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Journal of Health Policy & Outcomes Research

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e-Health

Telemedicine - a challenge rather than solution for payers and service providers in EU

K.Dziadek, G.Waligora

From the Editors

IN THIS ISSUE, WE FEATURE TELEMEDICINE AS A PART OF E-HEALTH, WHICH IS INTERESTING FOR BOTH PAYERS, MINISTRIES OF HEALTH OF ALL EUROPEAN UNION (EU) STATES AS WELL AS SERVICE PROVIDERS. IT SHOULD BE STRESSED THAT THE FASCINATION FOR THESE SOLUTIONS DOES NOT CORRESPOND WITH ADVERSITY, STEMMING FROM LEGISLATIVE BARRIERS IN MANY EU COUNTRIES. IN NOT ALL EU COUNTRIES LEGISLATION ALLOWS PROPER IMPLEMENTATION AND REIMBURSEMENT OF THE SERVICES.

Also featured in this issue is an overview of guidelines available in relation to real world data (RWD) methodology research. In conclusion, we need unified standards for evaluating RWD in Europe. However, medical practitioners in Poland who are important stakeholders involved in determining the future of RWE are interested in data about comparative drug effectiveness and safety (90%), about treatment and prescription patterns (75%) and in degree of patient compliance (70%).

Chronic obstructive pulmonary disease (COPD) is a life-threatening, debilitating lung disease that severely impacts normal breathing and daily activities. In 2012, more than 3 million people worldwide lost their lives due to COPD, accounting for 6% of all deaths globally for that year. Two articles - one from Greece (M. Geitona et al.) and the second one from Ukraine (V.Tolubajev et al.) show the problems of COPD, including also cost-effectiveness analysis of innovative drugs in these countries.

There has been extensive research into the QoL of patients with schizophrenia and it has been consistently reported that schizophrenia significantly reduces the QoL of patients and their caregivers in CEE countries. We feature an interesting article from international authors on stigmatization and discrimination patients with schizophrenia, and an associated impact on their QoL and that of their caregivers.

Our colleagues from Russia ISPOR Chapter present application of multi-criteria decision analysis (MCDA) and its alternatives in Russian Federation. There are presented pros and cons for this type of analysis, as well as their Western (Forsight) and Russian alternatives (rule of square of decision making, P. Vorobiev, 2003). There are also presented stages, questions and types of MCDA.

Finally, we would like to emphasize that in this issue you will find many other interesting papers.

We hope you enjoy this issue of Journal of Health Policy & Outcomes Research.

Editor-in-Chief   Deputy Editor-in-Chief
Prof. K. Jahnz-Różyk   Dr J. Lis

Telemedicine - a challenge rather than solution for payers and service providers in EU

K. Dziadek, MAHTA
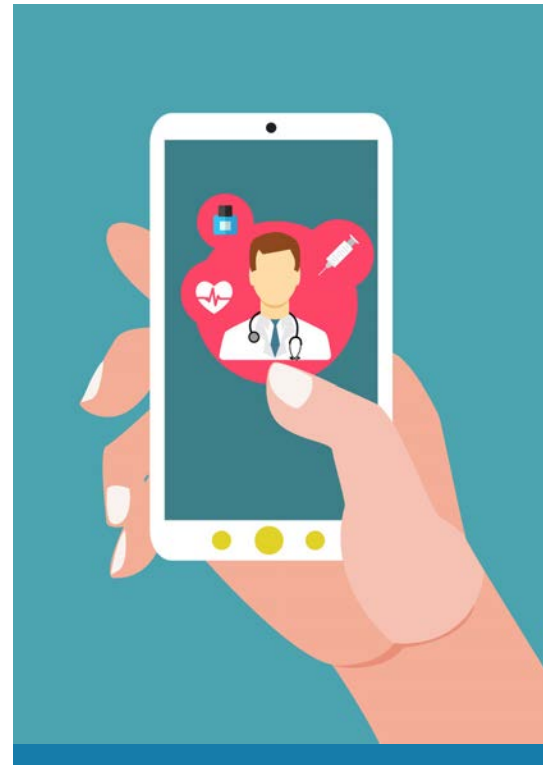**G. Waligora**

ABSTRACT

Telemedicine a part of E-health fascinates both payers, Ministries of Health of all European Union (EU) states as well as service providers. But fascination does not correspond with uptake of solutions implemented in EU states. The major obstacle in broad adoption of such services is legislation. Not in all EU countries legislation allows proper implementation and reimbursement of the services. Today the most common limitations are associated with necessity of the presence of a health care worker and the patient in the same place and legal problems in terms of reimbursement for telemedicine services to providers. France, Italy and Spain have powerful examples of successful implementation of telemedicine services mainly telemonitoring. However numerous clinical studies have proven significant improvement in compliance in chronically ill patients but also improvement in disease-specific clinical outcomes including mortality.

With the advancement of technology more and more new solutions have been introduced for widely understood e-health. Telemedicine is one of the components of this system. Defining of the concept of telemedicine by different organizations is not identical, however, a common component of these definitions is transmitting information over a distance when the patient and doctor are not in the same place. According to the definition proposed by the European Commission, telemedicine should be understood as providing healthcare services, using information and communication technologies (ICT) in a situation where the health professional and the patient (or two health professionals) are not in the same place. It includes transfer of data and medical information in the form of text, image, sound, or in other forms, which are necessary for the prevention, diagnosis, treatment and follow-up [1]. In the European Union telemedicine should be understood as providing services such as teleconsulta-

tion (including e-visits to the doctor, video-conferences between health professionals), telemonitoring, teleradiology and teledermatology. Some services like telesurgery, health information portals, electronic cards and electronic prescriptions are not always taken into account [2,3]. Telemedical services were originally performed primarily using stationary equipment, but currently thanks to continous development of mobile technology, some telemedicine services can be implemented using mobile devices like for example advanced smartphones.

Telemedicine services can be divided into two main types: one related to the implementation of medical procedures and telemonitoring.

Services related to the implementation of medical procedures refer to situations in which a doctor performs a medical act at a distance using specific information and communication technologies, eg. teleradiology - remote evaluation of X-ray images, telepathology - remote rating of biopsy sampling cells or tissues, teledermatology - remote evaluation of skin images sent by the patient or another doctor. This type of telemedicine is a typical example of B2B (business-to-business) service. Telemonitoring relates to the provision of medical care through a combination of specific desktop or mobile device with the corresponding sensors that allow to monitor the health status of the patient. Data can be collected automatically or a patient can input specific parameters to the device himself. Telemonitoring increases the frequency of contacts, that is the integration between a patient and his doctor without a necessity of face to face outpatient/ hospital visits (they are in the majority of cases linked with time consuming travelling). It ensures a better continuity of care in particular for patients with chronic diseases. The level of stress for a patient can be reduced. In addition, an early detection of abnormal parameters gives the possibili-

ty of rapid intervention and can prevent later complications. This can generate savings for healthcare system as through the use of this type of telemedicine services, not only the quality of care for chronically ill patients is improved, but also the frequency and duration of hospitalizations are reduced [2,4].

The implementation of telemedicine solutions enables the provision of more personalized medical care, focusing on adapting to the needs of each individual patient. At the same time it can help health systems with limited financial resources to face the challenges of aging populations, the multiple expectations of patients and increased mobility of patients and health care professionals. The main factors that in the near future may have an impact on the development of telemedicine services are: the relative increase in the number of patients with chronic diseases (including young adults), the increasing number of older people with decreasing revenues from constantly declining group of people paying taxes and finally decrease in the number of professionals in the field of medical care in

the European Union countries [4]. The global market for telemedicine services despite the economic crisis grew from 9.8 billion dollars in 2010 to 11.6 billion in 2011 and expected its value in 2016 is 27.3 billion dollars, which gives an average annual growth rate of 18,6% [5].

In the European Union (EU) legislation has been established. In the provisions of those legal acts the description of functioning of e-health systems, including telemedicine, both on individual countries as well as in the context of cross-border care is described.

However not in all EU countries, including Poland there are established legal frameworks which unable telemedicine services to be implemented. The most common limitations are associated with necessity of the presence of a health care worker and the patient in the same place and legal problems in terms of reimbursement for telemedicine services to providers [2].

However, there are already some member states with legislation for the provision of telemedicine services. Its range is very diverse – sometimes legal acts describe only a framework of courses of actions in relation to the implementation of telemedicine services to the health system, but in other cases legislation precisely regulates the functioning of the various telemedicine services in the system.

Poland is still lacking legislation. Thus as of today none of the services can be reimbursed by the public payer. There has been attempts to establish at least basic legal framework for introduction of telemedicine services within public healthcare system.

On a contrary, in France, the official regulations in the field of telemedicine already appeared in July 2009. In October 2010, a decree was published. In the document the main areas, that telemedicine coveres (including teleconsultation, teleex-

pertises, telemonitoring, teleasist, remote monitoring) as well as the rules of implementation and organization of telemedicine are described. The decree has been added to the Public Health Code and from a legal stand point, telemedicine services have become standard medical act. Also developed guidelines have been provided to a regional medical agencies for the development and implementation of telemedicine programs at the regional level [6]. Since October 2011, the telemedicine services have been reimbursed at the same level as a standard visits, if you can qualify them to one of the categories specified in the Social Security Code [7].

In Scotland there is no specific legislation regarding the use of the telemedicine technology in health and social care, but increasing attention to IT systems associated with the patients can be observed. The first strategy for eHealth was established in 2008. In December 2012 the document "National Telehealth and Telecare Delivery Plan for Scotland to 2015" was prepared which sets the strategic lines of action for telehealth and telecare [6].

Legislative solutions in the field of telemedicine in Spain vary depending on the region. For example, in Catalonia, the local level strategy for the development of telemedicine was implemented already in 2012. In addition, they implemented other strategies related to health or IT, which individual parts also refer to telemedicine eg. the treatment of chronic diseases from 2012, IT in health from 2008 [6].

In practice, European countries have already introduced many different activities in the field of telemedicine.

One of the most well-known project in the field of telemedicine in France is Cardiauvergne. It works in the Auvergne region, but it will be replicated in other regions. It is designed for patients with severe heart failure (stage III and IV NYHA) who were hospitalized at least once during the year prior to inclusion to the program. The program builds on telemonitoring system by which the current state of each individual patient is monitored, the messages are sent automatically to nurses' smartphones at intervals dependent on the severity of the disease also laboratory test results and information from the pharmacist are included. The data is entered into the electronic patient record and the IT system generates an alarm depending on defined parameters. The coordinating team takes appropriate action. In the first two years after introduction 558 patients were included into the system (mean duration of patient monitoring amounted to 355 days). Annual mortality decreased by 12% (which is more than twice better value than in traditional monitoring), whereas the incidence of hospitalization during the year decreased by 13.6% (while length of hospital reduced from 13 to 9.2 days) [6].

An interesting example of another regional implementation of telemedicine comes from Italy and is called "Telecardiology Puglia". The program has been performed in the region of Puglia. It focuses on supporting doctors in routine everyday clinical practice. In emergency cases, doctor or a trained person records 20 seconds of 12-lead ECG, and then sends the recordings to the center of cardiology (Cardio On Line Europe) available 24 hours, 7 days a week. In the mentioned above center cardiologist reads the recording and based on it and an interview performed during the teleconference, provides his opinion to the registering person and sends a corresponding report. On this basis, ambulance center determines the need of hospitalization for a patient. Five years after introduction, the system helped to reduce by half the mortality from acute myocardial infarction, as well as it helped to reduce the time from diagnosis to initiation of therapy. Additionally sav-

ings associated with avoiding unnecessary admissions to hospital were shown [6].

Today the most common pan-European telemedical service is teleradiology [2]. It involves the transmission of radiological images for interpretation or consultation. Teleradiology services are usually outsourced to external outsourcing centers, within the country as well as across borders. The European Society of Radiology published results of a study designed to evaluate the use of teleradiology in Europe. The study involved 368 specialists in radiology from 35 European countries. Of the surveyed doctors 65% were using teleradiology. The main advantages, that were pointed out are: the possibility of cooperation with other radiologists and efficient distribution of workload. In addition, 35% of specialists used outsourcing (65% of them using commercial services). The outsourcing biggest benefits were the ability to seek a second opinion as well as the possibility of telephone consultation. In general, most experts spoke positively about the future of teleradiology [4].

To identify advantages and disadvantages of the use of different types of telemedicine services numerous clinical studies have been founded. They evaluate both services using stationary equipment as well as mobile applications.

For example, in a systematic review from 2015, 107 studies were included. It focused on evaluation of the efficacy of m-health services (telemedicine services using mobile devices) in helping patients with chronic diseases. In the review usability, acceptability and preferences of patients in relation to the systems supporting adherence have generally been rated as high. In addition, 56% of randomized trials demonstrated a significant improvement in adherence and 39% of the studies showed a significant improvement in disease-specific clinical outcomes. The review identifies the large potential of the tools used in the context of m-health to improve adherence of people with chronic diseases, despite incomplete consistency of data. The authors suggest the necessity to carry out further studies to fully understand the tools by which the best results can be achieved [8].

As a part of the systematic review, the scientific evidence regarding telemedicine services used in the treatment of diabetes, gestational diabetes and diabetic retinopathy was evaluated. 73 studies meeting the inclusion criteria were identified. Applied forms of telemedicine services differed between studies, but the evidence obtained was consistent and showed a positive effect of telemonitoring and telescreening in relation to glycemic control, weight reduction and increased physical exercise. Furthermore, the authors highlighted the potential of telemedicine to changing behaviors and habits of patients, which is extremely important in controlling the disease, particularly in the case of diabetes type II and gestational diabetes [9].

As the payer in Poland together with some national consultants refer to low efficacy of expensive biologics and unnecessary hospitalizations in drug programs, implementation of telemedicine can be a solution.

One can assume, that the level of costly hospitalizations linked only with administering of drugs in drug programs can be significantly reduce. Also the compliance and adherence should improve.

Patients in drug programs can get medicine for the period of three months. M-health will provide greater control of administration. Reminder to administer the medicine will be send to each patient, every time. In case of questions televisit with a use of smartphone can be performed.

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Real world data guidelines - current status review

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ABSTRACT

Objective: to identify existing guidelines for real world data collection and analysis.

Methods: we performed Pub-Med search in literature for guidelines and recommendations for real world data studies.

Results: Based on the performed search we have obtained in total 97661 records. After analysis and selection we finally identified 40 publications fitting our search criteria and we found that only 2 were dedicated to RWD and provided some guidelines to researchers.

Conclusion: The published guidelines are usually focused on specific type of RWD studies and there are not many guidelines available in relation to real world data methodology research in general. In view of the potential use of RWD in decision making specific guidelines on how to conduct RWD research are needed.

INTRODUCTION

Randomized clinical trials (RCTs) are the gold standard in research and there are regulations in place about how to perform such studies, what the best methodology is, what the standards are to ensure good quality of delivered evidence and how to report the results. However RCTs cannot answer all scientific questions and real world data are those which can provide additional information in relation to medical treatments, especially taking into account the potential impact on decision making process at the time to provide access to new treatments. But yet there is a need to use the right methodology for data collection in order to ensure good data quality. This seems not to be that well defined when we are looking at the real world data studies.

This is the reason why as a follow up to our first paper related to real world evidence need we decided to search for existing guidelines or recommendations addressed to projects and studies where real world data is collected [1].

Objective: Our aim was to investigate what is recommended to perform good quality and reliable real world data studies. Are there any existing guidelines specific for RWD? What is the recommended methodology to collect and analyze RWD?

Methods: The performed search was based on the Internet. The Medline-PubMed databases have been reviewed and the search strategy was based on terms: "real world data" [All Fields] AND "guidelines" [All Fields] OR "guidance" [All Fields] OR "recommendation" [All Fields]. The initial search was performed in June 2015, however due to obtained findings not specific to guidelines related to real world we decided to perform an additional search in July 2015. The additional second search was focused on "real world data" [Title]. All the obtained   abstracts have been analyzed for the accuracy and the selected ones have been searched for the full publications.

Results: Based on the performed search we have obtained in total 97661 records. We have restricted the search to "humans" 69517 and then for publications within last 5 years which allowed to obtain 23597 records (diagram 1). When analyzing the obtained records we observed that they were not fulfilling our criteria, as most of the publications were related to clinical guidelines for treatment of different conditions, not methodological guidelines about how real world data studies should be performed. With the 2nd search, we decided to restrict the search only to titles with the words we were interested in and we obtained 67 records. We have restricted the search to "humans" which allowed to obtain 40 publications. Reviewing all obtained records from the performed search we analyzed in detail the abstracts and after analysis of the full texts we found 2 publications fulfilling our criteria (diagram 2). The final selection was done independently by 2 authors before the final inclusion decision was taken. Since we were not satisfied with the findings we continued searching additionally on the internet site of scientific organizations (ISPOR) and HTA organizations (NICE) where we found two additional publications which we decided to include in our discussion.
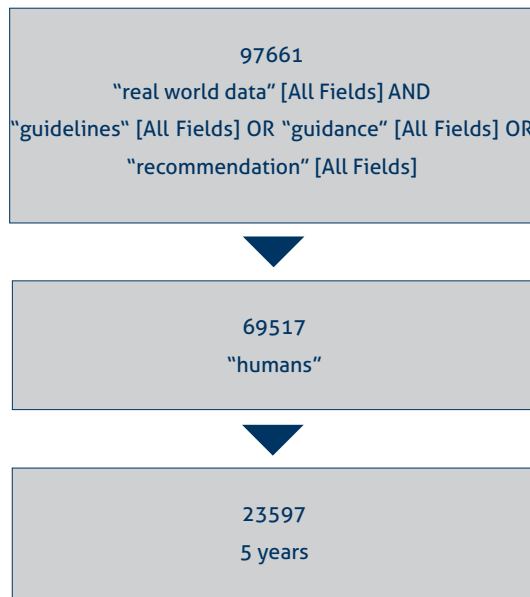

Diagram 1. First search strategies in the library database – PubMed

Diagram 2 – Second search strategies in the library database – PubMed

The RWD topic is in the area of interest of the ISPOR organization and their Task Force published the results in 2007 of the group work defining what we understand by real world data and also pointed out to the limitations in relation to RWD. The Task Force identified the need for good practices for collecting and reporting RWD and also the need for good process in using real world data in coverage and reimbursement decisions as well as the need to consider the costs and benefits of the data collection [3]. In the PubMed database search we found that already in 1999 Joel Hay raised the question about how we should evaluate RWD. The author saw the potential significant impact of real world data on decision making process as such information obtained from retrospective or observational trials can answer decision-makers questions. However there are limitations when collecting and analyzing data from real world. Hay provides examples of some retrospective analyses and discuss potential confounding factors and different factors influencing the results [2].

In his paper Willke recommends to learn from ISPOR publications about RWD however for those who start their interest in RWD he presents the "Ten commandments" for conducting and reporting CER based on analysis of RWD. In his paper the author provides an overview of what should be taken into account at the time of planning, analyzing and reporting results from real world research [4].

A recent publication by Roche, Reddel, Martin et al. focuses on the quality standards for real world research and helps to understand methodological issues related to comparative and observational studies when using clinical and administrative datasets. The authors provide the researchers and reviewers with a tool to be used both for conducting and reviewing RWD studies. The proposed checklist includes the key issues to be taken into account in relation to RWD projects. The authors divide the process whose aim is to ensure good quality of the data into preparation phase, analysis and reporting of results and the discussion of results [5].

DISCUSSION

With the growing interest in real world data as supportive element to the findings from randomized clinical trials we found relatively few published guidelines or recommendations on how to collect and analyze real world data. The reason could be that there are some guidelines focused on a specific type of RWD. There may exist guidelines for epidemiological studies, on how to report the results or guidelines for observational studies.

In 2007 there was an initiative called The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). Within this initiative recommendations on what should be included in an accurate and complete report of an observational study were developed. The STROBE recommendations covered three main study designs: cohort, case-control and cross-sectioal studies. There are also checklists for the different types of observational studies available [6].

In Brazil in view of the Brazilian Network for Health Technology Assessment recommendations to use observational studies

to develop economic evaluations a search was done to analyze to what extent RWD are used for HTA. The authors of the paper: "Real World data for Health and Technology assessment in Brazil: an unmet need" aimed to identify the requirements and needs for epidemiological data regarding HTA submissions in Brazil. After reviewing different sources such as HTA requirements, reports and dossiers, as well as local guidelines and regulations about principles for real world data requirements for HTA they found that in 11.8% of the submissions there were no real world data used and also lack of epidemiologic data was a common issue. The Authors concluded that for HTA in Brazil the use of real world data is an important need [7].

In relation to HTA analysis in UK NICE issued recently guidance for observational trials providing guidance which covers both aspects: for submission and review of observational data as part of the appraisal process. NICE being aware of the limitations in relation to observational data like bias in comparison to RCTs, patients selection, follow up and no pre-specified end-points prepared recommendations how the quality and transparency of assessments using observational data can be improved. The authors present an algorithm with the aim to support the best methods selection for the analysis [8].

CONCLUSION

Based on the performed search we can observe the growing interest in the real world data, however the published guidelines are usually focused on specific type of RWD studies and there are no many guidelines available in relation to real world data methodology research in general.

In view of the potential use of RWD in decision making specific guidelines on how to conduct RWD research are needed.

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The evolving landscape for Real World Evidence in Poland: physicians' perspective

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ABSTRACT

Real World Evidence is increasingly being demanded by national payers and HTA agencies to substantiate and validate outcomes from clinical trials. Yet, the access and quality of existing databases is often very limited, what creates hurdles to evaluate evidence in 'normal' healthcare setting. In Poland key stakeholders have not yet fully embraced RWE as an evidence source though they have growing need for more evidence to allocate scarce resources. The coming years are crucial for the shape and accessibility of RWE in Poland – however, the standpoint and the needs of the key stakeholders are not yet recognized. Therefore, an exploratory survey was undertaken to map current awareness and expectations of physicians related to practical outcomes data and to identify pharmaceutical industry's role in RWE generation. Consideration of stakeholder needs seems to be the natural step in the beginning of preparation for real world evidence system in Poland. The analysis showed significant physicians interest in practical evidence and broad spectrum of possible actions that can be undertaken to improve formal use of RWE in Poland. The differences in priorities between specializations are a good indicator of the unmet needs in certain therapeutic areas. Broadening doctors', payers', insurers' and service-providers' knowledge on RWE significance, raising awareness of practical implementation and improving accessibility could be crucial for shaping the RWE landscape in Poland and, consequently, for improving patient treatment results.

INTRODUCTION

Due to the rapidly changing range of medicines and therapies, the healthcare system stakeholders are increasingly turning to practical evidence for decision support. As a result there is a growing need for access to data that could explain reasons for initiation, combination and sequencing of different treatment options in non-trial setting (i.e. outside the framework of clinical studies). The starting point in estimating the effectiveness of a medical treatment is to collect key information about the number of exposed patients, drug utilisation, and the actual patient outcomes. In Poland, this kind of information is rare. Both medical practitioners and decision-makers in the healthcare system, at the local and national level, are not given the tools with which they

could effectively monitor the progress of therapy, or evaluate treatment outcomes in the long term. A rising need for new medical registers or structured databases is increasingly recognised, offering the opportunity to compare the effectiveness of existing therapeutic options in conditions more closely reflecting everyday medical practice.

DEFINITIONS, SOURCES AND USABILITY

In professional literature, this type of healthcare data is termed Real World Evidence (RWE) or Real World Data (RWD). This is a general term describing various types of data sets accommodating information about epidemiology, effectiveness, safety, and costs of treatment, generated and analysed outside the framework of randomised controlled trials (RCTs) [1]. In other words, RWE delivers insights into patient outcomes in real-life setting, in healthcare conditions other than meticulously arranged study conditions.

Real World Evidence (RWE)– data from the actual medical practice.
All evidence generated outside clinical setting referring to effectiveness, safety and costs of therapy delivered as part of standard patient care [1].

Figure 1.
Simplified model of placing a medicinal product on the market

Clinical trials are an obligatory part of the process of granting a marketing authorisation for almost every new medicinal product. Clinical trials are carried out to confirm safety and efficacy of an investigational medicinal product and to define its therapeutic effect in a study population. Phase III studies – the most important phase of a clinical trial that translates into future clinical recommendations – are typically conducted in a highly selected group of patients who grant an informed consent to take part in the study, while the progress of the study and the follow-up period (lasting several months to several years) are described in much detail in the study protocol.

In experimental setting, the quantitative measures with which the study sample is described (study end points) and the progress of the study are closely monitored and controlled to be able to prove that changes in the end point values result directly (and solely) from exposure to the investigational medicinal product.

Later on, a medicinal product authorised for marketing is used in a more general population of patients who can suffer from co-morbidities and other health problems, or use concomitant medications, while receiving medical care in a complex healthcare setting, determined for example by the structure of the healthcare system.

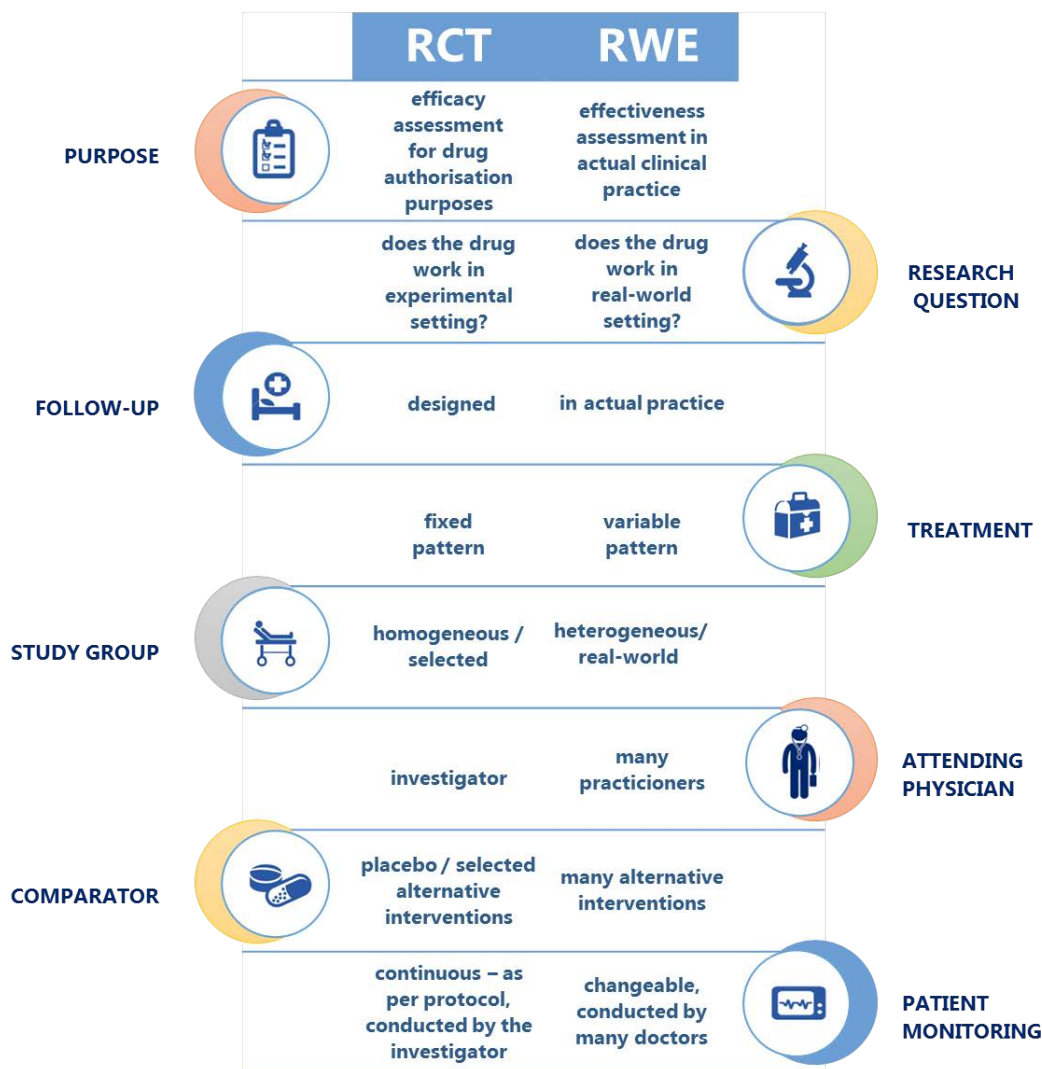|	RCT	RWE	
PURPOSE	efficacy assessment for drug authorisation purposes	effectiveness assessment in actual clinical practice	
	does the drug work in experimental setting?	does the drug work in real-world setting?	RESEARCH QUESTION
FOLLOW-UP	designed	in actual practice	
	fixed pattern	variable pattern	TREATMENT
STUDY GROUP	homogeneous / selected	heterogeneous/ real-world	
	investigator	many practicioners	ATTENDING PHYSICIAN
COMPARATOR	placebo / selected alternative interventions	many alternative interventions	
	continuous – as per protocol, conducted by the investigator	changeable, conducted by many doctors	PATIENT MONITORING

Figure 2.
Randomised clinical trials and real-world follow-up – main differences

Although they deliver best-quality scientific data, RCTs do not provide information about:

- treatment effectiveness in actual (everyday) medical practice, both in clinical and economic terms,
- effects of treatment on real-world, normal population instead of (selected) study population (i.e. where various inclusion and exclusion criteria apply to avoid enrolling patients with co-morbidities), or the prevalence of rare adverse effects, or drug-to-drug interactions;
- long-term data about correlations between safety and efficacy of therapy and real-world patient behaviour (e.g. patient compliance).

Unlike pre-marketing clinical studies investigating "efficacy", RWE provides information about "effectiveness". Based on tracing the 'real-world' medical history of patients dating many years back, data collected from a broader patient population, and evidence of real-life patient compliance, RWE is complementary to conventional data from RCTs, and as such it paints a wider picture of the methods used in preventing, diagnosing, and managing specific diseases, and of the long-term safety, effectiveness an costs of therapy. RWE appears to be an adequate response to the increasing demand of the healthcare system for more comprehensive evidence.

Apart from the scientific value it carries, information from medical registers that describe real-world treatment outcomes can serve as a basis for a system-wide economic and social assessment of medical technologies. Therefore in many countries across Europe, insurance institutions (payers), regulatory authorities, or agencies that evaluate the cost-effectiveness of medical technologies increasingly demand access to this type of information and knowledge – in addition to the outcomes of RCTs.

Real World Data can be derived from different types of registers (disease based, drug based), economic or social databases collected from medical practitioners or healthcare centres, patients, insurance companies (payers) and other entities that gather information about therapeutic effectiveness of drugs in everyday clinical practice (such as prospective observational studies), electronic medical records, National Health Fund (NFZ) reports, registers of epidemiological data, or questionnaire-based studies of patients.

For obvious reasons, scientific quality and validity of information generated from RWE depend on a number of factors, including data quality (completeness and representativeness), or the level of standardisation and clarity of the parameters measured (e.g. the underlying disease and its consequences). What is noteworthy, patient registers have a very special place among the sources of RWE as they meet both of these criteria.
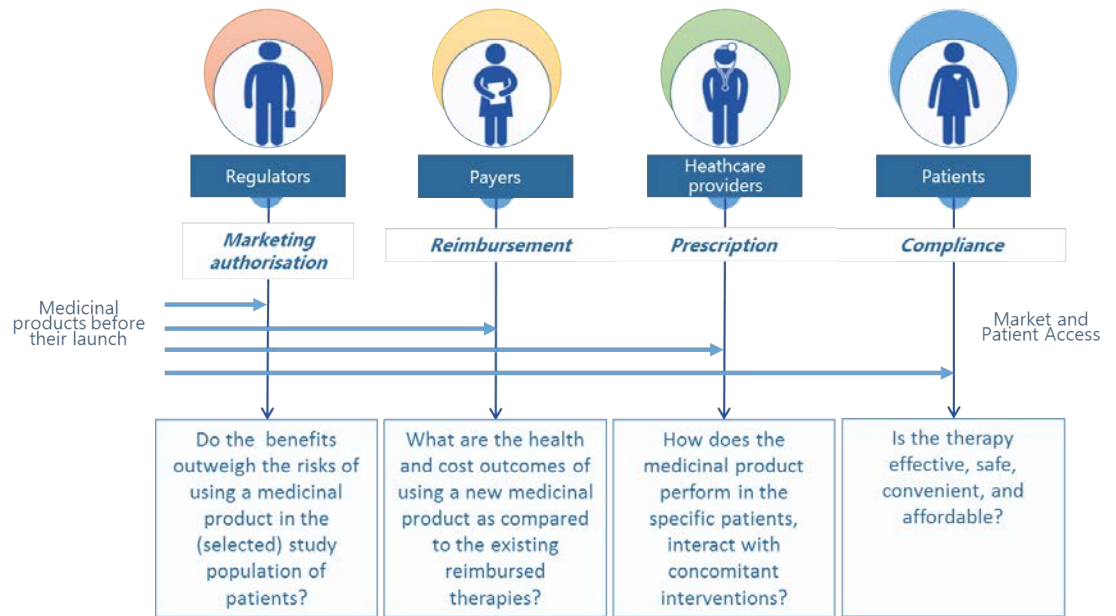
Figure 3.

*The perspective and demand for data among different stakeholders in the healthcare system
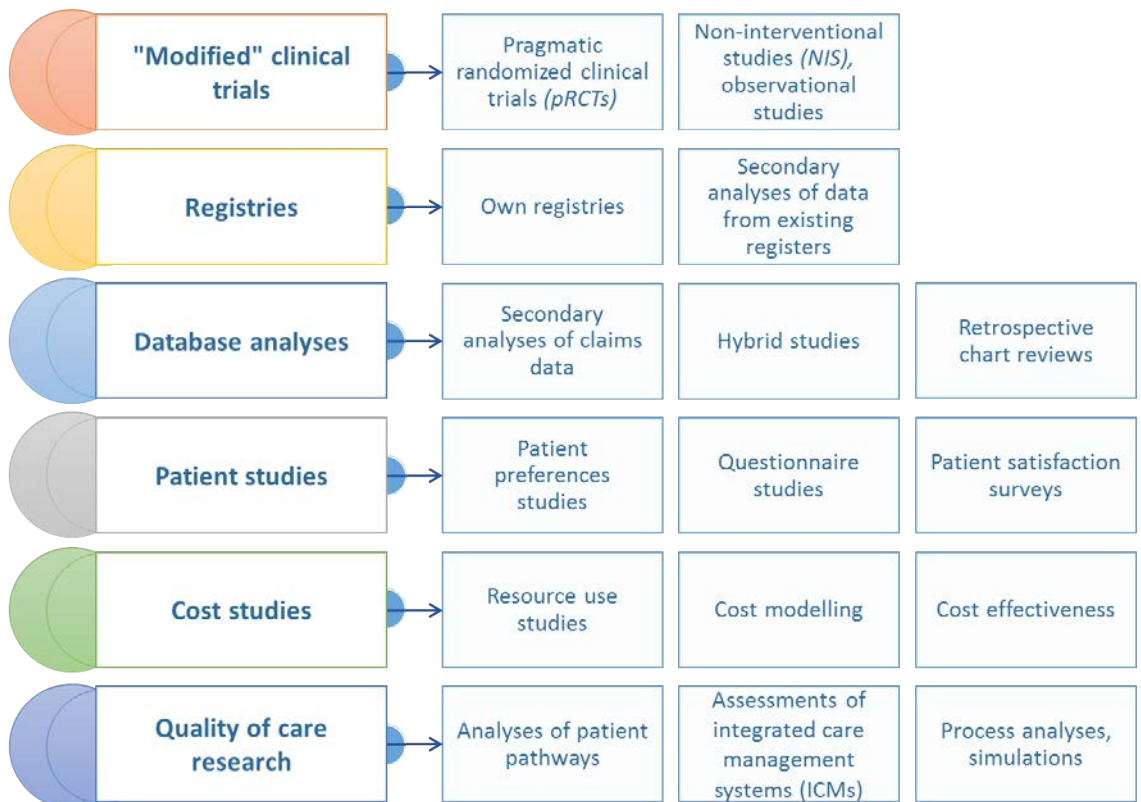(based on (2))*

Figure 4.

Examples of analyses based on real-world data

Implementation of well-designed RWE registers translates into benefits in many aspects of healthcare and paves the way for more general use of this data in:

- everyday medical practice – the data collected help evaluate real patient benefits of various treatment options,
- assessment of medical technologies in cases where clinical trials are difficult to conduct / impractical / unethical,
- research projects – practical treatment outcomes can supplement the existing body of evidence from clinical, epidemiological, and many other fields of science, such as health economics,
- agreements between payers and pharmaceutical companies under outcome-based risk-sharing arrangements to attain maximum control over reimbursement costs.

Registers can help evaluate the effectiveness and safety of therapy, identify patient needs, supplement HTA report, and support evidence-based reimbursement decisions, investigate the overall effectiveness of the healthcare system, or implement commercial and marketing strategies.

CURRENT STATE AND FUTURE PERSPECTIVE OF RWE IN POLAND

IDENTIFIED BARRIERS

In Poland, there is limited access to data that meet the criteria of RWE. The existing standardised registers, records, lists, inventories, or other structured sets of medical data are maintained mainly for settlement of accounts with the National Health Fund (NFZ). This entails a relatively narrow scope of information collected (in population and qualitative terms), data fragmentation among thousands of healthcare providers, and lack of surveillance over the scientific value of the registered data, all of which translates into poor practical value and limited usability of such data.

There are very few comprehensive medical registers in Poland, as they are typically limited to highly selected populations of patients or health conditions. These are mainly registers maintained by the Ministry of Health, e.g. the National Cancer Register (KRN), the National Cardiac Surgery Register (KROK), the Polish Register of Acute Coronary Syndrome (PL-ACS), and the relatively recent Medically Assisted Procreation Register and the Register of Non-malicious Large Salivary Gland Tumours.

NFZ also creates comprehensive medical databases, such as the Disease Treatment Register (RLC) and the Therapeutic Programs Monitoring System (SMPT) – these are dedicated modules of the NFZ IT systems where selected data for individual diseases is stored (i.e. solely the data relevant for and limited to NFZ-funded healthcare services, structured according to the ICD-10 code, treatment used, or clinical parameters belonging to a particular drug program, etc.).

Scientific associations also make attempts to collect data (for example, under the project "Long-term Safety and Effectiveness Assessment of Therapies used in Juvenile Idiopathic Arthritis" initiated by the Polish Rheumatic Disease Association).

The conditions for exploring the potential afforded by RWE have changed markedly with the introduction of a new drug reimbursement system. According to the new Drug Reimbursement Act [3] effective since 2012, "efficacy and effectiveness" are one of the criteria considered in deciding whether new medical technologies (and medicinal products) are eligible for reimbursement or not, and in consequence the new law makes room for therapeutic effectiveness data in the overall health technology assessments (HTA) system. The drug reimbursement law also mentions outcome-based pricing schemes as one of risk-sharing arrangements between the Ministry of Health and pharmaceutical companies, as part of the enrolment process of new medicinal products into reimbursement lists. However, public institutions have yet to take practical steps to implement these solutions.

In general, RWE development in Poland is being slowed down by a variety of obstacles. One crucial barrier is low awareness about RWE, and specifically about the benefits of collecting and analysing real world data, and about the needs RWE could satisfy, especially among top-level decision-makers

in the healthcare sector. Healthcare experts and the academic community, on the other hand, seem fully aware of the significance of RWE. In addition to research work based on data collected in Polish medical registers, there is also an increasing number of academic articles and public debate that bring the topic of RWE closer to the attention of decision-makers, advocating for more registers to be created in Poland, not only for the sake of actively taking part in the scientific development worldwide, but also in the hope for new system-wide solutions in Poland [4-6].

Another important issue involves formal limitations in medical data collection and processing arising from legal restrictions related to personal data protection and the resulting controversies over the ownership, processing, and dissemination of medical information. In accordance with legal provisions in force in Poland [7], processing of medical personal data is only permitted under explicitly defined circumstances and, as a rule, subject to the written consent of the data subject, except where otherwise stated:

- in separate regulations, for example those pertaining to the National Health Fund (NFZ) or the Social Security Office (ZUS),
- to protect the health status, provision of healthcare services, or patient treatment delivered by healthcare entities,
- for the purposes of scientific research (in a scientific article, personal data must be anonymous).

It seems most desirable for public medical registers to be set up on the basis of laws and regulations, in which case no consent would be mandatory from data subjects (which would also ensure sample representativeness and high quality of statistical data); it would also guarantee completeness and effectiveness of data collection by imposing a statutory obligation to report

data in the circumstances set forth in the relevant act, although this solution may be considered less favourable given the slow and complex legislative process in Poland.

In an attempt to accelerate the development of RWE, at some point registers were allowed to be created on basis of MoH regulations [8]. However, there was consid-

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erable uncertainty as to the outcome of this legal solution, and in December 2014, the Constitutional Tribunal declared the new rules unconstitutional.

The relatively low levels of computerisation of healthcare settings in Poland and restricted exchange of information among central systems (NFZ, KRN, and ZUS, etc.) present further obstacles to more extensive RWE collection on a nation-wide scale. Despite the comprehensive legislation adopted in 2011 [8] designed to reorganise the existing system for healthcare data collection, processing, and use, which was intended to streamline the development of e-health in Poland and to create a stable nation-wide information system – the strategy of upgrading the IT infrastructure and improving medical information ex-

change is still in its implementation phase. For example, the deadline for an obligatory transition from traditional to electronic form of medical records has been postponed few times. The implementation level of systemic solutions in this area, marked by lack of uniform standards for data content and quality review, or data exchange regulations and tools, directly translates into the degree of utilisation of the RWE potential.

Finally, creating databases (registers) requires considerable financial and organisational effort, which creates another significant impediment to the effective development of RWE in Poland, further aggravated by low awareness about RWE benefits on the one hand, and limited resources of the public healthcare system on the other hand.
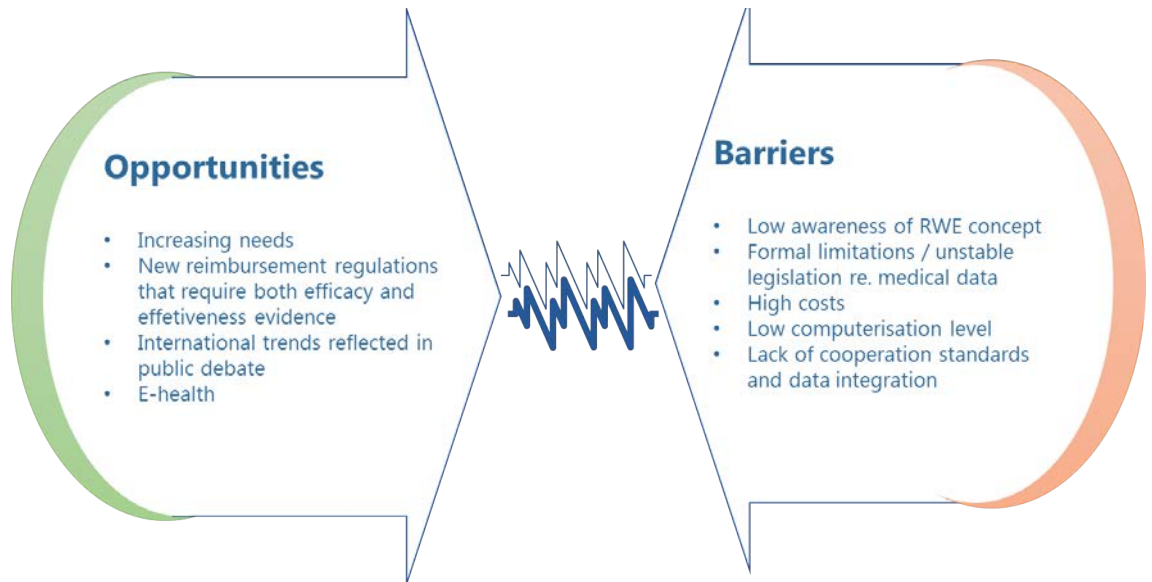
Opportunities

- Increasing needs
- New reimbursement regulations that require both efficacy and effetiveness evidence
- International trends reflected in public debate
- E-health

Barriers

- Low awareness of RWE concept
- Formal limitations / unstable legislation re. medical data
- High costs
- Low computerisation level
- Lack of cooperation standards and data integration

Figure 5.
Key determinants of RWE development in Poland

POTENTIAL SOLUTIONS

One solution to reduce obstacles to the development of RWE in the Polish healthcare system would be to establish rules and solutions based on multi-institutional partnerships among stakeholders involved in collecting and analysing real world medical data, as is the case in many European countries. For example, many European registers of therapies used in cancer and rheumatic diseases are maintained by scientific associations that cooperate with academia, while at least part of the funding is provided by pharmaceutical companies under terms and conditions similar to research grants [5,6].

Similar cooperation standards between the stakeholders (academia, governmental institutions, including MoH, Office for Registration of Medicinal Products, NFZ, and ZUS, commercial payers and insurers, and pharmaceutical companies) are still missing in Poland. As a result, the medical data collected and processed in Poland as part of the existing system has not been properly integrated; it is incomplete and difficult to access by the healthcare stakeholders, such as medical centres or institutions in charge of monitoring the healthcare system in Poland and the quality of medical services.

Restricted access to information offers little opportunities to compare clinical, epidemiological or cost indicators and parameters of the healthcare system from the geographic, patient and population point of view. In general, the existing registers, such as the SMPT (i.e. registers dedicated to detailed monitoring of drug programs by NFZ) should provide ample opportunities to control the size and selection of populations belonging to particular drug programs, to regularly assess and trace the program outcomes, and to monitor and evaluate indicators describing the effectiveness of drug technologies. However, such opportunities should not be limited to the institution that administers and collects the data concerned, not only on grounds of substance and for social reasons, but also from the sake of transparency in public spending.

` The following solutions can help improve the status of medical registers in the health-care system in Poland:

- Transforming the existing databases (e.g. SMPT) so that they collect and evaluate health outcomes for reimbursed drugs, involving risk sharing schemes and outcomes based agreements;
- Enabling private entities to get paid access to anonymised medical databases or registers, drawing on the experience from Hungary, Czech Republic, Sweden, or the UK. Paid access to statistical data would further improve data quality and stability of such initiatives in the long term perspective;
- Promoting public-private partnerships (between e.g. broadly understood payer or decision-maker and pharmaceutical companies, academia, healthcare providers) in terms of factual and financial involvement in setting up and maintaining medical registers.
- Setting up a group of experts bringing together representatives of payers, decision-makers, academia, patient organisations, and the pharmaceutical sector to work on the methodological assumptions for analysing and publishing data from medical registers or drug programs based in Poland.
- Setting up a strategic and analytical structure at the Centre of Health Information Systems (CSIOZ) to continuously analyse and present broadly defined aggregated medical data and to cooperate with the established players in the healthcare sector in the scope of commercial exchange of information.

Development of and access to RWE in the current legislative and structural framework in Poland largely depends on whether all stakeholders are able to take steps to:

- identify the demand of all healthcare system stakeholders for real-world evidence;
- develop rules for collecting and processing of data, and create tools and infrastructure dedicated to this process;
- the establishment of dialogue to set up transparent and functional rules of cooperation among stakeholders to achieve optimum use of the existing resources.

In order to implement these measures, it is necessary to be aware of the benefits of RWE-based data analyses as a 'multifunctional' source of information for the healthcare system.

Restricted RWE use in Poland is a consequence of the current regulatory framework, low levels of financial and IT resources in the healthcare sector, and lack of cooperation patterns among stakeholders.

This is why it is particularly important to identify the demand for and raise awareness about the potential afforded by RWE among all stakeholders, which will hopefully pave the way for a strategy of RWE development and improvement of access to data.

DEMAND FOR RWE AMONG MEDICAL PRACTITIONERS

Medical practitioners are important stakeholders involved in determining the future of RWE in Poland. These are the main beneficiaries of RWE used in professional development and in advancing the quality of therapy. So far in Poland we have already seen a dialogue among experts, along with some organisational changes in the Polish healthcare system influencing the shape and access to RWE in Poland; however, the attitude to and the demand for RWE among the key stakeholders – medical practitioners – are not yet known. Hence arose the need for a study to diagnose the demand for specific types of RWE and the awareness of the potential offered by RWE among medical practitioners in Poland.

Medical practitioners are one of the main beneficiaries of RWE. Still, their awareness and needs related to RWE have not been explored.

Diagram 1.
Percentage rate of interviews according to field of specialisation

The study was conducted all over Poland among medical practitioners from across different medical specialised areas: diabetics, infectious diseases, psychiatry, oncology, haematology, and a few non-specialised physicians working in outpatient and/or inpatient settings. The survey questionnaire included qualitative and quantitative questions on a large scope of topics: demand for real world data concerning treatment outcomes, interest in RWE data, or the most reliable sources of RWE information in Poland. The questionnaires were collected in the period from September to November 2014. A total number of 251 responses were received. Data was analysed using descriptive statistics.

The study broadly indicates that medical practitioners are generally dissatisfied with the level of access to real patient outcomes. Up to 90% of respondents declared they lacked access to real world evidence, and only 10% of the medical practitioners surveyed expressed the opposite opinion.

Most respondents stressed the importance of information directly related, but not limited to the practical aspects of therapy. For example, one out of five diabetologists chose "epidemiological data", both at national and regional scale, as the most important type of real world evidence they often missed in their respective field of specialisation. Haematologists and oncologists expressed similar opinions about "lack of registers" that might be used to analyse therapeutic patterns and treatment options in individual healthcare centres. Absence of "system-wide registers of drugs used by patients" has been brought up by oncologists. Diabetologists, psychiatrists, and infectious disease (ID) specialists shared a broader view on the demand for RWE information, declaring that they needed "access to follow-up information from other physicians, for example general practitioners" (diabetologists), "follow-up data – how the patient performed outside the outpatient settings (in the society)" (psychiatrists), "data about the health status of patients 'cured' more than 3 years before" (ID specialists). Some of this information has been systemically collected by NFZ and other healthcare institutions; however, access to this data is more problematic. The replies to the questionnaire show a broad spectrum of needs and interests of medical practitioners in this area.

When asked about the most desirable RWE data, the vast majority of respondents – over 90% – declared they were particularly interested in information about safety and comparative effectiveness of therapies. This clearly indicates that – from the perspective of medical practitioners – system-based registers collecting real world data should be primarily a source of information about therapeutic safety and effectiveness, complementary to the results of controlled clinical trials and observational studies.

The vast majority of respondents were not satisfied with the level of access to real world treatment outcomes.

In everyday medical practice, doctors were found to be very much in demand for comparative data about the safety and effectiveness of various therapies (new drug vs. new drug, instead of new drug vs. old standard).

The respondents almost unanimously considered effectiveness and safety of therapy as two most important aspects of RWE. Still, respondents from various fields of specialisation had divergent preferences for other types of RWE. Diabetologists declared high interest in data about treatment and prescription patterns (87% responses), haematologists preferred quality life data (87%), oncologists opted for patient compliance data (79%), infectious disease specialists were interested in indirect costs of treatment (68%), and psychiatrists demanded more information about direct costs of treatment (69%).

>90% HCP's are interested in data about comparative drug effectiveness and safety

75% HCP's are interested in data about treatment and prescription patterns

70% HCP's are interested in degree of patient compliance

Figure 6.
Most Demanded RWE – General Results

The respondents almost unanimously considered effectiveness and safety of therapy as two most important aspects of RWE. Still, respondents from various fields of specialisation had divergent preferences for other types of RWE. Diabetologists declared high interest in data about treatment and prescription patterns (87% responses), haematologists preferred quality life data (87%), oncologists opted for patient compliance data (79%), infectious disease specialists were interested in indirect costs of treatment (68%), and psychiatrists demanded more information about direct costs of treatment (69%).
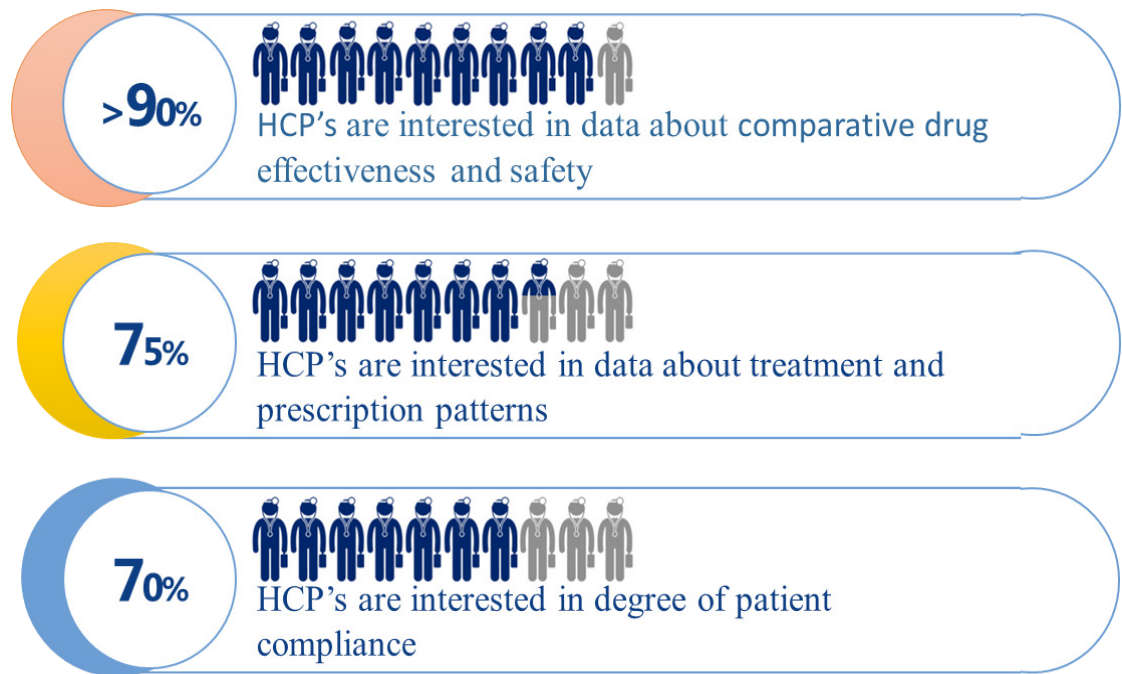
The prevailing majority of respondents indicated that they considered scientific societies as the most reliable and useful source of RWE (80% of respondents). Another important source of reliable RWE were case reports published in medical journals (63% of responses), especially among medical practitioners working in inpatient settings (67% vs. 48% of responses among medical practitioners

in outpatient settings). Practitioners in outpatient settings, as compared to inpatient care practitioners, were more likely to favour data from NFZ and ZUS, considering it highly reliable and useful. The lowest number of respondents listed as reliable data from market research and information provided by patient associations (26% and 20% respectively).

The survey also showed high support to the idea of creating RWE registers and RWE analyses carried out by independent institutions, set up either under the public law regimen or by non-governmental organisations.

The role of the pharmaceutical industry was also highly underlined. Respondents expected pharmaceutical companies to educate medical practitioners about RWE (80% of responses), share information about scientific publications based on RWE (51%), and partner with academia to raise the awareness of the scientific community about RWE (38%).

The medical practitioners surveyed declared that RWE registers should be maintained and the RWE data analysed by independent institutions.

In the opinion of medical practitioners, pharmaceutical companies should spread knowledge about RWE and keep medical practitioners informed about new scientific publications based on RWE

CONCLUSIONS

The potential of real world evidence appear to be increasingly recognised in Poland, although Poland lags behind other countries when it comes to implementing solutions for collecting, processing, and dissemination of information about the actual effectiveness, safety, and costs of therapy or epidemiological data. While there are areas where some RWE-relevant solutions have been operating, systemic solutions that promote RWE are still missing. Restricted RWE use in Poland has many causes and is a consequence of the current regulatory framework, low level of financial and IT resources in the healthcare system, and lack of cooperation patterns among stakeholders.

This is why it is particularly important to identify the demand for and raise awareness about the benefits by RWE among all stakeholders, which will hopefully contribute to the establishment of a strategy for RWE development and improvement of access to data.

The awareness of and demand for RWE among medical practitioners remained largely unrecognised, although they are among the main stakeholders in this area. The survey highlighted that the majority of respondents were dissatisfied with the level of access to real world patient outcomes. Among those who declared they were missing RWE-quality information, the majority believed that data about the relative treatment effectiveness are difficult to access in Poland. Respondents also pointed out the scarcity of data about real-world

1 All specialisations
Safety of therapy

2 All specialisations
Effectiveness of therapy

3 Haematologists
life quality of patients

3 Oncologists
patient compliance

3 Diabetologists
real-life treatment and prescription patterns

3 Psychiatrists
direct costs of therapy

3 Infectious disease specialists
indirect costs of therapy

Figure 7.
Top 3 Most Demanded RWE – by HCP's Specialization

Pharmaceutical companies have strong organisational skills to support successful collection and analysis of data

The process of data collection and analysis should be handled by independent institutions

Registers and databases should be maintained by public institutions or non-governmental organisations, whereas pharmaceutical companies should undertake analysis of data
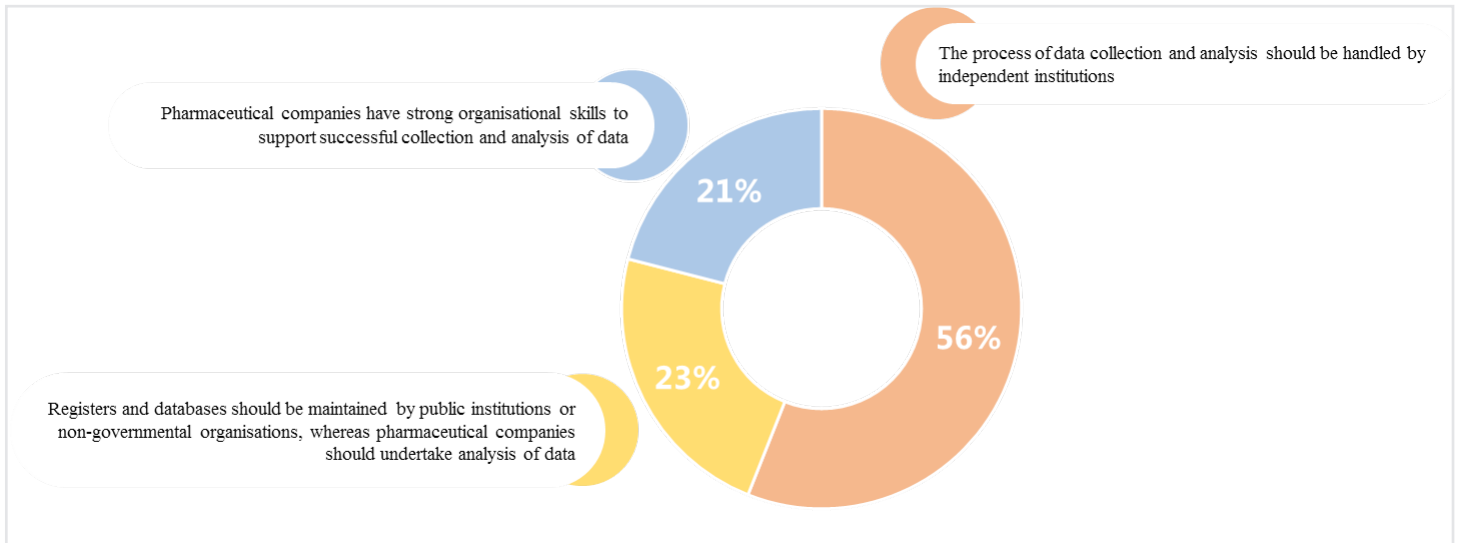
21%

56%

23%

Diagram 2.Opinions about the involvement of the pharmaceutical companies in RWE

costs of therapy, along with data on the patient quality of life and real-world treatment and prescription patterns. The missing data appears to be indispensable for taking evidence-based decisions about the most effective treatment strategies in everyday clinical practice or for monitoring patient outcomes. This leads to the conclusion that better access to RWE could have a positive impact on the decision-making process in all issues relating to patient therapy. The survey also proved that the need for information varies across different medical fields of specialisation, reflecting the specific nature of demand for information in various medical fields.

Medical practitioners in Poland were shown to have a clear opinion about the demand for and the range of data generated outside clinical trials. Systematic education about RWE among healthcare professionals

and other stakeholders, dissemination of knowledge about the benefits of RWE, and better access to RWE are of key importance in setting up the framework for the development of RWE in Poland, and the resulting improvement in patient outcomes.

Effective healthcare management requires access to up-to-date and reliable data (ranging from epidemiological data to information about the actual effectiveness of medical technologies in everyday medical practice, etc.), which is still few and far between in Poland. Keeping RWE registers and most notably analysing and disseminating RWE are preconditions for improvement of the quality and effectiveness in healthcare. Real world evidence about patients in Poland and the Polish healthcare sector would not only encourage scientific research, but also provide a solid ground for rationalisation of healthcare expenses.

SURVEY

Specialization: (open question) Care Setting: (multiple choice) Inpatient, Outpatient, Both Settings

1. Which areas related to the treatment outcomes do you consider the key ones to be improved in the Polish Health Care System over the coming 4-5 years?
(1 – minor to be improved, 5 – major to be improved, X-not applicable)

SCALE

A.Effectiveness of the therapy: i.e. maintain disease indicator on optimal level, overall survival, progression-free survival, adverse events.   1 2 3 4 5 X

B.Costs: direct costs: i.e. drug costs, hospitalization costs indirect costs: economic losses as a result of absence from work, disability and mortality.   1 2 3 4 5 X

C.Diagnostic and therapeutic process: documentation/administrative requirements, waiting time for treatment, primary care doctors' diagnostic and therapeutic capacity.   1 2 3 4 5 X

D.Access to therapy: access to physicians „in general", to specialists, to nursing care, to long-term care, to services.   1 2 3 4 5 X

E.Patient reported outcomes: i.e. self-control diaries, quality of life, social and family functioning.   1 2 3 4 5 X

F.Others: please specify   1 2 3 4 5 X

2. In which area should a pharmaceutical company provide support in order to improve practical treatment outcomes? (multiple choice, max 3).

SCALE

A. Support for prevention actions/programs   1 2 3 4 5 X

B. Support for diagnostics   1 2 3 4 5 X

C. Collect data from existing registries and publish results   1 2 3 4 5 X

D. Enhance patient education during therapy   1 2 3 4 5 X

E. Strengthen physician education   1 2 3 4 5 X

F. Develop new registries for monitoring therapy effectiveness   1 2 3 4 5 X

G. Support for patient compliance programs   1 2 3 4 5 X

H. Participate in the process of medical procedure improv   1 2 3 4 5 X

3. What type of evidence related to practical treatment outcomes (RWE) would you be interested in within your specialization, scale of 1 to 5 (1- least interested, 5 – most interested, X-not applicable)?

SCALE

A. Safety	1 2 3 4 5 X
B. Effectiveness	1 2 3 4 5 X
C. Costs C1. Direct costs C2. Indirect costs	1 2 3 4 5 X
D. Patient compliance	1 2 3 4 5 X
E. Quality of life	1 2 3 4 5 X
F. Treatment and prescribing pattern	1 2 3 4 5 X
G. Epidemiology data (prevalence, incidence, patient characteristics)	1 2 3 4 5 X

4. What evidence related to practical treatment outcomes (RWE) is missing with the reference to your specialization? (open question)

5. What sources of evidence regarding practical treatment outcomes (RWE) do you consider credible and useful in your specialization? (scale 1-5, 1 – lest credible and useful, 5 – most credible and useful, X- not applicable)

SCALE

A.Patient registries	1 2 3 4 5 X
B.Data gathered by patients organizations	1 2 3 4 5 X
C.Data from System of Monitoring Drug Programs „SMPT"	1 2 3 4 5 X
D.Data gathered by scientific societies	1 2 3 4 5 X
E.Data from Social Security Service ZUS (i.e. absenteeism, social security benefits)	1 2 3 4 5 X
F.Data from National Heath Fund NFZ (i.e. claims data, hospital DRGs)	1 2 3 4 5 X
G.Data on prevalence and hospitalization provided by National Hygiene Service PZH	1 2 3 4 5 X
H.Data such as "case study" published in medical press	1 2 3 4 5 X
I.Market research (i.e. survey, questionnaires)	1 2 3 4 5 X
J.Others (please specify)	1 2 3 4 5 X

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6. Do you think that pharmaceutical industry should be involved in the process of collection and analysis of evidence regarding practical treatment outcomes (RWE)? (multiple choice)

SCALE

A. Pharmaceutical industry has significant organizational capabilities that may help in the process of collection and analysis of data.

1 2 3 4 5 X

B.Registries and databases should be kept by public institutions and NGOs. However the analysis of data could be entrusted to pharmaceutical industry.

1 2 3 4 5 X

C. Process of data collection and analysis should be in competence of independent institutions.

1 2 3 4 5 X

7. What actions should be taken up by a pharmaceutical company that will contribute to the improvement of evidence about practical treatment outcomes (RWE)? (maximum 3 answers to be chosen)

SCALE

A.Develop new databases, patient registries.

1 2 3 4 5 X

B.Run analyses and publish results based on existing polish databases and registries (i.e. SMPT, Cancer Registry, healthcare provider databases).

1 2 3 4 5 X

C.Set up partnerships with academic centers in order to increase awareness about RWE.

1 2 3 4 5 X

D.Introduce physician education in relation to RWE.

1 2 3 4 5 X

E.Keep electronic record of major RWE sources available in Poland (indexation, wide description, quick access).

1 2 3 4 5 X

F.Share information about scientific publications prepared by a pharmaceutical company based on RWE data.

1 2 3 4 5 X

G. Scan of actions taken by scientific centers, scientific institutes with regard to RWE development.

1 2 3 4 5 X

[1] The term Real World Evidence within the meaning of real-life data generated by and in connection with the healthcare system is used interchangeably with the term Real World Data (RWD) – this is the convention used in this document. In some articles and discussions about data collected in actual clinical practice, the term RWE has a narrower meaning to denote a subset of structured and validated RWD used in the decision-making process about drug reimbursement, development, or marketing, etc.

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Multi-criteria decision analysis(MCDA) and its alternatives in health technology assessment

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ABSTRACT

Article presents application of multi-criteria decision analysis and its alternatives in Russian Federation. There are presented pros and cons for this type of analysis, as well as their Western (Forsight) and Russian alternatives (rule of square of decision making, P. Vorobiev, 2003). There are also presented stages of MCDA, questions of MCDA and types of MCDA.

In 2014, national standard GOST R 56044-2014 "Health Technology Assessment" was approved [1]. It is the first document, in which, in details, all the steps and approaches to the right decisions making are described, regarding the implementation of certain techniques in the health care system, both at the level of health management, so and at a medical institution. However, not all modern approaches included in this standard, some of the new technology of decision-making is discussed in this article.

Before you read this article, we must warn you that in it you will find quite a lot of philosophical and economic concepts, those of which we, being in a rush after simple solutions, have abandoned in recent years. Unfortunately – that is bad. Economy is a philosophical concept, although many see it more like bookkeeping. The economy is considered from the standpoint of cost as a system of social relations. It remains to recall that the cost - according to the classical works of Karl Marx – is the added utility of the product or service created by human work.

Word of the economy in the modern language has many meanings, and at least three of them should be mentioned:

• a set of relations connected with the economic activities of people: the market economy (which is hard to impose in Russia) and the administrative-command (which continues to rule the score in Russia, despite the fact that its place remains in the distant past), traditional (based on simple relations goods for money), socialist (when the human needs are placed in the center, not the problem goods for money) and mixed, which, in fact, is being developed and today in all the leading economies of the world.

• agriculture of particular region, country, group of countries, the individual associations of the countries (BRICS, the European Union) and the world at all large.

• scientific discipline that studies the economic life of the company or its segment.

The most common is the following definition: economy (from the Greek - house, farm) is the rules of farming [2]. Economy is the activity, but also a set of relations in the system of production, distribution, exchange and consumption of goods and services. Economics society is complex and all-encompassing factor that ensures the livelihoods of every individual and society as a whole. For experts in the field of clinical and economic analysis, it is important that any economy is a complex system that operates in a high degree of uncertainty, and that the medical component multiplies the degree of uncertainty.
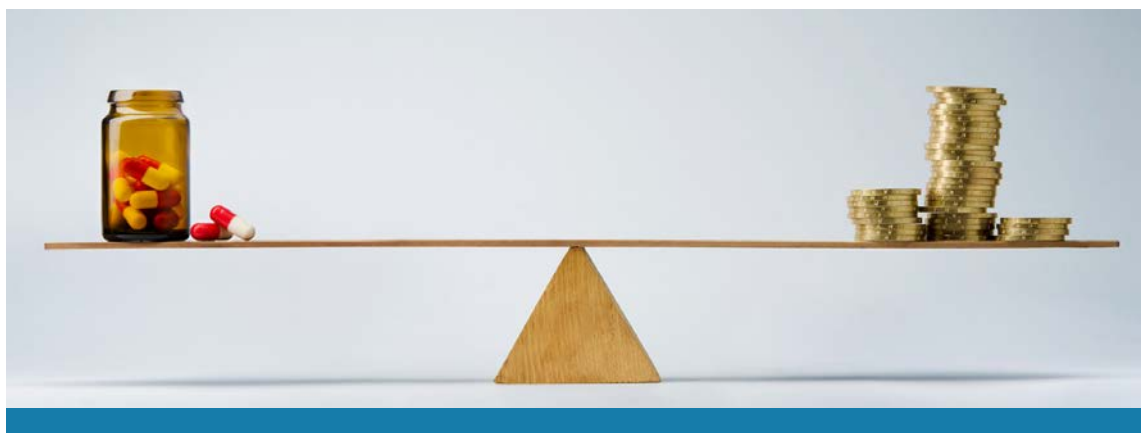
Today in the economy there are two approaches opposed - liberal and socialist. Liberalism - the desire for complete freedom of the individual - means that a person does everything by himself and society only helps him in this. Individual citizens can unite to achieve their goals, and the goals of each one of them may be different. Liberalization of the economy means that all subjects have complete freedom to buy and sell goods and services at any price, which will be willing to buy it, everyone is free to produce, sell and buy everything that can in principle be produced and sold, is not prohibited or doesn't bring harm to others. Access to all spheres of activity is open to all on an equal

footing and a special law (in Russia - the antimonopoly law) can stop individuals or groups of individuals to limit this access and freedom.

Let us return to uncertainty. The world exposed to contingency: it is stochastic. Vibrations of atoms, electrons, positrons are random, but they form an ordered pattern of molecules, which are in Brownian (random) motion. Randomly moving molecules form of matter - gas, liquid, solid objects. These chaotic motions are subjects to certain laws of physics, without these random fluctuations nor alive, neither living matter cannot exist.

Liberalism gives priority to the person, knowing that his actions only at first glance seem random. Set of countervailing actions are driven by progress. If stochastic processes, vibrations and collisions will be organized - everything stops and collapses. The situation of chaos turn into a void - in emptiness there is no movement. Lack of movement is nothing, it is vacuum.

Attempts to organize stochastic processes in society and fluctuations of individuals exist, and will exist. The desire to organize economic relations has taken shape during socialism, which puts the public good at the forefront: the interests of the group, of the society is above all implies the union of the overall effort to achieve common benefits. Even at the expense of the

benefits of individuals. The society (or the state, standing for the aspirations of society) forms goals and objectives, plans activities and creates the conditions for their implementation. Nowadays, health care is now completely socialistic, despite the existence in it of germs of market (liberal) relations.

We must not forget that socialism, by reduction to an absurd (it is only at first glance, in fact it is an objective development) always turns into totalitarianism. The question boils down to the limits of power, which depends on the decision of the distinction between liberal and totalitarian systems: the government identifies all the interests of individuals or identifies only some things, especially, formulating rules, guidelines, which regulate the economic behavior of individuals. In other words, it is a dictatorship of the law (the liberal model) - the rules are clearly defined and relatively unchanged or dictatorship of the group to change the law under the circumstances (the socialist model), so the rules change during the game.

It seems that the state should guide public consent or consensus, if consensus on the specific circumstances exists in the society. If there is no consensus - work on specific projects should not be performed! In any society, there are different interests that conflict with each other, which must be agreed, reaching consensus. These interests are expressed in terms of a large number of criteria can be quantified, for example, in monetary criteria, and exist on a qualitative level (related to quality of life, for example). Consequently, for the achievement of consensus must be taken into account these multicriteria differences.

The overall objectives of determining the trend of social (socialist) building, are called the "public good", "common interest". But is the most good and honest government able to cover all the infinite variety of human needs, competing in meeting their needs, determine the weight of each of them on a common (not abstract, but quite specific) scale. How far the multi-criteria approach to the assessment of the situation, that is related to the large number of uncertainties is adequate.

Human happiness (we equal it with satisfaction of all his needs) depends on a variety of reasons, countless combinations. Therefore, the government, ideally, should build just a hierarchy of objectives, the set of admissible models, algorithms in which every person will be able to find a place for satisfaction with each of their needs.

We grow from a planned economy - the highest achievement of the socialist state, in which most of us were born and raised. But in the process of planning is basically impossible to take into account the tendency of individuals and because of it a particular person in a planned economy acts as a tool used by the state to serve the "common good" is considered as a group of individuals, "certain categories of citizens".

What to do? Where strive to invest? Is it better to solve the problem of "socially significant" mass diseases or direct efforts towards rare diseases? And here again comes to the aid the economy: economic theory on the one hand trying to explain social phenomena, mechanisms of interactions in the society, on the other - makes it possible to anticipate trends in the economic behavior of individuals and society as a whole. The most important function of the economy is the scientific prediction of the future.

Now there is a new economic term Forsight - methodology of systematic evaluation of the future of science, technology, economy and society in order to identify areas of strategic research and implementation of technologies that bring the largest economic and social benefits.

Technologies, used in Forsight [3]

- Backcasting
- Bibliometical analysis
- Brainstorming
- Citizens Panels
- Cross-Impact Analysis
- Delphi
- Environmental Scanning
- Essays
- Expert Panels
- Futures Workshops
- Gaming
- Key Technologies
- Literature Review
- Megatrend Analysis
- Modelling and simulation
- Multi-criteria Analysis
- Scenarios
- Stakeholder Mapping
- SWOT Analysis
- Technology Roadmapping
- Trend Extrapolation

As it is shown in the scheme, multi-criteria analysis is only one of the methods in Forsight methodology. Multicriteria analysis (Multi-Criteria Analysis - MCA) is defined as the structuring process of evaluation and selection of alternatives under conditions of high uncertainty and a conflict of different social groups on the basis of a combination of quantitative and qualitative criteria for the evaluation and comparison of technologies in order to achieve mutual understanding and resolve conflicts between various stakeholders involved in the decision-making process.

Let us explain. It is obvious that in the process of decision-making in health care there are conflicts between providers and producers, consumers and payers, regulators. Of course, you can just sit down at the negotiating table, but obviously it is not always possible to agree on everything. The proposed method of multicriteria analysis - this is a consensus in the process of consultation, based on scientific, structured approach and compromise in the evaluation of pre-agreed criteria.

Pharmacoeconomics as a special case of the clinical and economic analysis (the latter term was proposed by P. A. Vorobiev in the late 90s) emerged in the late 80s of the XX century as a methodology that complements exclusively clinical and social studies when making decisions regarding the payment for medical technologies in the system of health care (reimbursement). Currently, clinical and economic analysis extended in the direction of decision-making on the various medical technologies - non-drug, organizational and others.

Existing in the methodology of clinical and economic analysis approaches that take into account different points

of view (the consumer, the provider of medical services and medicines manufacturer and payer) based on an approach of "economic effectiveness", and allow to compare the incomparable: generic with innovative drugs, different medical technologies (drug and non-drug) used in one disease, technologies for various diseases, the effectiveness of health systems in different countries. However, decisions about funding the one or the other medical technology based only on cost / effectiveness ratio, even in the case where the effectiveness is in the basis of the quality of life is not enough objectively.

The imperfection methodology of clinical and economic analysis was especially vivid manifested in diseases for which a purely economic approach is not applicable: medical technologies used in rare diseases. Taking into account only the incremental coefficient «ICER» (in fact - a profitable investment) in the evaluation of these technologies results in a denial of reimbursement for this medical technology and, the refusal to treat these patients. On the one hand, amount of these patients, with each pathology, is not so big, on the other - the number of rare diseases is quite great and if we sum up the total of the group – there is a few millions of patients in Russia. Moreover, how the question of the treatment or non-treatment of these patients is asked, because of the lack of resources seems blasphemous.

It is believed that the inclusion of the different criteria in deciding is the most close to real life, and structuring this technology allows you to make this approach scientific. Multi-criteria decision analysis in medicine is based on the following key assumptions (hypotheses):

- Lot of subjective assessments lead to one objective (this position causes justified doubts);

- Traditional clinical and economic approaches are not adequate enough to evaluate all medical technologies (that is absolutely fair);

- The main goal of decision-making in health care is ensuring fairness and equality for all patients (or at least the desire for it).

Multi-criteria decision analysis uses the following models [4]:

- Value measurement model: each of the criteria is defined in the numerical expression, compares the sum of criteria for each technology;

- Out ranking model: comparison of alternatives with each other for each criterion, amount of superiority by rating;

- Goal, aspiration, or reference-level model: for each of the criteria is determined the level below which model does not work, then there is comparison of the results of the application of each technology, calculated amount of remaining values.

These approaches are largely mechanistic, based on purely arithmetical values. However, not always simple mathematical formulas play a role in decision-making. In 2003 P. A. Vorobiev proposed an original model of multicriteria analysis – rule of square of decision making [5,6,7]. The essence of the model: to the decision maker, several factors have an impact - information, mathematical modeling, non-specific effects and resistance. The decision maker consistently analyzes these streams: selects from the entire array of information the relevant one, using mathematical apparat or logic models. In the case of health technology assessment results of clinical studies are mathematically estimated (meta-analyzes, systematic reviews), the models of decision making are built (Markov analysis, decision tree), simulation are being conducted.

Most often, this completes the decision-making process, and it is not optimal, since it ignores many other factors that may be important for the realization of what seems to be the right decision.

The main thing - is the impact of non-specific factors that are not captured when the model is being created. A simple example: you work on your computer and suddenly, in the middle of the biggest calculations, the electricity turns off. Not only is the result lost but also the background. In more complex cases, we can talk about the output of any administrative document, crisis, change in the political arena, the emergence of a new manager, natural and other disasters.

In the preparation of civil contracts, these factors are referred to as "force majeure", which means that these circumstances are exempt from the obligations of the contracting parties. However, as a rule, any obligations remain and have to be fulfilled by the contracting parties.
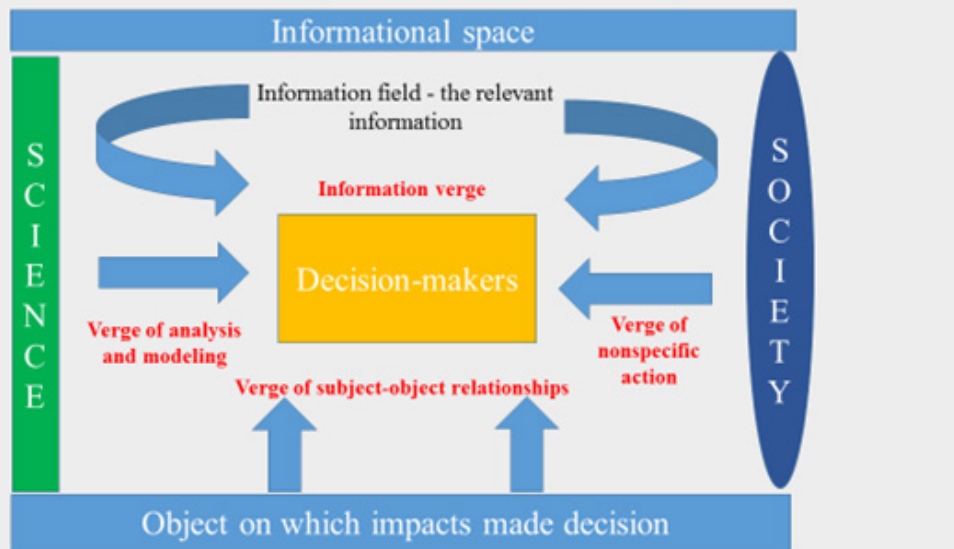
In the decision-making process, all non-specific factors can be identified and the probability of their influence can be assessed with the help of the refined model. Moreover, it is possible that offsetting of two or more non-specific factors (on the one side... on the other side...) or vice versa, a synergistic interaction of seemingly minor factors.

When taking decisions it must be remembered that any decision causes resistance of whom it is directed. A classic example - compliance with type 2 diabetes and hypertension: patients do not take drugs, not only because they forget, but also because they feel that there is no need for lifelong treatment. And in this situation neither they cannot be propagandized, nor, especially, made to.

Considering the fourth verge - verge of the subject-object relationship it is necessary to understand that health care providers, payers, consumers and regulators of health care can act as subjects and objects of the decisions taken. The relationship between subject and object always have the character of conflict. Conflict can be r solved by direct force (then the decision will not be en forceable if it remains disagreement, the decision only exacerbates resistance), but it can also be solved by finding resonance: push, release and push again to reach a consensus [8].

Alternative to MCDA – RULE OF SQUARE OF DECISION-MAKING (P.VOROBIEV, 2003)

Picture 1.
Rule of square of decision-making

As other decision methodology, multi-criteria analysis is performed stepwise [9]:

1. Identification of the decision situation.
2. Choice of the purpose of this decision.
3. Determination of criteria on the basis of detailed objectives, as well as the minimum level that will satisfy the decision maker.
4. Assigning weights to each criterion, depending on the preferences of the decision maker.
5. Getting information about the parameters for decision-making and the development of alternatives.
6. Evaluation of different options in accordance with established criteria.
7. Summing the products of different weights of criteria and sub-evaluations of individual options and assess the usefulness of different options. Option that receives the maximum number of points is the most rational option.
8. To confirm your choice, you can navigate through the various results of simulations.

Several of listed stages of multicriteria analysis cause questions. For example, the allocation of significant factors or criteria for the assessment. Any technology can be characterized by a huge set of criteria and which of them is a priority and is the most important – that is the big question. Of course, you can organize "rating voting" among of the experts and find out which, in their view, is an important criterion. However, we must not forget about the differences in the angles of various experts - payers, providers and consumers of health services. For some important criteria will be related to the budget, for others - to clinical efficacy, whereas for the third – to the quality of life. However, there may be criteria associated with an increase of life expectancy, which present an abstract concern to society as a whole and they are not as significant from the standpoint of, for example, the payer (short money).

For example, the criteria proposed for consideration in the evaluation of orphan technology by S. K. Zyryanov [10]:

1. Availability of affordable and effective drug therapy of specific disease.
2. Impact on survival prognosis of used therapy
3. Relationship of symptoms and quality of life.
4. The impact of the disease on livelihoods, reproduction, professional responsibilities and lifestyle.
5. The therapeutic effectiveness of innovative medicines.
6. The effect of a new drug on the prognosis of survival.
7. Safety the new drug.
8. Effect of an innovative medical technology on quality of life.

Therefore, even the selection criteria must include mechanisms for reaching consensus. Possible solution of this contradiction is the creation of an open list of criteria for defining to a greater or a lesser extent all medical technologies. This approach seems to be very complex and too little implemented.

The second issue is the formation of focus groups. Clearly, they should represent the various positions of the angles specified above. However, what are the requirements for members of the focus groups? Should it be persons who are far from decision-making procedures or, on the contrary, the persons immersed in this process in one way or another? From a particular solution of this problem can vary quite substantially the result of the evaluation. Selection of experts is arbitrary; we can assume that it is not difficult to find the "right" expert. In addition, experts are subject to the influence of other, external factors: personal experience, ethical preferences, the media, and the environment - it is all taken into account when forming focus groups?

In such a way, the skeptical view of the MCDA procedure allows us to formulate a few key questions to this procedure, while not denying the whole of its positive values and roles.

1. Who determines the criteria and who evaluates their weight?
2. How are focus groups created and who is in them?
3. How to compare different medical technologies with each other?
4. Should only the principles of justice and equality stand at the forefront of decision-making?
5. What should I do if there is unavoidable contradictions?

By a cursory acquaintance with the methodology of multicriteria analysis in decision-making in the first place - on reimbursement - it seems that the multicriteria analysis solves a problem of the verge of subject-object interactions, when seen through the prism of the "rules of the square." At the same time, all other verges "square of decision-making" remains outside of the purview of this type of analysis. Multicriteria analysis complicates the already difficult task of decision-making under conditions of high uncertainty. However, we must not forget about the rule of

"Occam's Razor": "Do not attract new entity unless it is absolutely necessary." "Keep it simple" - we say. It should be remembered that the simpler analysis is, the easier it is to play. Don't we leave this principle by introducing a multi-criteria analysis?

It is enough to recall the Resolution of the Government on August 28, 2014 N 871 "On approval of rules of formation of lists of drugs for medical use and a minimum range of medicines needed for health care" [11], which, though not fully, but is based on principles of multicriteria analysis. Among the criteria, there is the cost of treatment, which, in fact, should not be taken into account when making decisions. Life has shown shortcomings of this approach, when a full-time senior staff of the Ministry of Health discussed (with the whole process live on the Internet), which drugs should be included in the List, and which should not. The whole, formed mathematical base of surrogate multicriteria analysis was not considered.

At the Congress of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) in Amsterdam (November 2014), a joint meeting of representatives of pharmacoeconomic societies of Central and Eastern Europe on multicriteria analysis in decision making was held. Professor Z. Kalo (Hungary) suggested that this analysis should be a tool, not the rule. By using multi-criteria decision analysis, it is necessary to choose between the two approaches [12]:

1. In addition to the approach of "cost-effectiveness", which is based on existing criteria and processes in agencies for Health Technology Assessment. This reduces the role of the QALY and ICER when making decisions, and additional criteria are taken into account. With this approach, there is more transparency and reproducibility in the decision-making process.
2. Pure, when multicriteria analysis is the sole basis of decision-making

Thus, multi-criteria analysis should be in some form built into the system of decision-making, as the jury is built into court: their role is to say whether the one is guilty or not, and the role of experts of multicriteria analysis – whether technology is acceptable or not. In our view, multi-criteria analysis should be taken into account in the assessment of medical technology and is complementary to other approaches of decision-making, but cannot be decisive.

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Reaching Therapeutic Goals Impacts on Estimated Cost of Illness for Patients with Type 2 Diabetes in Poland

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ABSTRACT

Objective: To estimate savings for public payer and for society generated by reduction of diabetes mellitus complications through maintaining therapeutic goals set by Polish Diabetes Association (PDA).

Methods: Diabetes progress in lifetime horizon was simulated in a Polish cohort of newly diagnosed adults with type 2 diabetes mellitus (T2DM) using the IMS Core Diabetes Model. The natural course of disease (Uncontrolled patients) was compared to situation where patients meet therapeutic goals in the first year and keep it in following years (Controlled patients). Direct medical costs from public payer and patients perspective were complemented with indirect costs estimated using friction costs approach (FCA) and human capital approach (HCA).

Results: Mean life expectancy was higher for the Controlled vs Uncontrolled patients (11.3 vs 10.7 LYs). The average QALY was also higher for Controlled vs Uncontrolled patients (8.33 vs 7.87 QALYs).

Uncontrolled patients generated during lifetime total costs respectively 2053 PLN, 2826 PLN and 4417 PLN higher than Controlled patients, depending whether direct costs only or direct costs and indirect costs (FCA or HCA) were considered. Adopting the estimated mean annual savings per patient to 1.1 million of Polish patients with uncontrolled T2DM (HbA1c>7%) would result in 192 million PLN of total annual savings, if only direct costs were considered and 264 or 412 million PLN, if indirect costs (FCA or HCA) were also included.

Conclusion: Maintaining therapeutic goals in T2DM results in higher life expectancy and, through reduction of T2DM complications, reduces both direct and indirect costs per T2DM patient.

The study was financed by Sanofi-Aventis, Poland.

BACKGROUND

Type 2 diabetes (T2DM) is a social disease generating high costs for the patient, health care system and society. It is estimated that the 1.7 million of adult T2DM patients in Poland generated an annual cost of 4.3 billion Polish zloty (PLN) from the public payer and patients perspective in 2013, where 2.2 billion PLN was the direct cost of diabetes treatment (both drugs and medical care) and 2.1 billion PLN was the cost of specialist care related to diabetes complications. The cost of work productivity loss due to diabetes and its complications was estimated at 302 or 1779 million PLN depending if friction costs approach (FCA) or human capital approach (HCA) was used [1]. Keeping control of the disease reduces the risk of diabetes long term complications, such as heart disease, peripheral vascular disease or renal function impairment. The aim of the analysis was to estimate the savings generated by maintaining diabetes treatment goals set by Polish Diabetes Association (PDA) by the patients.

MATERIALS AND METHODS

Diabetes progress in lifetime horizon was simulated in a cohort of adult patients with newly diagnosed T2DM using the IMS Core Diabetes Model (8.0 version) [2], an extensively validated Markov's model replicating DM Type 1 and Type 2 course in one year cycles based on the data from clinical trials, including development paths of over a dozen of diabetes complications (each complication is simulated in a separate sub-model with an event-specific cycle length). The following complications and complication-related events were included in the model: myocardial infarction, coronary artery disease, heart failure, kidney transplant, hemodialysis, peritoneal dialysis, stroke, peripheral vascular disease, neuropathy, foot amputation, gangrene, foot ulcers, significant loss of vision, laser ther-

apy, cataract surgery, severe hypoglycemia, depression and others.

Patient characteristics at the diagnosis of diabetes (Table 1) were drawn from Polish study ARETAEUS and were complemented with data from UK Prospective Diabetes Study (UKPDS).

ARETAEUS was a cross-sectional questionnaire-based study conducted in 2009 in Poland. It involved patients with T2DM diagnosed within 2 years before the study. The aim of the study was to describe the baseline characteristics of patients with newly diagnosed T2DM and to assess to what degree diabetic control criteria recommended by the PDA clinical practice guidelines were met. 1714 patients recruited by randomly selected physicians were included in the analysis [3].

The UKPDS was a multicenter trial of glycaemic therapies among 5102 patients with newly diagnosed T2DM. It ran from 1977 to 1997. The study assessed impact of blood glucose and/or blood pressure control improvement on reduction of diabetes complications [4,5].

Table 1.
Characteristics of basal cohort of patients with T2DM

Parameter	Value	Source
Demographic data		
Age	59.7 years	ARETAEUS
Male %	49.83%	ARETAEUS
Time from diagnosis	0.8 years	ARETAEUS
Risk factors		
HbA1c	7.08%	UKPDS
Systolic blood pressure (SBP)	137 mmHg	ARETAEUS
Total cholesterol (TC)	209 mg/dl	UKPDS
High-density lipoprotein(HDL)	41 mg/dl	UKPDS
Low-density lipoprotein (LDL)	135 mg/dl	UKPDS
Triglicerides(TRIG)	208 mg/dl	UKPDS
Body Mass Index (BMI)	30.6 kg/m2	ARETAEUS
Smoking %	31.00%	UKPDS
Other		
Caucasian race %	100%	ARETAEUS
History of myocardial infarction %	10.40%	ARETAEUS
History of stroke %	4.03%	ARETAEUS
Microalbuminuria %	7.00%	ARETAEUS
Retinopathy %	17.59%	ARETAEUS
Uninfected foot ulcer %	1.70%	ARETAEUS

Two alternative scenarios were compared: one in which patients followed the natural course of the disease (Uncontrolled) and one in which they maintained disease control defined as keeping therapeutic goals set by PDA throughout the lifetime horizon (Controlled).

The natural course of disease was modeled using epidemiologic data from two large observational studies: UKPDS and Framingham Heart Study [4,6].

The therapeutic goals for the diabetic population set by PDA included maintaining certain levels of HbA1c, SBP, TC, HDL, LDL and TRIG as well as avoiding hypoglycaemia episodes [7]. The PDA recommendations that were used as Controlled patients treatment goals were presented in Table 2.

Table 2.
PDA goals for T2DM

Parameter	Value
HbA1c	7.00%
SBP	130 mmHg
TC	175 mg/dl
HDL	45 mg/dl
LDL	100 mg/dl
TRIG	150 mg/dl
Hypoglycaemic episodes	0

The assumption for the Controlled patients was that they would reach all the therapeutic goals in the first year of treatment and keep them during the whole analyzed period.

The direct costs were estimated from the public payer and patients perspective. The indirect costs were assessed from the societal perspective.

The direct cost comprised of the cost of drugs (diabetes treatment and prevention of diabetic complications) and cost of treatment related to particular diabetes complications (the state in particular sub-model).

The distribution of diabetes treatment type was taken from the Polish observational study [8] and included such active substances as acarbose, metformin, sulphonylurea and insulin (Table 3).

Table 3.
Distribution of diabetes treatment across newly diagnosed patients with T2DM in Poland

Active ingredient	Percentage
Acarbose	9.2%
Metformin	70.6%
Sulphynourea	62.1%
Insulin	37.1%

Patients were assigned frequency of prevention treatment of cardiovascular diseases (acetylsalicylic acid, ACE inhibitors, statins and alternatives to ACE inhibitors for patients who do not tolerate them) according to the frequency of its use observed in ARETAEUS [3] and POLKARD [9] studies.

The annual cost of drugs was assessed using the average price of the substances on Polish pharmaceutical market in 2014 [10].

The mean cost of treatment of diabetes-related complications such as angina pectoris, myocardial infarction, heart failure, peripheral vascular disease, stroke, renal failure, foot amputation, foot ulcer, gangrene, neuropathy, vision loss and hypoglycaemia was estimated using National Health Fund (NHF) statistical data [11]. The incidence of those events was based on results of UKPDS [4,5]. Parameters used in the model were presented in Table 4.

The indirect costs comprised of productivity loss (short-term absenteeism and work disability) due to angina pectoris, myocardial infarction, heart failure, peripheral vascular disease, stroke, haemodialysis, peritoneal dialysis, renal transplant, foot amputation, foot ulcer and its infection, gangrene, neuropathy, significant vision loss, cataract, depression and hypoglycaemia and its repercussions (see Table 5). No loss of productivity (absenteeism or work ability) was attributed to patients with T2DM without complications. The indirect cost of the event parameter comprised two categories: onset of event cost (productivity loss attributable directly to complication occurrence) and annual cost (absenteeism and work ability associated with the history of the event) accrued in first and following years after the event.

Data on work productivity loss due to complications were collected in a cross-sectional study of 920 patients with diabetes complications performed in various specialist ambulatory centers in Poland in 2014 [12] complemented by data from a wide-ranged survey among specialist treating such conditions and Central Statistical Office [13] and NHF data (DRG statistics) [11].

Two methods of indirect cost assessment were used: friction costs approach (FCA) and human capital approach (HCA). The first one assumed that productivity loss was produced only for a transitional period in which the workers substitute is found (3 months) and the latter estimated productivity loss in a broader time horizon (until reaching post-productive age of 67).

The unit cost of productivity loss was estimated using the average gross wages in Poland in 2013 [14]. The assumptions regarding the characteristics of labor market in Poland were based on Central Statistical Office methodology of economic activity estimation and were presented in Table 6.

The costs were not discounted, as the objective of the analysis was to represent the average annual cost of T2DM in Polish population of uncontrolled patients on various stages of the disease and at various

points from its onset, which was approximated by averaging the annual costs in the analyzed cohort throughout the lifetime simulation.

All costs were presented for 2014 in PLN (1EUR=4.26PLN). The incremental results were presented with 95% confidence intervals.

RESULTS

Mean life expectancy was higher for the Controlled vs Uncontrolled patients (11.27 vs 10.72 LYs, difference: 0.52, 95% CI: 0.05; 0.98). The average quality-adjusted life expectancy was also higher for Controlled vs Uncontrolled patients (8.33 vs 7.87 QALYs, difference: 0.45, 95% CI: 0.10; 0.79).

The difference in the average lifetime costs of disease between Uncontrolled and Controlled group amounted to 2053 PLN (95% CI: 266; 3935 PLN), 2826 PLN (95% CI: 496; 5295) and 4417 PLN (95% CI: -349; 9088) depending on type of costs taken in consideration: direct costs only, direct costs and indirect costs (FCA) or direct costs and indirect costs (HCA). The average lifetime cost of disease from the three perspectives were shown in Figure 1. Differences between the groups by cost categories were presented in Table 7.

Table 4.
Parameters – direct costs

Cost category	Costs [PLN]
Treatment of diabetes	
Treatment (annual)	814.76
Prevention of cardiovascular disease	
Statins	201.87
Angiotensin converting enzyme inhibitors	204.09
Stopping angiotensin converting enzymes due to side effects	119.26
Monitoring	
Screening for microalbuminuria	35.00
Screening for gastrin-releasing peptide	70.00
Eye screening	30.38
Foot screening program	35.00
Treatment of diabetes complications	
Myocardial infarction - 1st year	13363.54
Myocardial infarction – 2nd and following years	2942.84
Angina - 1st year	844.58
Angina - 2nd and following years	844.58
Congestive heart failure - 1st year	6709.70
Congestive heart failure - 2nd and following years	6709.70
Stroke - 1st year	12866.29
Stroke - 2nd and following years	437.86
Stroke - death within 30 days	3953.88
Peripheral vascular disease - 1st year	574.61
Peripheral vascular disease - 2nd and following years	574.61
Hemodialysis - 1st year	72194.55
Hemodialysis - 2nd and following years	69471.47
Peritoneal dialysis - 1st year	87537.72
Peritoneal dialysis - 2nd and following years	84814.64
Renal transplantation -1st year	60680.84
Renal transplantation - 2nd and following years	14447.91
Major hypoglycemia	117.18
Diabetic ketoacidosis event	2518.25
Lactic acid event	2518.25
Laser treatment	1692.86
Cataract operation	2423.03
Following cataract operation	60.77
Blindness - year of onset	2814.46
Blindness - 2nd and following years	260.77
Neuropathy - 1st year	724.94
Neuropathy - 2nd and following years	439.64

Cost category	Costs [PLN]
Amputation (event based)	8863.19
Amputation and costs of prosthesis (event based)	13110.06
Gangrene treatment	4803.70
Observation after healed ulcer	31.44
Infected ulcer	864.14
Standard uninfected ulcer	31.44
Healed ulcer history of amputation	144.29

Table 5.
Parameters – productivity loss

Category	Productivity loss (days)
Myocardial infarction - event	25.36
Myocardial infarction - annual	22.36
Angina - onset	16.92
Angina - annual	18.81
Congestive heart failure - annual	30.46
Stroke - event	56.85
Stroke - annual	25.46
Peripheral vascular disease - annual	5.58
Hemodialysis - onset	21.14
Hemodialysis - annual	15.32
Peritoneal dialysis - onset	11.27
Peritoneal dialysis - annual	10.08
Renal transplantation - onset	37.79
Renal transplantation - annual	12.32
Significant visual loss - onset	10.77
Significant visual loss - annual	30.08
Cataract - onset	14.98
Cataract - annual	8.99
Neuropathy - onset	0.15
Neuropathy - annual	27.49
Ulcer - onset	11.49
Ulcer - annual	50.16
Infected ulcer - onset	24.73
Infected ulcer - annual	59.08
Healed ulcer - annual	46.33
Gangrene - onset	26.89
Gangrene - annual	85.51
Amputation - event	31.52
Amputation - annual	14.26
Major hypoglycemia	2.62
Cataract - annual	44.70

Table 6.
Parameters regarding labor market in Poland

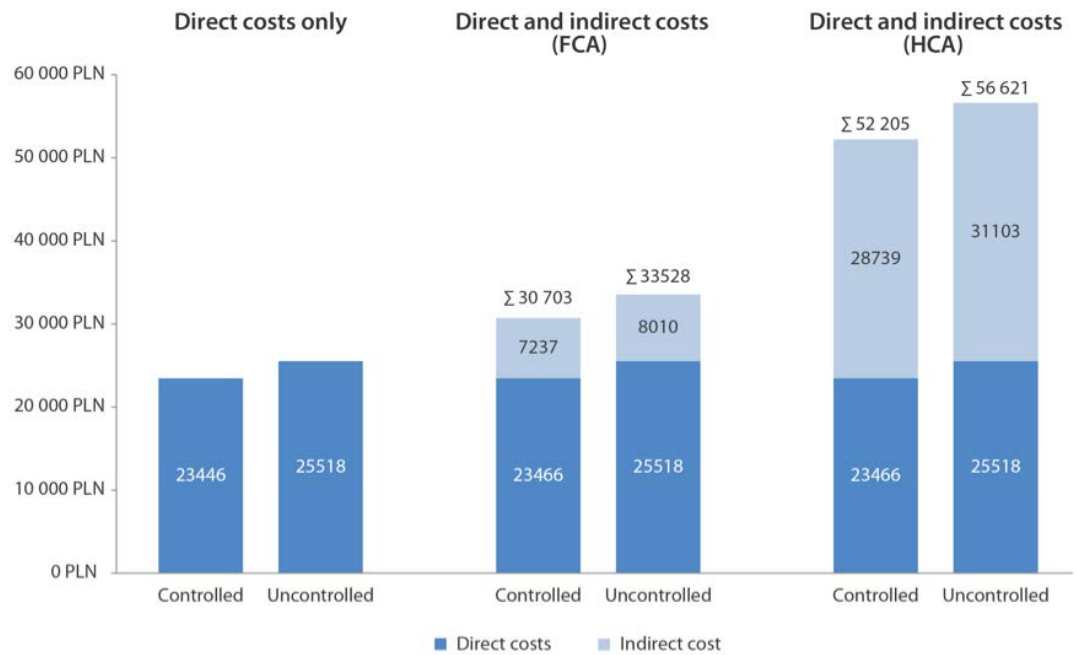| Category	Value
Retirement age	67 years
Age at first income	18 years
Mean annual salary	43800.72 PLN
No. work days/year	224
Months until substitution of productivity loss (FCA)	3

Figure 1.
Mean total lifetime cost of T2DM per Controlled and Uncontrolled patient [PLN]

Table 7.
The difference in average lifetime costs of T2DM between Uncontrolled and Controlled patients by cost categories [PLN]

Category	Controlled patients	Uncontrolled patients	Savings due to diabetic control
Diabetes treatment	8468	8140	-328
Prevention of CVD and diagnostics	2716	2638	-78
Complications -medical costs	12282	14739	2457
Total medical costs	23466	25518	2053
Complications - productivity loss (FCA)	7237	8010	774
Complications - productivity loss (HCA)	28739	31103	2364

Using lifetime costs per patient divided by average survival length obtained from the model mean annual costs of T2DM per patient were calculated for both cohorts to determine the value of annual savings for an average patient related to maintaining good diabetes control (HbA1c ≤ 7%). The results were then applied to the Polish population of patients with Type 2 diabetes who do not keep the sufficient disease control to simulate a hypothetical situation in which all the presently uncontrolled patients gain control in the first year of observation. The estimated mean annual savings per patient resulting from lowering the risk of diabetic complications by keeping PDA therapeutic goals by the whole uncontrolled population, estimated at 62.7% of 1.7 million Polish Type 2 diabetics, translated into significant amounts.

The average annual savings resulting from keeping the therapeutic goals summed up to 192 million PLN, in case where only direct costs were considered, 264 million PLN, if direct and indirect costs (FCA) were included, and 412 million PLN, if the analysis included direct costs and indirect costs (HCA).

DISCUSSION AND CONCLUSIONS

Type 2 diabetes and its complications generate a significant cost for the society in the long-term horizon. Many studies show that presence of diabetic complications is the most significant cost moderator which leads to the conclusion that preventing their development by maintaining control of the HbA1c levels, which influences strongly complications' incidence, would

result in significant cost reduction for the public payer and for the society. Our study confirmed that prolonged maintenance of the therapeutic goals reduced both direct and indirect costs per DM patient in lifetime horizon and affected both life expectancy and quality-adjusted life expectancy of T2DM patients by reducing the number of diabetes complications. It leads us to conclude that increasing the budget for education and treatment of the Polish population of diabetic patients, which would help them keep the therapeutic goals and improve their quality of life, in long term can also result in costs savings for the public payer and society. It is also important to note that the

paper did not aim at presenting methods for reaching diabetic control in the presumed period of time nor did it include the costs of said process, which undoubtedly could be significant. Its objective was to estimate the savings generated by controlling diabetes in the Polish T2DM population.

One of the limitations of the analysis may be the fact, that in both groups, the same cost of treatment, based on Polish observational study for whole T2DM population, was assumed. In practice, uncontrolled patients are probably treated with different regimens than patients that are controlled what can influence results of treatment. Moreover, patient's adherence was not taken into consideration which can also affect the results. However, assumptions concerning treatment regimens used in Polish population were based on best available data so influence of above restrictions on final results of the study seems to be negligible.

The main limitation of the study appears to be the assumption concerning PDA therapeutic targets which are constant over time of the analysis. In real life, goals of PDA are adapted to patient's age and condition. The aim of our study was to assess situation where patients reach general therapeutic goals apart from the fact that it is more difficult in older age. Therefore, the study presents savings in case of the best possible results of treatment.

This is the first Polish study assessing savings associated with effective treatment of diabetes not only in terms of direct but also indirect costs.
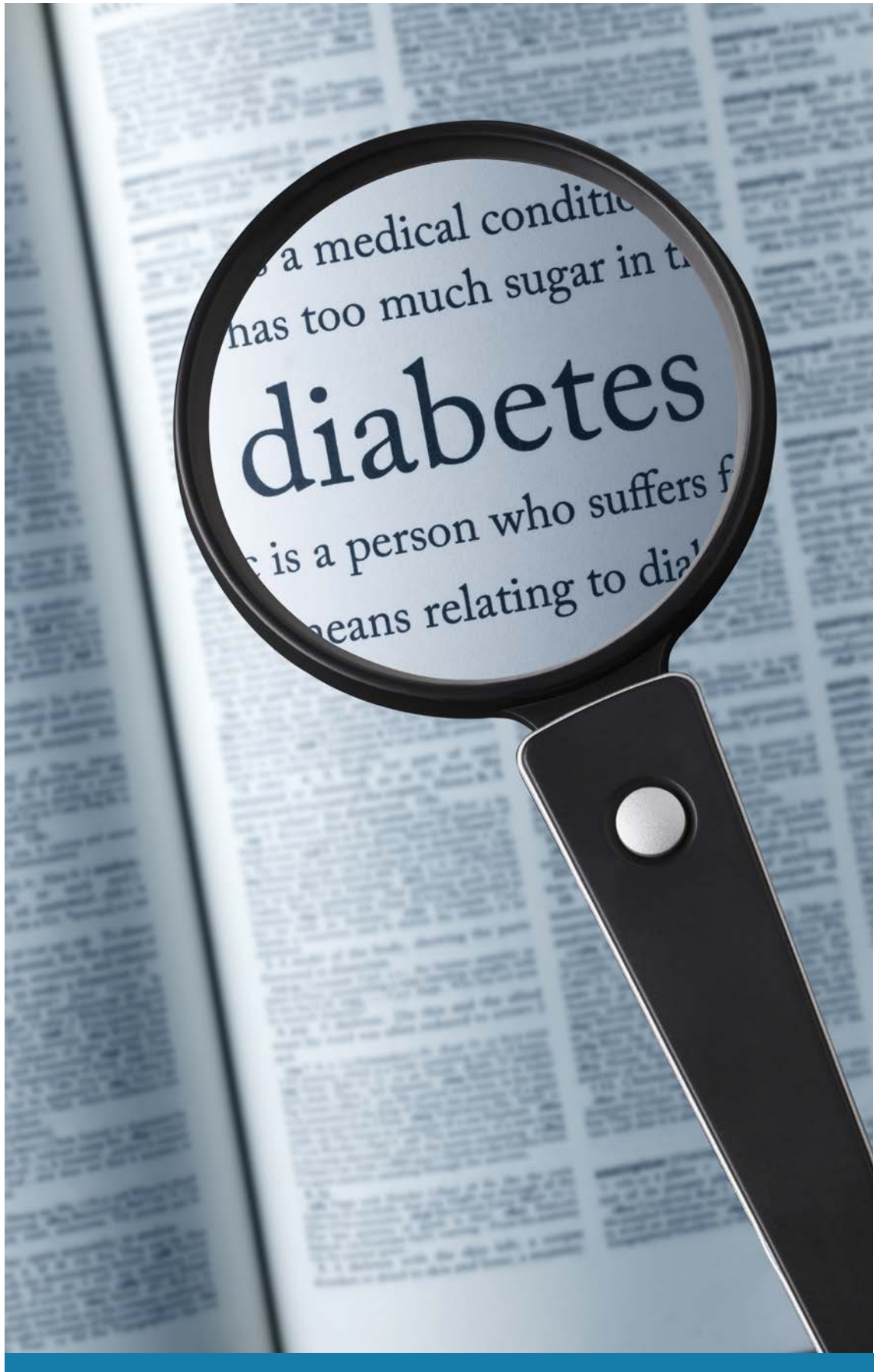
STUDY FUNDING AND CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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Cost effectiveness of the fixed combination of indacaterol / glycopyrronium versus salmeterol / fluticasone and tiotropium in the management of patients with COPD in Greece

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ABSTRACT

Background: This study aimed at estimating the cost-effectiveness of the fixed-dose combination indacaterol/gly-copyrronium (IND/GLY) 85/43μg versus salmeterol/ fluticasone 50/500μg (SFC) and tiotropium 18μg (TIO) in the management of patients with chronic obstructive pulmonary disease (COPD) in Greece.

Methods: A microsimulation model was developed in MS Excel. Effectiveness and utility data were obtained from the international literature and mortality data from the WHO database. Distribution of patients by severity stage of airflow limitation, maintenance costs and costs associated with severe/ non-severe exacerbations were taken from published Greek studies. Unit costs were taken from officially published sources (Price Bulletin, reimbursement list, diagnosis-related groups). The study perspective was that of the Social Insurance Fund; costs and outcomes were discounted at 3.5%,

and the outcomes are reported over time horizons of one, three, five and 10 years and over a lifetime. Deterministic and probabilistic sensitivity analyses were conducted to test robustness of model results.

Results: Treatment of COPD with IND/GLY is associated with increased efficacy both versus SFC (additional life years -LYs: 0.19; additional quality adjusted life-years -QALYs: 0.13) and TIO (additional LYs: 0.22; QALYs: 0.16). Although IND/GLY has a higher pharmaceutical cost (additional €2,626 vs. SFC; additional €2,679 vs. TIO), all other cost components (maintenance costs, severe and non-severe exacerbation costs) are reduced, resulting in a reduction of total costs by €5,204 compared with SCF and €7,126 compared with TIO.

Conclusions: IND/GLY was found to be a dominant treatment strategy compared to SFC and TIO for the management of patients with COPD in Greece, which could lead to savings for the healthcare system.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a life-threatening, debilitating lung disease that severely impacts normal breathing and daily activities [1]. In 2012, more than 3 million people worldwide lost their lives due to COPD, accounting for 6% of all deaths globally for that year [1].

COPD is a major cause of morbidity and mortality, with a significant cost and societal burden, especially in the developed countries [2–6]. Its significant economic burden on individuals and society originates from difficulties associated with correct diagnosis, its chronic nature, the acute worsening or COPD exacerbations, and the indirect costs associated with reduced ability to work [2–6].

The direct and indirect costs associated with the disease exhibit an increasing trend and vary significantly across countries [7]. In Greece, the disease prevalence in the population above the age of 35, with a smoking history of >100 cigarettes per lifetime, has been estimated at 8.4% [8], while the average cost of managing a COPD exacerbation is estimated at €1,711 [9].

The fixed combination of indacaterol/glycopyrronium 85/43µg (IND/GLY) is a once-daily inhaled combination of indacaterol maleate, a long-acting 2-adrenergic agonist (LABA), and glycopyrronium bromide, a long-acting muscarinic antagonist (LAMA). It is indicated by the European Medicines Agency (EMA, October 2013) as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD [10].

A recently published systematic review showed that IND/GLY provides significant and clinically meaningful improvements on several important COPD 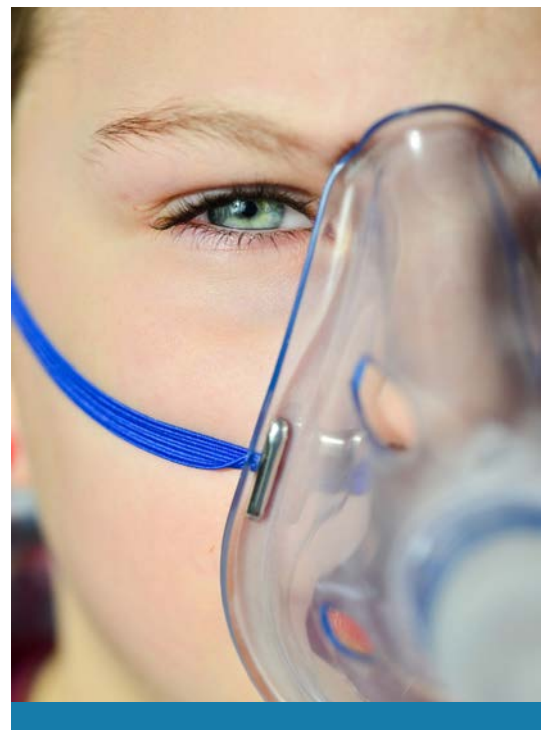outcomes. Relevant studies have demonstrated that therapy with IND/GLY is superior to therapy with a single long acting bronchodilator, even in patients who report symptoms despite being under treatment [11].

The purpose of this study was to compare the costs and outcomes of IND/GLY versus salmeterol/fluticasone 50/500µg (SFC) and tiotropium 18µg (TIO) in the management of patients with COPD in Greece.

METHODS
Model design

For the economic evaluation of IND/GLY versus SFC and TIO, a patient simulation model was developed in Excel 2010®, described in detail by Price et al [12]. The model time horizon varied across one, three, five and 10 years and over a lifetime; costs and outcomes were discounted at 3.5% annually [13,14]. The perspective of the analysis was that of the Social Insurance Fund (SIF), thus only direct medical costs reimbursed by the SIFs in Greece were taken into consideration. All costs are in 2014 Euros.

MODEL INPUTS
Clinical data

Effectiveness data used in the model were based on the results of three phase III randomized controlled trials: SHINE [15], SPARK [16] and ILLUMINATE [17]. In particular, inputs for IND/GLY versus SFC were based on ILLUMINATE [17], using the TORCH study [18,19] to calibrate against a placebo baseline. Inputs for IND/GLY versus TIO were based on of the results of SHINE [15] and SPARK studies [16].

Population and mortality data

Population data categorized by age and sex for Greece were taken from the Organization for Economic Cooperation and Development (OECD) Population Statistics 2012 (http://stats.oecd.org/). All-cause mortality data (life-expectancy, central death rates, the probability of dying and number of survivors by age group) were obtained from the World Health Organization (WHO life-tables for Greece 2012 (http://www.who.int/gho/mortality_burden_disease/life_tables/en/). Due to lack of Greek data on COPD-specific mortality, the hazard ratio was based on the study by Lindberg and colleagues [20].

Patient demographic characteristics (mean age entering the model and percentage of males versus females), as well as patient distribution according to airflow limitation as defined by the 2010 global initiative for chronic obstructive pulmonary disease (GOLD) classification [21] and mean FEV1% by GOLD stage were taken from studies in the Greek COPD population and are presented in Table 1.

COST DATA

For pharmaceutical costs, retail prices were taken into consideration (published in the Price Bulletin of the Ministry of Health and Social Welfare [23]), after subtracting patient co-payment (Table 2).

The costs associated with the management of severe and non-severe exacerbations were based on studies conducted on the Greek COPD population (Table 3). Severe exacerbations were defined as exacerbations requiring hospitalization. For severe exacerbations, the mean actual cost per exacerbation requiring hospitalization across all stages of the disease was taken into consideration. Both costs of severe and non-severe exacerbations were subsequently inflated with the Health Price Index (HPI) to reflect 2014 prices.

Maintenance costs included maintenance medication and non-medication costs (patient follow-up and lab tests), that do not relate to the management of exacerbations, after excluding pharmaceutical costs of the interventions compared (Table 4). Based on Greek leading experts' opinion, maintenance costs for GOLD stages I and II were negligible and thus excluded from the analysis. Costs for GOLD stages III and IV were based on published data by Geitona and colleagues [25]. The study estimated the cost of moderate-to-severe patients. This cost was broken down to moderate and severe patients based on the distribution of respective costs in the Swedish study by Price and colleagues [12] and was inflated with the HPI to reflect 2014 prices.

UTILITY DATA
Utility data were obtained from the Rutten-van Molken et al. study [26] and are presented in Table 5.

Table 1.
Patient demographic characteristics, distribution & mean FEV1% by 2010 GOLD stage

	Mean (s.d.)	Source
Age entering the model (years)	67.6 (10.2)	Papaioannou et al., 2014 [22]
% of males	71.3%	Papaioannou et al., 2014 [22]
Patient distribution by GOLD stage		Papaioannou et al., 2014 [22]
GOLD I	19.32%	
GOLD II	35.44%	
GOLD III	25.63%	
GOLD IV	19.61%	
Mean FEV1% by GOLD stage		Geitona et al., 2011 [9]
GOLD I	83.0% (5.2%)	
GOLD II	62.7% (11.3%)	
GOLD III	52.3% (16.5%)	
GOLD IV	38.8% (11.7%)	

Table 2.
Pharmaceutical costs

Drug	Cost per package (€)	Number of units per package	Cost per unit (€)	Number of units per day	Daily drug cost (€)
IND/GLY	53.20	30	1.77	1	1.77
SFC	29.99	60	0.50	2	1.00
TIO	29.63	30	0.99	1	0.99

Table 3.
Exacerbation costs

	Cost per occurrence (€)	Source
Non-severe exacerbation	572	Sonathi et al 2014 [24]
Severe exacerbation	1,839	Geitona et al. 2011 [9]

Table 4.
Annual maintenance costs

	Cost (€)	Source
GOLD I	-	
GOLD II	-	
GOLD III	3,205	Geitona et al. 2011 [25]
GOLD IV	10,72	Geitona et al. 2011 [25]

Table 5.
Utility values

Variables	EQ-5D Utility Score
Constant	0.688
Gender (male vs. female)	+0.057
Postbroncodilator therapy FEV1 % predicted	+0.003
BMI	-0.003
Number of concomitant diseases in the previous year	-0.01
Number of emergency department visits not resulting in hospital admission in the previous year	-0.029
Number of hospital admissions in the previous year	-0.02

Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were performed in order to investigate uncertainty around model results. The model inputs that were varied by +/-20% in the one-way sensitivity analysis were FEV1% improvement, exacerbation rate versus placebo, and disease severity of population (distribution of patients according to GOLD airflow limitation classification) at baseline. This range reflects habitually used ranges in the literature for one-way sensitivity analysis [27,28]. The probabilistic sensitivity analysis (PSA) was conducted for 1000 cohorts with 10,000 patients per cohort. The purpose of the PSA was to examine the effects of variability of effectiveness and cost data on the incremental cost-effectiveness ratio (ICER). Gamma distribu-

rates. The output of the PSA is presented in scatterplots of 1000 simulated ICERs on the cost-effectiveness plane.Source: Rutten-van Molken et al., 2006 [26]

RESULTS

Total per patient costs of managing COPD patients with IND/GLY over lifetime were estimated at €45,459 (Table 6). The respective costs for SFC and TIO were estimated at €50,663 and €52,585. Maintenance costs constitute the largest cost component, accounting for 81.9%%, 88% and 87.4% of total costs for treatment with IND/GLY, SFC and TIO, respectively.

Treatment with IND/GLY is associated with cost savings compared with both SFC and TIO from the 1st year of treatment and over three, five and 10 years, as well as over lifetime (Table 7).

Table 6.
Cost-effectiveness of IND/GLY versus SFC and TIO

	IND/GLY	SFC	TIO	Difference vs. SFC	Difference vs. TIO
LYs	9.87	9.68	9.649	0.19	0.22
QALYs	5.96	5.83	5.8	0.13	0.16
Total cost (€)	45,459	50,663	52,585	-5,204	-7,126
Drug cost (€)	5,859	3,233	3,181	2,626	2,679
Maintenance cost (€)	37,219	44,558	45,98	-7,339	-8,76
Exacerbation costs (€)	2,381	2,872	3,425	-491	-1,044

Table 7.
Incremental results of the base case cost-effectiveness analysis for IND/GLY versus SFC and TIO

Time horizon	1 year	3 years	5 years	10 years	Lifetime
IND/GLY vs. SFC					
Incremental total costs (€)	-453	-1,813	-2,997	-4,949	-5,204
Incremental LYs	0.00	0.01	0.02	0.08	0.19
Incremental QALYs	0.00	0.01	0.02	0.06	0.13
Exacerbations avoided	0.06	0.22	0.35	0.63	0.92
IND/GLY vs. TIO					
Incremental total costs (€)	-692	-2,624	-4,315	-6,988	-7,126
Incremental LYs	0.00	0.01	0.03	0.10	0.22

Overall, the analysis showed that IND/GLY is associated with increased effectiveness compared with SFC, both in terms of life-years (LYs) gained (0.19) and quality-adjusted life years (QALYs) gained (0.13). Similarly, treatment with IND/GLY is associated with more LYs (0.22) and QALYs (0.16) versus TIO.

Treatment with IND/GLY is also associated with a lower total cost compared with both SFC and TIO. In particular, although IND/GLY has a greater drug cost than SFC and TIO, this is completely offset by a reduced cost in maintenance treatment and management of (severe and non-severe) exacerbations (Table 6). The combination of increased effectiveness and reduced costs render IND/GLY a dominant treatment strategy versus SFC and TIO in the management of patients with COPD in Greece.

Sensitivity analyses results

Results of the one-way sensitivity analysis suggested that the parameters which had the most significant impact on the results were FEV1% improvement and the disease severity of the patients included in the analysis. The results of the PSA are presented in a cost-effectiveness plane of IND/GLY versus SFC and TIO in Figures 1 and 2, respectively. The PSA confirmed robustness of model results, as it showed that IND/GLY was dominant in the majority of iterations. The probability of being cost effective at a threshold of €30,000 per QALY gained was 99.9% and 97.1% versus SFC and TIO, respectively.
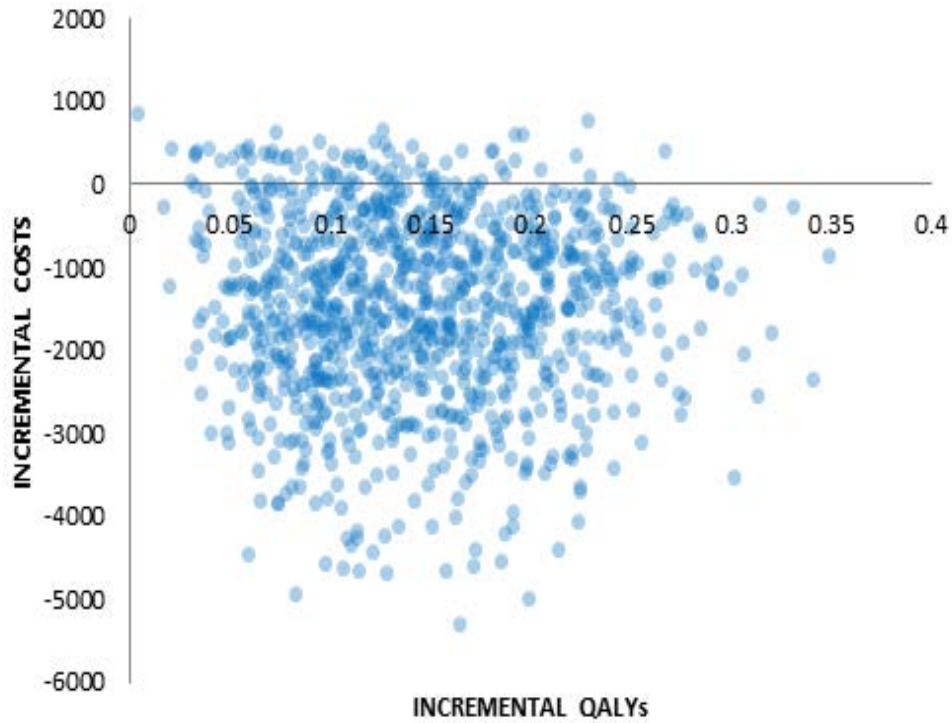
Figure 1.
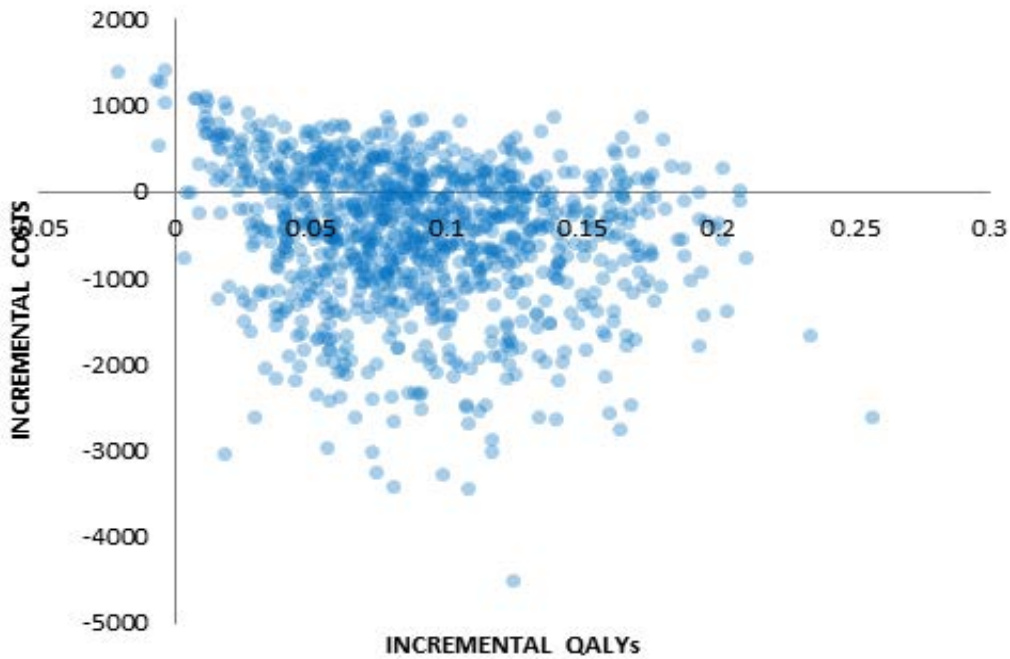Cost-effectiveness plane for IND/GLY versus SFC based on PSA

Figure 2.
Cost-effectiveness plane for IND/GLY versus TIO based on PSA

DISCUSSION

The results of the cost-effectiveness analysis showed that IND/GLY was associated with cost savings, and efficacy and safety benefits when compared with SFC and TIO, thus was found to dominate alternative treatments. In particular, the present study suggests that IND/GLY was associated with incremental cost savings at all time-horizons at a daily cost of €1.77.

The results of this analysis are comparable to results of the economic evaluation study of IND/GLY in Sweden. In particular, the study by Price and colleagues, suggested that IND/GLY is cost-minimising versus the free combination of indacaterol and glycopyrronium (IND+GLY) and dominates SFC in the maintenance treatment of COPD patients in Sweden [12]. In addition, previously conducted research on the costs of COPD treatments in the Greek health care setting has estimated the mean annual per patient cost of tiotropium at €2,504 [29], which is comparable to current results.

The present analysis had the following limitations. Mean FEV1% values by GOLD stage were taken from the study by Geitona and colleagues [9], which referred to a patient population with more severe disease (patients hospitalized due to COPD). This is of particular importance since disease severity is one of the key parameters impacting results. However, inputs on disease severity were tested in the sensitivity analysis and confirmed that even when only moderate patients were considered in the model, IND/GLY remained a cost-effective treatment strategy.

Another limitation of this study is that indirect costs were not included in the analysis. A Swedish study showed that annual indirect costs increased with disease severity, ranging from SEK 3,133 to SEK 118,517 for GOLD I to GOLD IV stages,

respectively [30]. The inclusion of indirect costs into our study would have provided a more complete picture of the true costs of COPD in Greece. However, the perspective of the present study was that of the SIFs, thus the study focused only on direct medical costs associated with disease management.

In Greece, pharmacoeconomic studies are currently not officially requested by Reimbursement Authorities. However, taking them into consideration could serve as an evidence basis for rational decision making and improvement of resource allocation. To the best of our knowledge this study is the first to evaluate the use of IND/GLY and the associated costs in the local treatment pathway and thus could help inform health care decision making.

CONCLUSIONS

This study suggests that IND/GLY is more effective (increases both LYs and QALYs) and less costly for Social Insurance Funds versus both SFC and TIO. Thus, IND/GLY is a dominant treatment strategy in the management of patients with COPD in Greece and could lead to savings for the health care system. The results of this study could support informed health care decision making and contribute to a more rational allocation of health resources.

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COPD in Ukraine: overview of the status and prospects for improvements and developments in health care system

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is an actual problem for healthcare systems in different countries taking in account it`s high morbidity, mortality, impact on quality of life and related costs. COPD in Ukraine could be one of the most valuable medical and socio-economic problems as for developing country, the human capital affected by COPD is the most important national asset. The access to drugs is critical especially for COPD patients, medications for basic therapy are very expensive, while intended for use permanently. This study was performed to investigate the status with COPD in Ukraine and determine possible ways for improvements and developments in COPD management and related processes in healthcare system in Ukraine. The following areas were investigated: epidemiological data, data in COPD management, health economics data and targeted literature review. Results showed that very limited epidemiological COPD data are available in Ukraine. There are favorable conditions for good COPD management in Ukraine because of availability of the adopted guidance and the unified clinical protocol that cover prophylaxis, diagnostics, treatment and rehabilitation of COPD patients. Ukrainian clinical guidance in COPD management has external validity and is expected to be updated on regular basis. There were several country-specific Health Economic studies focused on COPD but these studies have limitations due to substantial assumptions and extrapolations from small to large populations. More Health Economics large-scale studies needs to be performed in Ukraine. Results of current study, also, showed that COPD is a relevant topic for pulmonology research in Ukraine.

BACKGROUND

To investigate the status of COPD in Ukraine and determine possible ways for improvements and developments in COPD management and related processes in healthcare system in Ukraine.

METHOD

Overview of the following data was performed: data from Ukrainian epidemiological statistical reports and studies in COPD, health care legislative documents for COPD management, literature publications in international scientific database.

Search strategy: e-search was performed using the following key words and word combinations in Ukrainian and English languages: COPD in Ukraine; COPD prevalence in Ukraine; COPD morbidity in Ukraine; COPD mortality in Ukraine; health care for COPD patients in Ukraine; COPD costs in Ukraine.

Resources for e-search: Informational Portal of the Ministry of Health of Ukraine (https://www.moz.gov.ua/ua/portal/); web-database in healthcare standards of the State Expert Center of Ministry of Health of Ukraine (http://www.dec.gov.ua/mtd/index.html); web-database of the National Institute of Phthisiatry and Pulmonology (http://www.ifp.kiev.ua/index_ukr.htm); Ukrainian governmental legislative portal (http://zakon4.rada.gov.ua/laws); Embase (http://www.embase.com/).

Search period: 8-20 May 2015.
Search depth: Five full-scale years (2010-2015).

In addition, with the aim to assess the level of topicality and importance of the problem with COPD in Ukraine the targeted literature review was performed. For this purpose the "Ukrainian Pulmonology Journal" was selected as the web-database with the most relevant Ukrainian publications in pulmonology science in Ukraine. This journal is the only one that is selectively specialized in pulmonology area in Ukraine. Journal is established by the National Institute of Phthisiatry and Pulmonology n.a. V. Komisarenko. This institute is the core scientific institution of Ukrainian healthcare in phthisiatry and pulmonology. Search period: 1-2 June 2015. The search depth of three full-scale years (2012-2015) was selected with the aim to review and analyze the topics and key results of the recent publications are being considered as actual for today. Scope of search included results of the cost, economic, epidemiology and clinical studies.

RESULTS
Epidemiological data

The first official data on COPD prevalence, morbidity and mortality were introduced in 2010. It was 2009 report of the National Center of Medical Statistics had been created from 2009 data. Report was followed by the 2010 prevalence data in 2011. These reports are cumulative and included case data from the state (public) healthcare institutions (data from private healthcare providers were not included). COPD patient registries are not established in all state healthcare institutions in Ukraine, so statistical reports do not contain data from patient registries.

Unfortunately, no official reports were published after 2011 until now. Nevertheless, the presented reports did not contain the disease-related information on number of specialists' consultations (outpatient visits), number of disability days and hospitalizations frequency and lasting. According to the data from the National Center of Medical Statistics of the Ministry of Health of Ukraine (MoH), in 2009 the COPD prevalence was about 0.9% in Ukraine. The

number of COPD cases in population aged 18 and over was 377 267 with prevalence 998.70 for 100 000 population. In 2009 there were 29 928 first-diagnosed COPD cases. Average lasting of COPD hospitalization was 12.57 days with hospital mortality rate 0.88 for 100 000 [1]. In 2010 the National Center of Medical Statistics registered 420 083 COPD cases in population aged 18 and over.

According to opinion of the Ukrainian leading pulmonologists, COPD is under-diagnosed in Ukraine and it`s prevalence rate could reach 6% in general adult population [11]. Thus number of COPD patients in Ukraine could reach 1 930 000 patients.

Some epidemiological data were obtained from the prospective modeling for 2012-2020 are available in literature [8]. 2012-2020 dynamics of the key socioeconomic and COPD-related epidemiological indicators for general Ukrainian population were modeled based on data collected from MoH reports and data from World Health Organization (WHO). The best fit (least square) linear regression forecast was applied for that modelling. Results showed that in general population number of COPD patients could reach 1 731 332 in 2020. Cumulative 2012-2020 number of new COPD cases and COPD related deaths could be 1 230 750 and 56 207, respectively.

Data in COPD Management

COPD patients are being managed in Ukraine by GPs and Pulmonologists on outpatient and hospital levels of medical care. Management of COPD in Ukraine is regulated by the decree of MoH 555 from 27 Jun 2013 "About the approval and implementation of medical and technological documentation in standardization of medical care in Chronic Obstructive Pulmonary Disease". This decree implemented the adopted clinical guidance "Chronic Obstructive Pulmonary Disease" and unified clinical protocol of primary, secondary, tertiary (highly specialized) medical care and rehabilitation "Chronic Obstructive Pulmonary Disease". This decree required that the unified clinical protocol to be adopted locally in health care institutions throughout the Ukraine.

Clinical guidelines were adopted by Ukrainian multidisciplinary work group mostly from the following documents:

- GOLD (Global Initiative for Chronic Obstructive Lung Diseases (updated 2011))

- NICE 101 (Chronic obstructive pulmonary disease. Management of COPD in primary and secondary care (Jun 2010)).

Adopted guidance covers COPD diagnostics, management of stable COPD and exacerbation management. In addition, this document states the key measures to be implemented in healthcare system such as:

- diagnostic in age group over 35 years with appropriate clinical symptoms;
- confirmation of bronchial obstruction with post-bronchodilator spirometry;
- open access for spirometry;
- smoking cessation;
- treatment with effective bronchodilators;
- access to lung rehabilitation for any patient who needs it;
- usage of non-invasive ventilation in cases of COPD exacerbations with sustain lung hypercapnic insufficiency;
- appropriate exacerbation prevention (decrease the exacerbation frequency with inhaled corticosteroids, bronchodilators and vaccines) and adequate management (minimization of injury from exacerbation with: advises for early self-reporting of symptoms by patients; start of appropriate oral corticosteroids and/or antibiotics; use of non-invasive ventilation; inpatient-outpatient care combinations and early discharges);
- treatment by the multidisciplinary specialists.

Unified clinical protocol was created based on adopted clinical guidance for the following expected users: physicians, nurses and doctor-assistants, healthcare decision makers, patients and patient-support groups, authorized organizations and service providers. The aims of the protocol are: to ensure the quality, efficiency and access to medical care of COPD patients, according to evidence based medicine principles; to establish unified requirements for prophylaxis, diagnostics, treatment and rehabilitation in accordance with the guidance created with evidence based approach; to justify the human and material resources for healthcare institutions; to determine indicators for medical care quality assessment with the purpose of monitoring and audits of healthcare institutions. Date of creation: May 2013. Planned revision date: May 2016. Protocol

defines obligatory and desirable measures to be performed by healthcare professionals with appropriate justifications and reference to the adopted clinical guidelines.

Health Economics data

Some studies to determine socio-economic impact of COPD in Ukraine were performed by members of Ukrainian chapter of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). They were obtained in result of the literature e-search and are described below.

COPD data collection study with the Cost of Illness analysis were performed as a pilot project [9, 19]. Multi- center retrospective analysis (data from 12 months) of medical records (90%) and subjects' interview-lists (10%) was performed in three regions of Ukraine. Target population included

patients with II-III severity stage COPD. The main objective was to collect data is required for direct and indirect costs calculation: medical care (including routine practice for treatment) and services utilization data (Table 1). Tariffs for COPD related medical services were collected from the state (public) health care institutions. For tariffs, medians were calculated due to presence of outlier values and skewed data distribution (Table B). In result, total (direct + indirect) COPD costs were calculated for 2011. Direct costs included outpatient costs, hospitalization and inpatient care costs. Indirect costs included productivity loss (taxes from the lost average annual personal income and lost average annual income of companies) and disability compensations. Costs were calculated for 377 267 COPD patients from "Economically-active" age group by multiplying of cost units (Table 2) with the corresponding discounts.

Table 1.
Results of retrospective analysis of COPD related data from Ukrainian healthcare

Mean number of GP visits per 12 months (±SD)	2.63 (±1.45)
Mean number of Pulmonologist visits per 12 months (±SD)	1.18 (±1.1)
Number of lost working days due to COPD per patient, per 12 months	12.63
Frequency of COPD-related hospitalizations	0.53
Average duration of COPD-related hospitalization (days)	12.75

Table 2.
Direct costs units (tariffs) and indirect cost units (2011)

Unit	Price, €
GPs or specialists visit	0.61
Spirometry	3.59
Chest X-ray	4.17
Complete Blood Cells	2.92
ECG	2.27
Bacteriological Sputum Analysis	7.21
Hospital service (per person, per day)	11.52
1 lost working day	0.19
Disability compensation (per person, per day)	5.12
Annual Productivity loss because of presentism* (per person)	20.84

Total annual COPD costs were estimated as € 38 870 506 (€ 103.03 per patient) with € 28 448 213 (73.80% from total) direct medical costs and € 10 422 293 (26.20% from total) indirect costs in Ukraine.

The assessment of 2012 and projected 2020 COPD-related direct and indirect costs was performed [8]. Result showed that in 2012 in Ukraine direct COPD costs could be in 68.57% higher than indirect COPD costs and could reach € 326 367 598 vs. € 193 607 579.90, respectively. In 2020 indirect COPD costs may 1.47% exceed the direct costs and may reach € 496 997 427.80 vs. € 489 796 409, respectively. So, COPD-related productivity loss is expected to increase due to expected increase of economically active population proportion in general Ukrainian population.

Cost Benefit Analysis for salmeterol and tiotropium compared to standard intervention mix (routine practice of GPs) in economically active population with COPD was performed [10]. Results showed that per 1000 employed economically active COPD patients total annual COPD costs could reach € 498 052.34, € 441 697.07 and € 508 983.73 for usual COPD treatment practice of GPs, salmeterol and tiotropium, respectively. Reduction of annual exacerbation-related COPD costs compared to usual practice could amount €85 698.78 for salmeterol and € 114 380.78 for tiotropium per 1000 economically active COPD patients. Cost-benefit ratio for salmeterol calculated as 5.15 and for tiotropium as 4.45. Results of sensitivity analysis showed that in case of 27 % price drop salmeterol could become to be more beneficial than tiotropium.

Targeted literature review

The Ukrainian Pulmonology Journal reflects the whole spectra of scientific interests on Ukrainian pulmonology field. Articles had been published in 2012-2015 time-period were reviewed and sorted based on disease specificity (Table 3).
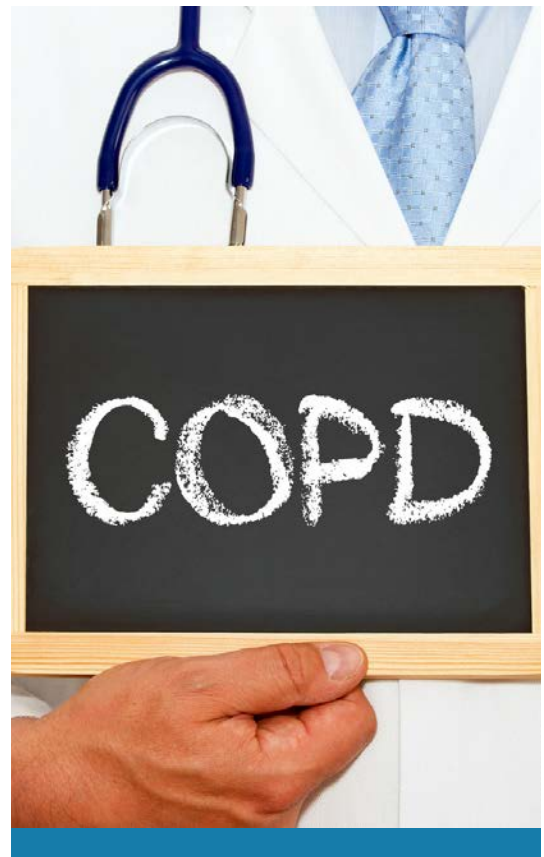

Table 3.

2012-2015 publications in Ukrainian Pulmonology Journal

Disease	2015/Q1	2014	2013	2012	Total
TBC	2	25	5	6	38
COPD	3	34	8	25	70
Sarcoidosis	1	3	1	-	5
Pneumonia	1	8	10	9	28
Asthma	3	6	2	10	21

The majority of articles (70 in total) are related to COPD as primary topic. Key messages/results from the articles have been written by lead Ukrainian experts in pulmonology are briefly described below:

Y. Feschenko noted [11] that according to official statistics, prevalence of COPD in Ukraine is about 1% of, but, according to local epidemiological studies, the prevalence of COPD in Ukraine can reach 6%. The main cause of this discrepancy of data is the low rate of early-diagnosed cases.

On the other hand, Y. Mostovoy presented data, according to which, the cause of prevalence data discrepancy could be inconsistencies in the forms of statistical reporting in inpatient and outpatient treatment levels of healthcare system [12].

T. Pertseva et al. [13] found that inflammation markers – cytokines and thromboxanes play an important role in the occurrence and development of COPD. Among them promising for the study is a factor lipoxins A4 as a marker of anti-inflammatory reserves of an organism.

N. Gorovenko et al. investigated the polymorphic marker for of adrb2, nr3c1, mdr1 genes relation with improvement of ICS/LABA therapy effect in COPD patients. Method could be used for prediction of ICS/LABA treatment efficiency in COPD patients [14].

L. Yudina in the study considered the antibiotics should be used for infectious COPD exacerbation. Author concludes that ciprofloxacin should be the medication of choice in cases of severe infectious COPD exacerbation with risk of P. aeruginosa colonization [15].

Current status and trends of disability of workable age population due to COPD and asthma is presented in the study of V. Shevchuk, et al [16]. In the conclusions authors stated that the average level of disability due to COPD in workable age population was 1.4 times lower than in Asthma. Analysis of disability due to COPD and Asthma revealed the lack of modern evidence-based health and social rehabilitation programs.

The article of K. Gashynova [17] provides factors that determine the prognosis of COPD. They are: the presence of systemic manifestations of the disease and comorbidities. Concomitant diseases increase the risk of hospitalization and death, increase the cost of medical care for such patients and reduce the quality of life. It was stated by the author that the majority (83.90%) of patients with COPD suffered from at least one concomitant disease. The most common comorbid conditions were cardiovascular diseases.

At the same time, A. Dovgan et al. [18] stated that COPD was associated with a development of somato-psychic disturbances – frequent neurosis 79.70%, reactive anxiety 41.80%, personal anxiety 76.70% and depression 23.30%.

DISCUSSION

For today in Ukraine, there is no appropriate COPD epidemiological statistical regular data that could be used to represent sufficiently the current COPD status in Ukraine [1,11,12]. Results of modeling could be used [8] but these data could have substantial level of uncertainty. Therefore, today, it is possible to perform only approximate assessment of prevalence morbidity and mortality levels when make the decisions in health care system in Ukraine. In addition, regular data about healthcare COPD-related resource utilization and tariffs for related medical services are not available and could be obtained

from the surveys or targeted analyses [9,19]. It could be useful to change the statistical datasets in regular reports with the purpose of support decision makers with the information required for efficient decisions on different levels of Ukrainian healthcare system.

To make clinical decision within the COPD management healthcare professionals in Ukraine have the adopted guidance and the unified clinical protocol as the tools are being powered by legislation. That documents are directly related to guidelines are being used throughout the world. Therefore, evidence-based part of prophylaxis, diagnostics, treatment and rehabilitation measures for COPD patients in Ukraine, in general, comply with other European countries.

The first economic assessment showed that total annual COPD costs in 2011 were estimated as € 38 870 506 (€ 103.03 per patient) with majority of direct costs 73.80% from total [8]. Results from cost study "Economic analysis of the Confronting COPD survey" was performed in U.S.A., Canada, the U.K, Spain, Italy, France and the Netherlands were published in 2003 [20]. In this study total per patient societal COPD costs ranged from $5646 in the U.S.A. to $1023 in the Netherlands. In all countries, except the France, direct costs dominated. The Countries had a particularly high proportion of indirect costs were the following: France, the Netherlands and the U.K., with 67%, 50% and 41% from overall costs, respectively. Compare to developed countries, Ukraine, as a country that is under developing, has lower incomes rates and lower rates of prices and tariffs. As result, there is substantial difference between per patient COPD-related costs between Ukraine and EU countries, U.K., USA, Canada.

The health economic studies on COPD [8,9,10,19] are only starting and need to be developed now in Ukraine.

The importance of those studies is extremely high. Results of Cost of Illness studies could valuate the losses related to COPD in money equivalent. Cost-Benefits analyses and Budget Impact analyses will show the possible benefits from purposeful implementation of different health technologies and will help to understand the real needs for reimbursement. However, conducting of costs studies requires appropriate datasets, which to be specific for Ukraine. Economic appraisals have been performed before [8,9,10,19] used substantial amount of assumptions and extrapolations from small to large populations. On the other hand, the cost structure and information collecting approaches were developed and implemented could be used as methodological basis for further studies.

Analysis of the specific publications showed that COPD is under active research in Ukraine. Large number of original publications on the epidemiology, pathogenesis, diagnostics, treatment and prevention of this disease are available for review. The lead Ukrainian experts in pulmonology are actively involved in research process [1,2,11-18]. Taking in account the majority in pulmonological disease-related publications, we can conclude that the problem of COPD in Ukraine is one of the most important in pulmonology. This indicates that COPD is not only a medical problem, but also social and economic. Today, scientists are looking for modern and effective methods for the treatment and diagnostic of COPD. Increase of COPD prevalence makes clinical, social and economic impact onhealth care system of Ukraine. Moreover, from publications we can see that COPD in Ukraine represents an enormous health problem for the community, affecting patients, state budget, employment sector, institutional network and hence society as a whole.

CONCLUSIONS

Statistical reports in Ukrainian Health care system should be changed with the aim to support healthcare professionals with COPD-related epidemiological and healthcare resource utilization information. These changes could increase the efficiency of COPD-related decisions in Healthcare system of Ukraine;

Ukrainian clinical guidance in COPD management has external validity and is expected to be updated on regular basis;

More Health Economics large-scale studies need to be performed in Ukraine. It will support healthcare system with important information and can help to establish reimbursement for COPD basis-drugs and improve patient's access to treatment.

COPD is actual problem for Ukraine that was confirmed by analysis of COPD-related publications in highly specialized Ukrainian scientific journal.

LIMITATIONS

Current review was performed using the e-search. Documents and articles were not published officially or were issued only on paper source are out of scope of current review. Literature search for 2015 year included only articles were published within the 1st quarter 2015. Journals specialized in internal medicine specialties other than pulmonology were not included in literature review.

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Assessment of quality of life in patients with schizophrenia and their caregivers in selected Central and Eastern European countries: A literature review

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ABSTRACT

Background: To investigate the impact of schizophrenia on quality of life (QoL) of patients and caregivers in seven CEE countries, by conducting a literature search.

Methods: Search was performed in publicly available databases to identify publications from 1995 to 2012 related to schizophrenia and QoL. Publications included those describing health-related QoL data of negative symptoms in patients with schizophrenia.

Results: Out of an initial search of 2882 abstracts, 1587 were excluded based on duplication or preliminary screening of titles, and a further 1550 publications were excluded based on screening of the abstracts (1510) or full-texts (40). Thus, 37 primary publications related to QoL of patients with schizophrenia and caregivers were identified. Due to differences observed in the identified studies, it was not possible to make direct comparisons nor to

pool data for analysis. However, it was consistently reported that schizophrenia greatly affected the QoL of patients and had a significant negative impact on the QoL of caregivers, such that their QoL was considered similar to the patients themselves. In addition, patients with schizophrenia experienced significant stigmatization and discrimination. In general, the presence of negative symptoms was not well-documented in the literature and available antipsychotics had limited impact on the treatment of negative symptoms.

Conclusion: Schizophrenia significantly reduces QoL of patients and their caregivers. Further research is needed to better understand the drivers of impaired QoL caused by schizophrenia, in particular the negative symptoms of schizophrenia, and how best the burden of illness and associated stigmatization and discrimination may be reduced.

INTRODUCTION

Schizophrenia is one of the most common psychiatric disorders, affecting approximately 1% of the world's population [36] and is a leading cause of disability [48]. Lifetime prevalence of schizophrenia is high, ranging from 0.4 to 1.4%, due to the early age of onset and chronic course of the disease [36].

The impact schizophrenia upon quality of life (QoL) has been an active area of research for many years. Schizophrenia is ranked among the op ten leading causes of disease-related disability in the world and has consistently demonstrated a major negative impact on QoL [48]. The chronic nature of schizophrenia particularly affects the social dimension of QoL. Decreased cognitive and social skills, and hypersensitivity to criticism and stress, can lead to patients becoming isolated from society and the object of stigmatization [35].

Therefore, treatment goals for patients with schizophrenia not only include reducing the frequency, duration and severity of episodes and overall morbidity, but also improving psychosocial functioning and QoL [34].

Assessment of QoL can provide an additional measure of treatment outcome for patients with schizophrenia. In recent years, a large number of scales have been developed to determine well-being and QoL in patients with schizophrenia [35]. Many individuals with schizophrenia rely on informal daily care, which is typically undertaken by family members, most often parents or siblings [2]. For family members who are caregivers, schizophrenia poses numerous challenges, including management of the patient's illness and adjustment to the negative impact on the patient's daily functioning.

OBJECTIVE

The aim of the study was to identify available information about the impact of schizophrenia, and particularly the negative symptoms of schizophrenia, on QoL in patients and caregivers across seven Central and Eastern European (CEE) countries. In addition, data on stigmatization and discrimination in patients with schizophrenia was obtained.

METHODS

A literature search was performed in seven CEE countries (Croatia, Estonia, Hungary, Poland, Serbia, Slovakia and Slovenia). The search strategy for MEDLINE via PubMed, Cochrane Library and Centre for Review and Dissemination databases was developed using the term 'schizophrenia' and its synonyms. A targeted search was performed using specific filters to identify:

- publications from key countries: the country name was combined with the schizophrenia synonyms search strategy
- relevant papers on the negative symptoms of schizophrenia: the term 'negative symptoms' and its synonyms were added as a filter
- publications concerning QoL: terms including 'health 'quality of life' and scale names (for example, 'EQ5D' or the European Quality of Life Scale [EuroQOL]) were added as a filter (this search was conducted only in MEDLINE via PubMed)
- publications concerning burden of schizophrenia: filters including 'stigmatization', 'discrimination', 'costs' and 'burden of disease' were used (this search was conducted in all databases).

In addition to a general search of publicly available databases, a search was conducted locally in each of the participating countries to include publications in local languages. The searched sources of data were: the local HTA agency databases, local patients registries, national medical journals, databases of national health services, national/central statistical office, national psychiatric association and other relevant sources (e.g. PhD thesis).

The search consisted of publications from 1995 to 2012 (primary studies, reviews and systematic reviews) on the QoL, stigmatization and discrimination of patients with schizophrenia (F20 in the International Classification of Diseases − Version 10 [ICD-10]). All publications that included QoL results were analyzed in relation to assessment of negative symptoms.

RESULTS
Quality of life

Out of an initial search of 2882 abstracts, 1295 were excluded based on duplication or preliminary screening of titles and a further 1550 publications were excluded during screening of the abstracts (1510) or full texts (40). The remaining thirty-seven primary publications from the seven CEE countries were included in the analysis (Figure 1; a PRISMA flowchart is provided in the appendix).
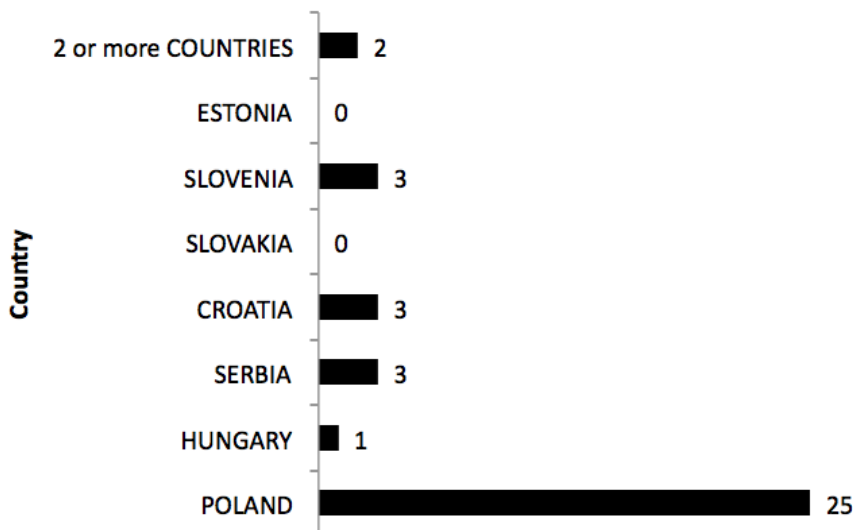

Figure 1.
Number of quality of life publications per country

Thirty-five of the studies were based in one country only and two were multinational European studies: StoRMi [12] (involved 22 countries including Croatia, Estonia, Poland, Slovakia and Slovenia) and EDEN [43] (based on five countries including Poland and Slovakia). A detailed list of all studies is presented in Table 1.

Table 1.
List of studies included in the analysis

Publication	Country	Instrument(s)	Number of time-points of QoL measurement*	Group evaluated**
Adamowski et al. 2009 [1]	Poland	Specific (MAN-SA)	3	Patients (F20-F29): inpatients vs day-care ward
Cechnicki et al. 2007 [5]	Poland	Specific (QoLI)	1	Patients (F20)
Chądzyńska et al. 2002 [7]	Poland	Specific (Mercier and Tempier Scale)	1	Patients vs family members
Chądzyńska et al. 2003 [8]	Poland	Specific (Mercier and Tempier Scale)	1	Patients vs family members
Czernikiewicz & Górecka 2003 [10]	Poland	Specific (QLS, SQLS)	1	Patients (F20)
Czernikiewicz et al. 2005 [11]	Poland	Specific (QLS)	1	Patients (F20)
De Marinis et al. 2007 [12]	22 countries (including Croatia, Estonia, Poland, Slovakia, Slovenia)	Generic (SF-36)	3	Patients (F20 or other psychotic disorder): conventional oral antipsychotic vs conventional depot antipsychotic before switching to long acting risperidone
Dernovsek et al. 2001 [13]	Slovenia	Specific + Generic (QLS, EQ-5D)	1	Patients (F20)
Główczak et al. 1997 [14]	Poland	Specific (Mercier and Tempier Scale)	1	Patients (F20)
Golubovic et al. 2010 [15]	Serbia	Specific (QLS)	8	Patients (F20 or schizoaffective disorders) treated with: atypical antipsychotics vs classical antipsychotics
Górecka & Czernikiewicz 2004 [16]	Poland	Specific (QLS)	1	Patients (F20)

Publication	Country	Instrument(s)	Number of timepoints of QoL measurement*	Group evaluated**
Górna et al. 2005 [17]	Poland	**Specific + Generic (SFS, WHOQOL-BREF)**	2	Patients (F20) vs healthy subjects
Górna et al. 2007 [19]	Poland	**Specific + Generic (SFS, WHOQOL-BREF)**	1	Patients (F20): with depression vs without depression
Górna et al. 2008 [18]	Poland	**Specific + Generic (SFS, WHOQOL-BREF)**	3	Patients (F20)
Hanuszkiewicz et al. 2007 [20]	Poland	**Specific (LQoLP)**	1	Patients (F20)
Jaracz et al. 2008 [22]	Poland	**Specific (SFS)**	3	Patients (F20)
Jarema et al. 1995 [25]	Poland	Generic (SF-36)	2	Patients (F20 or depression): inpatients vs day-hospital vs rehabilitation unit
Jarema et al. 1997 [24]		Generic (SF-36)	1	Patients (F20): inpatients vs patients from day-hospital vs patients from day-care centre
Jarema & Konieczyńska 2000 [23]	Poland	Generic (SF-36)	2	Patients (F20) (men vs women)
Jarema et al. 2002 [26]	Poland	Generic (SF-36)	2	Patients (F20) (men vs women)
Jukić et al. 2003 [27]	Croatia	**Specific (QLS)**	1	Patients (F20) treated with: conventional antipsychotics vs novel antipsychotics
Kasperek et al. 2002 [28]	Poland	**Specific (QoLQ)**	2	Patients (F20) from: social skills training group vs psycho-education group
Konarzewska et al. 2012 [29]	Poland	**Specific (QLS)**	1	Patients (F20 vs F20 addicted to alcohol)
Konieczyńska et al. 1997 [30]	Poland	Generic (SF-36)	3	Patients (F20)
Margetić et al. 2011 [31]	Croatia	Generic (Q-LES-Q-SF)	1	Patients (F20) vs relatives (key caregivers) vs healthy people

Publication	Country	Instrument(s)	Number of timepoints of QoL measurement*	Group evaluated**
Mihajlović et al. 2011 [35]	Serbia	Specific + Generic (SFS, SWLS, WHO-QOL-BREF)	1	Patients (F20) treated with: haloperidol depot vs risperidone long-acting
Opalić & Femić 2008 [37]	Serbia	Specific (combination of LQoLP and MANSA)	1	Patients (F20) vs healthy controls
Pąchalska et al. 2001 [38]	Poland	Specific (QLS)	1	Patients (F20) vs patients incurred a closed-head injury
Pentek et al. 2012 [45]	Hungary	Generic (EQ-5D)	1	Patients (F20) vs general population
Pesek et al. 2010 [41]	Slovenia	Generic (WHO-QOL- BREF)	1	Patients (F20)
Pesek et al. 2011 [40]	Slovenia	Generic (WHO-QOL- BREF)	1	Patients (F20)
Popławska et al. 2004 [42]	Poland	Specific (IMHC 2000)	2	Patients (F20 or depression) treated with: pharmacology and psychoeducation vs pharmacology
Priebe et al. 2011 [43]	5 countries (including Poland and Slovakia)	Specific (MANSA)	4	Patients (F20-F29, F30-F39, F40-F49)
Ružić et al. 2008 [45]	Croatia	Generic (Q-LES-Q)	1	Patients (F20-F29) who committed the crime of murder or attempted murder in state of insanity
Spiridonow et al. 1998 [46]	Poland	Specific (Mercier and Tempier Scale)	1	Patients (F20) vs healthy controls
Tomczak 2005 [50]	Poland	Generic (WHO-QOL- BREF)	1	Patients (F20) vs healthy controls
Tomczak 2006 [49]	Poland	Generic (WHO-QOL- BREF)	1	Patients (F20) vs healthy controls

*QoL could be evaluated once (at a specific time) or two or more assessments of QoL were carried out in different time period

**F20 = Schizophrenia (according to ICD-10)

We analyzed publications in terms of the number of estimates of QoL (time points), populations in which QoL was assessed and instruments used to evaluate QoL.

Four types of study design were observed, relating to study time-length and relationship factors (Figure 2). In the simplest approach the QoL of the analyzed group was evaluated once (at a specific time-point). In a more complex approach, two or assessments of QoL carried out at baseline and other pre-specified time-points were compared. Other studies compared the QoL in two or more groups of individuals, either at one time-point or at two or more time-points. The percentage distribution of the various types of studies is presented in Figure 2.
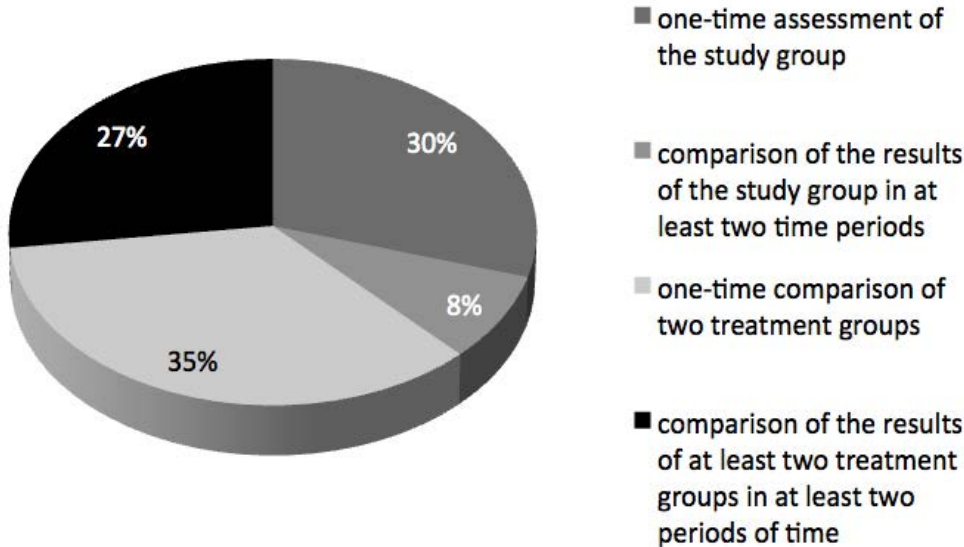

Figure 2. Distribution of studies according to design

The evaluation of patients' QoL was carried out most often by themselves (self-evaluation). However, in some studies, the assessment was made by healthcare professionals (doctors, nurses), caregivers or relatives. In 46% of the studies, QoL of other groups was also assessed, such as patients with mental disorders other than schizophrenia, caregivers of patients with schizophrenia, healthy people (trial sample) or a sample of age- and country-matched population (Figure 3).
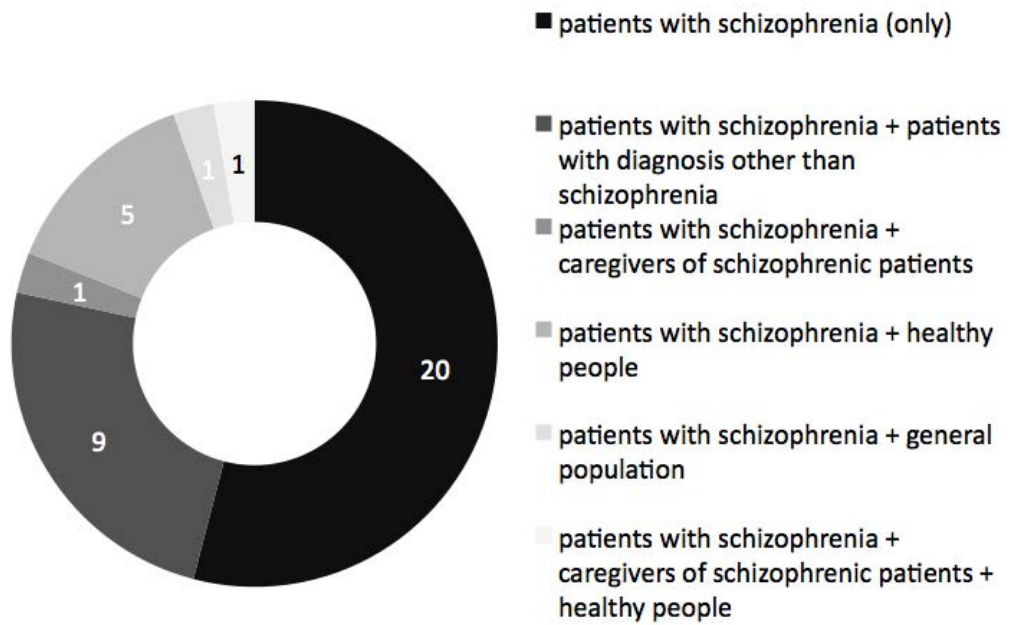
- patients with schizophrenia (only)
- patients with schizophrenia + patients with diagnosis other than schizophrenia
- patients with schizophrenia + caregivers of schizophrenic patients
- patients with schizophrenia + healthy people
- patients with schizophrenia + general population
- patients with schizophrenia + caregivers of schizophrenic patients + healthy people

Figure 3. Distribution of 37 studies by evaluated group

Schizophrenia was found to greatly affect the QoL of patients and had a significant negative impact on the QoL of caregivers. Both general QoL questionnaires and those specific for schizophrenia were reported. However, only a few instruments addressed the impact of negative symptoms on QoL (Figure 4).

Questionnaires not specific for schizophrenia were as follows (a detailed list of studies and instruments are presented in Table 1):

- EQ-5D: includes domains such as Mobility, Self-Care, Usual Activities, Pain/Discomfort And Anxiety/Depression
- Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (QLESQ-SF): measures satisfaction with domains such as physical health, mood, work and household activities on a 5-point scale
- 7-point Satisfaction with Life Scale (SWLS)
- Short Form-36 (SF-36) questionnaire: includes domains such as Vitality, Physical Functioning, Bodily Pain, General Health Perceptions, Physical Role Functioning, Emotional Role Functioning, Social Role Functioning and Mental Health
- World Health Organization Quality of Life Instrument – BREF (WHOQOL-BREF): includes domains for Overall QoL and General Health, Physical Health, Psychological Status, Social Relationships and Environment
- Quality of Life Questionnaire: includes domains for General Well-Being, Interpersonal Relations, Organizational Activity, Occupational Activity, and Leisure and Recreational Activity.

The disease-specific questionnaires used in assessment of QoL of patients with schizophrenia were as follows (a detailed list of studies and instruments are presented in Table 1):

- Lancashire Quality of Life Profile (LQoLP): an interviewer-administered instrument for patients with chronic mental illness
- Manchester Short Assessment of Quality of Life (MANSA): a questionnaire for patients with severe mental illness (includes some questions about satisfaction with leisure activities and the quality of social relationships based on a 7-point satisfaction scale)
- Quality of Life Interview (QoLI): an instrument dedicated to patients with mental illness
- Heinrichs Quality of Life Scale (QLS): schizophrenia-specific QoL instrument featuring a 21-item scale
- Schizophrenia Quality of Life Scale (SQLS): a brief self-report measure
- Social Functioning Scale (SFS): an instrument developed and validated on outpatients and conducted as a verbal interview.
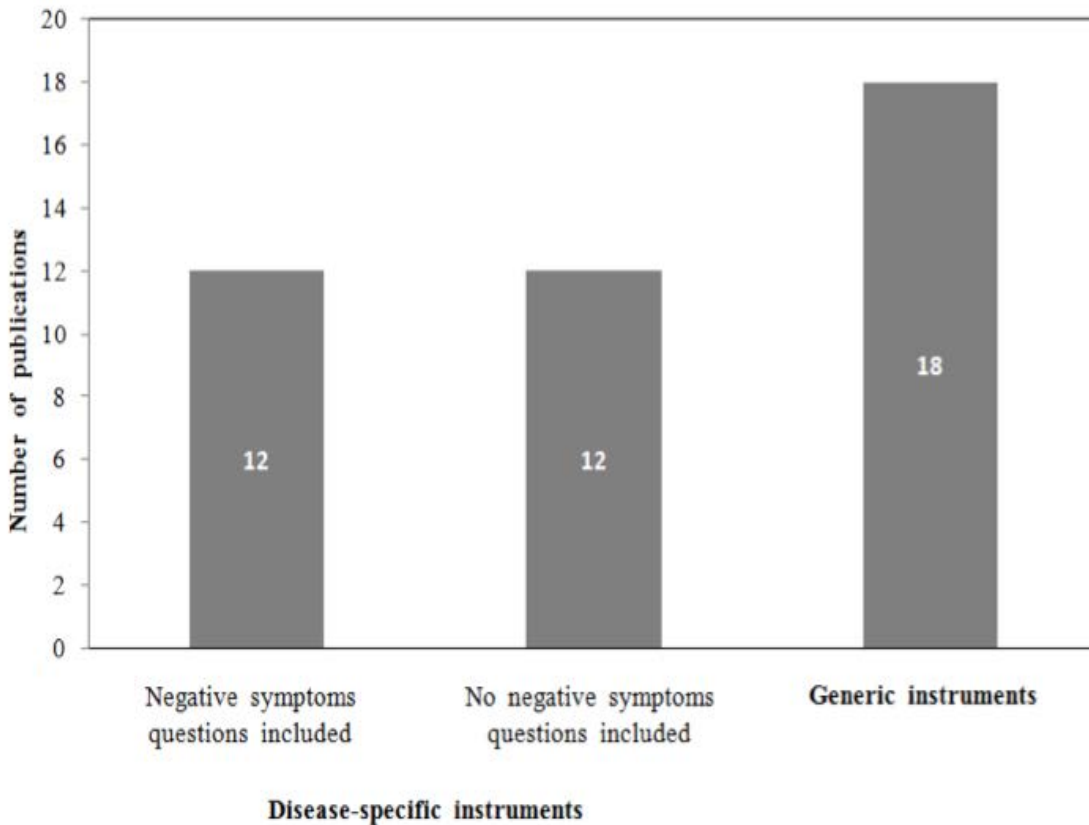

Figure 4. Number of studies with different types of questionnaires

Three other questionnaires less commonly presented in publications were also identified: the Liebermans' Quality of Life Questionnaire (QLQ), Mercier and Temp- ier Scale and IMHC 2000 (see Table 1). Only a few of the disease-specific QoL instruments measured dimensions relating to negative symptoms, as listed below:

- Lancashire Quality of Life Profile (LQoLP): an extensive interviewer-administered instrument for patients with chronic mental illness including schizophrenia, offering objective QoL indicators and subjective QoL estimates. in addition, the LQoLP assesses positive and negative affect, positive and negative self-esteem and global well-being
- Heinrichs Quality of Life Scale (QLS): a 21-item scale for patients with schizophrenia based on a semi-structured interview designed to assess deficit symptoms over the preceding 4 weeks. The items are grouped into categories: Intrapsychic Foundations, Instrumental Role and Common Objects and Activities
- Schizophrenia Quality of Life Scale (SQLS): a 30-item self-report questionnaire designed for patients with schizophrenia, consisting of three scales (Psychosocial, Motivation and energy, and Symptoms and side-effects)
- Social Functioning Scale (SFS): a 79-item questionnaire that can either be completed by the patient or interviewer and covers Social engagement, Interpersonal communication, Activities of daily living, Recreation, Social activities, Competence at independent living and Occupation/employment.

The literature confirmed that schizophrenia greatly affects quality of life of caregivers. Three publications demonstrated that the QoL of patients with schizophrenia and their caregivers is similar [7,8,31].

According to the literature, QoL significantly improves after a hospital stay, when compared with QoL at the time of admission [30,42]. However, there was no improvement in QoL for additional hospitalization after the initial hospital stay [13,17,28].

Stigmatization and discrimination

In addition to a lower QoL, patients with schizophrenia often experienced stigmatization and discrimination, although definitions of the two differed widely among the publications. Negative attitudes towards people with schizophrenia were also found to be prevalent in the CEE countries.

According to both international and country-specific publications, stigma related to schizophrenia can lead to rejection, discrimination, distress, social isolation, unemployment, homelessness, alcohol and drug abuse, and criminalization, factors which reduce the likelihood of clinical improvement and social reintegration [32,44,51]. As a consequence, stigmatization can also lead to poor attitudes towards physical health care, which is associated with higher mortality rates in patients with schizophrenia [52]. Those patients are often treated poorly with regards to their right to work, personal dignity, right to receive legal justice and equal access to medical treatment [6].

Stigmatization, together with other socioeconomic factors, is a key barrier to employment for patients with schizophrenia [33]. The number of professionally active or studying patients decreases by approxi-

mately one-half after initial hospitalization and the majority of patients receive a disability pension, indicating that vocational situation worsens in patients with schizophrenia during the first few years after hospitalization [22].

According to studies that cover populations from more than one country, the level of discrimination against patients with schizophrenia in European countries (including the seven selected CEE countries) was similar. In a multinational study [3], 42% of examined patients reported moderate or high levels of self-stigma (i.e. a personal response to perceived mental illness stigma) and 69% reported moderate-to-high levels of perceived discrimination. The majority of patients felt that the public hold negative attitudes towards mental health service users.

In a Polish study [4], the most common forms of discrimination experienced by patients were listed as: the feeling of being rejected by other people (87%), breaking off personal contact (50%), a negative public image of a mentally ill person in the media (38%), and problems in the area of employment (31%).

The burden of care on families with one or more family member with schizophrenia is very high [33]. Stigmatization and discrimination are key contributors to this burden in both patients with schizophrenia and their caregivers [9,47].
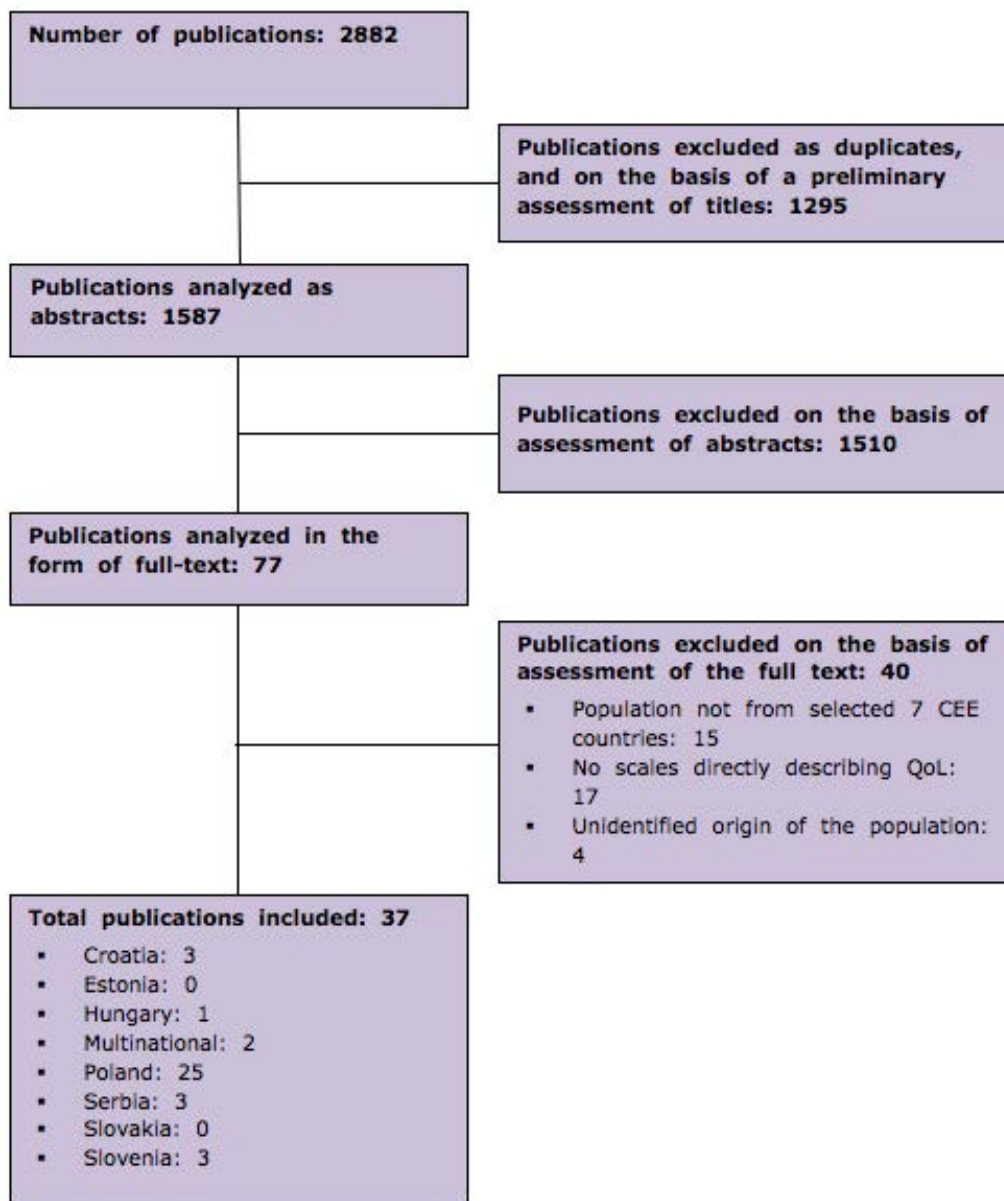
DISCUSSION

A wide variety of QoL publications were identified in this study. In the 37 articles analysed, 15 instruments had been used to assess the impact of schizophrenia on QoL (5 generic and 10 specific to schizophrenia or mental health disorders). Among the general scales, the World Health Organization of Life Instrument BREF (WHOQOL-BREF) (in eight studies) and SF-36 (in six studies) were most frequently used, whilst among schizophrenia-specific scales, QoL was evaluated most often by the Quality of Life Scale (QLS, Heinrichs, in eight studies) and Social Functioning Scale (SFS, Birchwood, in five studies).

A number of aspects of QoL have been investigated and reported in the literature, including:

- factors affecting the QoL of patients with schizophrenia, caregivers or healthy subjects
- factors influencing treatment choice
- correlations with mental condition, psychopathological symptoms or patient functioning.

The studies also differ significantly depending on their purpose, which influences the design, methodology and overall results. Aims of the studies reported are varied but typically include:

- identification of the factors affecting QoL
- comparison of the QoL of patients with schizophrenia versus other patients, caregivers or healthy subjects
- examination of whether QoL is correlated with mental condition, psychopathological symptoms, or patient everyday functioning
- evaluation of the influence of drugs or course of treatment on QoL

Number of publications: 2882

Publications excluded as duplicates, and on the basis of a preliminary assessment of titles: 1295

Publications analyzed as abstracts: 1587

Publications excluded on the basis of assessment of abstracts: 1510

Publications analyzed in the form of full-text: 77

Publications excluded on the basis of assessment of the full text: 40
- Population not from selected 7 CEE countries: 15
- No scales directly describing QoL: 17
- Unidentified origin of the population: 4

Total publications included: 37
- Croatia: 3
- Estonia: 0
- Hungary: 1
- Multinational: 2
- Poland: 25
- Serbia: 3
- Slovakia: 0
- Slovenia: 3

PRISMA Flow Diagram: Quality of life studies (MEDLINE via PubMed)

Due to the variety of data observed in the studies, it is not possible to make direct comparisons or pool data for analysis. However, it was consistently reported that patients with schizophrenia report worse QoL compared with the general population and that there is a significant negative impact on the QoL of caregivers, such that their QoL is similar to patients with schizophrenia. Furthermore, the QoL of patients with schizophrenia, after inpatient treatment, is significantly better than at time of admission to the hospital.

CONCLUSION

There has been extensive research into the QoL of patients with schizophrenia and it has been consistently reported that schizophrenia significantly reduces the QoL of patients and their caregivers. In CEE countries, patients with schizophrenia experience stigmatization and discrimination, and an associated impact on their QoL and that of their caregivers. There are a number of tools available to assess QoL, but many of these do not specifically measure the negative symptoms of schizophrenia, which are known to negatively impact QoL.

Further research is needed to consolidate the existing body of literature to better understand the drivers of impaired QoL in patients with schizophrenia. In particular, future research could investigate negative symptoms, and how best the burden of illness can be reduced for both patients and caregivers.

Conflict of Interest

The authors have no conflicts of interest or financial disclosures to declare, however those who are also employees of Roche had support from Roche for their travel to the project meeting, as part of their responsibilities in the project.

Appendix

PRISMA Flow Diagram: Quality of life studies (MEDLINE via PubMed)

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Adverse skin reactions induced by antibiotics: clinical and economic evaluation - an eleven - year retrospective study

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ABSTRACT

Background: The aim of the study was to clinically evaluate, as well as analyse the direct costs of treating patients hospitalised due to adverse skin reactions related to antibiotics use at the Department of Dermatology of the Military Institute of Medicine, Ministry of Defence in Warsaw, during the years 2002-2012.

Method: The study was carried out in a retrospective way on a group of 164 adult patients due to adverse skin drug reactions. The analysis was based on data from patient medical records and medical orders.

Results: The most common drugs that caused adverse skin reactions in the examined population between the 2002-2012 were antibiotics with 75 cases, in 39 cases non-steroidal anti-inflammatory drugs (NSAIDs), and in the case of paracetamol 6, in 44 cases other drugs. Amoxicillin was the most common described antibiotic (25.33%). It has been estimated that patient hospitalisation at the Department of Dermatology for adverse skin drug reaction generated costs averaging to an amount of 2784 PLN (662 EUR) per patient.

Conclusions: The most frequent form of drug-induced skin reactions, diagnosed in the study group, was the maculopapular rash - (52%). The most common drugs that caused skin lesions were antibiotics. Amoxicillin was the most common described antibiotic (25.33%). The largest average cost have been incurred due to clindamycin - 1059.91 PLN (252 EUR) and to amoxicillin - 1029.56 PLN (245 EUR). Following our analysis, treatment of skin adverse drug effects caused by antibiotics generates significant costs.

INTRODUCTION

Antibiotic-associated adverse events lead to hospitalization, and allergic reactions are the most common of these events [1]. Following the definition of the Directive 2010/84/EU of the European Parliament and the European Council on 15th of December 2010; adverse drug reactions (ADR) are noxious and unintended effects resulting not only from the autho-

rised use of a medicinal product at normal doses, but also from medication errors and uses outside of the clinical guidelines, including the misuse and abuse of the medicinal product. The incidence of adverse drug reactions is estimated at approximately 5 – 10% of all hospitalised patients [2], out of which, 30% include adverse skin reactions (ASR) [3].

The results of these studies are of significance, can support decisions, which implement new and/or modify actual therapeutic standards. Reviewing of international publications, a growing interest in the economic component of ADRs treatment is observed in many countries [4,5]. In Poland, some clinical pharmacology centres evaluate the efficacy and costs of therapies in broad pharmacoeconomic evaluation programmes [6,7]. However during literature searches, no analyses have been identified, dedicated to adverse drug reactions, associated with skin reactions and costs of their treatment under Polish conditions. Our study attempted to estimate the costs of therapy in cases of drug-induced skin reactions under Polish conditions.

OBJECTIVE

The aim of the analysis was to clinically evaluate, as well as analyse the direct costs of treating patients hospitalised due to adverse skin reactions related to antibiotics use at the Department of Dermatology of the Military Institute of Medicine, Ministry of Defence in Warsaw, during the years 2002-2012.

METHODOLOGY

It was a retrospective study, carried out in a group of 164 adult patients, hospitalised in Department of Dermatology, Military Institute of Medicine, during the years of 2002-2012 due to drug-induced skin reactions, including 57 men and 107 women.

The mean age of the patients was 53.7 years. All the included patients were hospitalized due to adverse, drug-induced skin reactions, regardless of administered therapy.

ANALYSIS

Direct costs of treatment of adverse skin drug reactions were evaluated. The analysis was based on data from the patients' medical records and from their medical order cards. All those documents provided information on used resources, such as diagnostic tests, specialist consultations, medicinal products used for treatment and the length hospitalisation. Based on the identified resources, used in applied treatment, the costs of therapy were estimated. Due to the lack of specific data on drug costs and diagnostic tests in 2002-2010, the analysis was based on the valuation procedures of 2012. The costs of pharmacotherapy were calculated on the basis of the wholesale prices for drugs, fixed for the year 2012. The unit costs of laboratory tests, consultations and hospitalisation days were taken from the hospital's internal pricelist, prepared by the Department of Medical Service Sales and Analysis of the Military Institute of Medicine for 2012.

RESULTS

The most frequent forms of drug-induced skin reactions, diagnosed in the study group, included maculopapular rashes - (52%), multiform erythema – 25%, nodal erythema – 15% and Stevens-Johnson Syndrome (SJS) – 4%. Other causes, which accounted for 4% of cases, included contact dermatitis and allergic urticaria.

The most common drugs that caused adverse skin reactions in the analysed population were antibiotics with 75 cases, in 39 cases non-steroidal anti-inflammatory drugs (NSAIDs), and in the case of paracetamol 6, in 44 cases other drugs. Amoxicillin was

the most common described antibiotic (25.33%). Cutaneous drug reactions appeared on average on day 6 (6.35) of the application of the drug. The average age of our patients was 48 years of age (47.9). Within the nonsteroidal anti-inflammatory drugs the most frequently reported changes were with the use of ibuprofen, after an average of 6 days after the administered treatment. The average age of patients was 55 years. The hospitalization for this reason, averaged 5 days (4.97).
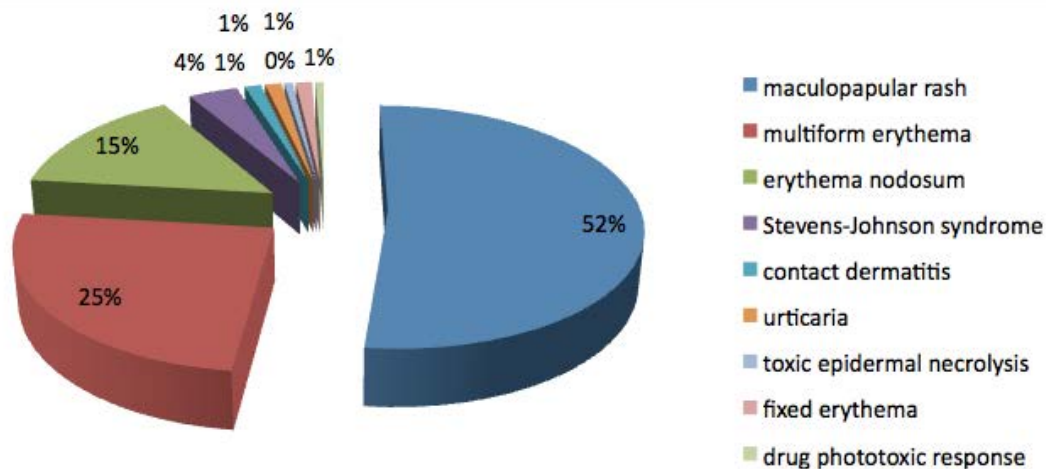

Figure 1.
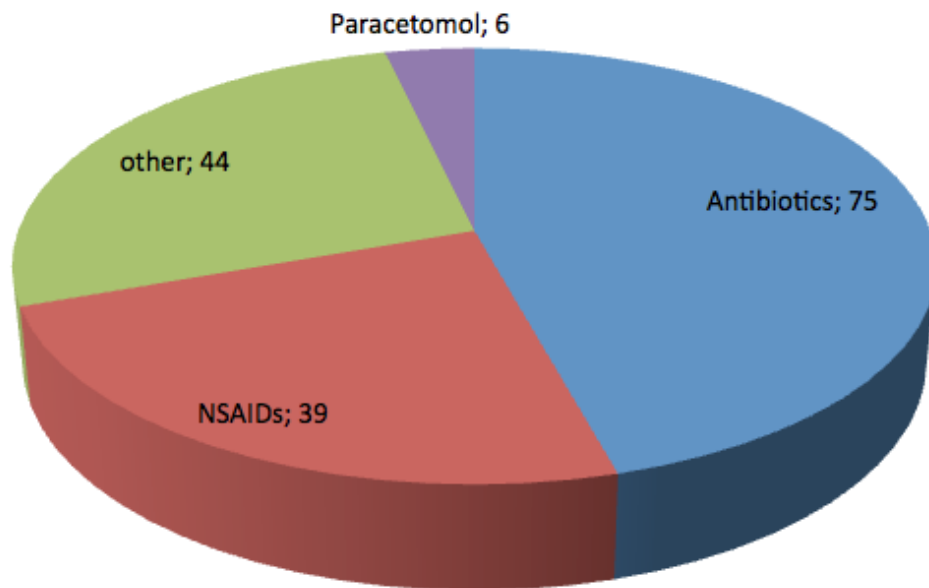*The most common skin adverse drug reactions*

Figure 2.
The most common drugs caused skin adverse drug reactions

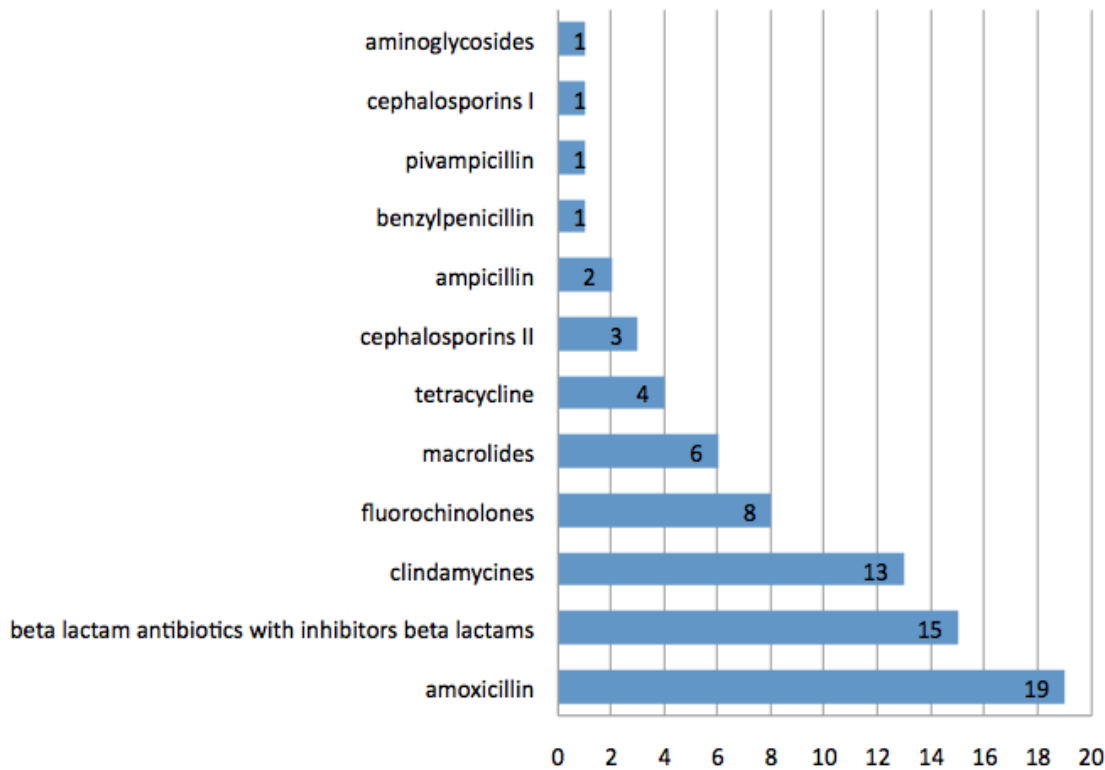The detailed division of antibiotics is shown on the graph below.

Figure 3. Detailed division of antibiotics

The 23 cases were beta-lactam antibiotics, of which there were 19 cases of skin reactions after amoxicillin, two cases - ampicillin, 1 - pivampicillin, 1 - benzylpenicillin, 15 cases - beta-lactams in conjuction with inhibitors of beta-lactamases, 3 - second-generation cephalosporin and 1 case of first-generation cephalosporins. There were 32 other instances from non-beta lactam antiobiotics. Within this one case of skin reactions was due to an aminoglycoside, 8 cases were caused by fluoroquinolones, 13 cases were due to clindamycin, macrolides in 6 cases and finally 4 cases were due to tetracyclines.

The total costs of hospitalisation in the analysed period, incurred by the Military Institute of Medicine and calculated according to the internal pricelist for the year 2012 for the analysed study group amounted to 456 624,64 PLN (108720 EUR). The average hospitalisation costs per patient was 2784 PLN (662 EUR). Analysing the direct medical costs from the medical provider's perspective, the total costs of performed diagnostic and laboratory tests (including haematology, biochemistry, urine tests, lipid profile, x-ray examination), incurred by the hospital, were calculated, amounting to 9873,36PLN (2350 EUR). The average examination and test costs per patient were 60,22 PLN (14 EUR). The total cost of pharmacotherapy was 14753,99 PLN (3512 EUR) and the average cost of pharmacotherapy per one patient was 89,96 PLN (21 EUR). The direct costs of cutaneous drug reactions induced by antibiotics amounted to − 214 838.75 PLN (51 152 EUR), NSAIDs − 108 543 PLN (25 843 EUR).

The largest average cost was incurred due to clindamycin - 1059.91PLN (252 EUR), amoxicillin - 1029.56 PLN (245 EUR), beta-lactam antibiotics with beta-lactamase inhibitor generated a cost amounting to 613.57 PLN 146 EUR) and macrolide 261.63 PLN (62 EUR).
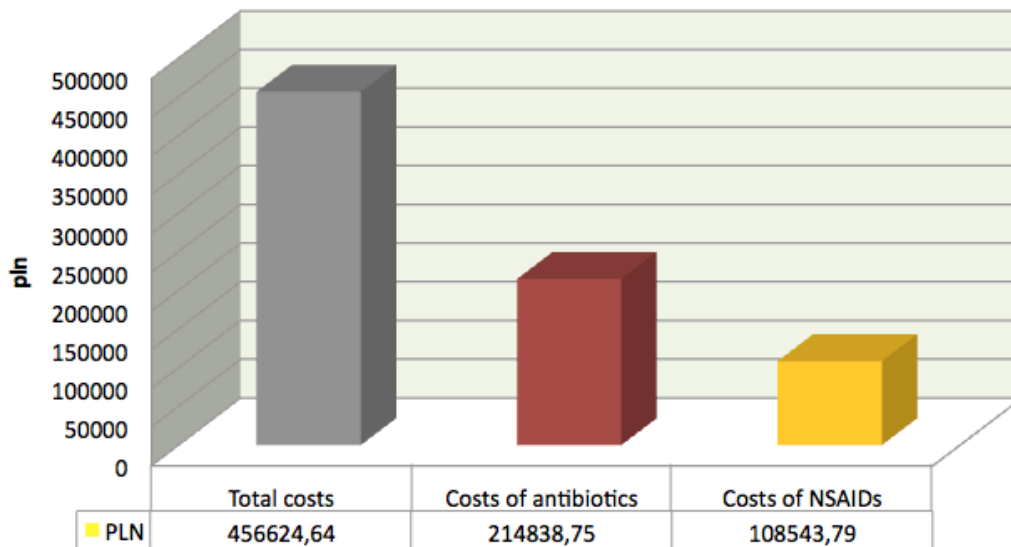
	Total costs	Costs of antibiotics	Costs of NSAIDs
PLN	456624,64	214838,75	108543,79

Figure 4.
Direct costs of skin adverse drug reactions

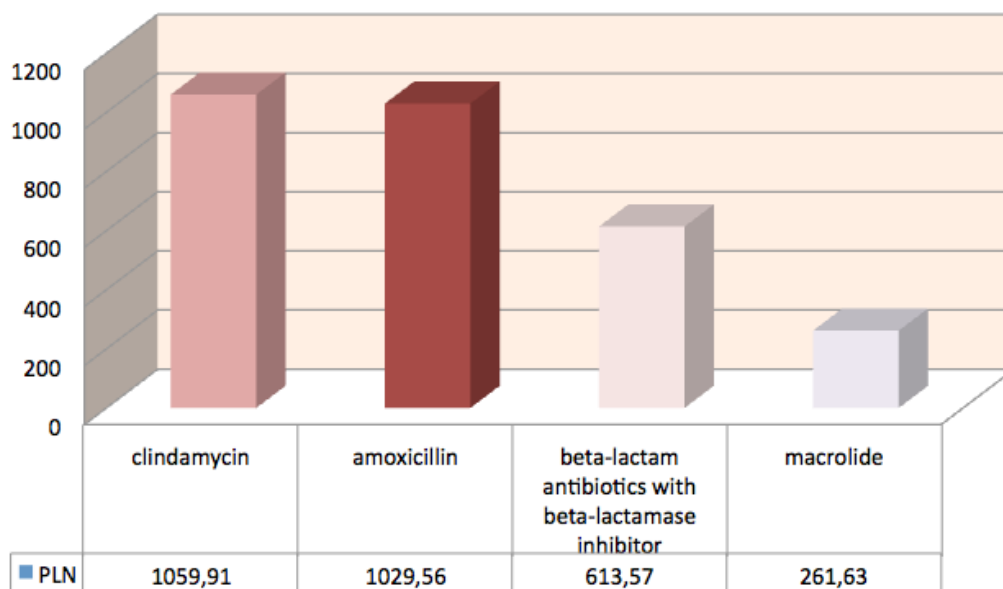|	clindamycin	amoxicillin	beta-lactam antibiotics with beta-lactamase inhibitor	macrolide
PLN	1059,91	1029,56	613,57	261,63

Figure 5.
The average costs of skin adverse drug reactions caused by antibiotics

DISCUSSION

In the era of liberal use of antibiotics on the market, the issue of drug-induced reactions is at an all time high. Patients with such changes will require treatment in the hospital environment. The diagnostics and therapy of the hospitalised patients require evaluations of these costs. Accordingly, we carried out an analysis of direct medical costs, incurred by the medical service provider in a group of 164 patients, hospitalised at the Department of Dermatology of the Military Institute of Medicine for antibiotics-induce adverse skin reactions in an eleven-year retrospective study.

The most common drugs that were the cause of cutaneous drug reactions in the analyzed study were still beta-lactam antibiotics and NSAIDs [8-11].

We did a clinical evaluation of drug-induced adverse skin reactions and an evaluation of the costs of their treatment.

Our study of the clinical data analysis can be compared with epidemiological analysis conducted in 2008 in the hospital of Pomeranian area. The patients with cutaneous drug reactions (386) were hospitalized from January 1996 to December 2006. The analyzed group was 4.25% of all hospital admissions over the 11 analyzed years. The Drugs that most frequently triggered cutaneous drug reactions (37.6%) were non-steroidal anti-inflammatory drugs. Amino-penicillin antibiotics, especially amoxicillin resulted to be the cause of skin reactions in 25.8% of cases. The most common figures that were reported: erythematous rash and maculopapular - rash (42%), acute urticaria together with Quincke edema (39.1%) and contact dermatitis (8%). Also diagnosed was erythema multiforme (7.3%). In addition, two instances of severe: toxic epidermal necrolysis and Stevens-Johnson syndrome (TEN and SJS). The maculopapular rash were usually caused by beta-lactam antibiotics with a beta-lactamase inhibitor (48.6%). Amoxicillin (21.4%) and carbamazepine (17.8%) were the cause of the reported cases of erythema multiforme [12].

Other examples of clinical analysis are the described below and performed in Thailand, India and Singapore.

In Thailand (Siriraj Hospital, Bangkok, Thailand) in the period from January 2002 to February 2012, in a population of elderly patients a retrospective analysis of cutaneous drug reactions was carried out. The results were similar and allowed for a comparison. The study included 400 medical records of history in patients above 60 years of age. Women accounted for 53% of all patients. Mean age was 73.6 years (62-96 years). The most common drug reactions included skin rash maculo - papular, which accounted for 65%. Most often they were caused by antibiotics (42.8%) and non-steroidal anti-inflammatory drugs (9,5%) in all the diseases described in 16.5% of patients, severe cutaneous drug reactions [13].

In another prospective study conducted in a large hospital in India in IGGMC and H analysing patients' data about cutaneous drug reaction we observed similarity of epidemiology in relation to our analysis. The analysis was conducted from 1st June 2005 to 31 May 2009. The group consisted of 2,693 patients, over 872 patients (33.4%) had cutaneous drug reactions, including 560 men and 312 women. The most common medicines, which caused 55.5% were antibiotics, glicocorticoids - 18.56% and NSAIDs - 12.61%. The most often observed ASR was maculopapular rash 37.73%, 17.2% fixed erythema and urticaria 14.56%. Attention needs to be drawn to the use of antibiotics and NSAIDs, because they accounted for at least one severe cutaneous drug reaction [14].

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) can be potentially life threatening.

Another study, performed in Singapore analysed data retrospectively for the period from January 2007 to December 2011. They analysed a total of 42 patients. The average age was 51.8 years (11-94 years). The gender distribution was equal (21). Most reported reactions occurred after exposure to antibiotics 50%, allopurinol - 14.3%, NSAID - 9.5%. SJS was observed most frequently (54.8%). Changes in the

skin after exposure to antibiotics was observed after an average of nine days. The symptoms of SJS were observed on average on the 22nd day. The band overlap SJS-TEN lesions were observed after only 5 days. In 38.1% of patients with systemic complications occurred. The most common were hypertransaminesemia (37.5%), disorders of the gastrointestinal tract and diarrhea (25%). In one case (overlap syndrome SJS-TEN complicated by pneumonia) lead to death [15].

In relation to the cost analysis we performed we were unable to obtain information about other direct costs of the treatment of cutaneous drug reactions caused by antibiotics in the available literature. A lot of reports dealt in terms of the cost of treatment of systemic side effects, but not the cutaenous.

Our analysis estimated that hospitalization in the Department of Dermatology Military Institute of Medicine due to drug reactions accounted for an average amount of 2784.30 PLN (662 EUR, 921 USD). Because of the absence of other cost analysis regarding cutaneous drug reactions in the Polish literature in order to enable the comparison with other published international analysis the costs results have been converted to EUR and USD (1 EUR - 4.20 PLN, 1 USD- 3.02 PLN).

In May 2013, a study on the costs of the treatment of cutaneous drug reactions in hospitalized patients in Taiwan was published. The data was collected by the medical center Chung Gung Memorial Hospital in northern Taiwan. In the analyzed group from 2005 to 2008 there were observed 700 patients with cutaneous drug reactions, including 370 men and 330 women. In the control group there were 3365 patients without cutaneous drug reactions, including 1785 men and 1580 women. Their mean age was 49 years and 48 years for the control group,

the average length of hospital stay amounted to 18 days for cutaneous drug reactions, and 7 days for the control group. The most common reactions were skin maculopapular rash 89.3%, and Stevens - Johnson 3.3%. The most common drugs that caused these reported reactions were antibiotics (57%). Others included antiepileptic drugs (9.8%), antipyretics (9.7%). Medical costs were estimated at an average of 916 USD. Compared with the control group (cost medical 318 USD) the costs are 2.5 times higher. In estimating costs of treatment, of critical importance was the length of hospitalizations and severity of condition of patients [16].

In 2014, an interesting publication on a retrospective analysis of ADR in the period from 1 January 2008 to 31 December 2012 in China appeared. All cases have been reported to the ADR Center database. The following data was obtained from the medical records of patients with the ADR. All cases of ADR were divided into two groups depending on the severity of adverse drug reactions. Group A included cases that resolve after cessation of treatment, that did not require further hospital intervention. Serious drug reactions and complications associated with them (including: death or life-threatening conditions leading to permanent disability) were included into group B. The study included 2,739 cases of drug-induced adverse reactions. The mean age of the patients was 48.51 ± 19.84 years (1 day of life - 99 years). Women accounted for 52.28% of all patients, 47.72% were

men. Antibiotics were the most common cause of ADRs (34.9%), mainly levofloxacin (7%). Most reported cutaneous drug reactions (31.69%), systemic ADR (30.56%) and gastrointestinal disorders (17.71%). Mild to moderate reactions were respectively 59.47% and 39.03%, only in 1.5% reported severe ADR. Not all types of diseases were analyzed in terms of epidemiology and cost. The direct and indirect costs of hospitalization in ADR were divided into the above-mentioned group A and B. The costs in group A were 43604.66 EUR, average 1616.18 EUR in group B was much higher in terms of the average cost 34,724.80EUR, medium 846.85 EUR [17].

Another article presents an analysis of the incidence of adverse reactions with the medications and the costs of their treatment in a hospital in Taiwan. This is a prospective study conducted during the period from 1st January 2002 to 31st December 2004. The study enrolled 564 patients from 142,295 patients hospitalized for ADR. Men constituted the majority in the study - 56.4%, the average age of the patients was 66 years. The most common cause of ADR were by antibiotics (38.8%), analgesics 11% and 9.9% cardiac drugs. The most common were cutaneous drug reactions, which accounted for 52.5% of all ADR, the maculopapular rash accounted for 30.5%, 6.6% erythema of site administration. Hematologic drug reactions were 10.8%. In this study, the average cost of hospitalizations associated with ADR was US 3489. These being the total cost of all the ADR, including those patients with cardiovascular complications [18].

In the available literature there are a lot of articles on pharmacoeconomic analysis related to treatment of other skin diseases which may impact on the economic system of hospitals [19,20].

Thanks to such work, an analysis of the cost of the treatment can be carried out,

support the decision about the choice of the medication that is the best for the patient and at the same time assess the burden of the hospital budget.

There are a lot of evaluations of studies also in terms of the quality of life of patients, the effectiveness of the treatment, costs of disease entities [21-25].

However, each patient is a separate case, even the same disease may require a longer or shorter stay in the hospital, or cheaper or more expensive laboratory diagnostics. These costs shall be borne by the provider in such a situation.

Therefore, the analysis of costs is extremely important when planning the budget, when implementing new billing systems of medical services and improving already existing ones. Such type of studies can be extremely useful management tools for departments through to the main hospital authorities.

Unfortunately, we did not find similar publications related to the cost of the treatment of cutaneous drug reactions caused by antibiotics within the available literature, which made it difficult to compare our results with other Polish departments of dermatology.

CONCLUSIONS

The most frequent forms of drug-induced skin reactions, diagnosed in the study group, was the maculopapular rash (52%). The most common drugs that caused skin lesions were antibiotics. Amoxicillin was the most common described antibiotic (25.33%). The largest average cost have been incurred due to clindamycin - 1059.91 PLN (252 EUR) and to amoxicillin - 1029.56 PLN (245 EUR). Following our analysis, treatment of skin adverse drug effects caused by antibiotics generates significant costs.

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Assessment of the financial barriers in access to cancer pain treatment with opioids in Polish settings

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ABSTRACT

Effective pain management and pain prevention is one of the fundamental obligations of doctors. The need to improve the management of pain is widely recognized in public debate in Poland.

Background: Identification and assessment of financial barriers in access to opioids in pain treatment of cancer patients in Poland.

Material and Methods: The main area of investigations was availability of opioids and cost of treatment for patients. The principles, conditions and procedures for reimbursement of opioids were recognized and analyzed from cancer patients point of view. All reimbursement lists announced by MoH were taken into account as well as data concerning reimbursed drug consumption and NHF spending's.

Results: Polish cancer patients have access to subsequent reimbursed opioids: morphine, fentanyl, oxycodone, methadone, buprenorphine, tramadol, dihydrocodeine.

In the case of opioids limit groups are narrow and very precisely defined and very compartmentalized. In practical terms, almost all patients may have access to opioids with limit price without additional co-payment.

Expenditures on opioids reimbursement between 2012 and 2014 increased from PLN 178M to 231M. Consumption of opioids increased faster than reimbursement expenditures between 2012 and 2014 because growth of consumption between 2012 – 2013 and 2013-2014 accounted for 17,7% and 23,4% respectively. Significant price decrease of opioids leaded to decrease of average patients co-payment for pack of opioids from PLN 9,63 to PLN 6,10.

Conclusions: Financial barriers in access to cancer pain treatment with opioids in Poland seems to be very limited.

INTRODUCTION

Effective pain management and pain prevention is one of the fundamental obligations of doctors. The need to improve the management of pain is widely recognized by many stakeholders as a hot issue in public debate in Poland. The Standing Committee of the Supreme Medical Court addressed the

appeal to doctors and dentists to ensure the effective pain management to all patients. Improvement of pain management in cancer patients seems to be most important need. Information and education program called "Pain free cancer" ("Rak wolny od bólu") is conducted by Patients Organizations in cooperation with Ministry of Health. According to experts from Fight against Pain (NGO) one of the barriers in pain treatment is fear of opioids as a results of ignorance and of the rules of using this group of medicines [1]. Many patients feel fear to take opioids. They are afraid to become drug addicted or even to be suspected. One of the main concerns of physicians when prescribing opioids is that the daily doses used for pain relief may predispose patients to drug dependence [2-4]. In 1986 the World Health Organization (WHO) presented the analgesic ladder as a framework that physicians could use when developing treatment plans for cancer pain. If cancer pain occurs, there should be prompt oral administration of drugs in the following order: nonopioids (aspirin and paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain. To maintain freedom from pain, drugs should be given "by the clock", that is every 3-6 hours, rather than "on demand" In the case of cancer pain in children, WHO recommends a two step ladder [5-7].

BACKGROUND

Identification and assessment of financial barriers in access to opioids in pain treatment of cancer patients in Poland.

MATERIAL AND METHODS

The main area of investigations was availability of opioids and cost of treatment for patients. The principles, conditions and procedures for reimbursement of opioids were recognized and analyzed from cancer patients point of view. Time horizon for observation was limited to years 2012-2014 because current reimbursement regulations were introduced in 2011 [8]. All reimbursement lists announced by the minister responsible for health matters (MoH) [9] were taken into account as well as data concerning reimbursed drug consumption and National Health Found (NHF) spending's, published by the Drugs Management Department of National Health Found [10]. Opioids consumptions were converted to DDD (define daily dose) [11] because the purpose of the DDD system is to serve as a universal tool for drug utilization research in order to improve quality of drug use. DDD system allows to study over time trends in drug consumption without the complication of frequent changes in the reimbursement system.

RESULTS

Assessment of the principle for opioids reimbursement in Poland

The reimbursement principles are regulated by Act of 12 May 2011 on the reimbursement of medicinal products, special purpose dietary supplements and medical devices [8].
Polish cancer patients have access to subsequent reimbursed opioids: morphine, fentanyl, oxycodone, methadone, buprenorphine, tramadol, dihydrocodeine. Drugs reimbursement for polish patients may be specified in four categories: drugs available in the pharmacy on prescription, drugs used in a regimen programme (drug programme), drugs used in chemotherapy and drug used within the other guaranteed procedures. All reimbursed opioids are drugs available in the pharmacy on prescription and administrative restrictions are limited to minimum in comparison to the rest kinds of reimbursement.

Reimbursed opioids are available to patients free of charge or for a lump sum fee 3,20 (~ € 0,8), but NHF reimbursed drugs

costs only to the limit price. If price of drug is higher than the limit price, patient has to pay the difference.

The criteria to set limit groups are not defined precisely. According to Article 15.2 Act of reimbursement, a drug which has the same international name or different international names, but similar therapeutic effects and similar mechanism of action and qualifies for inclusion in a limit group has to meet the following criteria: the same in-

dications or assignments, in which they are reimbursed; similar efficacy. This definition in many cases effects in creation of jumbo limit group e.g. all statins, all ACE-Is. In the case of opioids limit groups are narrow and very precisely defined and very compartmentalized. This means in practical terms that almost all patients may have access to opioids with limit price without additional co-payment. It looks as a patients friendly application of law. Overview of limit groups is showed below in Table 1.

International name (INN)	Limit groups	Payment
Morphine	149.1, Opioid pain killers –morphine orally administered - prolonged release form.	free of charge
Morphine	149.2, Opioid pain killers –morphine oral administered - prolonged release form	free of charge
Morphine	149.3, Opioid pain killers –morphine orally administered - normal release form.	free of charge
Oxycodone	150.1, Opioid pain killers – oxycodone	lump sum fee
Dihydrocodeine	150.2 Opioid pain killers – dihydrocodeine	free of charge
Methadone	150.3, Opioid pain killers – methadone	lump sum fee
Oxycodone + Naloxone	150.4, Opioid pain killers – oxycodone in combinations	free of charge
Fentanyl	152.1, Opioid pain killers – buccal form	lump sum fee
Fentanyl	152.2, Opioid pain killers – nasal form	lump sum fee
Buprenorphine	152.3, Opioid pain killers – sublingual form	free of charge
Buprenorphine,	152.4, Opioid pain killers – transdermal form	free of charge
Fentanyl	152.4, Opioid pain killers – transdermal form	lump sum fee
Tramadol	153.1, Opioid pain killers - tramadol – rectal form	free of charge
Tramadol	153.2, Opioid pain killers - tramadol – parenteral form	free of charge
Tramadol	153.3, Opioid pain killers - tramadol – oral form	free of charge
Tramadol + Paracetamol	153.3, Opioid pain killers - tramadol – oral form	free of charge
Tramadol	153.4, Opioid pain killers - tramadol – oral form – liquid	free of charge

Table 1. Reimbursement limit groups for opioids used in the treatment of cancer pain

Expenditures on opioids reimbursement were important and growing part of National Health Found reimbursement budget. Between 2012 and 2014 reimbursement expenditures on opioids increased from PLN 178M to 231M. Increase of reimbursement expenditures on opioid seems to have a constant trend, because the growth between 2012 – 2013 and 2013 – 2014 accounted for 15,2% and 12,7% respectively. Constant growing trend seems to be confirmed on monthly chart of expenditures (Figure 1).
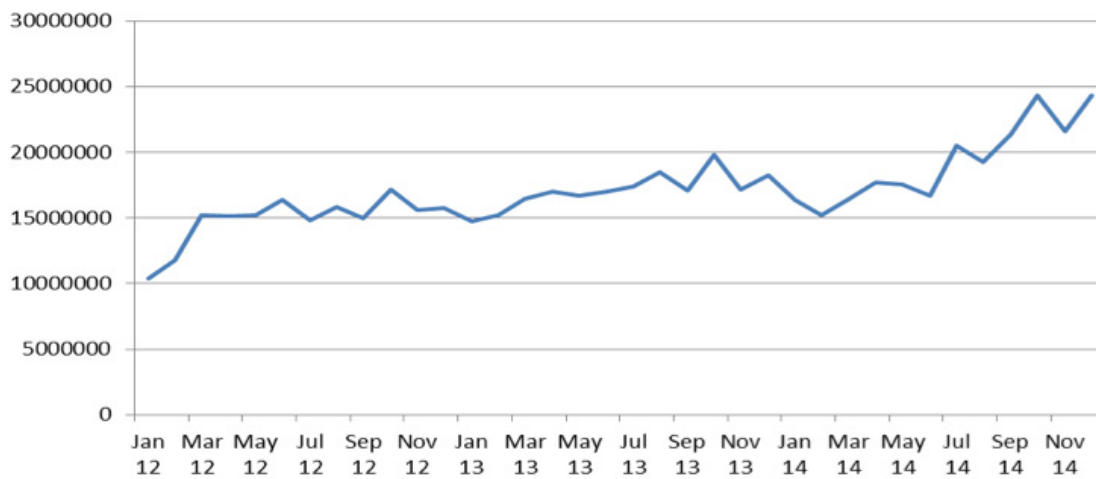

Figure 1. Monthly expenditures on opioids on NHF budget

This growing trend of opioid consumption is also confirmed by the growth expressed in DDD on monthly basis (Figure 2).
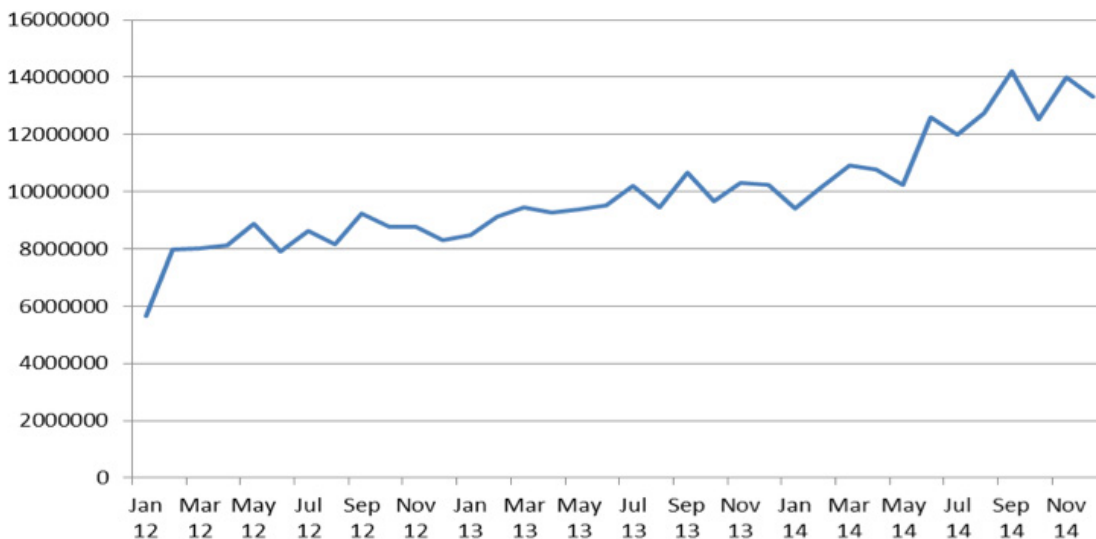

Figure 2. Opioids consumption in period 2012 – 2014 express in DDD

Consumption of opioids increased faster than reimbursement expenditures between 2012 and 2014 because growth of consumption between 2012 – 2013 and 2013-2014 accounted for 17,7% and 23,4% respectively when increase of expenditures accounted for only 15,2% and 12,2 % respectively (Table 2).

Table 2. Comparison of the growth of budget expenditures on opioids and growth of opioids utilization by patients

Year	2012	2013	2014
Number of DDD reimbursed by NHF	98 380 209	115 832 417	142 952 655
Growth		17,70%	23,40%
Costs of reimbursement for NHF budget (PLN)	178 154 144	205 310 655	231 398 054
Growth		15,20%	12,70%

This difference might be explained as a result of price decrease of opioids. During three years average price was decreased by 14,8% (Table 3).

Table 3. Results of comparison of prices decreases, limit price decreases and patients co-payment between 2012 and 2014

Period	2012	2013	2014	2012 - 2014
Average price decrease	-4,36%	-6,55%	-1,38%	-14,80%
Minimal price decrease	-0,72%	-0,66%	0,00%	-1,59%
Maximal price decrease	-32,07%	-19,57%	-17,11%	-64,31%
Average change of limit price	-0,20%	-8,86%	-0,51%	-9,62%
Minimal decrease of limit price	37,74%	-0,66%	0,00%	14,34%
Maximal decrease of limit price	-22,23%	-20,31%	-4,28%	-33,02%
Average change of patients co-payment	-11,00%	22,90%	-22,50%	-17,30%
Maximal increase of patients co-payment	159,10%	988,70%	283,80%	408,40%
Maximal decrease of patients co-payment	-100,0%	-45,30%	-100,0%	-100,0%

Significant price decrease of opioids leaded to decrease of average patients co-payment for pack of opioids from PLN 9,63 to PLN 6,10. (Table 4).

Table 4. Comparison of changes in patients co-payment for opioids pack between 2012 and 2014

	Beginning of 2012	Beginning of 2013	Beginning of 2014	End of 2014
Average patients co-payment (PLN)	9,63	6,9	8,2	6,1
Maximal patients co-payment (PLN)	103,14	30,6	74,36	29,8
Minimal patients co-payment (PLN)	0	0	0	0

CONCLUSIONS

Financial barriers in access to cancer pain treatment with opioids in Poland seems to be very limited, especially when compared to other drugs. Reimbursement limit groups for opioids are narrow and very precisely defined. Almost all patients may have access to opioids with limit price without additional co-payment. Average patients co-payment to one pack of opioids during last three year wat decrease only to PLN 6,10 (~ € 1,5). Increase on opioid consumption from 98 million DDD to 142 million DDD in three years indicates on lack of significant financial barriers in access to cancer pain treatment with opioids.

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The use of registries in primary immunodeficiencies: an example of rare diseases

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ABSTRACT

In the field of rare diseases, data on a significant number of patients can only be archived due to national and international collaboration. Data summarized from specialized centers are a powerful tool. Thanks to modern technology and networks, national and international databases can be constructed legally, with respect to ethical and safety principles. Currently registries for primary immunodeficiencies are established on different levels: single center, national collaboration involving specialized tertiary centers on the country level and on international level as for example ESID registry. Not all registries cover the same dataset, but generally allow to estimate prevalence of diseases, description of natural history, morbidity and mortality. Moreover registries can provide information of diagnostic criteria used, quality of care and management modalities. In the field of primary humoral immunodeficiencies is crucial to assess availability of immunoglobulin G substitution and to plan demand for this product. In other ultra-rare primary immunodeficiencies registries are the unique opportunity to compare different treatment interventions and strategies as hematopoietic stem cell transplantation. The review presents current published data from different registries of primary immunodeficiencies to underscore the need for founding polish registry.

INTRODUCTION

Rare diseases in European Union are defined as life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people. Although specific diseases as for example hereditary angioedema or criopirin associated periodic fevers occur rarely, altogether rare diseases can affect 27-36 million people in Europe and 26-60 millions in United States [1]. Up to 8000 rare diseases are described and due to progress in science their number is still growing. Moreover 72 medicinal products have a status of orphan drugs, most of them extremely expensive, which is a challenge for health care system. There is a great international need to work out a system for rare diseases diagnosis, management, quality and safety of treatment assessment, and drug foundation [2]. In the field of rare diseases, data on a significant number of patients can only be archived due to national and international collaboration. Primary immunodeficien-

cies (PIDs) are an example of rare disease in which some progress is possible to gain due to data gathered via different types of registries.

PRIMARY IMMUNODEFICIENCIES — BRIEF OVERVIEW

PIDs are a large and expanding group of over 230 diseases caused by inherited defect in function of innate or humoral immunology system leading to insufficient response for infections. If not treated PIDs are chronic conditions, leading to internal organ damage and premature death. Currently PIDs are classified into groups, depending on which component of immune response is affected [3,4]. The groups are: combined immunodeficiencies, combined immunodeficiencies with associated or syndromic features, predominantly antibody deficiencies, diseases of immune dysregulation, congenital defects of phagocytes number or function or both, defects in innate immunity, autoinflammatory disorders and complement deficiencies. The most common are predominantly humoral deficiencies. The main is common variable immune deficiency (CVID). It is a complex immune disorder characterized by the impaired B cell peripheral differentiation leading to hipogammaglobulinemia. The disorder involve wide spectrum of symptoms, with majority of subjects affected by recurrent serious infections. The course of disease if untreated deteriorates with age, leading to pulmonary chronic lung disease and irreversible damage. In 30% of patients with immunodeficiency paradoxically co-exist autoimmune complications and sometimes granulomatous inflammation [5-7]. Moreover patients with CVID are at higher risk of malignancy, mainly but not only lymphoma [8]. Other B cell immune deficiencies for which IgG are indicated includes agammaglobulinemia with classical X-linked (XLA or Brutton's agammaglobulinemia) or autosomal recessive pattern. Hyper IgM syndrome including defects of the CD40 ligand and rare forms caused by defects in enzyme required for the immunoglobulin class switching also lead to IgG deficiency. With presented heterogeneity of syndromes and their rarity is very difficult to gather representative data in only one center. The priority of collaboration in the field and importance of registries are the main of principles of care in PIDs.

NATIONAL REGISTRIES

Many countries across Europe developed national registries. The largest is established in 2005 in France: the Reference Center for PIDs (CEREDITH) [9]. According to data published in 2010 the registry comprised a total of 3,083 patients (mainly children), with an overall prevalence of 4,4 cases per 100,000 inhabitants. Predominantly B-cell immunodeficiencies were the most common diseases observed (43%) but the proportion of CVID was only14%. The data suggest that although referral to expert centers was fairly adequate for children, this has not been yet the case in France for adults. The distribution of primary immunodeficiencies (PIDs) varied significantly across distinct geographical areas and this suggested regional differences in patient care [9].

In Germany PID-NET is a federally funded clinical and research consortium (PID-NET, http://www.pid-net.org) [10]. The registry contains clinical and genetic information on PID patients and is set up within the framework of the existing European Database for Primary Immunodeficiencies, run by the European Society for Primary Immunodeficiencies (ESID). A central data entry clerk has been employed to support data entry at the participating centers. Regulations for ethics approvals have presented a major challenge for participation of individual centers and have led to a delay in data entry in some cases. Data on 630 patients, entered into the European registry between 2004 and 2009, were incorporated into the national registry. From April 2009 to March 2012, the number of contributing canters increased from 7 to 21. A total number of 1368 patients are included, of whom 1232 were alive. The age distribution of living patients differs significantly by gender, with twice as many males than females among children, but 15% more women than men in the age group 30 years and older. The diagnostic delay between onset of symptoms and diagnosis has decreased for some PID over the past 20 years, but has remained particularly high at a median of 4 years in common variable immunodeficiency (CVID), the most prevalent PID [10].

In Italy an Italian Network on Primary Immunodeficiencies (IPINet) has been set up in 1999 within the Italian Association of Pediatric Hematology and Oncology (AIEOP) to increase the awareness of these disorders among physicians. Further, diagnostic and treatment guideline recommendations have been established to standardize the best clinical assistance to all patients, including antibiotic prophylaxis, and for a national epidemiologic monitoring of PIDs [11]. The report which aimed to response for specific questions in defined PIDs have been published. A multicenter 5 year prospective observational study involving data of humoral deficiencies was conducted to identify prognostic markers, clinical co-morbidities and effectiveness of long-term Ig supplementation [12] In the study 201 patients with CVID and 101 patients with X-linked agammaglobulinemia were included giving over a cumulative follow-up period of 1,365 patient-years. Overall, 21% of the patients with CVID and 24% of patients with X-linked agammaglobulinemia remained infection free during the study. A reduction of pneumonia episodes has been observed after initiation of Ig replacement. During the observation time, pneumonia incidence remained low and constant over time. Patients with pneumonia did not have significant lower IgG trough levels than patients without pneumonia, with the exception of patients whose IgG trough levels were persistently

The Swiss National Registry for Primary Immunodeficiency Disorders (PID) was established in 2008, constituting a nationwide network of pediatric and adult departments involved in the care for patients with PID at university medical centers, affiliated teaching hospitals and medical institutions

[13]. The registry collects anonymized clinical and genetic information on PID patients and is set up within the framework of the European database for PID, run by the ESID. To date, a total of 348 patients have been registered in Switzerland indicating an estimated minimal prevalence of 4.2 patients per 100,000 inhabitants. Distribution of different PID categories, age and gender were reported. Predominantly antibody disorders (PADs) were the most common diseases observed (n=217/348, 62%), followed by phagocytic disorders" (n=31/348, 9%). PADs were more prevalent in adults than in children (78% vs. 31%). CVID diagnosis dominated (n=98/217, 45%), followed by other hypogammaglobulinemias (n=54/217, 25%). Among phagocytic disorders, chronic granulomatous disease (CGD) was the most prevalent PID (n=27/31, 87%). The diagnostic delay between onset of symptoms and diagnosis was high with a median of 6 years for CVID and more than 3 years for other hypogammaglobulinemias [13].

The United Kingdom national registry for PIDs (UKPID) is based on the adoption of the ESID on line platform [14]. Establishment of the Registry was supported by founding from the UK patients organization and further financial project support from the Healthcare Quality Improvement Partnership. In early 2008 a UKPID Registry management committee was established. The members of committee are representatives of medical and nursing stuff, patient's charities and the core registry team. The main aim of the registry is to act as a data repository that can provide longitudinal data. Clinicians may interrogate the database to answer questions relevant to clinical practice. Up to 36 of 38 centers responsible for PIDs care engaged to the project. According to published data in 2013, 27 centers actively collected data. To date 2229 patients have been enrolled, with still raising rate in recruitment. Of the 2229 registered patients, 2153 (96,5%) were alive. The

PADs make up the largest group accounting for (1364) 61% of registered patients. CVID accounts for 810 registered subjects. The minimal prevalence of all PIDs is estimated at 3,5 PID/100 000 of the UK population, PADs at 2,1 and CVID at 1,3. A total of 1358 patients were identified as receiving immunoglobulin replacement therapy [14].

INTERNATIONAL REGISTRIES

The ESID Registry is based on contribution by the following national registries: CEREDITH from France, REDIP from Spain, PID-NET from Germany, UKPIN from United Kingdom, IPINET from Italy, AGPI from Austria, registry from Czech Republic, Swiss and the Netherlands. Additionally in the ESID Registry contribute sites from 21 countries, including Polish centers [15]. The database is an internet based platform for epidemiological analyses as well as the development of new diagnostic strategies and therapeutic modalities [16]. According to data closed in 25 Jul 2014 there were 126 documenting centers an 19 355 patients reported. As in national registries PADs were the most prevalent: 10 966 cases (56,66%) with 6,476 on immunoglobulin therapy. In the last 2 years the ESID registry has been completely revised and reorganized. Data will be organized in three levels of data depth: level 1 - mandatory core data set, level 2- category specific data sets, level 3 - dedicated, specific studies with a fixed time frame and specific questions [17].

Similarly to ESID, The Latin American Society for Immunodeficiencies (LASID) has been promoting initiatives in awareness, research, diagnosis, and treatment for the affected patients in Latin America. These initiatives have resulted in the development of the LASID Registry (with 4900 patients registered as of January 2014) [18]. The first registry in United States was established in 1993, and later on included into the US Immuno-

deficiency Network (USIDNET). The USIDNET Registry contains 3,459 patients, with CVID being the most represented [19].

PROBLEMS AND CHALLENGES

Independent on the type of registries due to actual experiences the list of problems which have to be solved are identified [17]. First of all is the control of data quality. The participation in the PID registry is completely voluntary. The centers have to cope with limited human power for systematic documentation. In same registries special clerks are employed to support physicians working in centers.

Another issue is to prepare suitable classification criteria which cover all diagnoses in such heterogeneous group of diseases as PIDs. There is the possibility that patients with diagnosis confirmed genetically are reported more willingly. In the contest of natural history of diseases the more severely ill patients treated in tertiary centers are reported, while patients treated locally with uncomplicated course of disease are not covered in the registry what can bias severity assessments.

To gather valuable data PID registries have to be longitudinal, with no close-data. Reporting has to be provided without breaks with regular manner. Thus the real problem is to provide stable and secure funding. It has to be achieved from grants and public resources. Pharmaceutical companies can participate in the founding, but in majority they are interested in a given disease in a fixed timeframe.
Conclusions

CONCLUSION

Despite all limitations there is a common agreement that registries are valuable and necessary. They can capture data on rare diseases, which cannot be achieved in a single center perspective. They give Real World Evidence, important for physicians, patients, national payers and health care providers. Datasets covered in registries can support reimbursement decisions, especially in the field of rare diseases. Data on PIDs available up to date allowed to estimate PIDs epidemiology, and prove efficacy of Ig therapy. Revealed the need for organization of care for adult patients with PIDs through the whole Europe, the need for clear classification criteria and recommendations for treatment other than Ig supplementation (in ex. HSCT, antibiotics prophylaxis). In Poland the Nation Health Fund (NFZ) supports Drug Programs for specific innovative therapies. In 2015 the Drug Program has been initiated for adults with PIDs demanding Ig supplementation therapy. It contains selected datasets covering diagnosis, clinical parameters and treatment use. Moreover The Polish Working Group on PIDs attempts to create Polish National Registry for PIDs.

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PIDs are a large and expanding group of over 230 diseases caused by inherited defect in function of innate or humoral immunology system leading to insufficient response for infections. If not treated PIDs are chronic conditions, leading to internal organ damage and premature death. Currently PIDs are classified into groups, depending on which component of immune response is affected [3,4]. The groups are: combined immunodeficiencies, combined immunodeficiencies with associated or syndromic features, predominantly antibody deficiencies, diseases of immune dysregulation, congenital defects of phagocytes number or function or both, defects in innate immunity, autoinflammatory disorders and complement deficiencies. The most common are predominantly humoral deficiencies. The main is common variable immune deficiency (CVID). It is a complex immune disorder characterized by the impaired B cell peripheral differentiation leading to hipogammaglobulinemia. The disorder involve wide spectrum of symptoms, with majority of subjects affected by recurrent serious infections. The course of disease if untreated deteriorates with age, leading to pulmonary chronic lung disease and irreversible damage. In 30% of patients with immunodeficiency paradoxically co-exist autoimmune complications and sometimes granulomatous inflammation [5-7]. Moreover patients with CVID are at higher risk of malignancy, mainly but not only lymphoma [8]. Other B cell immune deficiencies for which IgG are indicated includes agammaglobulinemia with classical X-linked (XLA or Brutton's agammaglobulinemia) or autosomal recessive pattern. Hyper IgM syndrome including defects of the CD40 ligand and rare forms caused by defects in enzyme required for the immunoglobulin class switching also lead to IgG deficiency. With presented heterogeneity of syndromes and their rarity is very difficult to gather representative data in only one center. The priority of collaboration in the field and importance of registries are the main of principles of care in PIDs.

NATIONAL REGISTRIES

Many countries across Europe developed national registries. The largest is established in 2005 in France: the Reference Center for PIDs (CEREDITH) [9]. According to data published in 2010 the registry comprised a total of 3,083 patients (mainly children), with an overall prevalence of 4,4 cases per 100,000 inhabitants. Predominantly B-cell immunodeficiencies were the most common diseases observed (43%) but the proportion of CVID was only14%. The data suggest that although referral to expert centers was fairly adequate for children, this has not been yet the case in France for adults. The distribution of primary immunodeficiencies (PIDs) varied significantly across distinct geographical areas and this suggested regional differences in patient care [9].

In Germany PID-NET is a federally funded clinical and research consortium (PID-NET, http://www.pid-net.org) [10]. The registry contains clinical and genetic information on PID patients and is set up within the framework of the existing European Database for Primary Immunodeficiencies, run by the European Society for Primary Immunodeficiencies (ESID). A central data entry clerk has been employed to support data entry at the participating centers. Regulations for ethics approvals have presented a major challenge for participation of individual centers and have led to a delay in data entry in some cases. Data on 630 patients, entered into the European registry between 2004 and 2009, were incorporated into the national registry. From April 2009 to March 2012, the number of contributing canters increased from 7 to 21. A total number of 1368 patients are included, of whom 1232 were alive. The age distribution of living patients differs significantly by gender, with twice as many males than females among children, but 15% more women than men in the age group 30 years and older. The diagnostic delay between onset of symptoms and diagnosis has decreased for some PID over the past 20 years, but has remained particularly high at a median of 4 years in common variable immunodeficiency (CVID), the most prevalent PID [10].

In Italy an Italian Network on Primary Immunodeficiencies (IPINet) has been set up in 1999 within the Italian Association of Pediatric Hematology and Oncology (AIEOP) to increase the awareness of these disorders among physicians. Further, diagnostic and treatment guideline recommendations have been established to standardize the best clinical assistance to all patients, including antibiotic prophylaxis, and for a national epidemiologic monitoring of PIDs [11]. The report which aimed to response for specific questions in defined PIDs have been published. A multicenter 5 year prospective observational study involving data of humoral deficiencies was conducted to identify prognostic markers, clinical co-morbidities and effectiveness of long-term Ig supplementation [12] In the study 201 patients with CVID and 101 patients with X-linked agammaglobulinemia were included giving over a cumulative follow-up period of 1,365 patient-years. Overall, 21% of the patients with CVID and 24% of patients with X-linked agammaglobulinemia remained infection free during the study. A reduction of pneumonia episodes has been observed after initiation of Ig replacement. During the observation time, pneumonia incidence remained low and constant over time. Patients with pneumonia did not have significant lower IgG trough levels than patients without pneumonia, with the exception of patients whose IgG trough levels were persistently

The Swiss National Registry for Primary Immunodeficiency Disorders (PID) was established in 2008, constituting a nationwide network of pediatric and adult departments involved in the care for patients with PID at university medical centers, affiliated teaching hospitals and medical institutions

[13]. The registry collects anonymized clinical and genetic information on PID patients and is set up within the framework of the European database for PID, run by the ESID. To date, a total of 348 patients have been registered in Switzerland indicating an estimated minimal prevalence of 4.2 patients per 100,000 inhabitants. Distribution of different PID categories, age and gender were reported. Predominantly antibody disorders (PADs) were the most common diseases observed (n=217/348, 62%), followed by phagocytic disorders" (n=31/348, 9%). PADs were more prevalent in adults than in children (78% vs. 31%). CVID diagnosis dominated (n=98/217, 45%), followed by other hypogammaglobulinemias (n=54/217, 25%). Among phagocytic disorders, chronic granulomatous disease (CGD) was the most prevalent PID (n=27/31, 87%). The diagnostic delay between onset of symptoms and diagnosis was high with a median of 6 years for CVID and more than 3 years for other hypogammaglobulinemias [13].

The United Kingdom national registry for PIDs (UKPID) is based on the adoption of the ESID on line platform [14]. Establishment of the Registry was supported by founding from the UK patients organization and further financial project support from the Healthcare Quality Improvement Partnership. In early 2008 a UKPID Registry management committee was established. The members of committee are representatives of medical and nursing stuff, patient's charities and the core registry team. The main aim of the registry is to act as a data repository that can provide longitudinal data. Clinicians may interrogate the database to answer questions relevant to clinical practice. Up to 36 of 38 centers responsible for PIDs care engaged to the project. According to published data in 2013, 27 centers actively collected data. To date 2229 patients have been enrolled, with still raising rate in recruitment. Of the 2229 registered patients, 2153 (96,5%) were alive. The

PADs make up the largest group accounting for (1364) 61% of registered patients. CVID accounts for 810 registered subjects. The minimal prevalence of all PIDs is estimated at 3,5 PID/100 000 of the UK population, PADs at 2,1 and CVID at 1,3. A total of 1358 patients were identified as receiving immunoglobulin replacement therapy [14].

INTERNATIONAL REGISTRIES

The ESID Registry is based on contribution by the following national registries: CEREDITH from France, REDIP from Spain, PID-NET from Germany, UKPIN from United Kingdom, IPINET from Italy, AGPI from Austria, registry from Czech Republic, Swiss and the Netherlands. Additionally in the ESID Registry contribute sites from 21 countries, including Polish centers [15]. The database is an internet based platform for epidemiological analyses as well as the development of new diagnostic strategies and therapeutic modalities [16]. According to data closed in 25 Jul 2014 there were 126 documenting centers an 19 355 patients reported. As in national registries PADs were the most prevalent: 10 966 cases (56,66%) with 6,476 on immunoglobulin therapy. In the last 2 years the ESID registry has been completely revised and reorganized. Data will be organized in three levels of data depth: level 1 - mandatory core data set, level 2- category specific data sets, level 3 - dedicated, specific studies with a fixed time frame and specific questions [17].

Similarly to ESID, The Latin American Society for Immunodeficiencies (LASID) has been promoting initiatives in awareness, research, diagnosis, and treatment for the affected patients in Latin America. These initiatives have resulted in the development of the LASID Registry (with 4900 patients registered as of January 2014) [18]. The first registry in United States was established in 1993, and later on included into the US Immuno-

deficiency Network (USIDNET). The USIDNET Registry contains 3,459 patients, with CVID being the most represented [19].

PROBLEMS AND CHALLENGES

Independent on the type of registries due to actual experiences the list of problems which have to be solved are identified [17]. First of all is the control of data quality. The participation in the PID registry is completely voluntary. The centers have to cope with limited human power for systematic documentation. In same registries special clerks are employed to support physicians working in centers.

Another issue is to prepare suitable classification criteria which cover all diagnoses in such heterogeneous group of diseases as PIDs. There is the possibility that patients with diagnosis confirmed genetically are reported more willingly. In the contest of natural history of diseases the more severely ill patients treated in tertiary centers are reported, while patients treated locally with uncomplicated course of disease are not covered in the registry what can bias severity assessments.

To gather valuable data PID registries have to be longitudinal, with no close-data. Reporting has to be provided without breaks with regular manner. Thus the real problem is to provide stable and secure funding. It has to be achieved from grants and public resources. Pharmaceutical companies can participate in the founding, but in majority they are interested in a given disease in a fixed timeframe.
Conclusions

CONCLUSION

Despite all limitations there is a common agreement that registries are valuable and necessary. They can capture data on rare diseases, which cannot be achieved in a single center perspective. They give Real World Evidence, important for physicians, patients, national payers and health care providers. Datasets covered in registries can support reimbursement decisions, especially in the field of rare diseases. Data on PIDs available up to date allowed to estimate PIDs epidemiology, and prove efficacy of Ig therapy. Revealed the need for organization of care for adult patients with PIDs through the whole Europe, the need for clear classification criteria and recommendations for treatment other than Ig supplementation (in ex. HSCT, antibiotics prophylaxis). In Poland the Nation Health Fund (NFZ) supports Drug Programs for specific innovative therapies. In 2015 the Drug Program has been initiated for adults with PIDs demanding Ig supplementation therapy. It contains selected datasets covering diagnosis, clinical parameters and treatment use. Moreover The Polish Working Group on PIDs attempts to create Polish National Registry for PIDs.

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Estimation of stress resistance of medical students in Lviv, Ukraine

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ABSTRACT

High demands for speed and amount of students' trainings in health care education are among the stress causes. Presence of stress can negatively affect the state of progress and level of physical health of medical students. We have tested 275 students of II-IV years of the medical faculty (145 women, 130 men) using methods of Friedman and Rosenman modifications «tendency to stress» and «self-rating of stress resistance». Test results revealed: 34% of women and 29% of men showed below average level self-rating of stress resistance, including the group tendency to stressful situations. Average level was characterized for 39% of women and 27% of men. This indicates the sufficient resistance to stress and rejection as failure stress. Higher average level of stress resistance was observed for 15% of women and 26% of men. These students, despite the negative influence of different factors, fight stress and try to prevent it. High aptitude was recorded for 11% of women and 7% of men. Relatively high frequency of getting into stress was inherent for 25% of women and 21% of men. Presence of stress and attempts to avoid it were found for 29% of women and 40% of men. For 22% of women and 26% of men was found the ability to resist stress due to communicability and harmonic lifestyles. High level of self-regulation, the ability to achieve goals as the result of low aptitude to stress was inherent for 10% of women and 7% of men. Reducing adaptation to stress among medical students was registered. Formation of skills for stress resistance by implementation of health-saving technologies in student lifestyle is necessary.

IINTRODUCTION

The current period of social development raises the problem of human health as the global problem. According to numerous scientific data recently there has been a steady decrease of general health status, including students, while the society needs active, healthy, creative young people, who are ready to realize themselves in all spheres of life - first of all in the professional activity.

Students' health care is one of the major social problems in the society. University students are the future social-economic, intellectual and creative potential. However, students can be referred to the increased risk group, as the difficult age problems of modern students are named negative impact of the crisis almost in all major sectors of society and the state.

Nowadays significantly increased the interest of scientists and specialists to questions, related to professional stress – especially to the mechanisms of formation of human resistance to stress in different occupations. Such professional stress is often a reason, for what a significant number of highly educated employees leave their jobs, change professional areas, turn to consultants, psychologists and doctors.

METHODOLOGY
Materials and Methods

This study is a part of our scientific research "formation of healthy lifestyle of medical students". Sociological research was carried out among students at Lviv National Medical University by questionnaire "Self appraisals of mental states" (Eysenck) and our specifically elaborated sociological questionnaire "Self appraisals of medical students study", based on a random statistical population (n=275) where the error probability survey results did not exceed 5% (p<0.05). The mental status was assessed using the Eysenck Personality Questionnaire (EPQ) [*].

Study design

The aim of this work was to study introspection health status of medical students. The results, in our opinion, can be used for choosing the right tactics and methodology to preserve and strengthen the mental health of students.

Data collection

Both male and female students willing to participate were included in the study after explanation was given. We have tested 275 students from years II-IV of the medical faculty (145 women and 130 men) using methods of Friedman [*] and Rosenman [*] modifications «tendency to stress» and «self-rating of stress resistance». As well as our self-administered structured questionnaire was used for data collection. The forty item questionnaire comprised items pertaining to preference, awareness and consumption pattern.

Statistical analysis

All statistical analyses were carried out using SPSS version 11 and SPSS Statistics version 22. P-values < 0.05 were considered as significant.

The level of personal anxiety in the tested population was 41.4 ± 0.8 points [*]. Among the tested students there were some with both high and low personal anxieties, which determine their different reactions to examination stress. Based on the currently accepted interpretation of dividing people on levels of anxiety [*] 5.8% of the tested people have reduced personal anxiety (less than 35 points), about 5% have higher anxiety – above 55 points. About 90% of students have average personal anxiety from 35 to 55 points.

Intermediate reactive (situational) anxiety specified by Spielberger questionnaire, in a quiet position equal to 39.8 ± 0.7 points. Before the test, the figure increased significantly, reaching an average of 56.5 ± 0.8 points, indicating a rather high level of reactive anxiety in students before the exam (p<0.001).

RESULTS

According to recent studies, there are several factors that may affect stress situations during obtaining medical profession: the nature of medical work (constant involvement in human suffering), desire for independence in acquiring knowledge and rather rigid forms and methods of training specialists particular profile, acquisition and development of skills facing student in learning and development professional role socialization, personality problems and gender questions (Table 1).

Students also face social, emotional, physical, family problems, which may affect their ability to learn and progress. As stress factors act: student achievement, which has competitive influence at the ranking, lack of interaction teacher-student and absence of extracurricular activities (Table 2).

Table 1. Factors leading to stress for medical students

Stress factors	men (%)	women (%)
Individual adaptation to the curriculum	93.8	82.1
Economic problems	31.3	32.5
Work with patients	13.1	9.8
Collaboration with hospital staff	13.1	9.8
Lecturers	3.1	14.6
Test/examination fear	37.5	42.3
Family problems	25.0	6.5
Future work and employment	12.5	23.6

Table 2. The nature of stress among medical students during learning process

Stress levels	men (%)	women (%)
Do not feel stress	12.5	5.7
Minimum stress	25.0	26.0
Partial stress	12.5	25.2
Severe stress	21.9	13.8
Very strong stress	6.3	7.3

We conducted an investigation among medical students of the second study year to determine the level and nature of stress in students. For this purpose 275 students were tested. Analysis of the levels of stress among student contingent is presented in Table 2.

Test results revealed: 34% of women and 29% of men showed below average level of self-rating of stress resistance, including group tendency to stressful situations. Aveage level was characterized for 39% of women and 27% of men. This indicates the sufficient resistance to stress and rejection as failure stress. Higher average level of stress resistance was observed for 15% of women and 26% of men. These students, despite the negative influence of different factors fight stress and try to prevent it. High level of stress resistance was exposed only by 12% of women and 18% of men.

We have analyzed the impact on the success of medical students of stress and self-assessment of their health (Figure 1). The data show that the best success rates are observed in students who are more resistant to stress and lead a healthy lifestyle.

Gender differences in the aptitude to stress of medical students were identified. High aptitude was recorded for 11% of women and 7% of men. Relatively high frequency of getting into stress was inherent for 25% of women and 21% of men. Presence of stress and attempts to avoid it were found for 29% of women and 40% of men. For 22% of women and 26% of men it was found the ability to resist stress by communicative and harmony lifestyles. High level of self-regulation, the ability to achieve goals as the result of low aptitude to stress was inherent for 10% of women and 7% of men.
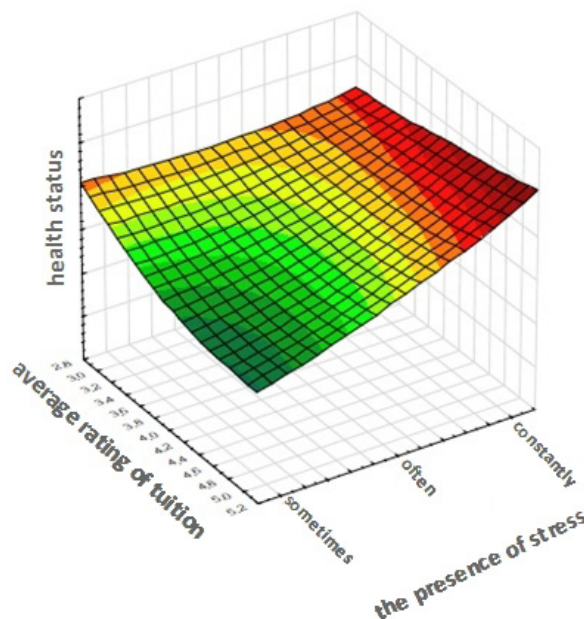

Figure 1. The relationship between presence of stress, average rating of tuition and self-assessment health score of the students

The presence of significant (p<0.05) relationship between material conditions of medical students and self-stress state (r=+0.34). That means, with the deterioration of the financial position there is an increase in stress level, which greatly affects the self-assessment of health of medical students (Figure 2).
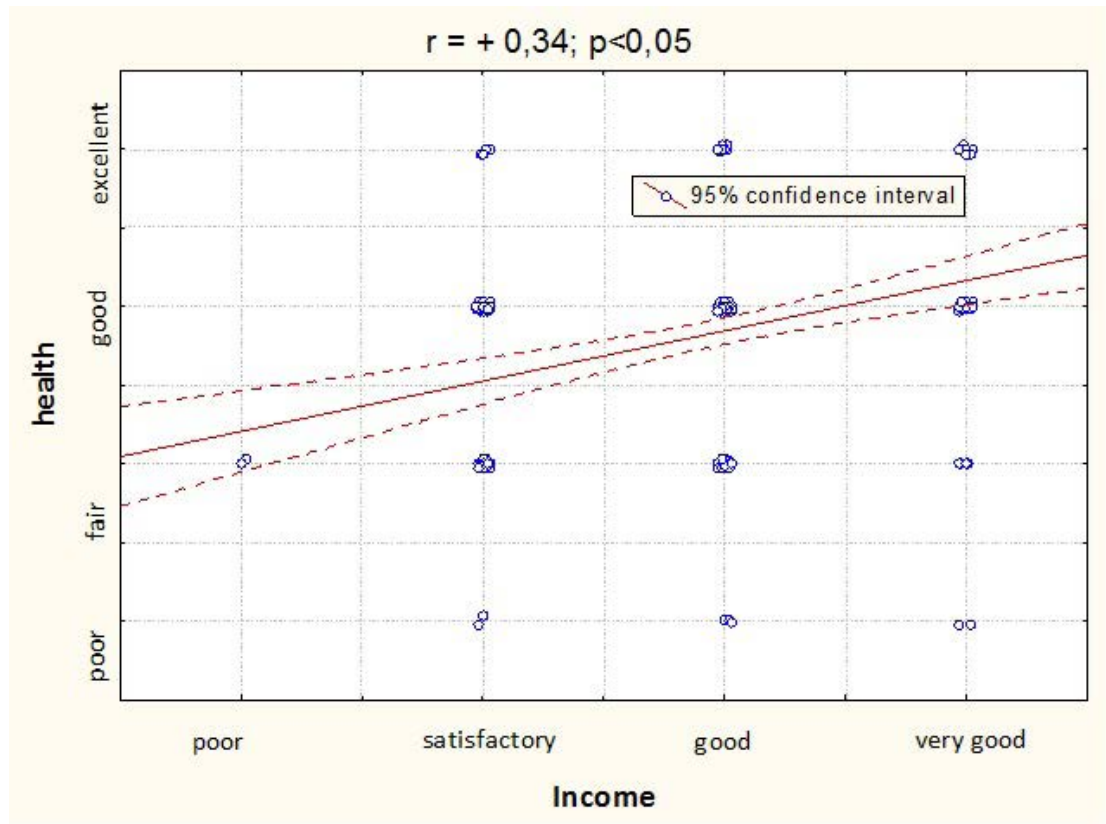
Figure 2. The relationship between material conditions and self-assessed health score of students

As the table 2 shows, the vast majority of students have minimal or partial stress, while a minimum and a very strong stress does not depend on gender identity. In conducting the correlation between gender and anxiety, frustration, aggressiveness and rigidity there is a weak correlation (Spearman correlation coefficient is 0.176, 0.103, 0.001 and 0.091 respectively). Female students often assess their mental state more negative than their male counterparts, or most likely during the test they tend to lower their assessment of mental state.
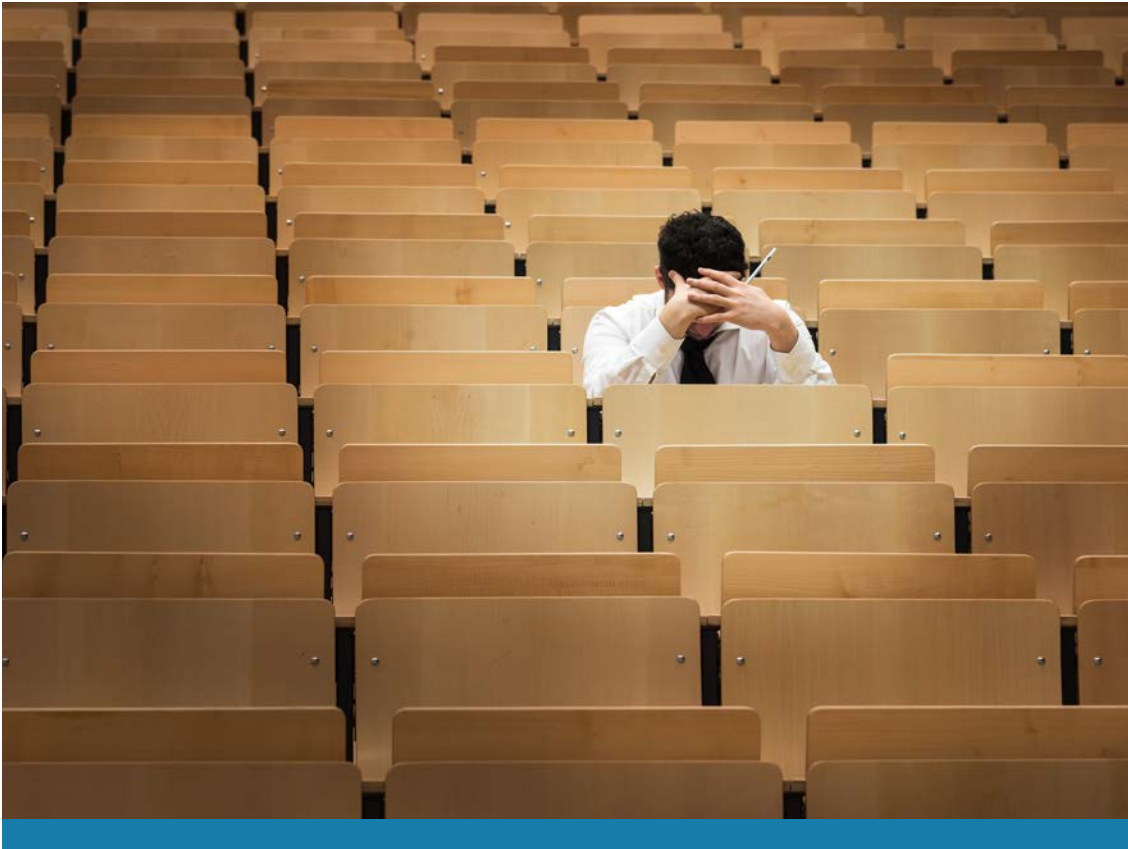
DISCUSSION

Determining the level of adaptation was made taking into account such factors as: the duration of professional activities, acquiring professional knowledge and skills to apply them in practice, the degree of autonomy in the profession, professional communication skills, etc. However, the forma-tion of stress-resistance is laid by student at a medical university level.

Healthy students develop the ability to learn through self-examination, self-observation and practical judgment. At the same time, they also develop the ability to form interpersonal relationships and work in team and society. Medical students and practitioners, compared with workers in other professions and the population in general, are prone to academic and professional stress, and therefore are susceptible to psychosocial health problems and some specific dysfunctions that may endanger their physical, mental and social health.

There are a lot of research studies about the relationship between education and lifestyle of medical students [*]. Implementation in the profession includes the image of the profession, especially at the stage of selecting professional field. The image of

the future profession combines emotional and evaluative and cognitive components. Compliance with these components makes reasonable choice of profession, especially taking into account the professional requirements of human potential. The level of student perceptions of the profession is directly related to the level of attitude to learning: the more students know about their future profession, the better is their attitude to learning. However, expanding the range of interests related to the chosen specialty increased their intellectual, aesthetic, moral and material needs.

Otherwise, in the consciousness of the future specialist negative experience is accumulated, some kind of solutions for tasks is formed, including ignoring of criticisms, evasion of solving problems, etc. [*].

Examination stress is one of the greatest among causes of mental stress among students. Very often exam is a factor, which may cause psychical injury or shock and may become a trigger to activate depression [*]. Recently strong evidence was obtained, indicating that examination stress has a negative effect on the students nervous, cardiovascular and immune systems [*]. According to many researchers during the examination sessions students marked disturbances of the autonomic regulation of the cardiovascular system, manifested the increase in heart rate and blood pressure, the growth of muscle and emotional stress [*]. Emotional stress can lead to activation of the sympathetic and parasympathetic divisions of the vegetative nervous system and to the development of transient processes involving violation of homeostasis and increased vegetative ability for reactions of cardiovascular system on emotional stress. After the exam physiological parameters do not immediately return to normal − usually it takes a few days for parameters of blood pressure to return to base quantities [*]. Recently it was proved, that examination stress, especially when combined with caffeine, may lead to further sustained

increase in blood pressure among students [*]. It should also be noted that the problem of exam stress affects every year hundreds of thousands of students all over the world, and to solve this problem the joint efforts of scientists from different disciplines – physiology, psychology, psychiatry, cardiology and health care- are necessary.

Investigation of the mechanisms of examination stress development and establishing the relationship of individual reactions to specific personal characteristics is a tool, with which may be disclosed linkages physiological and psychological aspects of human. Understanding of these mechanisms will develop more effective methods for correcting adverse functional states of human.

When stress is perceived negatively or becomes excessive, the students have physical and psychological deviation [*].

In order to understand the relationship between stress and medical training for future professional activities of physician the educational process should be considered more deeply. Studies show that the mental health of medical students compared to other students from other universities before admission to the university is about the same [*], but worse during the learning process. Each year the student is accompanied by new shocks with stressful career choices. For many significant amount of educational material during the first year is associated with the knowledge that the material cannot fully be digested [*]. That significantly affects the previous self-assessment of many students.

Although some degree of stress is a normal part of medical training and can be an incentive for some students, not all students consider stress to be constructive. For many of them stress causes fear, incompetence, guilt, anger and may be associated with both psychological and physical

morbidity. Elevated levels of stress can adversely affect the learning of the curriculum, prevent concentration, decision making and mastering other skills necessary for studying.

Studies, which have focused on identifying the sources of stress among medical students, in general, indicate 3 areas: academic pressure, social and financial problems, which range from 25% to 75%.

According to Bragina K.R. [*] during university studies one can identify medical students in three main critical periods - the first, fourth and sixth (last) years of study (existing till now system of training specialists). At the first year a change in the social role of student needs an adjustment of values, there is a need for more flexibility to adjust their behavior to adapt to the more stringent requirements of higher education, to establish relationships in the new team; for non-resident – to build up everyday life. Students often lack clinical medical experience and any possibility of self-realization as a future doctor, complaining of professional isolation [*].

For the undergraduates during their clinical training, where students are expected to experience stress associated with the beginning of their direct contact with patients, their intrusion into previously restricted areas, that are not common in social interaction, for example, examination of the patient, the study of his medical history, soul-searching, rethinking choice of specialty [*]. Medical students, with the advent of the program of clinical disciplines are beginning to feel a load of medical liability. The crisis of fifth (sixth) year is related to the future employment prospects and professional development within their chosen specialty. The lack of reserves of mental and physical health at each of these stages can lead to neurotic and adjustment disorders.

Gradually, students try to take more responsibility for the patients care. They need to be more competent, but still feel insecure. Students learning to overcome these feelings are sometimes arrogant and try to learn "all at once", challenge everything. Therefore, it may happen that a student cannot cope with the task, or cannot make the right decision at a given pace with high responsibility for the consequences of this decision, that there is an information overload - load that exceeds the capacity of the human subject to maintain high motivation and do the work.

CONCLUSIONS

1. Reducing adaptation to stress among medical students was registered.
2. Formation of skills for stress resistance by implementation of health-saving technologies in student lifestyle is necessary.
3. In order to accelerate and improve the adaptation of freshmen to university studies it's necessary:

- to create conditions for cognitive-information students adapt to a new environment, the structure of university, content and training requirements, duties;
- to get acquainted with the peculiarities of university training for creating a positive attitude towards their chosen specialty;
- to prepare students for new forms and methods of educational work in higher education.

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*FOOTNOTES

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Main Medical Library Databases

Wojciech Giermaziak, Main Medical Library

ABSTRACT

The current health policy is focused on use of various type of health data systems created for research, clinical trials and studies evaluate health care system. Databases collecting information in the field of medicine, related sciences and public health may be regarded as a specific type of registry. A well-known and highly respected example of this type of database is "Polish Medical Bibliography" (PBL), created in the Medical Information Center in Main Medical Library in Poland. Another data system functioning in the Main Medical Library is Thesaurus-MeSH (Tez-MeSH), which is the Polish version of the American Thesaurus, Medical Subject Headings (MeSH), carried out as a part of the Unified Medical Language System by the National Library of Medicine of the United States (National Library of Medicine-NLM).
Creation of Medical Information Center (CIM) in the Main Medical Library enabled continuation and updating highly specialized information databases, which allows CIM to qualify as an opinion-forming instrument tool in the government activities.

The Main Medical Library since 2002 functioning also as the World Health Organization (WHO) Documentation Center. WHO's publications in field of medicine and related sciences are collected, compiled and made available in the premises of the library. The Main Medical Library also allows the use of electronic databases of the fulltext journals.

IINTRODUCTION

Terminology about register in the health care system should not be limited only for the medical records systems of healthcare facilities, managed both electronically (computerized) and on paper. Databases collecting information in the field of medicine, related sciences and public health may also be regarded as a specific type of registry.

POLISH MEDICAL BIBLIOGRAPHY

A well-known and highly respected example of this type of database is "Polish Medical Bibliography" (PBL), created in the Medical Information Center in Main Medical Library in Poland. Polish Medical Bibliography is the oldest and most comprehensive abstracts medical database. Medical Information Center continues process of PBL creating, which was started originate by its founder Stanisław Konopka and automated

in the seventies of the 20th century by Scientific Medical Information Department set up for this purpose.

The system records polish scientific and clinical literature, professional in the field of medicine and related sciences, health care management, as well as popular literature in the field of health education. The database also contains monographs and unpublished doctorates and habilitations belonging to the collections of the Main Medical Library.

PBL database is not only a register of medical casuistry (described case studies), but also through a significant number of original published articles, shows, among other, the epidemiological picture of the Polish population and other countries, as well as describes the results of the effectiveness of various forms of prevention and treatment of diseases. Polish Medical Bibliography is appreciated worldwide bibliographic-abstracts database.

Experts from an international non-profit organization "the Cochrane Collaboration" which analyzed PBL database have found that close to 40 percent of randomized controlled trials records found in the database is not registered neither in Medline, neither in Embase, which testifies that system has got rich and valuable information resources. PBL is a valuable source of information for both health care system users, as well as public health researchers. It provides significant support for health care personnel in the process of diagnosis, treatment, analysis of the results of the practice guideline. It is also used as a very useful source of data for epidemiological and pharmacoepidemiological studies, in health care economics researches, with regard to a whole range of diseases.

The database includes over 400 000 records, making it one of the largest specific bibliography in Poland. The recorded data come from more than 250 Polish periodicals and about 200 foreign magazines. It is carried out in an automatic way since 1979, on a regular basis and updated every 3 months. Since 1991, Polish and English summaries of articles are entered into the database. The data included in the database are properly classified in order to optimize readabil-

ity of database records, facilitate access to information and reduce the time of target information searching. PBL is available for users for self-searching and also there is a possibility to prepare thematic summaries of literature on individual orders by GBL employees [1]. Searching may be carried out according to each significant element of the bibliographic and description of the content, for example: by the words of the title and abstract, descriptor, title, journal, year of issue, etc. (Fig.1).

TEZ-MESH DATABASE

Another data system functioning in the Main Medical Library is Thesaurus-MeSH (Tez-MeSH), which is the Polish version of the American Thesaurus, Medical Subject Headings (MeSH), carried out as a part of the Unified Medical Language System by the National Library of Medicine of the United States (National Library of Medicine-NLM). Mesh is functioning as an information-searching language of one of the most famous and recognized by the world medical system -

Medlarse /Medline. The database contains English and Polish nomenclature in the field of medicine, related sciences and health care system organization. Terminology included in the database along with indexing rules adopted from NLM, applies to prepare special documents – characteristics, which were introduced since 1979 to the PBL database and library catalogues. The implementation of Tez-MeSH Database to Polish Medical Bibliography (in 2007), greatly facilitated the process of searching in bibliographic database with the ability to use a descriptor tree [2].

Tez-MeSH system is available for free in the on-line version for medical schools libraries, other schools and medical institutions, academies of physical education and scientific research institutes of the Ministry of Health. Permanently it is used by more than 30 scientific and educational institutions. Figure 2 (Fig.2) presents methods of searching in the database.

Figure 1. The Polish Medical Bibliography Database – searching in system

Source:http://gbl.home.pl/cgi-bin/gblbase.pl/pblb09

Figure 2. The Tez-MeSH Database – searching of terminology in the system

WORLD HEALTH ORGANIZATION DATABASE

The Main Medical Library since 2002 functioning as World Health Organization (WHO) Documentation Center. WHO's publications in field of medicine and related sciences are collected, compiled and made available in the premises of the library. WHO Regional Office for Europe based in Copenhagen send systematically directly to the GBL or through the WHO Office in Poland, the latest publications from the World Health Organization institutions and development by experts from various fields carried out on behalf of the WHO organization. The Center currently offers more than 4000 publications and studies on various medical issues, statistics about health status and incidence of various types of diseases, a global health reports published annually by WHO and other development studies. Methods of searching in the database are presented below (Fig.3., Fig.4.).

FOREIGN BIBLIOGRAPHIC DATABASES – E-MAGAZINES

The Main Medical Library also allows the use of electronic databases of the fulltext journals; they are available at the premises of the library as well as in the GBL's branches. One of the most famous and appreciated database is the Medline Database, created by the National Center for Biotechnology Information at the National Library of Medicine in the USA. It is an electronic version of the Index Medicus, which began publication in 1966. Currently it registers more than 12 million articles from 4,600 journals from 70 countries. Its chronological range covers the period from 1966 to the present day. Since 2002 it is updated daily. About 2000 records are added per day. Approximately 52% of the records represent article published in the USA, 86% of articles are in English language. Medline is an essential component of PubMed Database. In addition to Medline it is also available:

Figure 3. T
he WHO Database

Source:
http://dosei.who.int/uhtbin/cgisirsi/Fri+Jun+19+04:00:43+MEST+2015/0/49

Figure 4.
WHO's documents – searching in the system

Source:
http://opac.gbl.waw.pl/cgi-bin/cgiip.exe/wo2_search.p?R=1&IDBibl=22&ID1=JILJKHNLN-
MKEEDGRKON&ln=p

Oldmedline - containing 1.5 million descriptions of articles from the years 1953-1965; Pubmed In Process - which includes articles prepared for inclusion in Medline and Pubmed As Supplied By Publisher - presents data on articles submitted by publishers. Pubmed contains 89% of records in English. It indexes magazines in 29 languages in addition to English magazines.

Another database is Embase, published by Elsevier. It is divided into: Embase Classic - Archival records of Excerpta Medica Abstract Journals (1947-1973) and Excerpta Medica - since 1974 to the present day.

It provides access to bibliographic records of articles from 7,000 journals, of which 1,800 biomedical journals is not indexed by Medline. Profile of indexed journal is more international than Medline, since 1989, with a particular focus on European literature [3,4].

The next system is an Elsevier Database, which presents electronic versions of Elsevier scientific journals published since 1995, including tables of contents, bibliographic data, abstracts and full text articles along with graphics. It contains 1,901 titles of magazines, including 1480 updated on a regular basis every week and 421, which are no longer updated. Another shared thematic platform is created by Wiley Online Library, since 2010. It includes electronic publications from a combination of earlier operating databases Blackwell Synergy and Wiley Interscience. It contains resources of publishes such as John Wiley & Sons, Wiley-Blackwell, Wiley-VCH, Jossey-Bass. On the platform there are more than 4 million articles from 1500 scientific journals. The database increases by almost 200 new records each month [5]. The Springer Database, in turn, every day updates 419 journals publishing by Springer Verlag. Next database, EBSCO is existing since 1994. It is a company's platform of scientific journals published by EBSCO. It includes, among others, databases such as: Medline Complete - the world's most comprehensive source of full text medical journals, contains articles from over 1,800 journals indexed in Medline. The full text articles date back to 1857.

The other available databases also should be mentioned, such as (Fig.5.):

- *Academic Search complete – database of 8500 full text journals, indexes and abstracts of 12500journals chronological range from 1887;*
- *Health Source - contains 550 full text scientific journals;*
- *Oxford Journals - electronic versions of 95 medical journals published by Oxford University Press (base archives date back to 1996);*
- *Lippincott, Williams & Wilkins - electronic versions of 104 medical journals;*
- *BMJ - 28 medical titles of full text journals published by BMJ Publishing Group. Since 1998, it was the electronic version of the printed journal British Medical Journal, published since 1840. In 1999, BMJ Publishing Group as the first magazine greatly extended versions of selected articles published in the Internet [6];*
- *Karger - a collection of 76 biomedical Karger full text journals; offering access to current numbers immediately, before publishing on paper;*
- *Informa Healthcare - 160 periodicals published by Informa Healthcare with a chronological range from 1997 to the current issue;*
- *Nature - allows access to the electronic version of the prestigious, existing since 1869 the British scientific journal Nature; Base chronological range extends from 1997 to the current issue.*

Figure 5. E-magazines in Main Medical Library.

MEDICAL INFORMATION CENTER

The current health policy is focused on use of various type of health data systems created for research, clinical trials and studies evaluate health care system. Many institutions change profile activity, concentrating on collecting, processing and purposeful use of available scientific information, which allows using them as a tool in the government activities. The care about the reliability of sources of information and the quality of such data seems to be significant.
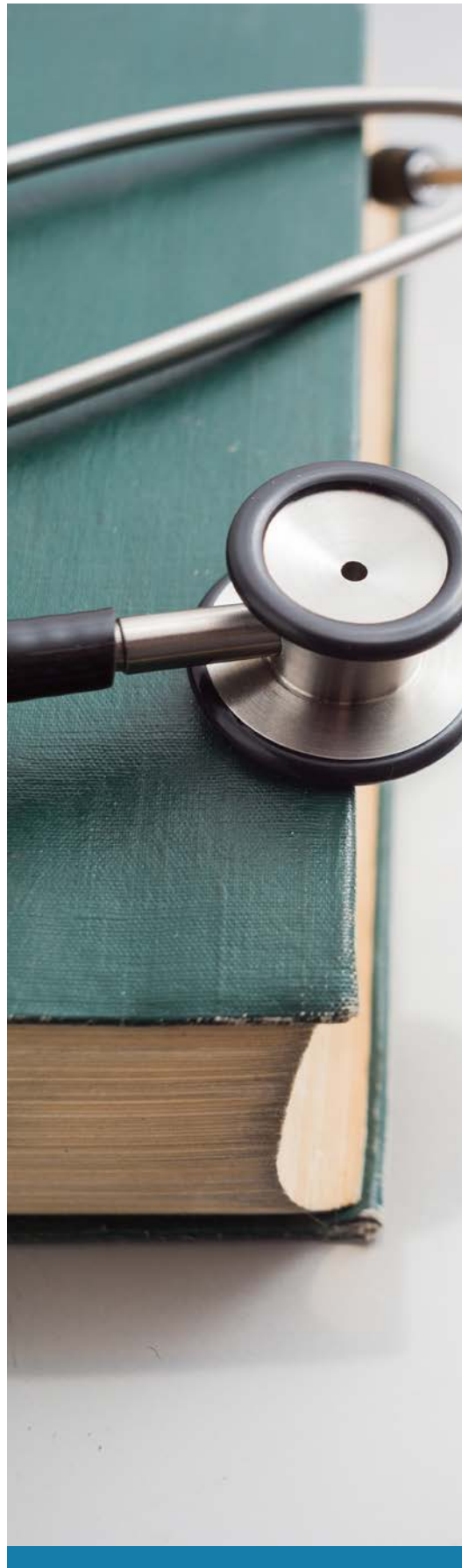
Creation of Medical Information Center (CIM) in the Main Medical Library enabled continuation and updating highly specialized information databases, which allows CIM to qualify as an opinion-forming unit (independent of lobbying influence), auxiliary tool in making decisions process about changes and procedures in the Polish health care system. The functioning of the CIM assume using the potential of individuals, such as GBL, AOTM, HTA and Medical Audit Agency. The Medical Information Center turns out to be an innovative instrument in shaping the administrative decisions concerning for example medicinal products market. PBL Database is a reliable source of current information concern all aspects of the Polish pharmaceutical market. The Main Medical Li-

brary is also the general distributor of World Health Organization's scientific information. The data system allows access to the Polish and global scientific achievements. Information obtained through the database is used in CIM for: professional preparation the most optimal system solutions in health care; creation of tips which could improve registration and authorization of food supplements and medical devices on the Polish drug market system; as well as substantive justification for the change or creation a new medical law by identifying the most secure solutions in the assessment of international research that should be implemented into national law. The aim of CIM is also cooperation with European Union members and global range, to optimize solutions in the Polish health care system as part of integrated systems in Europe, including variety aspects; for example immunization by vaccination.

The proper functioning of health records systems require their constant evolution, depending on the changing needs and expectations of users. Continuous improvement of systems is a necessity, especially if we take into account the promotion of international studies comparing the quality of care and efficiency of health care systems. All these activities should serve a common purpose health policy - strengthening the information infrastructure.

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Polish Pharmacoeconomic Society activities' review 1/2015

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The Polish Pharmacoeconomic Society, as in previous year, cooperated with the Journal of Health Policy and Outcomes Research (JHPOR) and supported the organization of the 2nd Scientific Conference dedicated to "Patients Registries - the role of the health system, new trends and hopes for Polish patients". The conference took place in Warsaw on 19th March 2015 and the President of the Scientific and Organizing Committee, prof. Karina Jahnz-Różyk opened the discussion followed by presentations of clinical experts from different therapeutic areas who shared their experience with disease registries.

There was a special session with Ministry of Health, HTA Agency (AOTM) and National Health Fund representatives participation. The invited guests discussed not only the current experience but also the existing challenges for RWD use and registries implementation in Poland.

The conference ended with an interesting interdisciplinary panel discussion where some of that challenges have been addressed and also the real world data needs in Poland have been discussed. Among other there were questions about the benefit for patients from collecting RWD, potential impact of the generated evidence on the health system and the therapeutic standards and drug policy. Some data already exists but do we really use it to improve the functioning of health care in Poland? How can we obtain more benefits from registries? Not all databases are registries however when collecting individual patient data there are legal aspects to be fulfilled, e.g. related to privacy of data and patient consent. Are we legally prepared for the wide registries implementation? What is the best way to successfully implement registries?

The conference will be followed by the postulate of the "seven milestones", presenting recommendations for the role of Patient Registries functioning in Poland.

Recent news from the Polish Pharmacoeconomic Society sections are that they started 2015 with new ideas and in addition to keep working on ongoing projects some new activities have been initiated.

The Therapeutic Programs, Pharmaceutical Care and Pharmaceutical Law Section (TPPCPL) continue to analyze adverse events costs based on therapeutic programs examples and in parallel started working on a pricing lexicon with the aim to explain pricing related terms in Polish language.

The Quality of Life Section having successfully edited English-Polish/Polish-English QoL Dictionary, started working on a QoL lexicon to provide more detailed explanation to QoL terms in Polish.