EU Clinical Trials Register, 2020).

The pharmaceutical industry, by making significant investments in the development of new medicines, not only makes huge profits on these investments, but also contributes to public health. As shown in recent studies(Yang & Lee, 2018), the cost of Research and Development (R&D) investment in the pharmaceutical industry is increasing and the productivity is stagnant. For this reason, the demand for innovation is growing. It is also estimated (DiMasi, Grabowski, & Hansen, 2016) that the cost of developing a new drug has increased from USD 800 million (in 2000) to USD 2.87 billion (in 2013).

Introduction of new medicines on the market is only possible after an extensive research, involving high risks. On average, it takes 12-13 years to market the development new medicines since synthesising the first active substance. The cost of a new chemical or biological substance is around EUR 1.059 billion. Out of 10 000 new synthesised substances, only one or two becomes a marketable product (The European Federation of Pharmaceutical Industries and Associations, 2020).

Investment in research and development in the pharmaceutical industry in Europe reached more than EUR 35 300 million in 2017. The dominant positions of the United State of America (USA) in the R&D market over the past decade has led to a significant shift in economic and research activities to this country. Moreover, Europe is facing an increasing competition with emerging economies such as Brazil and China, so the geographical balance of the pharmaceutical market in the research and development area is expected to gradually shift to developing countries. Spending on R&D in the pharmaceutical industry in Europe has been growing by 3.8% annually since 2014, compared with the USA, where this indicator has been growing at a much faster rate of 8.6%. In 2018, the global pharmaceutical and biotechnology sector in the R&D field ranked first in the world at 15%, compared to the R&D intensity of the general sector. The number of employees involved in pharmaceutical R&D in Europe in 2018 was about 115 000 (The European Federation of Pharmaceutical Industries and Associations, 2020).

Aim of the research is to analyse economic factors of clinical trials of medicines in countries with small population, taking Latvia as an example. Object of the research: economic factors of clinical trials of medicines. The principle of

snowball has been used to make the selection of the participants' survey. The empirical analysis and evaluation of economic factors in unique clinical trials of medicines are based on the qualitative research method of semi-structured individual (in-depth) interviews.

Characterization of Clinical Trials of Medicines in Latvia

Despite the fact that Latvia's population is *small*, there is stable increase in clinical trials. On average, 67 permits for clinical trials have been issued over the last 10 years and, on average, 264 clinical trials have been conducted (see Fig. 1).

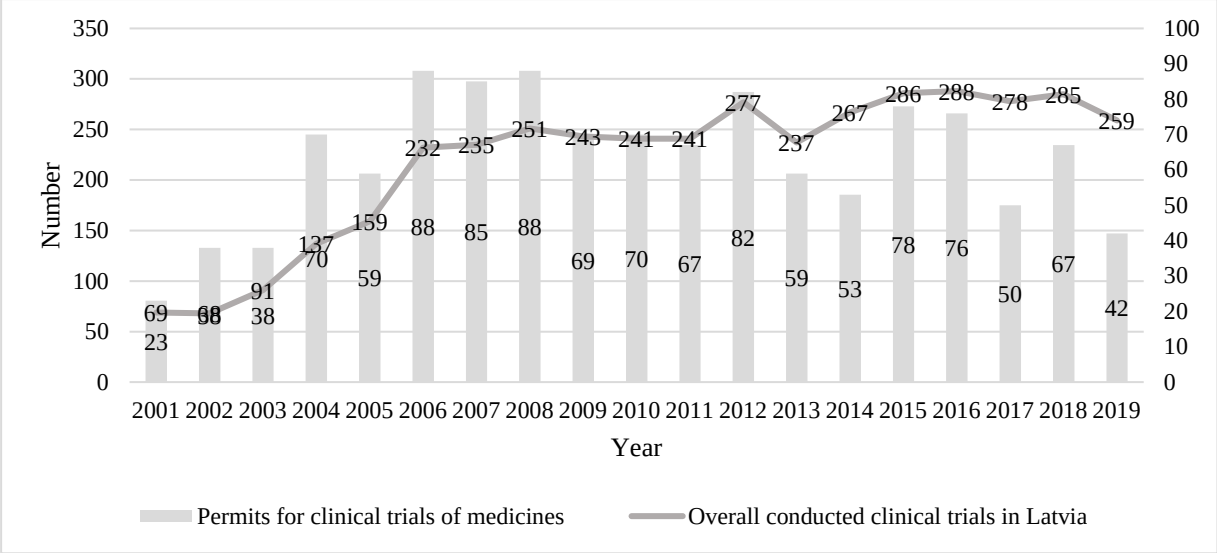

Figure 1 ***Clinical Trials in Latvia*** (The State Agency of Medicines of Latvia A, 2020; The State Agency of Medicines of Latvia B, 2020)

A rapid increase in permits for clinical trials took place in 2004, resulting in bigger volumes of clinical trials in 2005 and 2006. Such an increase in clinical trials could be attributed to Latvia's accession to the European Union (EU), a very good infrastructure, skilled medical professionals and many treatment “naïve” patients.

The permitted clinical trials of medicines by phases are reflected in the number of issued permits, as the number of patients increases significantly with every next phase of the trials (see Fig. 2).

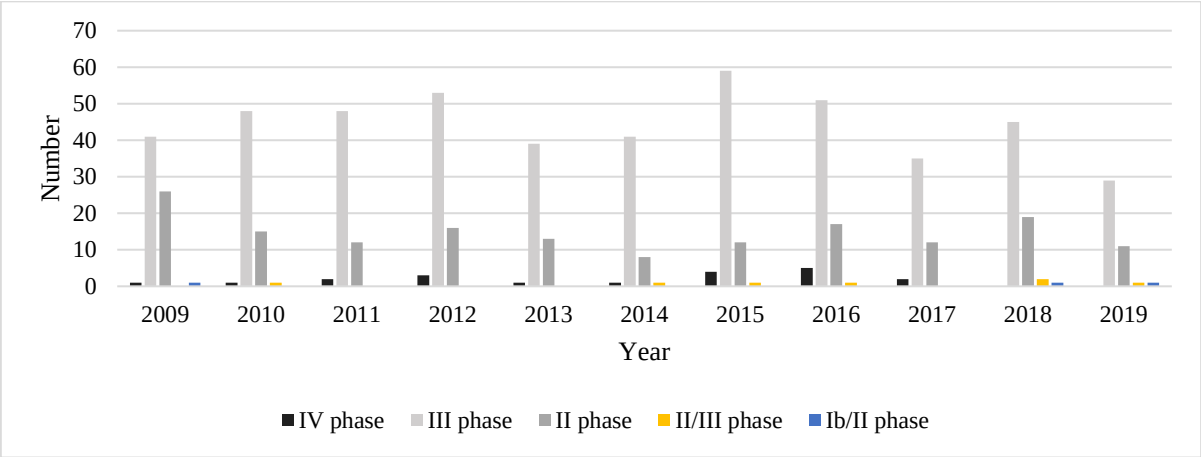

Figure 2 ***Number of Clinical Trials by Phases in Latvia*** (The State Agency of Medicines of Latvia A, 2020; The State Agency of Medicines of Latvia B, 2020)

Since 2009, 24% of all clinical trials of medicines have been the phase II research and 72% the phase III research.

During the last ten years, the biggest number of permitted clinical trials in Latvia was in the following sectors: oncology, pulmonology/allergology/ physiatrics, psychiatry/neurology, endocrinology, rheumatology, gastroenterology (see Fig. 3).

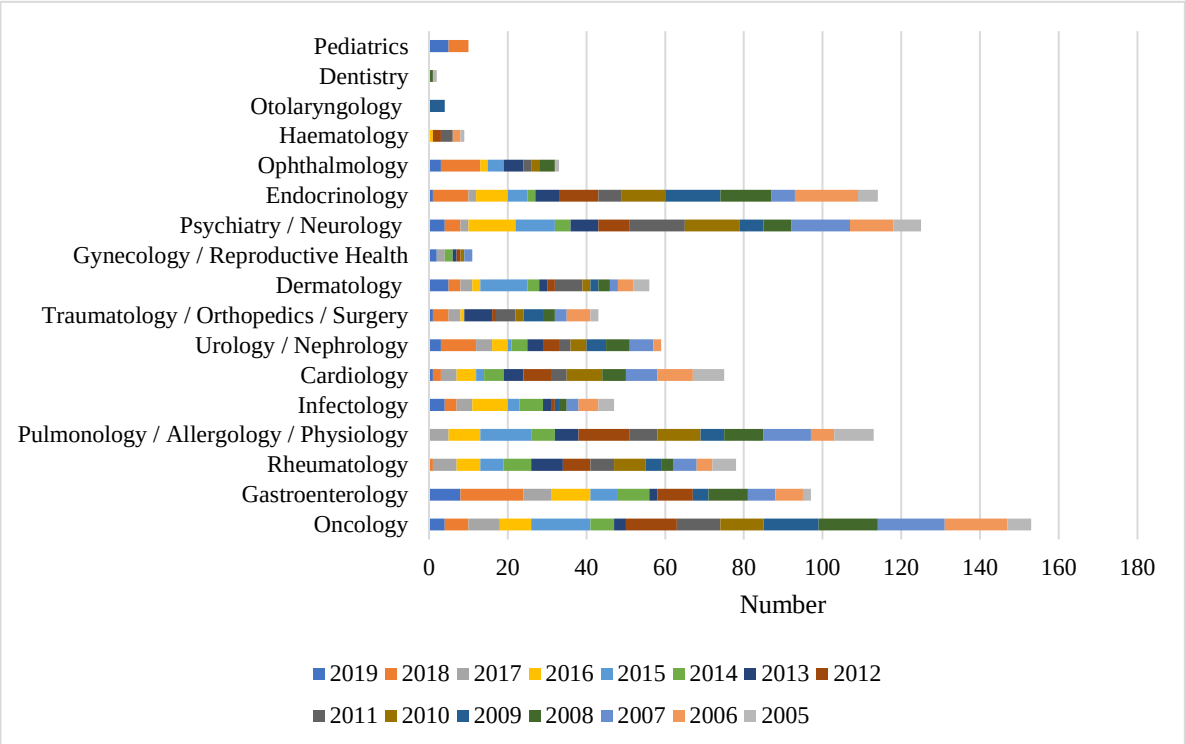

Figure 3 ***Clinical Trials of Medicines in Different Sectors of Therapy*** (The State Agency of Medicines of Latvia A, 2020; The State Agency of Medicines of Latvia B, 2020)

The sectoral breakdown of clinical trials of medicines is very similar to the world tendencies where oncology is leading in terms of the number of studies.

There are a lot of publications devoted to clinical trials of medicines (Abdel-Kader & Jhamb, 2020; Sakamaki et al., 2020; Thiers, Sinskey, & Berndt, 2008), including in Latvia (Logviss, Krievins, & Purvina, 2018), but various economic aspects of clinical trials are subject to continuous changes (Kramer, J. M.;Schulman, 2012; Petitti, 2009; Pinto, Willan, & O'Brien, 2005; Ramsey et al., 2015).

According to approximate estimates of PricewaterhouseCoopers, salaries of internal and insourced staff constitute 31%, support services (including couriers, accommodation, travelling, translations, etc.) – 8%, remuneration of researchers – 31%, remuneration of sites – 11%, fees of Ethical Committees – 2%, Central Clinical Trial Registry – 1%, medical costs (other than drugs, i.e. lab tests, scans, etc.) only 2% and other expenses 14%. More than a quarter of revenues from clinical trials come as a tax contribution to the state budget (PwC, 2020).

The most obvious economic factors can be segmented into benefits for state and medical institutions. Costs of clinical trials are covered by sponsors – medicines for patients, examinations, as well as the work of doctors and nurses, etc.

Structure of payments by clinical research centres includes all three elements of the economic factors directly or indirectly. Direct economic factors include national charges, both as labour force taxes and corporate taxes, made by researchers and Clinical Research Associates (CRA) within the framework of clinical trials. In addition, the direct economic effect may include resources that are not paid by the state for medicines and bed day costs for medical treatment of patients. Socioeconomic factors are also manifested as benefits for medical and scientific authorities as deductions for the use of infrastructure and archiving services, which are further directed to develop the clinical and scientific base.

The process of selecting healthcare services is currently being organised in accordance with Cabinet Regulation No. 555 adopted on 28 August 2018 "Procedures for the Organisation and Payment of Health Services" (Cabinet of Ministers, 2018). Hospitals are still paid through a combination of "earmarked service programs", Diagnostic Related Groupings (DRGs) and payments according to the actual number of bed days (Strizrep & Alaka, 2016). Accordingly, fees and charges for bed days take place in accordance with at least this regulatory enactment. Archiving and deductions for the use of infrastructure are determined in accordance with contracts for the respective clinical trials. The bilateral agreements set also salaries of Clinical Research Associates and physicians-researchers.

In spite of the obvious significance of direct economic factors in clinical trials of medicines, other economic factors, which are not of minor importance, are also required (see Fig. 4).

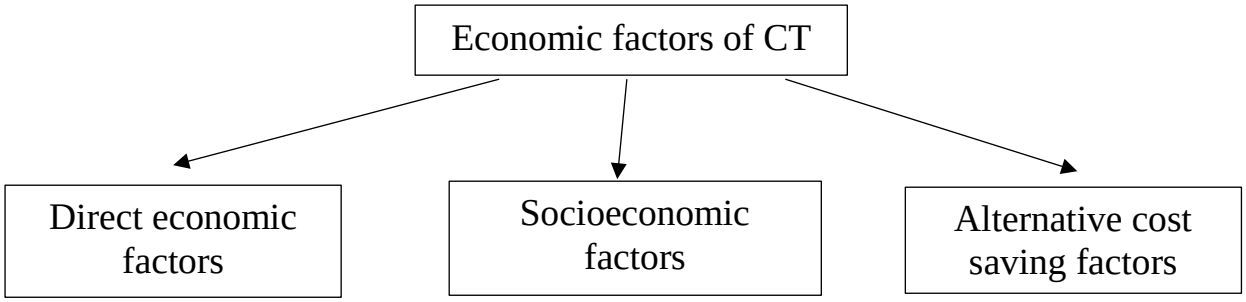

Figure 4 ***Economic Factors of Clinical Trials of Medicines*** *(made by the authors)*

The provided categories have been grouped according to the following three economic factors: direct economic factors, socioeconomic factors and alternative cost savings factors (Kalashnikov, 2004; Lin, Sokolov, & Orlov, 2015; Melihov, 2006).

Material and Methods

Identification of economic factors. Types of economic factors of clinical trials of medicines have been identified based on an analysis of scientific and practical literature. Three types of economics factors have been identified.

An empirical research is based on a systemic approach to investigate the maximum possible manifestation properties of the object. This increases the probability of acquiring general knowledge about the object of research. Every type of economic factors of clinical trials, in terms of content, is comprehensive; therefore, expert opinion is used to identify and group economic factors of clinical trials of medicines. The authors have selected a model that allows evaluating economic factors of clinical trials of medicines in fifteen categories: *direct economic factors* (contribution to the state budget; employment opportunities; economic incentives for other supportive businesses; additional revenues of medical institutions; provision and improvement of medical infrastructure of clinical trials), *socioeconomic factors* (access to the new standards of Good Clinical Practice (GCP); access to the latest treatment methods and preparations; improved patient care (time used per patient); in-depth patient care after a treatment course; access to examinations not available in Latvia; exchange of experience, transfer of knowledge on the most innovative treatment methods; professional development of researchers and doctors and work experience) and *alternative cost savings factors* (contribution to the national economy (retaining

of working capacity and contribution to the Gross Domestic Product (GDP) increase); saving of healthcare and social resources; family contribution to the national economy (taxes and GDP increase).

Search strategy. The principle of snowball has been used to make the selection of the participants' survey. As participants with information and understanding of what clinical trials are and what the economic factors of clinical trials are that could provide useful information, we have used snowball sampling so that we could set up a network to find each of the next participants in the survey. The empirical analysis and evaluation of economic factors in unique clinical trials of medicines are based on the qualitative research method of semi-structured individual (in-depth) interviews. A content analysis has been used to process the resulting data. A method of logical analysis has been used to reflect the conclusions of the empirical study.

Survey groups. A case study method has been selected for the research to analyse the activities of several *subjects* in three groups. This research method can be applied in both developing of new scientific knowledge and solving various practical situations. Attention is paid to the subtlety and complexity of the individual case. Pauls Stradiņš Clinical University Hospital (PSKUS) is the second largest clinical university hospital in Latvia, where the biggest number of clinical trial research centres in Latvia is attracted. The validity of the choice of the case study research method and the research subject is ensured by: 1) PSKUS doctors-researchers involved in conducting clinical trials; 2) administrative staff ensuring clinical trial processes at PSKUS; 3) CRA that supervises researches at PSKUS. Patients are not selected as research subjects because their responses to the economic factors of clinical trials are expected to be highly biased and, above all, personal benefits from clinical trials will be mentioned as an economic factor. In view of the specific niche of clinical trials, random respondents are not included in this survey, since the overall understanding of the economic factors of clinical trials may be very low.

Research Results

Matrix of economic factors. All three groups of respondents have been also analysed in the context of the entire group. In total, 23 respondents have participated in this research. For confidentiality purposes, respondents have been coded and only their codes have been used in the work – Group 1 (A1 – A9), Group 2 (B10 – B16), Group 3 (C17 – C23). Each participant in the survey was asked to code each economic factor from 1-15.

Table 1 ***Summary of the Research Results***

Type of economic factor		Category of economic factor	Code	Weight factor (Index)
Direct economic factors	State	Contribution to the state budget	107	0.36
		Employment opportunities	144	0.48
		Economic stimulus for other supportive businesses	86	0.29
	Medical institution	Additional revenue of medical institutions	137	0.46
		Provision and improvement of medical infrastructure of clinical trials	137	0.46
		Total sum of the codes:	611	
		Average index of the factor		0.41
Socio-economic factors	For patients	Access to the new standards of Good Clinical Practice (GCP)	212	0.71
		Access to the latest treatment methods and preparations	**297**	**1.00**
		Improved patient care (time used per patient)	259	0.87
		In-depth patient care after a treatment course	235	0.79
		Access to examinations not available in Latvia	219	0.73
	For researchers	Exchange of experience, transfer of knowledge on the most innovative treatment methods	255	0.86
		Professional development of researchers and doctors and work experience)	235	0.79
		Total sum of the codes:	1712	
		Average index of the factor		0.82
Alternative cost savings factor		Contribution to the national economy (retaining working capacity and contribution to the GDP increase)	105	0.35
		Saving of healthcare and social resources	118	0.39
		Family contribution to the national economy (taxes and GDP increase)	74	0.25
		Total sum of the codes:	297	
		Average index of the factor		0.33

The research has resulted in the creation of matrices that separate types of economic factors, categories of economic factors, codes and the weight factor (Index). Table 1 summarises the research results (emphasis on the weight factor (Index)). First of all, based on the determined code values, the index (weight factor) has been calculated for each category of the economic factors where the sum of codes for each category is divided by the maximum code of one of the categories (e.g. 107/297; 297/297; 74/297, etc.). The maximum code of the categories (the sum of answers of each respondent) is the economic factor category - "Access to the latest treatment methods and preparations", 297, in total. This allows ranking values of the category of economic factors of clinical trials.

Secondly, this shows the level of significance of each type of the factor, i.e. respondents have identified the topic categories as relevant. The significance of each type of factors is indicated as the average weight factor (Index). The average

weight factor (Index) has been calculated as the average Weight factor (Index) of each type of economic factors.

Characteristics of the categories of economic factors. For each category of economic factors, the Weight factor (Index) has been estimated. The most important category for identifying economic factors in clinical trials is the "Access to the latest treatment methods and preparations" (Index max 1). Next most important indexes are the "Improved patient care (time used per patient) - 0.87, "Exchange of experience, transfer of knowledge on the most innovative treatment methods" - 0.86, "In-depth patient care after a treatment course" - 0.79 and "Professional development of researchers and doctors and work experience" - 0.79. The index "Access to examinations not available in Latvia" has been estimated as 0.73 and "Access to the new standards of Good Clinical Practice (GCP)" as 0.71. All estimated weight factors (Indexes) belong to the category of socio-economic factors of economic factors, pertaining to both patients and researchers.

Other most important economic factors are direct economic factors. Respondents believe that a positive contribution to the economy is the "Medical institution" subfactor – "Additional revenue of medical institutions" and "Provision and improvement of medical infrastructure of clinical trials" - index 0.46. Then follows the "Employment opportunities" category of the "State" subfactor - 0.48. Weight factor (Index) of "Contribution to the state budget" is 0.36 and of "Economic stimulus for other supportive businesses" 0.29.

Weight factor (Index) of "Saving of healthcare and social resources" is 0.39 and of "Contribution to the national economy (retaining working capacity and contribution to the GDP increase)" 0.35.

The least important economic category in clinical trials is "Family contribution to the national economy (taxes and GDP increase)" (Index 0.25).

Characteristics of types of economic factors. Another important result is the total amount of codes in the context of identifying economic factors in clinical trials. The interpretation and conceptualisation of the research data have revealed that the type of economic factors - "socioeconomic factors" has the biggest sum of codes (1712 in total), the average index of the factoris 0.82 The type of economic factors - "direct economic factors" has shown 611 in total, the average index of the factor is 0.41, while the type of economic factors - "alternative cost savings factor" has the smallest sum of codes (297 in total), the average index of the factor is 0.33.

Conclusions and Discussion

Taking into account the results of the survey, financial revenue from clinical trials is not the most significant economic factor. The respondents believe that

exactly socioeconomic factors give primary economic benefits from clinical trials of medicines in a society with small population. Certainly not only in countries with a small population, the largest beneficiaries of clinical trials are patients, but also researchers. Exchange of experience, transfer of knowledge on the most innovative treatment methods and professional development of researchers and doctors and work experience are two most significant benefits from clinical trials. Financial benefits from clinical trials are of great importance to the national economy. Its revenue from clinical trials contributes to the development of a more rapid scientific research base for medicated institutions. In the form of different national taxes and unpaid medicines, even a country with a small population has benefited in terms of several million euro. Although the "Alternative cost savings factor" is underestimated on the part of the respondents, this factor can be considered as having hidden potential in the context of its economic contribution, as it cannot be estimated with account of the high probability of the outcome.

When assessing how a society with a small population evaluates the primary economic benefits from clinical trials of medicines, it can be clearly concluded that all categories of the surveyed groups believe that the socioeconomic factor is the most significant. Patients in clinical trials are overly beneficial because they have access to the latest treatment methods and preparations, and patients benefit from the improved patient care. The alternative cost savings factor is the least significant in the context of the economic factors of clinical trials.

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