Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

PHD THESIS SUMMARY

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SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

CONTENTS

LIST OF PUBLICATIONS
LIST OF ABBREVIATIONS

Introduction

I. Theoretical considerations

1. GENERAL ASPECTS ON RHEUMATOLOGICAL DISEASES
   1.1. Definition of rheumatological disorders
      1.1.1. Triggering factors for rheumatic disease
      1.1.2. Clinical signs and symptoms
   1.2. Classification and characteristics of rheumatological disorders
      1.2.1. Criteria used as diagnostic tools for rheumatic diseases
      1.2.2. Methodological and statistical considerations regarding the criteria for classification of rheumatic diseases
      1.2.3. Specific criteria for classification of rheumatic diseases
   1.3. Assessment of severity of rheumatic diseases and pain
   1.4. Rheumatic diseases addressed in the context of the research program
      1.4.1. Rheumatoid arthritis
         1.4.1.1. Definition and classification
         1.4.1.2. Diagnostic methods
         1.4.1.3. Medication in rheumatoid arthritis
         1.4.1.4. Phases of treatment in rheumatoid arthritis
         1.4.1.5. Socio-economic impact on the patient
         1.4.1.6. Rheumatoid arthritis in the context of the research program
      1.4.2. Other rheumatological disorders addressed in the research program
         1.4.2.1. Clinical features and diagnostic methods
         1.4.2.2. Treatment and social impact
   1.5. Methods of self-management of the disease
      1.5.1. Impact on the patient
      1.5.2. Impact on society

2. PHARMACOECONOMIC INSTRUMENTS
   2.1. Pharmacoeconomics: concepts and methods
      2.1.1. Common types of economic studies
      2.1.2. Adherence
         2.1.2.1. Definition and issues
         2.1.2.2. Classification of adherence
         2.1.2.3. The importance of adherence in drug treatment
         2.1.2.4. Methods for measuring adherence
      2.1.3. Social cognitive models of rheumatic diseases
         2.1.3.1. Brief history
         2.1.3.2. The conceptual model of Planned Behaviour Theory: terms, applications and limitations
         2.1.3.3. Considerations regarding the connection between therapeutic adherence and the theory of planned behaviour
      2.1.4. Pharmacoeconomic instruments used in rheumatic diseases; defining the PRO (Patient-Reported Outcomes)
         2.1.4.1. CQR-19 Questionnaire (Compliance Questionnaire for Rheumatology)
         2.1.4.2. The PDSQ Questionnaire (Psychiatric Diagnostic Screening Questionnaire)
         2.1.4.3. Potential of electronic pharmacoeconomic instruments (ePRO)
   2.2. Pharmacoeconomics: applications
II. Personal contributions

3. Working hypothesis and general objectives
   3.1. Defining the working hypothesis
   3.2. Defining objectives

4. Study 1: Translation and cultural adaptation of the Compliance Questionnaire for Rheumatology (CQR19)
   4.1. Introduction (working hypothesis and specific objectives)
   4.2. Material and method
       4.2.1. Description of patient sample
       4.2.2. Translation procedure
   4.3. Results
   4.4. Discussions
   4.5. Conclusions

5. Study 2: Optimization by statistical methods of the CQR-19 Questionnaire applied to patients with rheumatic diseases in Romania
   5.1. Introduction (working hypothesis and specific objectives)
   5.2. Material and method
       5.2.1. Description of patient sample
       5.2.2. The treatment prescribed to the patients participating in the study
       5.2.3. Statistical analyses performed
   5.3. Results
   5.4. Discussions
   5.5. Conclusions

6. Study 3: Evaluation of depression and anxiety in patients with rheumatic diseases using pharmacoeconomic instruments
   6.1. Introduction (working hypothesis and specific objectives)
   6.2. Material and method
       6.2.1. Description of patient sample
       6.2.2. Research tools
       6.2.3. Statistical methods implemented
   6.3. Results
   6.4. Discussions
   6.5. Conclusions

7. Study 4: Development of a virtual tool for analysis and optimization of pharmacoeconomic results obtained in the treatment of rheumatic diseases
   7.1. Introduction (working hypothesis and specific objectives)
   7.2. Material and method
       7.2.1. LabVIEW – graphical programming environment
       7.2.2. Virtual tool for analyzing and optimizing patients’ adherence to the treatment of rheumatic diseases
           7.2.2.1. Front panel of the virtual instrument
           7.2.2.2. Block diagram of the virtual instrument
           7.2.2.3. How the virtual instrument works
   7.3. Obtained results
       7.3.1. Results obtained for all questionnaire items originally coded
       7.3.2. Results obtained for all questionnaire items (some recoded)
       7.3.3. Results obtained for the selected questions
   7.4. Discussions
   7.5. Conclusions

8. Conclusions and personal contributions

BIBLIOGRAPHY

ANNEXES
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

KEY WORDS

Adherence, Rheumatic diseases, Pharmacoeconomic instruments, Optimization, Statistics

SUMMARY

Currently, in Romania rheumatic diseases hold a central place in the area of chronic diseases, with serious effects on the quality of life of the population. In order to alleviate the effects of these conditions, it is of particular importance that besides the medication prescribed by the specialist, the patients should consider their attitude towards it.

In order to achieve high therapeutic goals a complete strategy is needed, which can be implemented at all decision-making levels; likely to lead to the patients' high adherence to the physician's recommendations. A low adherence to treatment can result in disease progression, increased disability and, ultimately, expensive medical therapies; all these requiring substantial costs.

The use of pharmacoeconomic instruments (patient-reported outcomes measures – PRO) in rheumatologic research is widespread, however, the use of data to assess the quality of rheumatologic care is less known.

Diseases-specific and generic tools used in rheumatology have progressed over time and more of them reflect what parts of the medical process is important for patients' quality of life.

The paper is structured in terms of content into two main parts presented below.

The first part of the paper represents a general part describing the current stage of topic-related knowledge, and it includes the general and theoretical aspects of the two fields which the research studies cover.

General aspects of rheumatologic diseases are presented in the first chapter and they refer to: triggering factors for the diseases, clinical signs and symptoms, specific criteria for classification and severity assessment. Also, the rheumatic diseases addressed in the context of the research program are reviewed. The pharmacoeconomic instruments used to analyze patient adherence to treatment (more particularly, rheumatic treatment) are addressed in Chapter Two.

General notions about adherence (definition, classification, importance for treatment, measurement methods) are defined, as well as the types of pharmacoeconomic instruments used in the research thesis. The concept of PRO (Patient Reported Outcomes) designates
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

The management of information taken directly from patients in the form of questionnaires.

The second part constitutes the main component of the research thesis and it includes the original personal contribution to the program (materialized in four studies).

Chapter Three sets out the working hypotheses and general research objectives. Since in Romania there is a lack of pharmacoeconomic instruments that evaluate the results obtained in the treatment of rheumatic diseases, we drew on the CQR-19 (English version) questionnaire which we translated, adapted and optimized to the specific conditions of our country. The overall objectives of this thesis underpin the increase the benefits of treatment and medical services with the help of pharmacoeconomic instruments adapted from a cultural point of view to the Romanian population by measuring patient adherence.

Chapter Four includes Study 1, which aims to translate and adapt the CQR-19 questionnaire to the Romanian culture in order to be administered to a group of patients with rheumatic diseases. For this purpose, a translation and adaptation methodology consisting of five stages involving a two-way (English-Romanian-English-Romanian) translation. The resulting questionnaire is administered to a sample of 24 patients diagnosed with rheumatic diseases (vertebral spondylosis, osteoarthritis, articular rheumatism, etc.), aged between 26 and 74 years old, having different backgrounds (20 patients are from the urban area and 4 patients from the rural area). The study of translation and cultural adaptation resulted in a final Romanian version of the questionnaire.

The pilot test shows a low adherence (3 patients are adherent with scores between 87-89%); this, besides translation and cultural adaptation of the questionnaire, indicates the need for another study, in which statistical analyses are carried out in order to increase the level of adherence of the patients.

In the second study presented, we developed and optimized a Romanian version of the CQR-19 questionnaire for patients with rheumatoid arthritis and other rheumatic diseases. In this study we used a number of 140 patients, of which 103 were provided with conventional treatment and 37 patients with biological treatment. As a data analysis tool, IBM SPSS (Statistical Program for Social Sciences) was used to work out descriptive statistical analyses for the patient sample characterization and exploratory factorial analysis by modeling structural equations.
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

In order to optimize the questionnaire obtained from Study 1, we used the statistical analysis in relation to two methods: the first one is called the method of recoding and the second the method of eliminating uncorrelated questions with the adherence score.

**Method 1** - recoding some of the questions that lower the initial adherence, by calculating it using the 19 questions quoted in the Likert scale. Another option of this method is that some questions (Q4, Q12, Q9), uncorrelated with the adherence score, following analysis based on the Pearson and Spearman correlation coefficients, are recoded. The third option of the method uses the importance of weight formula when the SPSS program considers or not certain questions with a weight based on the value of the given answers. In this case, the adherence value is given by the SPSS correlation. The results obtained are presented in Table 1.

**Table 1. Adherence of patients to treatment in three options (Output from SPSS)**

<table>
<thead>
<tr>
<th></th>
<th>Adherence of patients treated with conventional drugs (Standard deviation)</th>
<th>Adherence of patients treated with biological drugs (Standard deviation)</th>
<th>Low adherence (% of patients treated with conventional drugs are less than 80% adherent)</th>
<th>Low adherence (% of patients treated with biological drugs are less than 80% adherent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial version – all 19 questions queried Likert</td>
<td>57.13 (7.71)</td>
<td>65.86 (7.15)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Recoded questions (5-Q4, 5-Q12, 5-Q19)</td>
<td>56.16 (8.56)</td>
<td>73.49 (10.41)</td>
<td>97%</td>
<td>89%</td>
</tr>
<tr>
<td>Weighted questions (Q4, Q8, Q9, 5-Q12, 5-Q19)</td>
<td>63.13 (10.90)</td>
<td>77.98 (12.98)</td>
<td>92%</td>
<td>51%</td>
</tr>
</tbody>
</table>

Analyzing the data in the table above shows an increase on the score of adherence especially for patients treated with biological drugs (from 100% non-adherent initially to 51% non-adherent after optimization).

**Method 2** – *exploratory factor analysis* is used in the case that the questionnaire as a multivariate statistical procedure for reducing the number of variables (questions) and optimization them. The basic criteria for optimizing the questionnaire is given by the value of the Cronbach alpha index. This is a function of the number of patients in the study; average covariance between questionnaire questions and total score variation (measured adherence).
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

The factor analysis allows us to interpret the self-reporting questionnaire and reduce a large number of scale elements (19 questions) to a smaller and more manageable number (only 9 questions). The factor analysis results in a number of 5 own values (components or queries) having an Eigen total greater that 1; this is also graphically observed in Figure 1,a.

![Fig. 1. Diagram of values for all components considered by the SPSS program (Cattell Test-Scree Plot) for: a) the initial questionnaire with 19 questions, b) the questionnaire with 9 questions](image)

The table below displays the results obtained by the SPSS program for the five remaining questions sets.

<table>
<thead>
<tr>
<th>Component (question group)</th>
<th>Rotary Element Matrix Questions</th>
<th>Cronbach Alpha Coefficient for selected Questions</th>
<th>Cronbach Alpha if one of the questions is deleted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Q1, Q5, Q6, Q15, Q16, Q17, Q19</td>
<td>0.683</td>
<td>0.861 (if Q19 was deleted)</td>
</tr>
<tr>
<td>2</td>
<td>Q2, Q3, Q4, Q13, Q14, Q18</td>
<td>0.615</td>
<td>0.834 (if Q4 was deleted)</td>
</tr>
<tr>
<td>3</td>
<td>Q6, Q7, Q11, Q12</td>
<td>0.251</td>
<td>0.722 (if Q12 was deleted)</td>
</tr>
<tr>
<td>4</td>
<td>Q1, Q8, Q9, Q19</td>
<td>0.019</td>
<td>0.499 (if Q1 was deleted)</td>
</tr>
<tr>
<td>5</td>
<td>Q3, Q10, Q11</td>
<td>0.391</td>
<td>0.471 (if Q11 was deleted)</td>
</tr>
</tbody>
</table>

After the sequential analysis of the Exploratory Factor, Measure of Sampling Adequancy (MSA) and Exploratory Factor weight were recalculated. The table below shows the results obtained for each new type of CQR questionnaire when removing certain
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

questions (items). The notations used in the table are: CQR-19,16,15,12,9=Rheumatology adherence questionnaire with the number of articles (questions) considered; MSA=sampling adequacy measure.

**Table 3. Exploratory Factor Analysis of Complete and Reduced Versions of Rheumatology Compliance Questionnaire (CQR) – results from SPSS**

<table>
<thead>
<tr>
<th>Factor Analysis-Number of Questions (Items)</th>
<th>Value KMO</th>
<th>Numer of items removed</th>
<th>MSA value for removed questions</th>
<th>Importance of questions removed</th>
<th>Number of components</th>
<th>Total variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-CQR19</td>
<td>0.870</td>
<td></td>
<td></td>
<td>5</td>
<td>64.028</td>
<td></td>
</tr>
<tr>
<td>2-CQR16</td>
<td>0.864</td>
<td>Q4 Q12 Q19</td>
<td>0.303 0.474 0.520</td>
<td>4</td>
<td>63.761</td>
<td></td>
</tr>
<tr>
<td>3-CQR15</td>
<td>0.862</td>
<td>Q7</td>
<td>0.376</td>
<td>4</td>
<td>65.123</td>
<td></td>
</tr>
<tr>
<td>4-CQR12</td>
<td>0.859</td>
<td>Q1 Q3 Q10</td>
<td>0.376 0.309 0.309</td>
<td>4</td>
<td>65.781</td>
<td></td>
</tr>
<tr>
<td>5-CQR9</td>
<td>0.855</td>
<td>Q8 Q9 Q11</td>
<td>0.192 0.192 0.479</td>
<td>3</td>
<td>62.892</td>
<td></td>
</tr>
<tr>
<td>6-CQR9</td>
<td><strong>0.865</strong></td>
<td></td>
<td></td>
<td>2</td>
<td>66.778</td>
<td></td>
</tr>
</tbody>
</table>

The chart of the values for the 9 components resulting from SPSS optimization (Cattell-Scree Pot) is illustrated in (Figure 1,b). It can be seen from the figure that the last CQR-9 (with 9 questions) has two components with an Eigen value higher than 1, which reflects the adherence results. The final value of the 0.852 KMO for the CQR-9 suggests a very good internal reliability of the scale for this questionnaire.

Both groups of questions that remained at the end of the SPSS analysis showed a very good internal reliability: 0.849 for group 1 and 0.853 for group 2. Questions in group number 1 (Q5, Q6, Q15, Q16, Q17) emphasize the trust that patients put in the rheumatologist and also in the treatment that s/he prescribes. Questions in group number 2 (Q2, Q13, Q14, Q18) highlights that patients undergo the prescribed treatment of the physician for fear of any aggravating consequences of the illness they have been suffering from.

In addition to improving the adherence score (patients treated with biological drugs had an adherence average of 81.08% versus 65.86% initially), this method also provides other useful information about the motivations of the patients interviewed regarding the treatment taken.

The adherence value obtained by using the CQR-9 questionnaire was closer to reality, in the sense that some patients treated with biological drugs became even 100%
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

adherent. Also, the two subscales of the new CQR-9 optimized questionnaire point out that psychosocial factors, especially perceptions, are strong predictors of adherence to anti-rheumatic drugs.

The main objectives of study 3 presented in Chapter Six are to determine the connection between low adherence of patients to rheumatologic treatment and mental disorders that may occur (the degree of depression and anxiety). In order to determine this correlation, two questionnaires (CQR-19 AND PDSQ-psychiatric screening questionnaires) are used as instruments for pharmacoeconomic measurement; the group of 119 patients with rheumatic diseases was divided into two study groups: a group of 40 patients with biological treatment and 79 patients with conventional treatment. For statistical processing is used the program SPSS and the following tests: independent T-test, Mann-Whitney U test and Kolmogorov-Smirnov test.

Table 4 presents the subscales of the questionnaire PDSQ with the correlations (p) calculated with Man-Whitney U test using the SPSS program.

Table 4. PDSQ scores for the two groups of patients (Man-Whitney U test – output from SPSS)

<table>
<thead>
<tr>
<th>PDSQ subscales</th>
<th>Critical point</th>
<th>Group 1 (Mean±SD)</th>
<th>Group 2 (Mean±SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depressive Disorder (MDD)</td>
<td>9</td>
<td>0.65±1.59</td>
<td>3.95±4.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Posttraumatic Stress Disorder (PSD)</td>
<td>5</td>
<td>0.44±1.22</td>
<td>1.25±2.11</td>
<td>0.013</td>
</tr>
<tr>
<td>Bulimia/Binge-Eating Disorder (BD)</td>
<td>7</td>
<td>0.27±0.73</td>
<td>1.20±2.31</td>
<td>0.015</td>
</tr>
<tr>
<td>Obsessive-Compulsive Disorder (OCD)</td>
<td>1</td>
<td>0.71±1</td>
<td>0.55±1.34</td>
<td>0.079</td>
</tr>
<tr>
<td>Panic Disorder (PD)</td>
<td>4</td>
<td>1.52±1.40</td>
<td>1.33±1.77</td>
<td>0.217</td>
</tr>
<tr>
<td>Psychosis (P)</td>
<td>1</td>
<td>0.14±0.47</td>
<td>0.35±0.95</td>
<td>0.135</td>
</tr>
<tr>
<td>Agoraphobia (A)</td>
<td>4</td>
<td>0.62±0.91</td>
<td>0.55±1.48</td>
<td>0.081</td>
</tr>
<tr>
<td>Social Phobia (SP)</td>
<td>4</td>
<td>1.32±2.25</td>
<td>1.80±3.10</td>
<td>0.583</td>
</tr>
<tr>
<td>Alcohol Abuse/Dependence (AD)</td>
<td>1</td>
<td>0.28±0.64</td>
<td>0.40±0.87</td>
<td>0.660</td>
</tr>
<tr>
<td>Drug Abuse/Dependence (DD)</td>
<td>1</td>
<td>0.37±0.86</td>
<td>0.75±1.46</td>
<td>0.131</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder (GAD)</td>
<td>7</td>
<td>1.33±1.98</td>
<td>1.45±2.32</td>
<td>0.683</td>
</tr>
<tr>
<td>Somatization Disorder (SD)</td>
<td>2</td>
<td>0.65±0.79</td>
<td>0.88±1.11</td>
<td>0.411</td>
</tr>
<tr>
<td>Hypochondriasis (H)</td>
<td>1</td>
<td>0.46±0.75</td>
<td>0.63±1.10</td>
<td>0.610</td>
</tr>
</tbody>
</table>
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

It is noteworthy that major depressive disorder and post-traumatic stress disorder are more likely encountered in the group of patients treated with biological rather than in those treated with traditional ones. This is because the clinical picture of the disease was more serious than in the patients provided only with conventional treatment.

For those in group 2, the awareness of the evolution of the disease with irreversible functional and structural damage can lead to depression. Bulimia as a defense mechanism against depression appears distinctly between the two groups, being higher in the group of patients treated with biological drugs. Only for 3 PDSQ scores: major depressive disorder (MDD<0.01), post-traumatic stress disorder (PSD=0.013), bulimia disorder (B=0.015), we found statistically significant differences between the two groups. The conclusion of this study is that in order to increase the effectiveness of the treatment prescribed by the rheumatologists, there is a constant need to supplement this treatment process with psychological care, which implies an approach in a general social context for each individual patient.

**Chapter Seven** of the thesis consists in detailed information about and structure of a virtual instrument originally designed and achieved; with the help of which the patients' adherence to rheumatoid arthritis treatment can be efficiently assessed. This complex tool allows for both building a database containing information about patients (name, surname, age, sex, education, occupation, etc.)

As a working hypotheses for carrying out this study, the information provided by the CQR-19 questionnaire (translated and culturally adapted in Study 1) is used to calculate the adherence to treatment of a number of 40 patients with rheumatic diseases from the Rheumatology Clinic of Craiova County Hospital, Romania. The graphical programming environment LabView (Laboratory Virtual Instrument Engineering Workbench) is exploited to create the virtual instrument which is considered and accepted as a standard in the field of graphic programming. In (Fig. 2) the five front panels of the virtual instrument that constitute a user-friendly interface are presented. With their help, all the operations necessary for the study can be carried out in a simple and fast way, ranging from the data entry, the building of a complex and complete database to the intended on-line or off-line analyses.

When a button is pressed, the processing results are displayed immediately in numeric, tabular or for easy interpretation in graphical form and in histograms.
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

With the help of this virtual tool, the level of adherence of a patient to a certain treatment can be calculated and displayed immediately, depending on his/her answers to the items of a questionnaire. An analysis can also be performed using statistical tools (Spearman and Pearson correlation) in order to optimize the questionnaire used by recoding or eliminating those questions that are not correlated with the adherence score. (Fig.3.a) presents the results of the analysis carried out from which it results that question number 12 has a poor negative association regarding the adherence score for the sample of 40 patients questioned: graph-direction is negative; numerical-Pearson and Spearman correlations have small, negative values; in contrast, question 18 has a strong positive association (Fig.3.b).

The virtual tool makes it easy to perform recoding or deleting questions that are not related to adherence; the results obtained are displayed immediately so that conclusions can be drawn regarding the fairness of the decisions made (in order to optimize the questionnaire so as to reflect as accurately as possible the patients’ adherence to the prescribed medication).
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

In (Fig. 4) an example is provided, which illustrates the operation of the instrument for a global assessment of patient adherence. Thus (Fig. 4,a) presents the situation in which all 19 questions, uncoded are considered. In this case, all the 40 patients interviewed are non-adherent (i.e., 100%). When selecting a number of 10 questions out of the 19 (see Fig.4,b) it is observed that the number of patients not adhering to the treatment (with an adherence below 80%) decreases to 18 patients (2 with 56%, 2 with 60%, 2 with 63%, 4 with 66%, 4 with 70%, 2 with 73% and 2 with 76%), representing 45% of the total patients; the number of adherent patients increases to 22 patients (representing 55% of the total).

Fig. 3. Analysis of the correlation of adherence to the questions: a) weak negative association for no. 12; b) strong positive association for question no. 18

Fig. 4. Global adherence analysis for: a) all questions, unrecoded; b) selected questions, not coded
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

The results obtained by data processing can be offered immediately or can be stored for future use; it can be said that we have also built a computer tool, with applications in the medical-pharmaceutical area.

The results of the analyzes obtained using various methods confirm the fairness and validity of the instruments used (the results are comparable between them). The conclusions, the personal contributions as well as the potential use of the research-driven results are highlighted in Chapter Eight, which shows the fulfillment of the main objective of the thesis, namely the development and optimization of some tools for measuring the pharmacoeconomic results obtained in the treatment of rheumatic diseases in Romania.

The obtained results point out to a thorough understanding of all the factors that influence the adherence of patients with rheumatic diseases to the treatment, equally indicating the less favourable aspects that the healthcare providers should take into account. These concerns are considered very important in the current context in Romania, characterized by an increase in patients’ non-adherence to treatment due to several factors, including education. This research program has shown that adherence to drugs is a complex process involving several models, all of which ultimately lead to informed decisions, balancing the benefits of a particular treatment and the costs incurred.
SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases

SELECTED BIBLIOGRAPHY


SUMMARY of the thesis: Development and optimization of pharmacoeconomic instruments and results obtained in the treatment of rheumatologic diseases


