University of Szeged

Faculty of Pharmacy

Institute of Pharmaceutical Technology and Regulatory Affairs

IMPORTANCE OF PATIENT REPORTED OUTCOME MEASUREMENTS IN THE DEVELOPMENT AND REGULATION OF TREATMENT STRATEGIES OF CHRONIC DISORDERS

Ph.D. Thesis

Helga Fekete

Supervisor:

Prof. Dr. Ildikó Csóka

2020

Table of Contents

List of Publications and lectures iv

Full papers related to the thesis iv

Scientific conference poster presentations related to the thesis iv

Scientific conference verbal presentations related to the thesis v

Abbreviations vi

1. Introduction and aims 1

2. Literature background 5

2.1 Osteoarthritis 5

2.2. Non-Insulin Dependent Diabetes Mellitus 7

2.3 Chronic Ophthalmic Disorders 7

2.4 Cardiovascular Diseases - Oral Anticoagulant Therapy 8

2.5 Health Related Quality of Life Questionnaires 10

2.5.1 Generic Health Related Quality of Life tools 10

2.5.2 Disease Specific Health Related Quality of Life tools 11

2.6 Quality by Design 12

3. Methods 13

3.1 Adaptation and validation of QAKHQoL for the Hungarian population 13

3.1.1 Study design 13

3.1.2 Questionnaire Translation and the cross-cultural adaptation process 14

3.1.3 Questionnaire Validation process 15

3.2 Not-Insulin Dependent Diabetes Mellitus - study design 16

3.3 Chronic Ophthalmic Disorders study set up 17

3.4 Cardiovascular Disease - Oral Anticoagulant Treatment survey methods and materials 18

3.5 Quality by Design – method development of QbD-TOM 19

3.6 Ishikawa diagram 20

4. Results and discussion 21

4.1 Osteoarthritis Knee and Hip Quality of Life survey results 21

4.1.1 Translation and content validity 21

4.1.2 Sample 21

4.1.3 Score distribution 23

4.1.4 Reliability 25

4.1.5 Known-group validity 25

4.1.6 Construct validity – convergent validity 27
4.2 Audit of Diabetes Dependent Quality of Life survey results 28
4.3 Chronic Ophthalmic Study main results 33
4.4 Cardiovascular Disease - Oral Anticoagulant Therapy survey main results 40
4.5 QbD-TOM model development main results 44
5. Conclusion, Discussion 47
6. Summary 50
8. References 52

List of Publications and lectures

Full papers related to the thesis

H. Fekete, F. Guillemin, E. Pallagi, R. Fekete, Z. Lippai, F. Luterán, I. Tóth, K. Tóth†, A. Vallata, C. Varjú, I. Csóka „Evaluation of Osteoarthritis Knee and Hip Quality of Life (OAKHQoL): adaptation and validation of the questionnaire in the Hungarian population" Therapeutic Advances in Musculoskeletal Disease DOI: 10.1177/1759720X20959570 – *accepted for publication*

Viola R, Fekete H, Csoka I. „Patients' knowledge on oral anticoagulant treatment in Hungary. Int J.Clin.Pharm". 39(6):1265-1272, (2017) - *published*

Helga Fekete, Róbert Fekete, Ildikó Csóka „Patient adherence and factors influencing quality of life in the case of osteoarthritic patients" Acta Pharmaceutica Hungarica DOI: 10.33892/aph.2019.89.126-132 - *published*

Helga Fekete, Tivadar Bíró, Edina Pallagi, Zoltán Aigner, Ildikó Csóka „Implementation of Patient Reported Outcome Measures (PROMs) in QbD based formulation development in ophthalmology" – Acta Pharmaceutica Hungarica - *accepted for publication*

H. Fekete, E. Pallagi, K. Tóth, I Csoka „Életminőség mérése hazai 2-es típusú Diabetes Mellitussal diagnosztizált betegek esetében" – Gyógyszerészet - *accepted for publication*

Edina Pallagi, Helga Fekete, Ildikó Csóka - "Quality by Design for Therapy Outcome Management (QbD-TOM): A new method for the risk based evaluation to improve Health Related Quality of Life" International Journal for Quality in Health Care – *under review*

Fekete Helga – „Kommunikáció Cukorbetegekkel" Magyar Családorvosok Lapja, Asszisztens Különszám/2019 nyár; 8-10 - *published*

Scientific conference poster presentations related to the thesis

1.H. Fekete, R. Fekete, I. Csóka, „Evaluation of patient adherence influencing factors in case of Hungarian osteoarthritic patients of the South Plain Region", Who-lof Esceo: World Congress On Osteoporosis, Osteoarthritis And Musculoskeletal Diseases, Florence, Italy, March 23-26, 2017 - OSTEOPOROSIS INTERNATIONAL 28 : Suppl. 1 pp. S422-S422. Paper: P710, 1 p. (2017)

2.H. Fekete, R. Fekete, I. Csoka, „Cross-Cultural adaptation of the „Osteoarthritis Knee and Hip Quality of Life " disease specific questionnaire — methods and results of the Pilot phase 1.", 7th BBBB International Conference on Pharmaceutical Sciences, Balatonfüred, Hungary, Oct. 5-7, 2017 - pp. 224-224. Paper: P2H-2, 1 p.

3.H. Fekete, E. Pallagi, Y. Bilici, I. Csoka, „Human aspects of Quality by Design based pharmaceutical development" 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Granada, Spain, Mar 19 - 22, 2018 - Paper: P 266, 2 p.

4. H. Fekete, E. Pallagi, I. Csóka „Translation Pharmacy in Diabetes care: human aspects based product and care design on QbD basis" European Federation for Pharmaceutical Sciences - EUFEPS- Annual Meeting, Athens, Greece, May 24-26, 2018

5. H. Fekete, T. Biró, J. Soos, E. Pallagi, Z. Aigner, I. Csóka „ Implementation of Patient Reported Outcome Measures (PROMs) in QbD based formulation development in ophthalmology "12th Central European Symposium on Pharmaceutical Technology and Regulatory Affairs and Satellite Symposium on Pharmaceutical Biotechnology", Szeged, Hungary, Sept. 20-22, 2018

Scientific conference verbal presentations related to the thesis

l. Fekete H.: „Ízületi gyulladásos betegek életminősége és adherenciája", Gyógyszertárműködtetés 2017. XXII. Konferencia Egerszalók, Magyarország, 2017. március 10-12.

2.Fekete H.: „Retrospektív vizsgálat — a régió alsó végtagi arthrosissal diagnosztizált betegeinek életminőségét, együttműködését befolyásoló tényezők, rizikó faktorok és általános betegségterhek" A rehabilitációs osztály 10 éves fennállásnak jubileumi tudományos ülése BKMK SZTE ÁOK Kiskunfélegyházi Telephelye, Kiskunfélegyháza, Magyarország, 2017. április 7.

3.Fekete H.: Magyarországi osteoarthrosisos populáció betegségterheinek, költségeinek felmérése - módszertan és vizsgálati szempontok" Osteológiai kongresszus, Balatonfüred, Magyarország, 2017. május 25-27.

Abbreviations

Audit of Diabetes Dependent Questionnaire – ADDQoL

Body Mass Index – BMI

Cardiovascular Diseases – CVDs

Confidence Interval – CI

Critical Process Parameter – CPP

Critical Quality Attribute – CQA

Design of Experiments – DoE

Design of Interventions – DoI

European Medicines Agency – EMA

Food and Drug Administration – FDA

General Practitioner – GP

Health-Related Quality of Life – HRQoL

International normalized ratio – INR

Intraclass Correlation Coefficient – ICC

National Institute for Health and Care Excellence – NICE

Non-Vitamin K Antagonist Oral Anticoagulant – NOAC

Non-Insulin Dependent Diabetes Mellitus – NIDDM

Non-Steroidal Anti-Inflammatory Drug – NSAID

Oral Anticoagulant Therapy – OAT

Osteoarthritis – OA

Osteoarthritis Knee and Hip Quality of Life – OAKHQoL

Over-The-Counter – OTC

Patient Reported Outcome – PRO

Patient Reported Outcome Measurement – PROM

Quality by Design – QbD

Quality Life Target Profile – QLTP

Quality Target Product Profile – QTPP

Risk Assessment – RA

Risk Estimation Matrix – REM

Time Trade Off – TTO

Visual Analogue Scale – VAS

Vitamin K Antagonists – VKA

World Health Organization – WHO

World Health Organization Quality of life Questionnaire – WHOQoL

Years Lived with Disability – YLD

1. Introduction and aims

In today's society, patients cannot be treated as they were earlier. Based on the possibilities of the Internet and the countless online health platforms, patients require being involved in their treatment, or at least they would like to feel that despite the information asymmetry between them and the health care providers, they are treated as an equal party regarding their health status. Patients are unable to provide objective feedback about the effectiveness of the received therapy, but their subjective opinion is very important in order to evaluate how the treatment in question affects the patients' everyday life. The subjective health value judgement of patients determines the quality of life, even their disorder, how they are able to fulfill their role in the family, on the labour market and in the society. Asking patients to provide self-perception regarding their health status makes them feel important and an active party in influencing their health. Incidentally, they provide feedback for health care providers, for research and development, for early treatment formulation and for competent authorities who are responsible for the marketing authorization of each new treatment. Besides, it is important to improve patients' health literacy, in other words their knowledge about the background of their status. Asking for the patients' opinion also helps to determine their health literacy, and this information may lead to finding possible points of intervention in order to develop the knowledge. Presumably, if patients' health literacy improves, they will provide higher adherence to their treatment, which will contribute to the success of therapy outcomes and quality of life improvement [1].

We live in an ever-aging society, which entails the fact that human beings are affected by more and more chronic disorders. Patients who have some symptoms visit health care providers, who determine their status, perform the necessary tests, prescribe medicines or suggest over-the-counter (hereinafter: OTC) medications. Patients are able to visit general practitioners, general or specified clinics or hospitals, they use out-patient or in-patient services, or go to the pharmacy. As it is seen, a patient spends a lot of time at different points of the health care system. At these different points of the system, they receive a lot of information, which they either do not understand or forget, and in several cases, patients are unable to select from among the information. This process consumes considerable time, energy, and money as well. In the end, most patients just follow their doctors' treatment suggestion as a passive party without being aware of its rationale, so they do not show adherence to their treatment. The communication among the affected parties – patients, doctors,

researchers and developers, formulation technologists, pharmacists – is not complete, the feedback from patients to the other parties involved is not ensured, not part of routine practice.

To improve patient centered care, feedback must be ensured to all other parties, and thereby the individuals' Health Related Quality of Life (hereinafter: HRQoL), adherence to treatment and health literacy can be improved as well. An adherent patient takes an active part in his/her therapy and understands the background of the requirements necessitated by the treatments, and in this case HRQoL can turn in a positive direction despite the chronic disorders and the need for lifelong treatment.

The definition of HRQoL based on the World Health Organization's (hereinafter: WHO) health definition is: *„a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity"*[2]. Almost all chronic disorders mean lifelong treatment for the affected patients. Adapting to long-term therapy and lifestyle changes is quite a challenge, and patient adherence to treatment and their persistence in the long term are essential for a successful therapy. In view of this fact, it is important to consider the patients' perceptions from the very beginning in the early development phase in order to fulfill Patient Centered Care and to ensure HRQoL. According to competent authorities (European Medicines Agency (hereinafter: EMA) and Food and Drug Administration (hereinafter: FDA), the term Patient Reported Outcome (hereinafter: PRO) is an umbrella term, which covers single and multidimensional measures as well in connection with the general health status of the patients, satisfaction with the treatment, adherence to the treatment, symptoms and HRQoL [3,4]. In addition, PROs evaluate all the subjective perceptions of the patients obtained directly from them [5]. These feedbacks offer information to the health care team to find the possible intervention for health status improvement, to develop the individualized and patient centered therapy and could also be useful for the researchers or the academics during the early development process [6,7,8,9,10,11,12,13,14,15,16]. Patient Reported Outcome Measurements (hereinafter: PROMs) are performed mostly via self-reported questionnaires. Generic and disease specific questionnaires are used for detecting PROs [17]. The importance of PROMs is documented, they have been used in the field of clinical trials for several years. In several cases, the use of PROs is required by the competent authorities for the authorization of a new pharmaceutical drug or a new indication [18,19,20,21,22]. According to the WHO's Quality of Life Questionnaire (hereinafter: WHOQoL), the influencing factors are divided into 4 domains: 1. Physical health (e.g. mobility, pain and discomfort, work capacity), 2.

Psychological (e.g. negative, positive feelings, religion, personal beliefs), 3. Social relationships (e.g. social support, sexual activity), 4. Environment (e.g. financial resources, transport, freedom) [2]. These dimensions cover all the relevant factors of HRQoL and could be useful to separate the influencing factors from the patients' point of view.

Based on the importance of the patients' point of view regarding the effectiveness of a used treatment, the aim of the Ph.D. research was to evaluate patients' HRQoL, their adherence to treatment and the burden of the disease in many different ways. To achieve this aim, the research team completed the evaluation through public/national health endemic disorders. The evaluated endemic disorders were selected in accordance with the prevalence and incidence of the chronic diseases. The Ph.D. work analyzed, as pilot studies, the different disorders in different ways, how to receive the patients' perceptions as regards their conditions and how to provide the information received to the different parties concerned. The observed disorders were the following: Osteoarthritis (hereinafter: OA), type 2 diabetes mellitus, in other words non-insulin dependent diabetes (hereinafter: NIDDM), chronic ophthalmic disorders, and cardiovascular diseases (hereinafter: CVDs). CVDs constitute a very huge category of disorders, therefore from the group of CDVs patients affected by deep vein thrombosis were analyzed, those who need to be treated with oral anticoagulant therapy (hereinafter: OAT). Because of the different disorders, the research team worked together with various parties in the system, which means that all pilot studies centered on the patients, while the other party was different, such as formulation technologists, academia, doctors and pharmacists. Based on the conclusions the research team developed a Quality by Design (hereinafter: QbD) based method in order to provide a general tool which can be used in all chronic disorders for measuring patients' perceptions, and which method can provide feedback to all the parties who are involved in patient care in some way. Figure 1. summarizes the basic points of the research work performed.

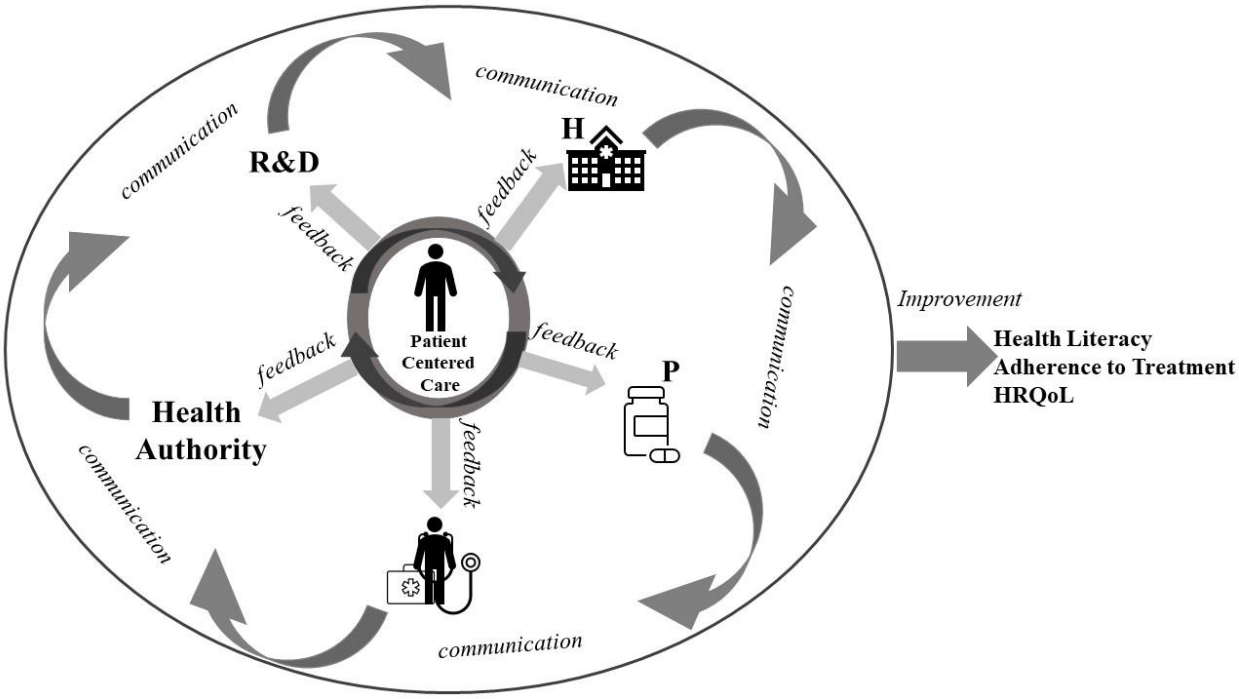


Figure 1. – Intervention points for Patient Centered Care improvement

2. Literature background

2.1 Osteoarthritis

Among chronic conditions, diseases affecting the musculoskeletal system are on the rise; besides the basic disease, they cause several other diseases, loss of quality of life, loss of working capacity on the labour market, etc., and thus they put an increasing burden on the patients concerned and on the society both regarding quality of life and in economic terms. OA, including coxarthrosis and gonarthrosis, is a major cause of severe pain, limited mobility and disability resulting in a significant reduction in quality of life [23,24,25]. It means increasing costs for the individuals and for the society as well [26,27,28,29]. According to the Global Burden of Disease 2010 Study, OA accounts for 17.1 million of the total global years lived with disability (hereinafter: YLDs), which supposedly means the 11th leading cause of disability in the world [30,31]. The affected patients have incapacity for work, difficulty in applying for a job or early retirement [32]. An estimated 9.6% of males and 18% of females aged over 60 years old are affected worldwide and this prevalence increases with age [33,34,35,36,37]. In Hungary, the number of patients affected can only be estimated; during the European Health Interview Survey of 2014, 17% of the people asked were found to have arthrosis-related joint pain, which can mean the involvement of about 1,600,000 people nationwide [38]. The Global Burden of Disease 2015 Study stated that the prevalence (thousands) of OA increased from 178,665 (2005) to 237,369 (2015) [39].

The importance and the severity of the issue were recognized worldwide, and the 'Decade of Bones and Joints' was proclaimed in 2000, which was extended until 2020 due to its success, and several other European organizations have also taken steps to focus attention on the disease [40,41,42]. Hungary was the first to join the program on state level and achieved major success in many areas [43,44]. In spite of all these efforts, very few Hungarian studies have been made and published on OA (erosion of articular cartilage).

Arthrosis is the leading cause of disability and pain all over the world and was ranked as the 6th most common cause of disability in 2003, estimated to be the 4th in rank in 2020 [34,45,46].

The measurement of the quality of life and adherence of patients suffering from OA is complicated by several factors, which are the following:

- The disease is usually diagnosed when it is already in an advanced stage, i.e., when there are severe symptoms. The therapeutic options are limited; what can be achieved is mainly the alleviation of the symptoms for a longer or shorter period [47,48, 49].

- As opposed to other musculoskeletal disorders, no well-proved disease-modifying active ingredient is available [50,51].
- Due to the complex nature of the disease, the patient's active and conscious cooperation with the healthcare professionals involved in the treatment is essential.

The therapy is described in the National Institute for Health and Care Excellence's (hereinafter: NICE) guideline [52], which divides the tasks into three separate parts. The first and foremost is the education of patients during treatment, both by doctors and pharmacists, which includes the promotion of a healthy lifestyle, the incorporation of sports into everyday life, i.e. health-conscious behavior; and also adopting the so-called Mediterranean diet [53]. All these reduce the risk of the most important risk factor, obesity, as well as the development or worsening of cardiovascular diseases, diabetes mellitus and mental illnesses, which are also risk factors in the incidence of OA. Another element of therapy is the use of non-pharmacological therapies, which include electrical impulse therapies, manual therapies and balneological therapies. Currently, these provide the longest asymptomatic period. Paracetamol and non-steroidal anti-inflammatory drugs (hereinafter: NSAIDs), usually applied topically then orally, are the drugs of first choice in medicated therapies. If they fail to be effective, the administration of the opioid analgesic tramadol is recommended. Most of the active ingredients mentioned in the first group are also available in drugs without a prescription, so the extent of their use cannot be measured in this disease; it is well-known that their excessive and combined use generates several adverse effects and causes additional burdens. The protocol does not recommend the use of chondroprotective drugs, although patients often expect these "miracle drugs" to rebuild cartilage. Commercially available products are available to users through a number of distribution chains, frequently bypassing healthcare professionals; this can result in uncontrolled use if communication between the parties is inadequate during patient care.

The rational use of the great number of over-the-counter drugs and chondroprotective preparations can be controlled only by the pharmacist, who can provide information to the family doctor and to the specialist, and can also recommend the patient to visit the doctor.

On the other hand, physicians and physiotherapists can inform the pharmacist about the patients' medical history, who can then dispense the medication with this knowledge.

In the light of all these facts, it can be hypothesized that adherence can be improved if OA patients' burdens affecting therapeutic cooperation are explored. With the improvement of adherence, patient satisfaction and cooperation with therapy improve, which in turn has a favorable influence on specific parameters of quality of life, resulting in improvements at individual, family and social levels. Given the complexity of the therapy, this can be achieved only through the collaboration of the healthcare professionals participating in the treatment, which will improve therapeutic efficiency.

2.2. Non-Insulin Dependent Diabetes Mellitus

DM is a public disease in today's society. The ever-growing patient number and the co-morbidities basically improved influencing factor of the disorder on the society. The WHO survey *"Global Diabetes Report"* dated 2014 estimated that the number of patients over 18 years of age living with diabetes was 422 million worldwide, compared to 108 million in 1980, which is a drastic increase within 35 years. Almost 90% of the patients were affected by NIDDM, which caused the death of 1.5 million people in 2012. According to the WHO, DM is going to be the 7th leading cause of death by 2030. DM affected 8% of the Hungarian population aged 19-70 in 2014. [54,55,56]. NIDDM develops over long years, typically after the thirties. The evolved co-morbidities should be considered at the time of the diagnosis. NIDDM is a complex disorder, a number of individual-dependent parameters and lifestyle traits contribute to the likelihood of its development and/or exacerbation. Among members of the society, the following people are most at risk: those who have a Body Mass Index (hereinafter: BMI) above 25kg/m^2, who live a life without doing sport activities, or who smoke. The disorder has macrovascular and microvascular co-morbidities. Macrovascular co-morbidities include coronary diseases such as acute myocardial infarct, cerebrovascular diseases such as stroke or peripheral artery disorders. Microvascular co-morbidities include retinopathy, nephropathy, neuropathy, or the so-called diabetic leg [56]. NIDDM is a chronic disorder necessitating lifelong treatment, and this fact basically influences the affected patients' everyday life and has a huge impact on their quality of life.

2.3 Chronic Ophthalmic Disorders

The eye is one of the most important human organs of sense. Any disorder which affects vision leads to the patients' frustration, anxiety and also an unsatisfactory quality of life. Chronic

ophthalmic disorders such as glaucoma or chronic dry syndrome probably mean lifelong therapy as well, similarly to OA and DM. The treatment of eye disorders, especially in the long term, is very complex due to the anatomical characteristics of the eye and the patients' compliance, or in the case of long-term therapy better to use the term persistence. Drug formulation is challenging for pharmaceutical technologists because of the lipophilic – hydrophilic nature of the eye at the same time and its extreme sensitivity. In chronic eye disorders the main target is mostly the posterior segment of the eye, such as the lens, vitreous humour, retina sclera and optic nerve. Although mostly invasive routes of administration such as intravitreal and subconjunctival injections are used for treating the posterior segment, there are also publications regarding non-invasive posterior treatment methods, but obviously very few options are available [57,58,59,60,61,62,63]. There is a need for a more non-invasive treatment option which could be performed by the subject, without needing a qualified caregiver, and could be used chronically. Non-invasive methods are in the first line of topical eye drugs, like eye drops and eye lotions. Currently, the patients' role and adherence are crucial in the case of these types of eye medications. To create non-invasive eye drugs which are capable of reaching the posterior segment, besides the pharmaceutical technology aspects, it is very important to take into consideration the patients' feedback and their point of view. The patients' perceptions can be summarized by using an appropriately designed method, and thereby feedback can be provided to pharmaceutical technologists, who can implement the results in the early phase of drug formulation. The QbD based approach may be a sufficient tool to achieve this process. The QbD based method can bridge the gap between different stakeholders, such as patients, health care professionals and technologists. With this approach, a final product can be produced which contains all the interested parties' perceptions and expectations, and also there is possibility for better patient adherence and positive HRQoL.

2.4 Cardiovascular Diseases - Oral Anticoagulant Therapy

CVDs are the leading cause of death globally, approximately 17.9 million people died of CVDs according to a WHO report in 2016. CVDs constitute a huge group of disorders. All diseases affect the heart and the blood vessels. Among others, CVDs include the following: cerebrovascular, coronary heart disease, peripheral arterial disease, rheumatic heart disorders and deep vein

thrombosis. Based on our unhealthy lifestyle in today's society (smoking, lack of sport activities, junk food, workaholic behavior), almost each human being is at risk for CVDs [64].

Thromboembolism has special epidemiologic significance. Despite effective tools being available for its prevention and treatment, its mortality and morbidity rates have not changed as desired [65,66]. Vitamin K antagonists (hereinafter: VKAs), such as acenocoumarol and warfarin, form the basis of their oral anticoagulant therapy, while there has been a recent trend of gradually increasing the use of novel non-vitamin K antagonist oral anticoagulants (hereinafter: NOAC), such as dabigatran, rivaroxaban, or apixaban [67,68]. Safe and effective OAT is achieved in highly compliant patients only. Persistence in OAT is facilitated by the adequately informed, well-educated patient's participation in the therapy [69]. Several studies indicate that reduced adherence to the therapeutic regimen and low level of patient knowledge about OAT are the main causes of complications (e.g. major bleeding) and suboptimal clinical outcomes (e.g. INR value outside the therapeutic range) [69,70,71,72,73,74,75,76]. In Hungary, general practitioners (hereinafter: GPs) manage most patients requiring OAT. In the Hungarian health care system, traditionally the main role of out-patient pharmacists/pharmacies is dispensing the prescribed medication and providing basic instructions regarding their use, but pharmacists are generally not involved in therapeutic decision making, they have limited access to patient's health care data and therefore limited option to "treat" the patients and improve their health literacy. Studies suggest that wider sources of patient education within the health care system efficiently improve knowledge and adherence resulting in better clinical outcomes [77,78]. In addition, the aim of the survey regarding OAT treatment adherence was to access patient knowledge in connection with OAT and reveal knowledge gaps. A further goal was to identify any groups of patients at risk of having critically low levels of knowledge of OAT. These findings could reveal the specific areas to focus on during an effective patient education program in daily pharmaceutical care.

2.5 Health Related Quality of Life Questionnaires

Generic and disease specific questionnaires as part of PROMs are useful tools to evaluate patients' perceptions about their health status, their current treatments, or their HRQoL. These types of questionnaires are promising tools for the evaluation of the burden-of-illness, the diagnosis, or the treatment options – as noted in the Introduction section. To fulfill the basic aim of the research work, several general and disease specific questionnaires were applied [79].

2.5.1 Generic Health Related Quality of Life tools

Among generic HRQoL questionnaires, the widely used EQ-5D-3L and the WHOQoL-BREF questionnaires were part of the research work. Based on the reviewed scientific literature, in each case where generic HRQoL was used as a reference, these tools were part of the research work, and otherwise these questionnaires validated the Hungarian adaptation, which was also an important aspect from the technical point of view.

2.5.1.1 EQ-5D-3L

EQ-5D-3L is a generic HRQoL measurement tool, available in more than 170 languages, including the Hungarian language. This questionnaire is divided into 5 dimensions, each with one item: mobility, usual activities, self-care, pain/discomfort and anxiety/depression, resulting in a simple descriptive profile about the individual's perceptions of the health status, ranging from 0 (bad health value) to 1 (good health value). However, the range is defined between 0-1, the calculation could result a value under 0, which means that there are several health statuses which affect the patients harder than death. Within each dimension, there is a three-level response option. Level 1: No problem, Level 2: Moderate problem, Level 3: Severe problem. 3^5 =243 health statuses can be stated by calculating the EQ-5D index. Based on the given responses, an official online calculator considers the EQ-5D index number as regards Visual Analogue Scale (hereinafter: VAS) and Time Trade of Method (hereinafter: TTO). Several countries in Eastern and Central Europe have no individual national value set for calculation, and neither does Hungary. In this case, the British value set is recommended to be used for the Hungarian calculation according to the practical proposals in the relevant literature. The VAS is part of the EQ-5D, mentioned as a health status thermometer, ranging from 0 to 100 for the patients to evaluate their current general health status. 0 represents the worst possible health status and 100 represents the best possible health status [80,81,82,83,84,85,86]. EQ-5D-3L questionnaire was used in the case of arthritic specific questionnaire in the Hungarian adaptation and validation process, in the case of NIDDM

evaluation among patients in pharmacy practice, and dimensions of EQ-5D-3L were the bases of the QbD based method development.

2.5.1.2 WHOQoL-BREF

WHOQOL-BREF is the abbreviated version of the World Health Organization's generic HRQOL questionnaire, available in the Hungarian language [87]. This tool is made up of 26 items, divided into 4 domains: physical health (7), psychological health (6), social relationship (3), environment (8) and two independent items – one about the individual's overall perception of quality of life and one about the individual's overall perception of his/her own health. The Likert response scale was used with the range from 1 (worst status) to 5 (best status). Domain scores were scaled in a positive direction – higher scores reflected higher quality of life. Within each domain the mean score of items was used to calculate the domain score. Based on the guideline, the domain score result was transformed to a 0-100 scale. The evaluation was constructed according to the WHOQoL-BREF instruction guideline [88,89,90,91].

2.5.2 Disease Specific Health Related Quality of Life tools

Disease specific tools are used in order to analyze specific characteristics of the disorders in question. By using this type of questionnaires, it is possible to monitor how specific disorders affect quality of life.

2.5.2.1 Osteoarthritis Knee and Hip Quality of Life Questionnaire

The "Osteoarthritis Knee and Hip Quality of Life questionnaire (hereinafter: OAKHQoL), developed by French researchers, is multidimensional and covers all the dimensions which are highlighted for patients affected by lower limb OA [92,93,94,95]. The OAKHQoL disease specific questionnaire has been translated into different languages and proved to be a successful instrument for measuring quality of life in the case of knee and hip OA patients [96,97,98,99,100,101,102].

2.5.2.2 Audit of Diabetes Dependent Quality of Life

Based on the scientific literature's review, the Audit of Diabetes Dependent Quality of Life questionnaire (hereinafter: ADDQoL) was selected for the evaluation of the targeted Hungarian population, suffering from NIDDM. ADDQoL was developed by British scientists and has many years of experience, and it was adapted and validated for several languages, among others for Hungarian as well [103,104]. This tool assesses the impact and the importance of DM on various aspects of HRQoL for diabetic patients. Based on the results of impact and importance scores, the weighted impact (WI) score is calculated by multiplying them. By averaging all the weighted

scores, the average weighted impact (AWI) score is obtained and is interpreted as the overall weighted impact score of DM on HRQoL. Prior to the research work, the developer of the questionnaire gave official permission for the use of the tool and provided the guideline for the evaluation of the results.

2.6 Quality by Design

The QbD approach of the developments was used generally in the pharmaceutical industry and its application was forced by regulatory authorities as well. The original Quality by Design (QbD) concept is a risk, knowledge and preliminary design focused manner of pharmaceutical development [105]. The concept places the emphasis on the critical points based on accurate prior planning, where the critical points are defined by risk evaluation. QbD is also described as a holistic and systemic quality management method according to the relevant ICH guidelines (ICH Q82R, Q9 and Q10) [106,107,108]. According to the guidelines, it begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. The first step in the case of a QbD based pharmaceutical development is precise target definition [105], which is based on the therapeutic role and performance of the product. Quality Target Product Profile (hereinafter: QTPP) forms the basis of product development design. It is a prospective summary of the quality characteristics of the product that will be achieved ideally, including patient-relevant product performance and professional requirements based on regulation. After defining the QTPP, the identification of Critical Parameters (called Critical Quality Attributes, CQAs, if related to quality and Critical Process Parameters, CPPs, if related to the process selected previously) is the next step, followed by Risk Assessment (RA), which is the key element of the whole QbD based development process. The identification of potential CQAs means the selection of those characteristics which influence the final product's performance and quality. The collection and systemic evaluation of the influencing factors is called "Knowledge Space Development" [108]. These steps are followed by setting up the control strategy related to the critical factors, and a new circle starts in order to achieve continuous quality improvement. In all cases, the product should be designed to meet patients' needs and the intended product performance. As this QbD method is highly recommended by the regulatory authorities, it is more and more commonly used in pharmaceutical industrial developments and research, having advantages for all stakeholders (patient, industry and competent authority). It offers a better understanding of product and process for manufacturers,

and also provides regulatory flexibility and increased assurance of product quality for the patients. The extension of this model was made to the early phases of pharmaceutical research, emphasizing the role of knowledge based pre-formulation design, in order to select the proper active agent and dosage form based on the unmet clinical needs and patient expectations as well [109]. Besides quality and safety issues, patients also have preferences and subjective decisions on therapeutic adherence [110], which should be taken into consideration in the very early phase, when decision is made on the administration route and dosage forms [111,112]. The era of "patient centered care" has started with this [113,114], resulting in new approaches in health care delivery and scientific research [115], involving the consideration of PROs as well [116].

3. Methods

3.1 Adaptation and validation of OAKHQoL for the Hungarian population

3.1.1 Study design

This prospective study was performed among patients diagnosed – by the doctors, acting as the expert panel of this study – with OA of the lower limb. The recruitment was performed between June 2017 and November 2017, in six hospitals situated in six different geographical regions of Hungary. The participating hospitals were selected in a way to represent different geographic and cultural areas of the country; the patients were selected randomly by the doctors of the given sites after evaluating the inclusion criteria, which were as follows: age over 18 years, clinically/doctor diagnosed knee and/or hip OA, native Hungarian language, the ability of self-filling and completely filled patient data sheet. Exclusion criteria was age under 18 years, other type of OA, psychiatric disorders and those who had surgeries within 1 month, or who were incapable of filling in the forms.

This research was evaluated and approved by the Hungarian Medical Research Council, acting as the National Ethics Committee, its registration number is: 24950-3/2016/EKU. Printed Patient Information Sheet was provided to each participating patient, patients had enough time to think over the participation, had opportunity to ask questions and their questions were answered, then the participating patients gave verbal informed consent. Each participating patient received the Patient Data Sheet. The Patient Data Sheet contains questions related to patients' demographic characteristics: gender, year of birth, height and weight – to calculate the BMI, residence type (urban or rural), education level, marital status, OA duration, income level, type of OA (knee, hip,

both). In accordance with the reviewed international and national literature and the evaluated parameters, the research team made the following hypothesis: Participants with higher ages will suffer more from OA, and more females will be affected.

3.1.2 Questionnaire Translation and the cross-cultural adaptation process

The adaptation process of the OAKHQOL questionnaire was conducted according to the published guidelines, based on the instructions and cooperation with the researchers of the original questionnaire [117,118,119]. The committee of the procedure was composed of: (1) Translation committee (4 members), (2) Team of the University of Szeged, as moderator (4 members), (3) Expert panel (6 doctors of the study sites: orthopedists, rheumatologists, musculoskeletal rehabilitation doctors).

Step 1: The original French questionnaire's English version was translated into the Hungarian language by two translators independently of each other. The using of the English version of the original questionnaire for the adaptation process was recommended by the developer as it is equivalent with the French one. One of the translators was a health care professional and the other one was a professional bilingual translator based on the guideline.

Step 2: The two created versions – TH1 and TH2 (translated-Hungarian) – were merged into one (named TH1.2.) by the expert panel, based on their experience with the Hungarian patients.

Step 3: The expert panel suggested some changes which made the questionnaire fit to national characteristics. Hungarian language limitations justified the merging of two questions. This was approved by the developers of the questionnaire and the local professional panel too: two pairs of questions were merged, and two new ones were added.

Step 4: The content validity of the TH1.2. pre-final version was tested within a focus group by interviewing 34 patients. This formed the pre-testing procedure. This TH1.2. version was translated backward by two native English-speaking persons independently (backward-English - BE1 and BE2), and then this was synthetized by the research group to form the final OAKHQoL-HUN version. (The TH1.2 version and OAKHQoL-HUN are the same, the former is in Hungarian and the latter is in English).

Step 5: This step was the pilot testing procedure in order to evaluate the psychometric properties of the questionnaire. 99 questionnaires – from the initial 125 – met the requirements of complete filling, and 30 of them were ready to participate in the re-testing procedure (re-fill) after one month.

From the 125 questionnaires, 26 were excluded as they did not meet one of the inclusion criteria, namely, in these cases the patient data sheets were not completely filled in.

3.1.3 Questionnaire Validation process

3.1.3.1 OAKHQoL:

The original OAKHQoL questionnaire contains 43 items, where 40 items are divided into five domains: physical activity (16), mental health (13), pain (43), social support (4), social activity (3) and three independent items about professional life, sexual activity and relationships [92,93]. Each question was responded by a 0-10 response scale, where 0 determined the worst status and 10 determined the best status. The score of each dimension is standardized to a 0 (worst level of quality of life) to 100 scale (best level of quality of life). In accordance with the guideline, if missing items are below 5% within a domain, the domain is evaluable. The code number for the missing items was "99".

3.1.3.2 Statistical analysis

The statistical evaluation of data was made by means of the 23.0 version of the SPSS program. The adapted OAKHQoL-HUN questionnaire items were grouped into the five dimensions and three independent questions, then the standardized scores (0–100) were calculated in case of each dimension based on the scoring sheet. The descriptive analysis was determined by mean, standard deviation, missing items, and the observed and theoretical range. Validity and reliability were evaluated as well [120,121].

3.1.3.3 Validity assessment

Content validity was performed by the doctors forming the expert panel. The doctors evaluated how understandable the questionnaire was. This process represented *Step 4*. Construct validity and discriminant validity (otherwise known-group validity, hereinafter: known-group validity) were evaluated as well. Construct validity is used when similar dimensions of the different measurement tools are measured with the same construct (convergent validity), [120,121,122,123]. In this way, the OAKHQoL-HUN 5 domains were compared to two generic quality of life questionnaires' domains (WHOQoL-BREF and EQ-5D). Correlation with other musculoskeletal tools was not possible due to the fact that at the time of the practical part of this research (2017), there was no OA specific questionnaire available in Hungary. The determination of the correlation was calculated by using Pearson's correlation coefficients (r). The correlation was evaluated as poor (0-0.2), fair (0.2-0.4), moderate (0.4-0.6), very good (0.6-0.8), and excellent (0.8-1.0) [122,123].

To determine known-group validity, the OAKHQoL-HUN 5 dimensions' values were evaluated in connection with gender, age groups and OA duration. The Mann-Whitney test was used to analyze known-group validity [124,125].

Due to content validity, it was assumed that patients will understand the items and the content of the questionnaire. The basis of this assumption was that the terminology of the items was simple, clear, and the sentences were not too long or difficult. With regard to construct validity, the next hypothesis was that the items related to the physical, pain, mental and social parameters could be measured dependably. In these cases, at least good correlation (p=0.6-0.8) was assumed. However, there were doubts regarding the comparability of the independent questions of the questionnaire. The team predicted significant difference (significance level p=0.05) regarding the patients with higher age and higher duration of OA in comparison to physical conditions as described by known-group validity.

3.1.3.4 Reliability assessment

Reliability was evaluated with the following methods: internal consistency was analyzed by means of Cronbach's alpha ($\alpha>0.7$ – acceptable, $\alpha>0.8$ – good, $\alpha>0.9$ – excellent) [120,121,122,123]. The Intraclass Correlation Coefficient (hereinafter: ICC) was derived from a two-way analysis of variance with a random effect [126]. In accordance with the 95% confident interval of the ICC estimate, values showed < 0.5 (poor), between 0.5-0.75 (moderate), between 0.75 - 0.9 (good), and >0.90 (excellent) reliability.

Reliability was measured by two methods, first by determining Cronbach's alpha and by ICC. Internal consistency was hypothesized to be at least good ($\alpha>0.8$) in connection with all 5 domains. The ICC was assumed to be at least good (by 95% IC above 0.7).

3.2 Not-Insulin Dependent Diabetes Mellitus - study design

The evaluation was performed in 3 Hungarian pharmacies with the cooperation of an undergraduate pharmacy student. ADDQoL was used as a disease specific tool and the EQ-5D – 3L was used as a generic HRQoL questionnaire. In addition to the questionnaires, the creation of a Patient Sheet was also completed. The inclusion criteria were age over 18, males and females, diagnosed NIDDM within one year from the patient interview, therapy used for at least 4 weeks prior to the interview and ability for the self-completion of the questionnaires. Participation was completely anonymous, the patients were received subject information sheet in order to be informed about the purpose and the details of the research. The ADDQoL contains 19 + 2 items.

The first question asks about the patient's quality of life in general, where the patient must put an X on a scale for the most characteristic condition between excellent and extremely bad. The second item focuses on the patient's perceptions about their QoL in the absence of NIDDM. These 2 items cover the so-called "Present QoL score". The following part of the tool covers DM specific items, called diabetes dependent score. Each item has to be evaluated at two levels: level "a" and level "b". Part "a" of the items determined if the patients were not affected by NIDDM, how different the area of their life in question would be. By completing part "b" of the items, patients decide how important the particular area covered by part "a" is for them. As for items related to workplace or sexual life, patients have the option to respond "no", meaning not applicable to them, and with this answer they can skip the item in question. At the end of the questionnaire there is a so-called open item, where patients have the opportunity to add any other relevant information regarding their feelings about the disorder. All 19 items, both parts "a" and "b", are coded by numbers. The evaluation of the questionnaires was completed according to the official guideline provided by the developer of ADDQoL [104,127,128].

3.3 Chronic Ophthalmic Disorders study set up

Chronic eye disorder related PROMs were reviewed and those chronic ophthalmic disorders were selected which can be treated with eye drops (glaucoma, chronic dry eye syndrome). Based on the evaluation, these measures were selected on the basis of the influencing factors which are crucial for the improvement of HRQoL in the case of patients affected by the chronic ophthalmic disorders mentioned above [129,130,131,132,133,134,135,136,137,138]. These factors were classified according to the WHO dimensions of HRQoL. As the next step, QTPP and Knowledge Space Development were defined. QTPP was selected with careful planning and the consideration of the relevant needs and special requirements in chronic ophthalmic disorders. The defined QTPP included the following elements: 1. Eye discomfort (itching, redness, smarting, tearing, dryness, irritation, swelling) 2. Anxiety, 3. Daily routine, 4. Health literacy, 5. Social support, 6. Work capacity. Then CQAs were determined; these critical quality parameters were defined in terms of patient outcome. The following CQAs were selected: 1. Lifelong therapy, 2. Topical administration route, 3. Dosage form (eye drop), 4. Local effect, 5. Dissolution profile (residence time), 6. Device for administration, 7. Microbiological stability, 8. Physicochemical stability. Finally, CPPs were identified. In this special case, the targeted observation process was aimed at the Medical Product Application. In this patient focused theoretical research, the selected CPPs

were: 1. Storage (temperature), 2. Regimen (frequency of administration), 3. Device applicability, 4. Long-term stability, 5. Long-term sterility, 6. Application without decreased vision, 7. Hygienic circumstances, 8. Mobile application (alarm system). The RA was performed by using Lean QbD Software (QbD Works LLC., Fremont. CA, USA, qbdworks.com). According to the design of the software, the connections between QTPP elements, CQAs and CPPs were thoroughly evaluated. The interdependence between QTPPs and CQAs, as well as between CQAs and CPPs was structured and evaluated one by one, then rated on a three-level scale. This scale reflects the impact of the parameters' interaction on the product as high (H), medium (M) or low (L). The probability of the occurrence of critical factors was also estimated by using the same three-grade scale. As the output of the RA evaluation, Pareto diagrams were generated showing the ranked parameters according to their critical effect on the aimed product. In the case of CQAs and CPPs, Ishikawa diagrams were set up as well for the visualization of the selected influencing factors. In order to determine the influencing factors as CQAs in the case of a chronic ophthalmic disorder (effect), four major causes were selected according to the WHO HRQoL classification: 1. Physical health, 2. Psychological, 3. Environment, 4. Sociological relationship. To achieve the optimal ophthalmic formulation (effect of selecting CPPs), the following dimensions and causes were determined: 1. Stability, 2. Formulation, 3. Efficiency, 4. Active ingredient, 5. Preparation, 6. Patient adherence.

3.4 Cardiovascular Disease - Oral Anticoagulant Treatment survey methods and materials

A cross- sectional study was carried out including patients in OAT, aged at least 18 years, who visited one of the seven out-patient pharmacies in Hungary selected for participation. The on-site survey period for data collection took 3 months, from September until November 2015. A self-developed structured questionnaire was used to access the patients' knowledge on OAT. Demographic and clinical data were extracted from prescription and questionnaire data. The study was approved by Hungarian Medical Research Council, Scientific and Research Committee and was in full accordance with the Declaration of Helsinki. Approval No: 44498-2015/EKU 0333/15, Hungarian Medical Research Committee.

The development was based on 4 validated tools, used in previous relevant studies [139,140,141,142]. The development process involved: (1) bilingual translation; (2) field-testing for face and content validity and (3) assessment of the instrument's reliability (internal consistency). A bilingual expert panel (three Hungarian pharmacists, one GP, one cardiologist, all fluent in English) translated each of the above-mentioned questionnaires to select the relevant

items for the first-ever Hungarian tool on OAT. Field test interviews were conducted by an expert pharmacist involving 40 randomly selected patients on OAT. After completing the questionnaire, the interviewer asked the participants about the content and understandability of the items. Statistical analysis was performed by using SPSS v23.0 software. Internal consistency was also determined by the calculation of Cronbach's α (values above 0.70 indicate that the items included in the scale are adequately related). The level of anticoagulant knowledge was expressed as a percentage: patients' score of correct responses/total score x 100=%. The knowledge level was categorized into 3 classes: over 70%, between 50-70% and below 50%, and was graded as good, average and poor, respectively, in accordance with scientific literature [16]. Descriptive statistics were employed to characterize demographic and clinical variables. Values were expressed as mean ± standard deviation (SD) for continuous data and percentages for categorical data. The association between the study variables and the knowledge level was assessed by using univariate analysis (Chi-square test). Binary logistic regression analysis was carried out to determine the association of poor OAT knowledge level with the variables found to be significant during the univariate analysis. P values of 0.05 and below were considered as statistically significant.

3.5 Quality by Design – method development of QbD-TOM

The purpose of the development of QbD-TOM was to develop a QbD and risk based new method for the approximation of HRQoL investigations, based on all pilot research studies completed as part of this Ph.D. work. In the method development process, the following quality management tools were applied: (a) Ishikawa diagram. The Ishikawa diagram was chosen as a proper tool for the collection, visualization and analysis of the influencing factors and for better understanding the cause and effects relationships among the factors with a potential impact on the quality of life of patients affected by chronic disorders. The influencing factors were divided into 5 main groups according to the EQ-5D dimensions. (b) The process map building (or flowchart construction) was also used in this study as a tool helping in the imaged description of the steps or the flow of a process. The steps, elements and characteristics of the newly developed QbD based method were visualized through this tool. (c) The Risk Estimation Matrix (hereinafter: REM) was applied as a quality management tool during RA in the interdependence rating step. In REM, the effect of the potential risk elements on each other was evaluated according to their severity. During REM creation, the relations between the factors (factor pairs) were estimated and their interactions were categorized as "high" (marked in red), "medium" (marked in yellow) or "low" (marked in green)

by severity. (d) Pareto charts are bar graphs that display variances by the number of their occurrences. Variances are shown in their descending order to identify the largest opportunities for improvement, and to select the critical ones. The results of the RA, namely the ranking of the influencing factors by their critical effect on the QoL, were graphically presented in Pareto charts. The Lean-QbD® software (QbD Works LLC, Fremont, CA, USA) was used for the RA process. The first step of RA was to carry out an interdependence rating among the elements of the QLTP and life quality CQAs and also among the CQAs and CPPs of the therapy or treatment process. A three-level scale was used to describe the relation between the parameters. Accordingly, the interaction between the elements was described as “high” (H), “medium” (M) or “low” (L). The dynamism of this interdependence rating is presented in REM tables generated by the software.

This was followed by the probability rating step, in which CPPs were estimated and categorized on the same three-grade scale. Finally, Pareto charts were generated by the software, presenting the numeric data and the ranking by the critical effect of the CQAs and CPPs on QoL.

3.6 Ishikawa diagram

The Ishikawa, cause and effects, or fishbone diagram is a widely used quality improvement method. The Ishikawa diagram illustrates possible causes of a problem and classifies ideas into categories. According to the expected effect, all the factors can be summarized and grouped as inputs or causes. It is advised to form 4-6 major cause categories, and minor causes are classified based on these [143,144,145].

4. Results and discussion

4.1 Osteoarthritis Knee and Hip Quality of Life survey results

4.1.1 Translation and content validity

After reviewing the first two translated versions (TH1+TH2), the expert panel made the following modifications: questions 13 and 14 ("I need to pace myself" and "It takes me longer to do things") sound in the same way in the Hungarian language, therefore they were merged. The new question in English is the following: "*I have slowed down my usual pace, so it takes me more time to complete my tasks"*. Questions 19 and 20 *("I am anxious" and "I am depressed")* had almost the same meaning in the Hungarian language, so they were also merged. The suggested question by the expert panel was: *"I often feel anxious, sometimes I am even depressed".* Based on the expert panel's opinion, two new questions were included. The first one in the physical domain: "*I must use knee support (e.g. orthresis) to avoid pain",* the second one in the mental health domain*:" I have difficulty practicing my treatment".* Finally, the expert panel also suggested some changes in the order of the items, while the number of items within the domains was not changed. The back-translated and synthetized final version called OAKHQOL-HUN met the requirements of the back-translation procedure. As the final step, the expert panel evaluated the results of the interviews of 34 patients performed in the focus group and accepted the content and face validity of the adapted questionnaire.

4.1.2 Sample

99 questionnaires were completed properly (78 females and 21 males). The average age of the sample was 66.6 years (SD: 12.1), they were mostly obese (48.5%), low educated (47.5%), with a low level of income (53.5%) and married (55.6%). The average duration of OA was more than 10 years (59.6%). The results proved the previous hypothesis based on the average age of the evaluated population and the number of the participating females. Detailed information is presented in Table 1.

Table 1. Sociodemographic and clinical characteristics of patients with knee and hip osteoarthritis participating in the study

Characteristics	Total sample (N[a]=99)	Male (N=21)	Female (N=78)
Age (years; mean ±SD[b]) Range	66.6(12.1) 28-99	62.1(9.9) 38-81	67.8(12.4) 28-99
Age groups; number (%) ≤55 56-65 66-75 ≥76	 18 (18.2%) 26 (26.3%) 30 (30.3%) 25 (25.3%)	 3 (14.3%) 10 (47.6%) 6 (28.6%) 2 (9.5%)	 15 (19.2%) 16 (20.5%) 24 (30.8%) 23 (29.5%)
BMI[c] (kg/m$^{2;}$;mean ±SD) Range	29.5(4.9) 17.1-43.1	31.3(4.4) 24.4-42.3	29.0(4.9) 17.1-43.1
BMI groups (kg/m^2; number (%) ≤18.5 (underweight) 18.51 – 24.99 (normal) 25.00 -29.99 (overweight) ≥30.00 (obese)	 1 (1.0%) 19 (19.2%) 31 (31.3%) 48 (48.5%)	 0 (0%) 1 (4.8%) 8 (38.1%) 12 (57.1%)	 1 (1.3%) 18 (23.1%) 23 (29.5%) 36 (46.2%)
Residence; number (%) Urban Rural	 61 (61.6%) 38 (38.4%)	 10 (47.6%) 11 (52.4%)	 51 (65.4%) 27 (34.6%)
Education level; number (%) Low Medium High	 47 (47.5%) 35 (35.4%) 17 (17.2%)	 9 (42.9%) 9 (42.9%) 3 (14.3%)	 38 (48.7%) 26 (33.3%) 14 (17.9%)
Family status; number (%) Single Married Widowed Divorced	 9 (9.1%) 55 (55.6%) 25 (25.3%) 10 (10.1%)	 1 (4.8%) 17 (81.0%) 2 (9.5%) 1 (4.8%)	 8 (10.3%) 38 (48.7%) 23 (29.5%) 9 (11.5%)
Income level; number (%) Low Medium High	 53 (53.5%) 42 (42.4%) 4 (4.0%)	 7 (33.3%) 13 (61.9%) 1 (4.8%)	 46 (59.0%) 29 (37.2%) 3 (3.8%)
OA[d] duration (years; number (%) <5 years 5-10 years >10 years	 17 (17.2%) 23 (23.2%) 59 (59.6%)	 3 (14.3%) 8 (38.1%) 10 (47.6%)	 14 (17.9%) 15 (19.2%) 49 (62.8%)

OA involvement (body area; number (%)			
Knee	15 (15.15%)	5 (33.33%)	10 (66.67%)
Hip	9 (9.09%)	2 (22.22%)	7 (77.78%)
Both	75 (75.76%)	14 (18.67%)	61 (81.33%)

a: Number of the sample; *b*: Standard deviation; *c*: Body mass index; *d:* Osteoarthritis

4.1.3 Score distribution

In accordance with OAKHQoL domains, lower values were predicted, so lower HRQoL for Physical activities and pain and higher HRQoL value for Social domains were expected. The mean values of the domains are presented in Table 2. The lowest value belongs to the domain "Physical activity", (38.39), as predicted. This means severe physical dysfunction as in the evaluating score between 0-100, 0 means the worst possible health status. The best quality of life (74.15) was observed in the case of "Social support". Previously, higher quality of life was predicted for Social domains, which was partially confirmed by the results in the domain of Social support. The other 3 domains had values around average. Missing items were detected below 5% for the 5 domains. On average, 30-50% of the participants did not give evaluable answers in the case of the three independent items (38.4 % for "Professional activity", 37.4 % for "Spouse relation", and 48.5% for Sexual activity). The research team analyzed the floor and ceiling effect as well. The evaluation of the floor and ceiling effect means analyzing, item by item, what percentage of patients answered by giving the lowest (floor) or the highest (ceiling) value.

Relatively high floor and ceiling effects were observed in some cases; namely, the highest floor effect for the item "Knee support" (47.5%). 20% was the floor effect for items 33, 36, 37 and 38. As regards ceiling effects, the highest value was observed in the case of item 42 "Feel support from those close to me" (51.5%).

Table 2.– Distribution and reliability coefficients for the five subscales of the OAKHQoL-HUN

OAKHQoL[a] domains	Number of items	Mean	SD[b]	Missing items NO (%)[c]	Floor effect[d] (%)	Ceiling effect[e] (%)	Observed range[f]	Theoretical range[g]	Cronbach's A[h]	ICC[ji](95%CI)
Physical activity	16	38.39	19.88	2.25(2.27)	0	0	8.00-89.38	0-100	0.93	0.908(0.869-0.938)
Mental health	13	54.06	21.45	1.85(1.86)	0	0	11.54-92.50	0-100	0.91	0.892(0.851-0.924)
Pain	4	44.07	25.56	1.25(1.26)	4.04	2.02	0-100	0-100	0.89	0.881(0.834-0.916)
Social support	4	74.15	19.32	1.5(1.52)	0	6.06	10-100	0-100	0.62	0.579(0.416-0.704)
Social activities	3	50.84	19.19	1.67(1.68)	2.02	0	0-93.33	0-100	0.57	0.551(0.331-0.699)

a Osteoarthritis Knee and Hip Quality of Life Questionnaire

b Standard Deviation

c Number and percentage of the patients with some missing items in the subscale, and this ratio in parentheses is the missing items of the questionnaire.

e Percentage of the lowest modality summarized by domains

d Percentage of the highest modality summarized by domains

f The range of the observed lowest and highest value of each subscale.

g The range of the possible lowest and highest value, which was determined by the evaluation guideline.

h Internal consistency was evaluated in the case of each subscale with the use of Cronbach's α coefficient

I Intraclass correlation coefficient and confidence interval (95%)

4.1.4 Reliability

The reliability results are presented in Table 2. The questionnaire has good or excellent internal consistency based on the values of Cronbach's α in the case of Physical activity (0.93), Mental health (0.91), and Pain (0.89). Lower values (0.62 and 0.57) were observed for Social support and Social activities. The hypothesis was proved in the case of 3 domains, but the internal consistency of 0.8 was not observed in the Social support and Social activities domains. The results of test-retest reliability were evaluated with 95% Confidence Interval (hereinafter: CI) and found to be excellent for Physical activity (0.908) and good for 2 domains: Mental health (0.892) and Pain (0.881). Moderate values were observed for the other two dimensions: Social support (0.579) and Social activities (0.551). These results partially supported our prediction because similarly to internal consistency, the ICC was not observed above 0.7 in the case of the Social domains.

4.1.5 Known-group validity

The validity of the questionnaire was evaluated in connection with the different demographic factors (Table 3.). Significant differences were predicted between the Physical activity domain and the different age groups, and also between the duration of OA and the 5 domains. Based on the results, a significant difference was detected only in the mean score between Physical activity and Age groups ($p=0.048$). Younger patients (< 55 years) have a significantly better physical status.

Table 3. -– Known-group Discriminant validity analysis of the OAKHQoL-HUN

	Physical activities			**Mental health**			**Pain**			**Social support**			**Social activities**		
	Mean	SD[a]	P[b]	Mean	SD	P	Mean	SD	P	Mean	SD	P	Mean	SD	P
Gender (N)			0.51			0.76			0.72			0.94			0.66
Male (21)	40.90	17.01		52.79	22.61		45.87	23.23		73.85	19.95		49.21	16.69	
Female (78)	37.65	20.63		54.41	21.26		43.59	26.27		74.23	19.28		51.28	19.88	
Age (years)			**0.048**			0.655			0.613			0.355			0.780
≤55	49.90	25.77		56.31	23.77		49.31	28.36		79.03	18.27		52.59	19.39	
56-65	37.62	20.23		49.82	23.58		40.47	24.82		69.74	25.06		52.69	21.91	
66-75	34.85	17.16		54.03	19.74		41.75	24.94		72.58	17.51		47.89	16.50	
≥76	34.94	15.27		56.89	19.90		46.90	25.58		77.10	14.55		51.20	19.76	
BMI[c] (kg/m^2)			0.910			0.482			0.516			0.949			0.700
≤18.5	46.88	.		56.92	.		45.00	.		75.00	.		43.33	.	
18.51-24.99	40.70	26.39		56.98	24.01		46.58	32.03		74.47	23.28		53.51	16.27	
25.00-29.99	37.43	20.55		57.60	19.59		48.63	21.08		75.67	17.68		52.79	20.53	
≥30.00	37.81	16.82		50.56	21.65		40.12	25.56		73.02	19.19		48.68	19.64	
OA[d] duration (years)			0.088			0.685			0.158			0.541			0.822
<5	44.44	23.49		57.52	16.16		49.56	28.58		75.05	20.20		51.57	24.10	
5-10	43.06	15.12		55.18	21.92		50.43	22.07		70.22	18.49		52.75	12.50	
>10	34.74	19.89		52.63	22.73		40.01	25.53		75.42	19.50		49.89	19.99	

a: Standard deviation; *b*: Significance level (p=0.05); *c*: Body mass index, *d:* Osteoarthritis

4.1.6 Construct validity – convergent validity

Good correlation (r= 0.6-0.8 p=0.01) was determined between Physical activity and EQ-5D-VAS (r=0.615**), Mental health and EQ-5D-VAS/TTO (r=0.643, 0.633**), Pain and EQ-5D - VAS/TTO (r=0.676, 0.670**) and Professional activity – Physical health (r=0.621**). Moderate correlation (r=0.4-0.6) was observed in many cases, e.g. Physical activity – Physical health (r=0.599**), Mental health – Psychological (r=0.594**), Mental health – Environment (r=0.575**), Pain – Physical health (r=0.589**) and Physical activity – EQ-5D-TTO (r=0.587**). In addition, the social dimensions weakly correlated with the WHOQoL-BREF dimensions and EQ-5D (Table 4.).

Table 4. - Construct validity of the OAKHQoL-HUN with correlation of WHOQoL-BREF and EQ-5D-3L generic quality of life questionnaires

	OAKHQoL[a]							
	Physical activity	**Mental health**	**Pain**	**Social support**	**Social activities**	**Professional activity**	**Spouse relation**	**Sexual activity**
WHOQoL-BREF[b]								
Physical health	0.599**	0.502**	0.589**	0.018	0.106	**0.621****	0.284*	0.470**
Psychological	0.308**	0.594**	0.447**	0.253*	0.104	0.455**	0.182	0.378**
Social relationships	0.126	0.352**	0.241*	0.227*	0.098	0.250	0.339**	0.431**
Environment	0.448**	0.575**	0.501**	0.180	0.127	0.385**	0.313*	0.242
Overall QoL perception	0.272**	0.356**	0.272**	0.071	0.090	0.284*	0.201	0.226
Overall health perception	0.378**	0.296**	0.229*	-0.212*	-0.074	0.291*	0.060	0.134
EQ-5D[c]								
EQ-5D-TTO[d]	0.587**	**0.633****	**0.670****	0.028	0.197	0.538**	0.251*	0.443**
EQ-5D-VAS[e]	**0.615****	**0.643****	**0.676****	0.037	0.177	0.588**	0.249*	0.452**
VAS[f]	0.363**	0.423**	0.377**	0.038	0.215*	0.246	0.067	0.264

** Correlation is significant at the 0.01 level

*Correlation is significant at the level 0.05

a: Osteoarthritis Knee and Hip Quality of Life Questionnaire; *b*: World Health Organization Quality of Life – BREF; *c*: EQ – 5 dimensions 3 levels; *d:* EQ-5D index, calculated by using time trade off method (EQ-5D-TTO) – The United Kingdom values were used in Hungary; *e*: EQ-5D index, calculated by using visual analogue method (EQ-5D-VAS) – The United Kingdom value set was used in Hungary; *f*: Visual Analogue Scale

Construct validity is indicated by Pearson's correlation coefficient, r (P value) and the indicated instruments.

4.2 Audit of Diabetes Dependent Quality of Life survey results

A total of 150 patients showed willingness to participate in the research. Of 150 questionnaires, 89 were evaluable. A questionnaire was rated as evaluable if the patient data sheet was complete regarding the demographic characteristics. Table 5. summarizes the characteristics of the analyzed population.

Table 5. – Demographic characteristics

	Male; NO (%)	**Female; NO (%)**	**Total; NO (%)**
Gender	40 (44.94)	49 (55.06)	89 (100)
Age groups			
≤45	2 (5.0)	3 (6.1)	5 (5.6)
46-55	5 (12.5)	4 (8.2)	9 (10.1)
56-65	16 (40.0)	8 (16.3)	24 (27.0)
66-75	11 (27.5)	20 (40.8)	31 (34.8)
≥76	6 (15.0)	14 (28.6)	20 (22.5)
BMI (kg/m^2)			
<18.5 underweight	0 (0.0)	0 (0.0)	0 (0.0)
18.6-25 normal	3 (7.5)	4 (8.2)	7 (7.9)
25.1-29.9 overweight	23 (57.5)	19 (38.8)	42 (47.2)
30 < obese	14 (35.0)	26 (53.1)	40 (44.9)
Living area			
Countryside	14 (35.0)	18 (36.7)	32 (36.0)
Town	26 (65.0)	31 (63.3)	57 (64.0)
Graduation status			
Low	22 (55.0)	30 (61.2)	52 (58.4)
Medium	5 (12.5)	12 (24.5)	17 (19.1)
High	13 (32.5)	7 (14.3)	20 (22.5)
General income			
Below HUF 100,000	7 (17.5)	14 (28.6)	21 (23.6)
HUF 100,000-250,000	27 (67.5)	32 (65.3)	59 (66.3)
Above HUF 250,000	6 (15.0)	3 (6.1)	9 (10.1)
Medicine costs of the income			
10%- 20%	34 (85.0)	42 (85.7)	76 (85.4)
20%-40%	6 (15.0)	7 (14.3)	13 (14.6)

Marital status			
Unmarried	3 (7.5)	2 (4.1)	5 (5.6)
Married	28 (70.0)	24 (49.0)	52 (58.4)
Widow	6 (15.0)	19 (38.8)	25 (28.1)
Divorced	3 (7.5)	4 (8.2)	7 (7.9)

No relevant difference was observed between the genders, almost half of the participants were under 65 years, which means they were active members of the labour market. In their case, NIDDM can cause their lack of capacity to do their job, which negatively affects both the patient and the society. More than half of the patients were married (58.43%). Marital status can predict better quality of life because it is much easier to face a disorder with the support of a family member. The income of the sample is considered low, moreover, patients added that a huge amount of their income is spent on medicines, travelling to periodic check-ups, professional health care or doing sports activities. Based on their responses, sometimes they have to decide which of their medicines to buy. Almost all the evaluated patients have abnormal BMI, which is one of the most important risk factors of NIDDM. Co-morbidities were evaluated as well. In addition, 3 of the mentioned co-morbidities were outstandingly high. Hypertension (92.13%), musculoskeletal disorder (47.19%) and high cholesterol level (44.94%). Besides these, patients mentioned heart failure, psychological disorders, respiratory system abnormalities, kidney disorders and gastro-esophageal disorders as co-morbidities.

The most important part of the research was to evaluate the HRQoL of the patients by using EQ-5D-3L and ADDQoL. The patients' demographic characteristics were analyzed by comparison with the EQ-5D-VAS method (Table 6.). Utility values were calculated within one index number by using a special program. This method makes it possible to compare the relative values of different statuses with the total value. In Hungary, no reference measurement has been performed, so Hungary officially uses the value set of the United Kingdom. Values are always between 0-1, moving towards 0 they get worse, moving towards 1 they get better and better. The results of the research revealed no significant differences between the genders. By older ages, the values are lower, which means lower HRQoL. Moving from higher incomes towards lower incomes, the index value takes a lower value, which may be related to the fact that individuals with a higher income are able to pay for the services provided in the private health care system, where health

care providers have the opportunity to pay more attention to them. More attention makes patients feel better and trigger their HRQoL.

Table 6. – EQ-5D index values compared to demographic characteristics

		EQ-5D-VAS[b]	
	N[a]	Scale value	SD[c]
Gender			
Male	40	0.79	0.17
Female	49	0.74	0.21
Age group			
<45	5	0.91	0.12
46-55	9	0.80	0.17
56-65	24	0.80	0.16
66-75	31	0.77	0.19
76<	20	0.64	0.21
General income			
Low	21	0.69	0.23
Medium	59	0.77	0.17
High	9	0.87	0.16
Marital status			
Unmarried	5	0.85	0.14
Married	25	0.73	0.19
Widow	52	0.75	0.20
Divorced	7	0.83	0.17
DM related co-morbidities			
No	29	0.74	0.20
Yes	60	0.77	0.19

a: case number; *b:* EQ-5D-VAS: EuroQol – 5-dimension questionnaire – visual analogue scale method; *c*: Standard Deviation

The two introductory items (general HRQoL and DM dependent HRQoL) were compared to the demographic characteristics which predicted significance difference in HRQoL. The scale range was between 3 (as excellent) and -3 (as extremely bad). Diabetes dependent HRQoL was evaluated on a 5-response scale, where -3 counted as “much better” and 1 counted as “worse”. The results are summarized in Table 7.

Overall, HRQoL was evaluated by patients between 0-1 (0= good, 1=neither good, nor bad). Diabetes dependent HRQoL was estimated within the range of -1 and -2 (-1= little better, -2= better). Middle-aged patients (56-65) rated their QoL with the highest value (0.92). The lowest HRQoL was observed in the age group over 76 years, and this age group felt the most that their

HRQoL would be better if they were not affected by DM (-1.65). In case of the general income, an important difference was observed between edge categories compared to HRQoL. The value was 0.29 for the lower income category and above 1 for the high income category, indicating "good" or "very good" HRQoL. Relevant result was observed for HRQoL depending on the existence of DM related co-morbidities ("Yes": HRQoL – 0.52, "No" HRQoL – 0.78).

Table 7. – ADDQoL Present QoL score compared to demographic characteristics

		General HRQoL		**DM depending HRQoL**	
	N	Scale value	SD	Scale value	SD
Gender					
Male	40	0.88	0.61	-1.43	0.90
Female	49	0.55	0.54	-1.57	0.82
Age group					
<45	5	0.80	0.45	-1.40	1.14
46-55	9	0.78	0.67	-1.00	0.87
56-65	24	0.92	0.72	-1.54	0.83
66-75	31	0.65	0.49	-1.55	0.81
76<	20	0.45	0.51	-1.65	0.85
General income					
Low	21	0.29	0.46	-1.76	0.62
Medium	59	0.75	0.51	-1.49	0.87
High	9	1.33	0.71	-1.00	1.00
Marital status					
Unmarried	5	0.80	0.84	-1.60	0.89
Married	25	0.40	0.50	-1.64	0.81
Widow	52	0.81	0.59	-1.50	0.87
Divorced	7	0.86	0.38	-1.00	0.82
DM related co-morbidities					
No	29	0.52	0.51	-1.72	0.84
Yes	60	0.78	0.61	-1.40	0.85

The results of the responses for diabetes specific items (19 items in total) are summarized in Table 8. The highest number of the impact score was observed regarding "freedom to drink" (-1.97) and "freedom to eat" (-1.93). The results perfectly reflect how much patients' everyday life is influenced by taking care what to drink and what to eat. Society's reaction does not have a high impact (0.31), which is a good result because patients do not feel that they are on the margin of

the society. Based on the importance score results, almost all activities are at least "important" (code 2) for the patients. The highest value was found for "working life" (2.41). Although less than half of the patients gave response to this item, active members of the labour market voted that "working life" was very important for them. "Local or long-distance journey" (1.89) and "Physical appearance" (1.87) were the least important for the analyzed sample.

The average weighted impact (AWI) score was calculated using the results of impact and importance scores. Score values were between -9 and 3. In addition, "freedom to drink" (-4.85) and "freedom to eat" (-4.73) had the highest impact on the patients' HRQoL. Incidentally, it should be mentioned that none of the items had a value above 0, which draws attention to the fact that every part of the lives of diabetes patients is influenced by the disorder.

Table 8. - Evaluation of ADDQoL diabetes dependent items

Item number	HRQoL domain	Impact score (mean, SD)	Importance scale (mean, SD)	Weighted impact score (mean, SD)	NA options; %
1	Leisure activation	-1.09(0.97)	1.90(0.74)	-2.20(2.28)	-
2	Working life	-1.03(0.96)	2.41(0.69)	-2.65(2.80)	58.4
3	Local or long-distance journey	-0.91(0.96)	1.89(0.83)	-1.79(2.17)	-
4	Holiday	-1.21(0.78)	2.29(0.69)	-2.76(1.95)	57.3
5	Physical status	-1.18(0.96)	2.21(0.63)	-2.66(2.44)	-
6	Family life	-0.60(0.84)	2.33(0.60)	-1.33(2.02)	2.2
7	Social life	-0.54(0.84)	2.00(0.73)	-1.15(1.89)	-
8	Private life	-0.83(0.90)	2.36(0.55)	-1.86(2.26)	34.8
9	Sexual life	-1.16(1.02)	2.02(0.84)	-2.64(2.76)	49.4
10	Physical appearance	-0.70(0.80)	1.87(0.74)	-1.30(1.63)	-
11	Confidence in ability	-0.61(0.78)	2.03(0.66)	-1.21(1.82)	-
12	Motivation	-0.64(0.83)	2.00(0.72)	-1.35(1.92)	-
13	Society reaction	-0.31(0.67)	1.93(0.78)	-0.64(1.46)	-
14	Feelings about future	-0.89(0.86)	2.00(0.72)	-1.84(2.18)	-
15	Financial status	-0.84(0.80)	2.25(0.59)	-1.87(1.81)	-
16	Living conditions	-0.87(0.79)	2.21(0.59)	-1.88(1.76)	-
17	Dependence	-0.72(0.89)	2.25(0.71)	-1.52(2.25)	-
18	Enjoyment of food/freedom to eat	-1.93(0.88)	2.31(0.76)	-4.73(2.92)	-
19	Freedom to drink	-1.97(0.87)	2.34(0.71)	-4.85(2.96)	-

4.3 Chronic Ophthalmic Study main results

This research work evaluated the key intervention possibilities in chronic ophthalmic disorders from the patients' point of view to find the points where adherence can be increased in this situation needing lifelong treatment. First, the QTPPs were identified as follows: patients who suffer from chronic eye disorder and need lifelong therapy, the aimed administration route was topical, and the selected dosage form was the solution (eye drop). The expected effect was a local effect, and the intermediate dissolution of the active ingredient was needed as the residence time in the eye is limited to the physiological environment and state. The device was also the element of the QTPP as it should protect the formula and helps to preserve microbial and physicochemical stability. The long-term protection of microbial and physicochemical stability has financial advantages and helps in the patient's everyday life if the medicinal product has no special requirement for storage, handling, etc. The selected QTPPs and their target, justification and explanation are summarized in Table 9. After the previous and profound QTPP determination, cause and effects diagrams (Figure 2., Figure 3.) were set up for the visualization of the most relevant influencing factors related to the development of ocular drug delivery systems (Figure 3.), which helped to identify potential critical factors. Figure 1. was the basis of CQA selection. As there are originally determined and regulated critical factors (pH, viscosity, osmolality, surface tension), the critical quality factors determined in this study as CQAs were the ones which could be modified according to patients' expectations and perceptions. The selected CQAs are "patient focused" quality attributes in our present case. The identified CQAs were the following: 1. Eye discomfort (itching, tearing, redness, dryness, irritation, smarting, swelling), 2. Anxiety (caused by lifelong treatment and loss of vision), 3. Daily routine, such as household, reading, shopping, 4. Health literacy, which is determined by education level and current mental capacity or status, 5. Social support, first of all family members and friends, 6. Work capacity, which could result in productivity loss or impairment of work performance. From the researchers' point of view, first of all the technological parameters determined the production of a drug, which was mentioned above as pharmaceutical standards. In this case, the production steps of an eye-drop formulation are fixed, the composition and preparation depend on the physicochemical attributes of active ingredients and additives. The final formulation needs to meet the strict physiological requirements, such as pH, osmolality, viscosity and surface tension. The preparation must be made under aseptic

conditions to ensure a sterile product and proper microbiological stability during the storage and the application of the eye drop.

As product manufacturing has specific defined elements, in our present study "the application of the medicinal product by the patient" was identified as the process, and its critical attributes were identified as CPPs. The selected CPPs were the following: 1. Storage conditions, e.g. temperature, 2. Regimen, which is characterized by the frequency of the drug application, 3. Device applicability, which is determined by the complexity of the drug application, 4. Long-term stability, 5. Long-term sterility, 6. Application without decreased vision – this means the shortest time between the application and the perfect vision capacity to continue the daily routine, 7. Hygienic circumstances, e.g. clear hands, 8. Mobile application, which functions as an alarm system to pay attention to the application of the next dose. The selected QTPPs, CQAs and CPPs were applied in the initial RA process. In the initial item of RA, interdependence ratings were performed. Interdependence was evaluated step by step for each pair of the CQA and QTPP elements, then for each pair of the CQA and CPP items. The effects of the pairs on each other were estimated by using the three-grade scale, as the potential effect can be rated as high, medium or low. Figure 4. presents graphically the results of the interdependence rating as part of RA between QTPP elements and CQAs as well as CQAs and CPPs. CQAs and CPPs are also presented in Pareto charts (Figure 5.) generated by the software, which also show the numerical data of the selected critical factors and their ranking.

Figure 6. shows the relative severity – relative occurrence diagram. It has four quarters, which present the estimated occurrence and the estimated severity of critical factors related to the application process from the patients' point of view. The most important one is the "relative high occurrence – relative high severity" quarter. In this study, this quarter contains the factors such as regimen (the frequency of product use), hygienic circumstances (e.g. purity of hands and environment), and storage conditions (temperature). The most important outcome of the research is that if there is a specific chronic eye disorder as a target, the target product profile and its desired quality can be determined in the first step by using the QbD approach. Then, based on the QTPP and related knowledge from the literature and practice, CQAs and CPPs can be identified. After performing risk assessment, the design of experiments can be made, and later the DoE-based experimental work will result in the determination of the design space. The information needed for the QbD based formulation design can originate from the scientific literature and directly from

patients via PROMs. In our specific case, those questionnaire items (more specifically, the issues covered by the items) were used which are the most common regarding chronic ophthalmic disorders. The presented method helps to systemize the available information on a risk-based manner.

Table 9. - Selected QTPP elements, their target, justification and explanation

QTPP element	Target	Justification	Explanation	
Therapeutic indication	Chronic eye disorder	Globally more than 253 million people suffer from vision impairment	Therapeutic indication is a suggested QTPP by the ICH Q8	**Investigated in the RA of this study**
Target population	Patients who need lifelong therapy	Lifelong therapy determines the patients' everyday life, decreases the HRQoL and leads to non-adherent patient behavior	Target patient group is a suggested QTPP by the ICH Q8 in the clinical settings	
Administration route	Topical (eye)	Topical use avoids systematic effects and drug-drug interactions. Administration of drug by avoiding first-pass-metabolism, Blood Retinal Barrier and Blood-Aqueous Barrier. Expert competence is not needed for application	The route of administration has to be evaluated as a QTPP according to the ICH Q8 guideline	
Dosage form	Solution (eye drop)	Local irritation is decreased, permeability of drug is increased compared with suspension formulations	Dosage form is an essential QTPP element by the ICH Q8	
Site of activity	Local	Local effect is usually a general requirement of products for eye treatment. It is influenced by the solubility properties of the active pharmaceutical ingredient (API), mucosal adsorption and wettability	It is critically related to the quality, safety and efficacy of the medicinal product. Being a QTPP is a therapeutic requirement	
Dissolution profile	Immediate release	Immediate effect is usually a critical expectation for locally administered products. The residence time of the formula is limited on the surface	It is critical from the patients' point of view	
Device	Proper for eye administration	Easy application, dose reproducibility are the main requirements. It is also linked to the microbial stability of the product	It is critically related to application safety and product quality	
Microbial stability	Long-term microbial stability	Antimicrobial stability is essential in ocular drug delivery, considering the sensitivity of human eyes	It is critically related to application safety and product quality	
Physicochemical stability	Long-term physicochemical stability	It is critically related to the efficient and safe application of medicinal products	Default quality requirement	
pH	pH=7-9 pH=5-9	pH= 7-9 (optimal) pH= 5-9 (acceptable, not painful)	Default quality requirement	**Not investigated in the RA (strict regulated factors)**
Viscosity	30mPa*s	Should be under 30 mPa*s	Default quality requirement	
Osmolality	300mosm/kg	Should be close to isotonic level	Default quality requirement	
Surface tension	43mN/m	Surface tension of tear is about 43mN/m. It should be similar in the product because of optimal spreadability and therapeutic effect	Quality requirement	

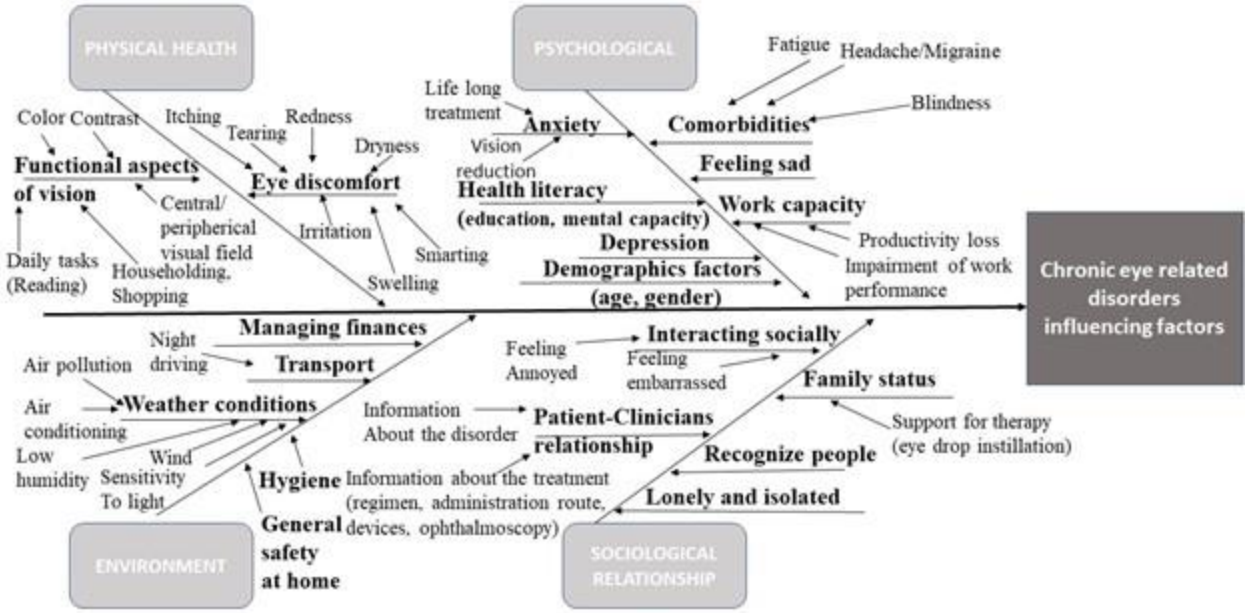


Figure 2: Ishikawa diagram of influencing factors related to the chronic eye disorders

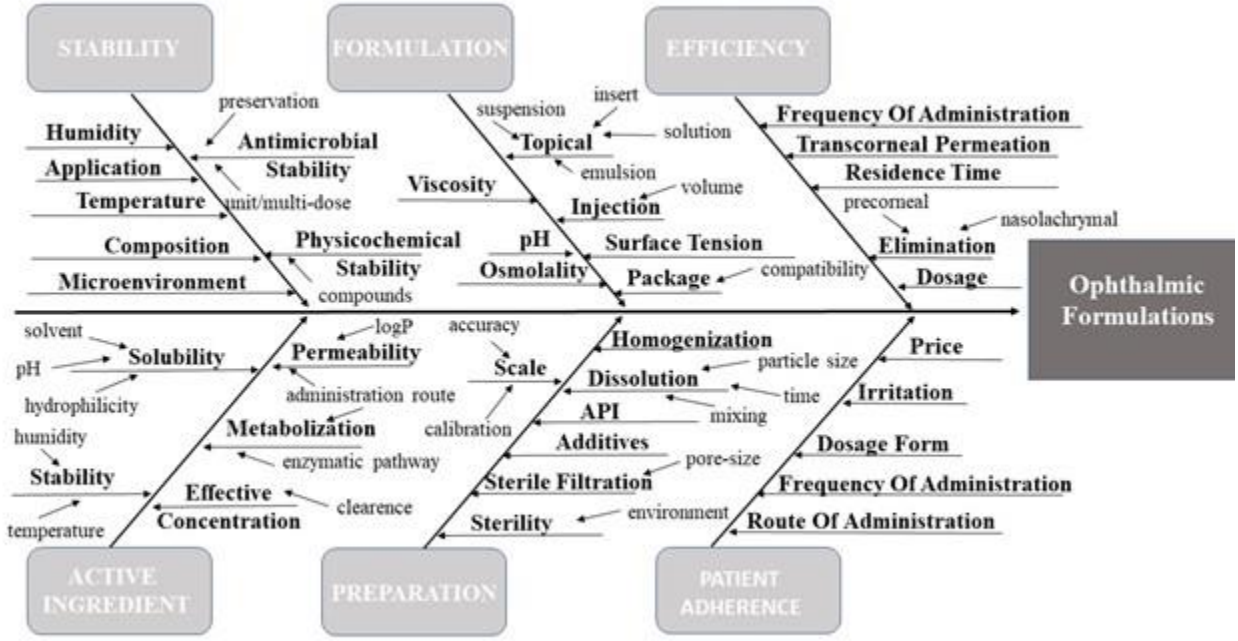


Figure 3: Ishikawa diagram of influencing factors related to the ophthalmic formulation development

QTPP – CQA

CQA	QTPP	(II) Life-long therapy	(II) Topical administration route	(M) Dosage form (eye drop)	(II)Local effect	(M) Dissolution profile (residence time)	(II)Device to the administration	(II) Microbiological stability	(II)Physicochemical stability
Eye discomfort	28%	High	High	Low	Low	Low	Low	High	High
Anxiety	14%	High	Medium	Medium	Low	Low	Low	Low	Low
Daily routine	12%	High	Low	Low	Low	Low	Low	Low	Low
Health literacy	13%	Medium	Medium	Medium	Low	Low	Medium	Medium	Medium
Social support	16%	High	Medium	Medium	Low	Low	Medium	Low	Low
Work capacity	18%	Medium	Medium	Low	Low	Low	Low	High	High

CQA – CPP

Process		Drug Product Application Process							
CQA	CPP	Storage (temperature)	Regimen (frequency of the administration)	Device applicability	Long-term stability	Long-term sterility	Application without decreased vision	Hygienic circumstances	Mobile application (alarm system)
		17%	30%	9%	6%	6%	21%	21%	12%
Eye discomfort	28%	Low	High	Low	Low	Low	High	High	Low
Anxiety	14%	Low	High	Medium	Low	Low	Medium	Low	Low
Daily routine	12%	High	Medium	Low	Low	Low	High	Low	Medium
Health literacy	13%	High	Medium	Medium	Medium	Medium	Low	High	High
Social support	16%	Medium	Medium	Low	Low	Low	Low	Medium	Low
Work capacity	18%	Medium	High	Medium	Low	Low	High	Low	Medium

OCCURANCE

CPPs	CPP Occurrence	CPP Severity	CPP relative occurrence	Occurrence Severity
1. Storage (temperature)	High	17%	20%	1.22
2. Regimen (frequency of the administration)	High	30%	20%	0.68
3. Device applicability	Medium	9%	7%	0.79
4. Long-term stability	Medium	6%	7%	1.18
5. Long-term sterility	High	6%	20%	3.54
6. Application without decreased vision	Low	0%	2%	-
7. Hygienic circumstances	High	21%	20%	0.98
8. Mobile application (alarm system)	Low	12%	2%	0.19

Figure 4. – Results of the interdependence rating between CQAs and QTTPs as well as between CQAs and CPPs together with the occurrence of CPPs

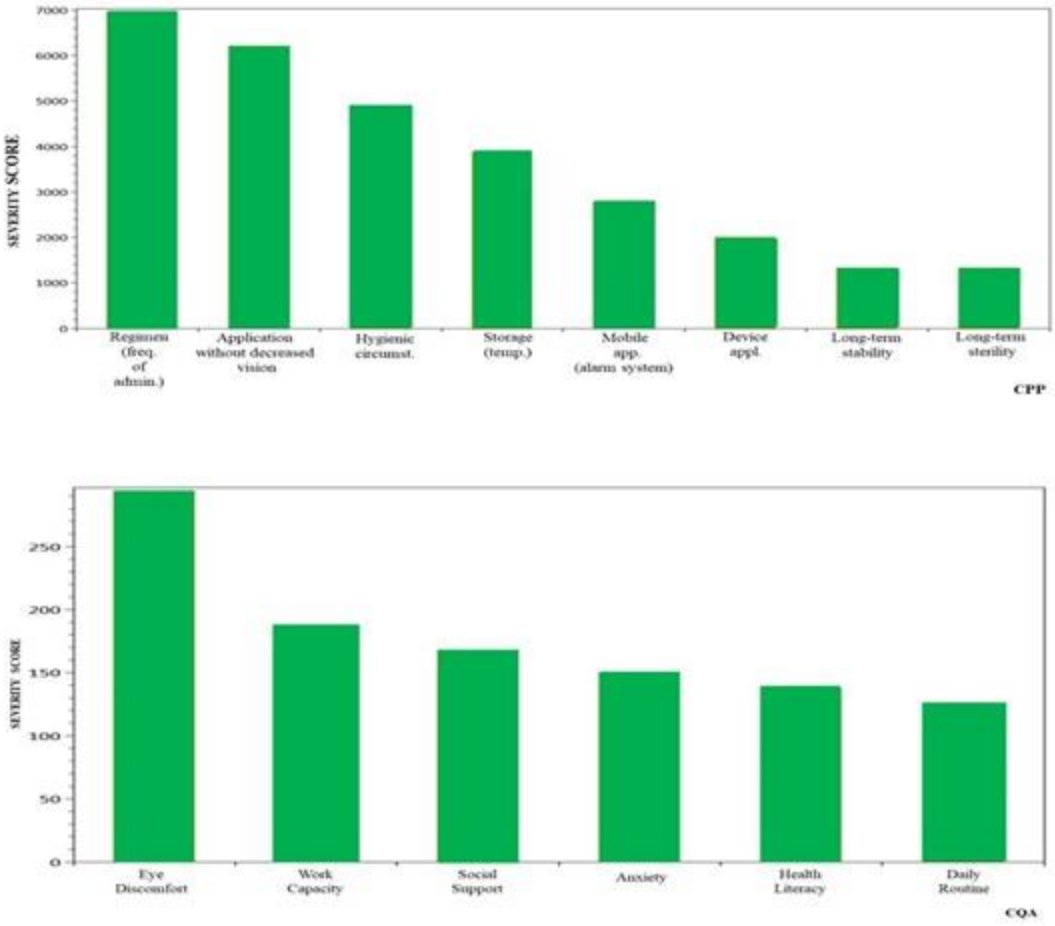


Figure 5. – Pareto charts according to numeric data of CQAs and CPPs

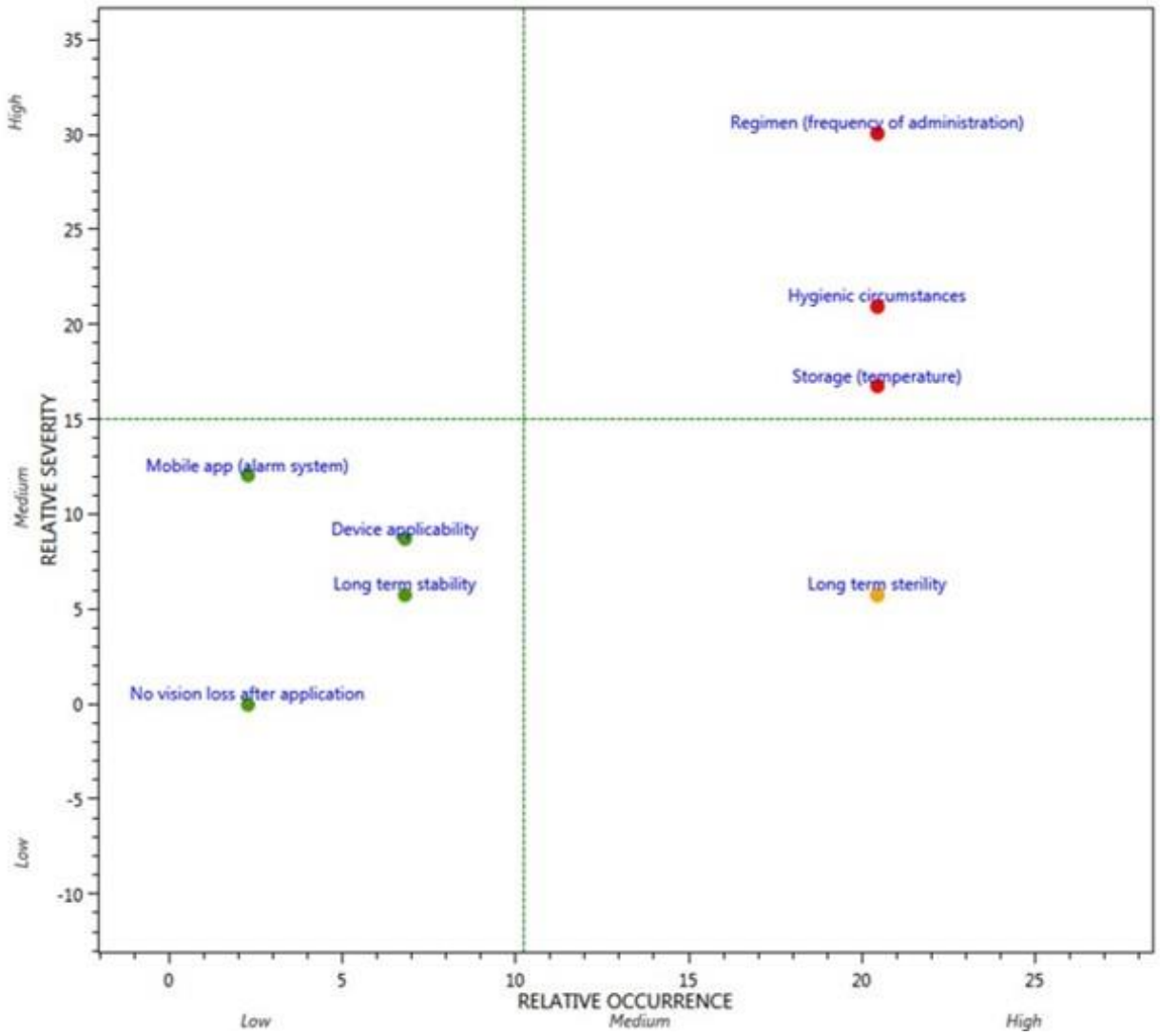


Figure 6. – The application process dependent relative severity – relative occurrence, based on selected CQAs

4.4 Cardiovascular Disease - Oral Anticoagulant Therapy survey main results

All participants, 40 patients in total, completed the test questionnaire within 10 minutes, no assistance was needed. The final version developed for patients on VKA therapy consisted of 17 multiple choice questions regarding the awareness of OAT indication (1 question), basic drug information (7), side effects (1), interactions (2), INR monitoring (2) and diet (4). Patients on NOAC therapy were given a shorter version of the knowledge assessment questionnaire (10 questions) because dietary and INR monitoring items are less relevant for NOAC therapy. Internal consistency, evaluated by determining Cronbach's α coefficient, was 0.795, indicating the

adequate interrelatedness of the items. After the pilot testing, the developed questionnaire was tested on a high number of sample size. In A total of 427 completed questionnaires were analyzed. Besides the developed tool, a patient data sheet was provided to patients as well in order to determine the evaluated population's demographic and clinical profile. Most of the patients were treated with acenocumarol (68.6%) and the indication of OAT was mostly atrial fibrillation (63.2%). Only 1.4% of the patients purchased newly prescribed anticoagulant medication at the time of the survey, while the rest had been on OAT for a certain period of time. The mean duration of OAT was 5±5.46 years (range 0-40 years). A switch in OAT medication, from a VKA to NOAC, was implemented for eleven patients (2.5%). The mean percentage knowledge score was 59.39 (±17.62), the minimum score was 3.33 and the maximum was 94.12. As expressed by the generally accepted categories, about one-third of the patients (29.0%) had a poor level of knowledge on OAT, while 41.2% had an average and 29.7% had a good level of therapy-related knowledge. Assessing the different domains of the questionnaire revealed that the highest frequency of the incorrect responses was related to items about drug interactions (mean score: 34.99). The best scores were achieved for the side effects domain. Over half of the patients marked common side effects of OAT correctly. Regarding diet in the case of VKA treatment, patients had the most difficulty in answering the multiple-choice item on vegetables with high vitamin K content: only 11.4% of the respondents gave the correct answer. Although 83.5% of the patients on VKA medication were aware of requiring regular INR monitoring, the target INR range was answered correctly by only 48.0%. Most patients (87.3%) do not consider it important to share information with the pharmacist about being on OAT when they purchase OTC or herbal medicines. The majority of patients (83.6%) had adequate knowledge on the indication of their OAT. Those who marked their indication for treatment correctly had higher knowledge scores (61.63 ± 16.29) than those who gave incorrect answers (48.20 ± 19.20). The Chi-square test showed a significant difference between these subgroups, suggesting that an adequate knowledge on the indication of OAT has a positive predictive value. These results are detailed in Table 10. The survey evaluated the association of the different variables with knowledge score categories, too. Patients with a low level of education, those aged > 75 years, diagnosed with atrial fibrillation (AF) and those with inadequate knowledge on OAT indication had significantly higher rates of poor knowledge scores. Male gender and starting OAT within a year were also associated with higher rates of poor knowledge scores, but this was not statistically significant. The binary logistic regression model

was determined as part of the research work (Table 11.). Binary logistic regression confirmed that suffering from atrial fibrillation, having an inadequate knowledge of OAT indication and low education have a significant impact on poor knowledge on OAT. The impact of older age (75 + age group) was confirmed by the univariate analysis only.

Table 10. - Summary of the answers to specific questions of the questionnaire assessing knowledge

Domain	Question	Percentage of patients (%)			Mean knowledge score
		"I don't know"	Indicating a wrong answer	Indicating the correct answer	
Indication	Aware of the indication of OAT	5.4	11.0	83.6	n.a.
Basic drug information	How OAT benefits the patient	6.8	23.2	70.0	73.32
	Planned length of therapy	16.4	9.6	74.0	
	When to take doses	13.8	39.8	46.4	
	What to do in case of missed doses	12.2	10.8	77.0	
	Cases of urgent contact with the physician	13.3	40.3	46.4	
	Necessity of informing healthcare providers about being on OAT	2.1	85.3	12.6	
	Recognizable signs of ineffective OAT	30.1	17.2	52.7	
Side effect	Possible side effects	23.0	18.2	58.8	74.96
Interactions	Factors influencing the effectiveness of OAT	34.4	37.7	27.9	34.99
	Type of pain killers that interact with OAT	49.4	40.4	10.2	
INR monitoring	Frequency of required monitoring	4.0	12.5	83.5	64.74
	Range of intended INR	35.3	16.7	48.0	
Diet	Type of foods which interact with OAT	21.4	24.7	53.9	64.93
	Necessity of a special diet	18.1	8.5	73.4	
	Recognizing vegetables with a high vitamin K content	23.2	65.4	11.4	
	Impact of alcohol intake on OAT	21.1	10.6	68.3	

on OAT

Table 11. – Logistic regression for prediction of poor knowledge level regarding OAT (Overall model fit: Nagelkerke R^2 = 0.109; goodness-of-fit: Hosmer and Lemeshow Test p=0.001; classification table: Correct predictions =74.7%)

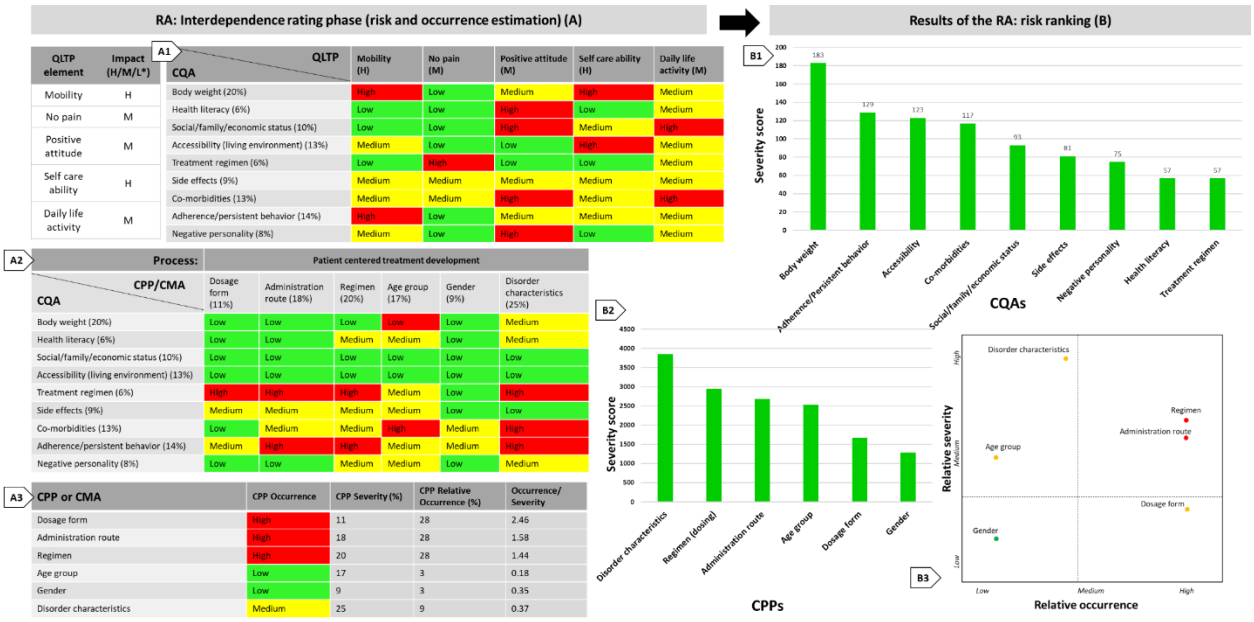
	B[a]	**S.E.[b]**	**Wald**	**df[c]**	**p**	**OR[d]**	**95% CI for OR[e]**
Age > 75 years	0.149	0.244	0.372	1	0.542	1.160	0.719-1.871
AF diagnosis	0.474	0.245	3.750	1	0.025	1.606	0.994-2.595
Low education level	0.807	0.235	11.749	1	0.001	2.241	1.413-3.555
Unaware of the indication of OAT	0.972	0.279	12.181	1	0.000	2.643	1.531-4.563
Constant	-1.722	0.227	57.789	1	0.000	0.179	-

a: regression coefficient; *b*: standard error; *c*: degree of freedom; *d*: odds ration; *e*: confidence interval

4.5 QbD-TOM model development main results

This newly developed method was named by the authors as "QbD in the therapy outcome management (QbD-TOM)". The original QbD describes the determination of the QTPP of the aimed product as the first step, while in this new method this was named "Quality Life Target Profile" (hereinafter: QLTP) by the authors. QLTP shows the required, targeted and aimed Quality of Life, e.g. no pain, self-care ability, etc. Here, Critical Quality Attributes (CQAs) are related to the given disorder and should be identified. In this case potential CQAs were related to the 5 dimensions of the EQ-5D questionnaire connected to the HRQoL. The Critical Process Parameters (CPPs) in this new method were linked to the treatment process and should also be identified. When applying this method, Risk Assessment (RA) can be performed similarly to the original QbD. RA is followed by the next step, which is here Design of Interventions (hereinafter: DoI) in the therapy. DoI replaces the original Design of Experiments (hereinafter: DoE) phase of the classic QbD. It is followed by the alternative pair of the Design Space named by the authors as "Therapy or Life Interventions" in this case. Control Strategy, which originally means the planned set of control in order to ensure the required product quality, can be interpreted in this new method by measuring the HRQoL after the interventions made in the therapy or life conditions. The last item of the procedure description of the QbD-TOM method is Continuous Improvement, as the most important point of quality management philosophy in every case. In fact, this QbD-TOM method can be combined with all types of generic and disease specific questionnaires to determine CQAs. The following CQAs were selected regarding QoL related to patients suffering from a chronic disorder: body weight, health literacy, social/family/economic status, accessibility of the living environment, treatment regimen, side effects, co-morbidities, adherence (persistent behavior) and negative personality. As the next step, CPPs should be selected. The CPPs selected were: dosage form (changing or development of a new one), administration route (changing it if possible), dosing regimen (modification of the dosing regimen if possible, e.g. by using the same medication or active agent but with modified drug release from the dosage form), age group, gender (in connection with preferences, adherence, health related behavior) and finally the special characteristics of the disorder. These can be critical to the outcome of the therapy. After the determination and selection of the QLTP, CQAs and CPPs described above, RA was performed. The RA process had several steps which had to be completed to achieve the RA results. First, the impact of each determined QLTP element was scored on the three-grade scale (H/M/L) (Fig. 7-

A), then the interdependence rating was made between the QLTP elements and CQAs (Fig. 7-A1) as well as between CQAs and CPPs (Fig. 7-A2). These interactions are presented in REMs (Fig. 7-A1-A2). The next step in the Lean-QbD® software-based investigation was the occurrence rating of the selected CPPs, as it can be seen in the bottom of the figure (Fig. 7-A3). The same three-grade scale (H/M/L) was used in each phase of risk estimation. RA resulted in the ranking of CQAs and CPPs related to the chronic disorders. These rankings are presented in the Pareto charts (Fig. 7-B) generated by the RA software applied. The results of RA, namely the theoretical rankings of CQAs and CPPs according to their severity score (Fig. 7-B), show that the most critical factor in general life quality is body weight, which is followed by the patient's adherence, co-morbidities, social/family/economic status. A lower impact was found related to side effects, negative personality, health literacy and treatment regimen (Fig. 7-B1). The results also show that in the patient centered treatment development process, the crucial factor from the patient's point of view is the characteristics of the given disorder (Fig. 7-B2), and it requires the greatest attention. It is followed by dosing regimen, administration route, age group, dosage form and gender. The software also generates a relative occurrence-relative severity diagram (Fig. 7-B3), which highlights the previous finding, namely that the special characteristics of the given disorder have the highest impact. In the following line, the modification in the dosing regimen and the changing of the administration route can have a critical effect on therapeutic outcome from the patients' point of view in improving their quality of life. The patients' age group and gender have a lower effect on therapy development, and the dosage form also seems to be less important.



QLTP element	Impact (H/M/L*)
Mobility	H
No pain	M
Positive attitude	M
Self care ability	H
Daily life activity	M

CQA \ QLTP	Mobility (H)	No pain (M)	Positive attitude (M)	Self care ability (H)	Daily life activity (M)
Body weight (20%)	High	Low	Medium	High	Medium
Health literacy (6%)	Low	Low	High	Low	Medium
Social/family/economic status (10%)	Low	Low	High	Medium	High
Accessibility (living environment) (13%)	Medium	Low	Low	High	Medium
Treatment regimen (6%)	Low	High	Low	Low	Medium
Side effects (9%)	Medium	Medium	Medium	Medium	Medium
Co-morbidities (13%)	Medium	Medium	High	Medium	High
Adherence/persistent behavior (14%)	High	Low	Medium	Medium	Medium
Negative personality (8%)	Medium	Low	High	Low	Medium

CQA \ CPP/CMA	Dosage form (11%)	Administration route (18%)	Regimen (20%)	Age group (17%)	Gender (9%)	Disorder characteristics (25%)
Body weight (20%)	Low	Low	Low	Low	Low	Medium
Health literacy (6%)	Low	Low	Medium	Medium	Low	Medium
Social/family/economic status (10%)	Low	Low	Low	Low	Low	Low
Accessibility (living environment) (13%)	Low	Low	Low	Low	Low	Low
Treatment regimen (6%)	High	High	High	Medium	Low	High
Side effects (9%)	Medium	Medium	Medium	Medium	Low	Low
Co-morbidities (13%)	Low	Medium	Medium	High	Medium	High
Adherence/persistent behavior (14%)	Medium	High	High	Medium	Medium	High
Negative personality (8%)	Low	Low	Medium	Medium	Low	Medium

CPP or CMA	CPP Occurrence	CPP Severity (%)	CPP Relative Occurrence (%)	Occurrence/ Severity
Dosage form	High	11	28	2.46
Administration route	High	18	28	1.58
Regimen	High	20	28	1.44
Age group	Low	17	3	0.18
Gender	Low	9	3	0.35
Disorder characteristics	Medium	25	9	0.37

Figure 7: Process elements and results of RA in the case of chronic disorders in general: interdependence rating and occurrence estimation step (A1-A2-A3), ranking results of CQAs and CPPs by their severity scores in Pareto charts (B1-B2) and the relative occurrence-relative severity diagram of the CPPs of the patient centered treatment (B3)

5. Conclusion, Discussion

Based on the evaluated endemic disorders, the research team reached different patients with different disorder characteristics. During the years of the research, the patients' perceptions were evaluated regarding Health Related Quality of Life, satisfaction with the received treatment and adherence to treatment. Three main aspects of the patients' attitude towards pharmaceutical treatment were evaluated and their interrelation was compared according to the major risks within the therapeutic process for different disorders, namely, health literacy, adherence and health related quality of life. The research work can also be understood as some kind of stakeholder segmentation, according to economics. The patient centered care paradigm has economic aspects as well, and in order to develop proper therapeutic guidelines, in line with patients' characteristics, economic aspects should be taken into consideration, so-called "co-creation" needs to be applied.

One of the most important outcomes of the Ph.D. work is the OAKHQoL questionnaire adaptation and validation process. At the time of the research, there was no available tool in the Hungarian language for the evaluation of the HRQoL of patients affected by OA. The research work had a pilot part where the content of the tool was analyzed, and then validity and reliability were evaluated. The patients were interviewed in 6 Hungarian rehabilitation clinics, in 6 different parts of the country. In the process of the adaptation, the doctors acted as an expert panel and provided a lot of feedback based on their experience.

In parallel with this work, patients receiving oral anticoagulant therapy were interviewed regarding their knowledge about their health status, and their adherence to treatment was evaluated as well. This work was performed in 7 different pharmacies in the Southern Plain region of Hungary. In this case, the pharmacists were provided information about their aspects. After these surveys, another relevant chronic disorder, type 2 diabetes mellitus was focused on, and the patients affected were evaluated with general and disease specific questionnaires in 3 different out-patient pharmacies and in a clinic as well (due to limitations of text length, this examination was not detailed in this Ph.D. thesis).

As the next step, the research team aimed to cooperate with the academia and research work was initiated with formulation technologists. The selected chronic disorder was chronic ophthalmic disorders, and the research was carried out with the QbD based approach. Based on this experience, the team decided to improve an individual QbD based approach which could be applied to all

chronic disorders. In this manner, the authors linked the QbD approach and the human aspects related to chronic disorders.

The authors wanted to evaluate the integration possibilities of risk assessment-based thinking and the improvement potentials in this field. The main hypothesis was that the parameters with potential risks can be identified based on the 5 dimensions of the EQ-5D as a HRQoL tool, and the intervention points can be found in a risk-based manner. A further hypothesis was that by means of RA, the critical factors which have the greatest effect on the improvement of the patients' health can be predicted in order to elevate their status from the lowest 3rd level to the 1st level in the case of the selected EQ-5D questionnaire.

A new model was developed based on the previous knowledge (knowledge space according to the R&D QbD general model) and the evaluation of the results of the pilot studies, which is to be the first publication in this interdisciplinary field. The adaptation process of the QbD based model to therapy outcome management is summarized in Figure 8. However, the developed method has to be tested in practice. Basically, it is an objective tool which can be easily adapted to each chronic disorder and can also be provided to competent authorities in order to be applied when they make decisions on the level of the support for a therapy or during the marketing authorization process, in which fields the patients' perceptions are becoming increasingly important. This QbD based manner is the most important outcome of the Ph.D. work.

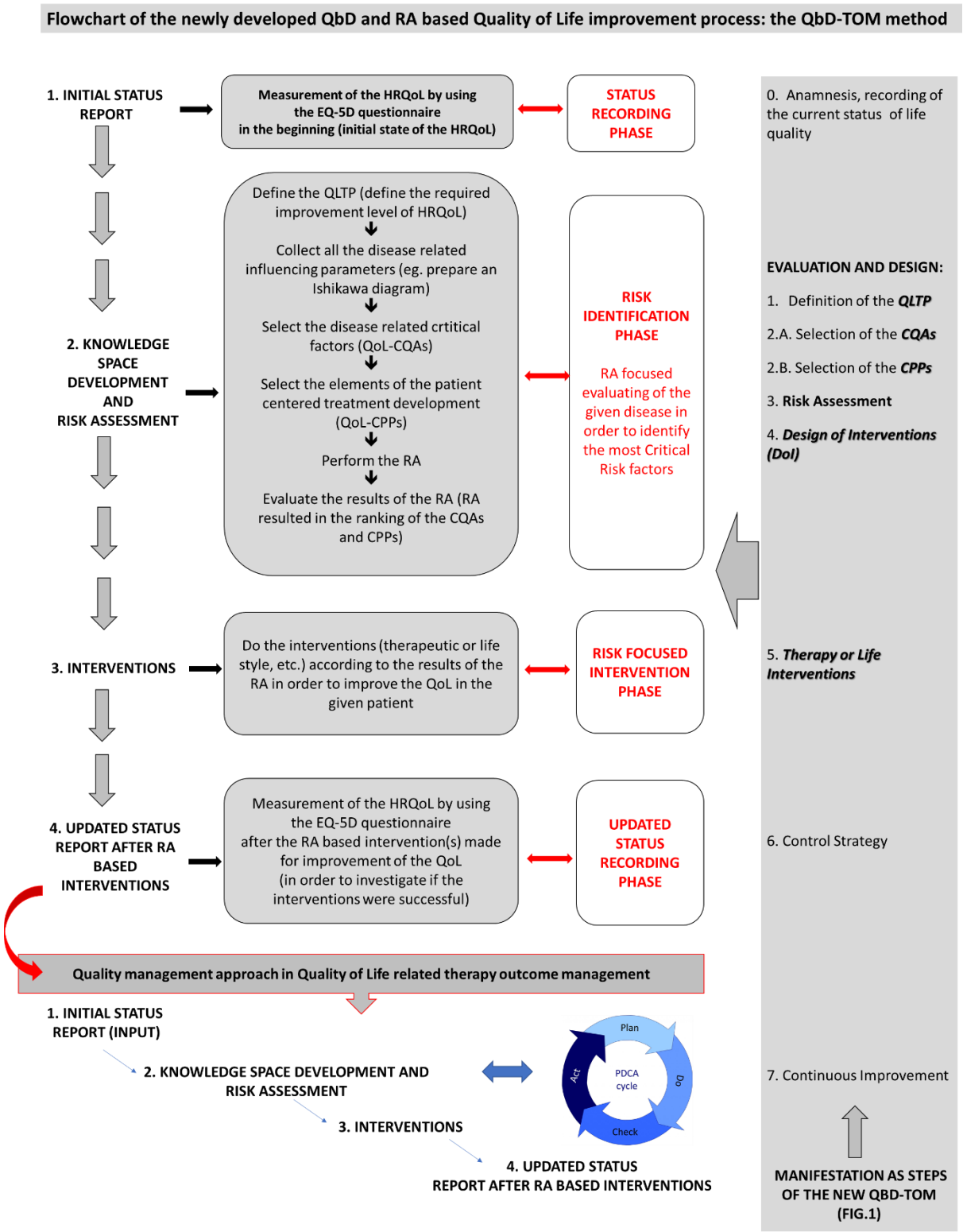


Figure 8. Flowchart of the adaptation of the classic QbD into the therapy outcome management for quality of life improvement process

6. Summary

The Ph.D. work focuses on the patient as an individual whose role in his or her own therapy has changed in recent years because of the rapid spread of information, the ever-aging society and lifelong treatments based on chronic disorders. In order to improve patient centered care, all affected parties need to be involved, from research and development to the patients themselves. Feedback from the patients due to their self-perception regarding the received treatments is the most important method to evaluate the real effectiveness of a treatment's outcome. When patients enter the health care system, they spend a lot of time, energy and money over the years, and mostly none of the health care providers are interested in their feelings, they just provide information about the required treatment protocol. Patients take more and more medicines, and they follow their doctors' instructions as passive parties without real knowledge of their health status and the rationale for their therapies. All these factors have a negative influence on patients' lives. Measuring Health Related Quality of Life is a promising tool for providing feedback to the parties involved and for finding potential points of intervention in general and according to specific disorders as well. Based on patients' feedback, the gaps between them and health care providers can be determined. Effective communication is expected to improve health literacy and the patients' adherence to their treatment, so they can be active participants in their own therapy, which can make them more satisfied, more interested in their own health status and turn their quality of life in a positive direction. If an individual has positive HRQoL and is satisfied despite the chronic disorder, he or she will feel their importance in the society, which is important for the nation and for the individual as well.

This complex issue was raised by the Ph.D. work and analyzed from different aspects. The patient was the center, their perceptions were evaluated in relation with academia, pharmacies and the hospital area. Based on the conclusions of the pilot studies, an objective method was developed based on the QbD approach, which is the most important outcome of the Ph.D. work. Despite the strengths of the work, there are several limitations as well. The developed method has to be tested in practice in order to have more real-life evidence that the method is satisfactory, therefore further examination is needed.

7. Acknowledgements

I would like to express my sincere gratitude to my supervisor **Prof. Dr. Ildikó Csóka** for the continuous support of my Ph.D. study and related research, for her motivation and huge knowledge. Her guidance helped me during the time of research and writing of this thesis.

I owe my special thanks to **Dr. habil. Edina Pallagi** for her continuous support as a friend and co-author in many of my research article.

I owe my special thanks to the Doctors who were provided the patients to the main research of this thesis. Namely: At the first line to my father **Dr. Róbert Fekete**, **Dr. Cecília Varjú**, **Prof. Dr. Kálmán Tóth** – rest in peace-, **Dr. István Tóth**, **Dr. Zoltán Lippai** and **Dr. Ferenc Lutherán**. I would like to thank **Prof. Dr. Francis Guillemin**, **Prof. Dr. Lajos Kullmann** and **Prof. Dr. Clare Bradley** for their permission to use the questionnaires, developed by them.

I owe my thanks to all my colleagues for their help and useful advice and for all the fun we have had in the last couple of years.

Finally, I would like to thank my family and friends for supporting me and never letting me give up during my Ph.D. studies.

8. References

[1] Zheng M, Jin H, Shi N, Duan C, Wang D, Xiaoge Y, Xiaoning L, The relationship between health literacy and quality of life: a systematic review and meta-analysis, Health and Quality of Life Outcomes. 2018.16:201

[2] WHOQOL Group WHOQOL- Measuring Quality of life https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/ (accessed: 19 Jun 2019.)

[3] Acquadro, C., Berzon, R., Dubois, D., Leidy, N.K., Marquis, P., Revicki, D., Rothman, M., PRO Harmonization Group., Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration. Value Health. 2003.522, 31. https://doi.org/10.1046/j.1524-4733.2003.65309.x

[4] European Medicines Agency, 2005. European Medicines Agency (EMA) Reflection paper on the regulatory guidance for the use of health related quality of life (HRQL) measures in the evaluation of medicinal products. https://www.ema.europa.eu/en/regulatory-guidance-use-health-related-quality-life-hrql-measures-evaluation-medicinal-products (accessed: 19 Jun 2019)

[5] Doward, L.C., McKenna S.P., Defining patient-reported outcomes. Value Health. 2004.1,S4-8. https://doi.org/10.1111/j.1524-4733.2004.7s102.x

[6] U.S. Department of Health and Human Services FDA, Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual. Life Outcomes. 2006.11,4:79. https://doi.org/10.1186/1477-7525-4-79

[7] Arpinelli, F., Bamfi, F., The FDA guidance for industry on PROs: the point of view of a pharmaceutical company. Health Qual. Life Outcome. 2006.4,85. https://doi.org/10.1186/1477-7525-4-85

[8] Hudon C, Fortin M, Haggerty JL, Lambert M, Poitras M. Patient-Centered Care : A Systematic Review of Tools for Family Medicine. Ann Fam Med. 2011;9:155-164. doi:doi:10.1370/afm.1226. International Alliance of Patients' Organizations. What is Patient-Centered Healthcare-A review of definitions and principles. 2007:1-37.

[9] Clarke S, Ells C, Thombs BD, Clarke D. Defining elements of patient-centered care for therapeutic relationships: a literature review of common themes. Eur J Pers Centered Healthc. 2017;5(3):362-372.

[10] Liu F, Ranmal S, Batchelor HK, et al. Patient-centred pharmaceutical design to improve acceptability of medicines: Similarities and differences in paediatric and geriatric populations. Drugs. 2014;74(16):1871-1889. doi:10.1007/s40265-014-0297-2

[11] Williams K, Sansoni J, Morris D, Grootemaat P. Patient-Reported Outcome Measures Literature Review.; 2016.

[12] Bingham CO, Noonan VK, Auger C, Feldman DE, Ahmed S, Bartlett SJ. Montreal Accord on Patient-Reported Outcomes (PROs) use series e Paper 4 : patient-reported outcomes can inform clinical decision making in chronic care. J Clin Epidemiol. 2017;89:136-141. doi:10.1016/j.jclinepi.2017.04.014

[13] Adams RJ. Improving health outcomes with better patient understanding and education. Risk Manag Healthc Policy. 2010:61-72. doi:10.2147/RMHP.S7500

[14] Marshall S, Haywood K, Hons D, Fitzpatrick R, Fitzpatrick R. Impact of patient-reported outcome measures on routine practice: a structured review. J Eval Clin Pract. 2006;12(5):559-568.

[15] Hung DY, Glasgow RE, Dickinson LM, et al. The Chronic Care Model and Relationships to Patient Health Status and Health-Related Quality of Life. Am J Prev Med. 2008;35(35):S398-S406. doi:10.1016/j.amepre.2008.08.009

[16] Fagerlind H, Ring L, Brülde B, Feltelius N, K LA. Patients ' understanding of the concepts of health and quality of life. Patient Educ Couns. 2010;78:104-110. doi:10.1016/j.pec.2009.05.016
[17] Dawson, J., Doll, H., Fitzpatrick, R., Jenkinson, C., Carr, J., Nuffield, A., The routine use of patient reported outcome measures in healthcare settings. BMJ. 2010. 340,186 https://doi.org/10.1136/bmj.c186
[18] Brundage, M., Bass, B., Davidson, J., Queenan, J., Bezjak, A., Ringash, J., Wilkinson, A., Feldman-Stewart, D. Patterns of reporting health-related quality of life outcomes in randomized clinical trials: implications for clinicians and quality of life researchers. Qual. Life. Res. 2011.20,653. https://doi.org/10.1007/s11136-010-9793-3
[19] Lacey L, Bobula J, Rüdell K, Alvir J, Leibman C. Quality of Life and Utility Measurement in a Large Clinical Trial Sample of Patients with Mild to Moderate Alzheimer ' s Disease : Determinants and Level of Changes Observed. Value Heal. 2015;18(5):638-645. doi:10.1016/j.jval.2015.03.1787
[20] Policy H. Multimorbidity in chronic disease : impact on health care resources and costs. Risk Manag Healthc Policy. 2016:143-156.
[21] FDA, CDER, CBER, CDRH. Guidance for Industry Use in Medical Product Development to Support Labeling Claims Guidance for Industry. 2009;(December).
[22] Storf M. The impact of FDA and EMA guidances regarding Patient Reported Outcomes (PRO) on the drug development and approval process Wissenschaftliche Prüfungsarbeit. 2013.
[23] World Health Organization (WHO). The burden of musculoskeletal conditions at the start of the new millennium (WHO Technical Report Series 919). Geneva: World Health Organization; 2003.
[24] Reginster JY The prevalence and burden of arthritis Rheumatology 2002;41:3–6.
[25] EULAR, Musculoskeletal Health in Europe Report v5.0 Summary 2013, www.eumusc.net/.../Musculoskeletal%20Health%20in%20Europe%2. Accessed: 17 April 2018.
[26] Salaru V, Sadovici V, Mazur-Nicorici L, Bannwarth B, Bijlsma J, Dieppe P et al. Total Costs and Their Predictor Factors in Patients with Knee Osteoarthritis Ann Rheum Dis 2015;74:378.
[27] Xie F, Kovic B, Jin X, He X, Wang M, Silvestre C, Economic and Humanistic Burden of Osteoarthritis: A systematic Review of Large Sample Studies Pharmacoeconomics 2016;34:1087-1100.
[28] Puig-Junoy J, Zamora AR Socio-economic costs of osteoarthritis: A systematic review of cost-of-illness studies Semin Arthritis Rheum 2015;44:531-541.
[29] Chen A, Gupte C, Akhtar K, Smith P, Cobb J The Global Economic Cost of Osteoarthritis: How the UK Compares Hindawi Publishing Corporation 2012.
[30] Cross M, Smith E, Hoy D The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study Ann Rheum Dis 2014;73:1323-1330.
[31] Turkiewicz A, Petersson IF, Björk J, Hawker G, Dahlberg LE, Lohmander LS et al. Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032 Osteoarth Cartil 2014;22:1826-1832.
[32] Ricci A, Stewart WF, Chee E, Leotta C, Foley K, Hochberg MC Pain exacerbation as a major source of lost productive time in US workers with arthritis Arthritis Rheum 2005;53:673–81.
[33] World Health Organization (WHO). The burden of musculoskeletal conditions at the start of the new millennium (WHO Technical Report Series 919). Geneva: World Health Organization; 2003.
[34] Allen KD, Golightly YM Epidemiology of osteoarthritis: state of the evidence Curr Opin Rheumatol 2015;27:276-283.

[35] Johnson VL, Hunter DJ The epidemiology of osteoarthritis Best Pract Res Clin Rheumatol 2014;28:5-15.
[36] Litwic A, Edwards MH, Dennison EM, Cooper C Epidemiology and burden of osteoarthritis Br Med Bull 2013;105: 185–199.
[37] Picavet HSJ, Hazes JMW Prevalence of self-reported musculoskeletal diseases is high. Ann Rheum Dis 2003;62:644-50.
[38] Hungarian Central Statistical Office – European Health Interview Survey 2014. https://www.ksh.hu/docs/hun/xftp/stattukor/elef14.pdf Accessed: 17 April 2018.
[39] Vos et al. – Global, Regional, and national incidence, prevalence, and years lived with disability for 310 disease and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet 2016;388:1545-602.
[40] Stoffer MA, Smolen JS, Woolf A et al. Development of patient-centred standards of care for osteoarthritis in Europe: the eumusc.net-project Ann. Rheum. Dis. 2015;74: 1145-1149
[41] Jordan KM, Arden NK, Doherty M et al. EULAR Recommendations 2003: An Evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) Ann Rheum Dis. 2003;62: 1145-1155
[42] EUROSTAT Musculoskeletal Health In Europe Report V5.0 Available from: https://www.google.hu/search?q=eumusc.net&ie=utf-8&oe=utf-8&client=firefox-b&gfe_rd=cr&ei=01wtWbOHLIqBX8PMvbAH#q=eumusc.net+report+v5.0 [Accessed: October 10, 2016]
[43] Bone and Joint Decade, Global Alliance of Musculoskelatal Health, Available from: http://bjdonline.org/ [Accessed: November 30, 2016]
[44] Csont és Ízület évtizede (2010-2020) Magyarországon, Available from: http://www.sulypont.hu/blog/gyogytestneveles-kategoria/csont-es-izulet-evtizede-alapitvany-2010-2020-magyarorszagon [Accessed: November 30, 2016]
[45] Palazzo C, Nguyen C, Lefevre-Colau MM et al. Risk factors and burden of osteoarthritis Ann. Phys. Rehab. Med. 2016; 59(3): 134-138
[46] Silverwood V, Blagojevic-Bucknall M, Jinks C et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis, Osteoarthritis and Cartilage 2015; 23(4): 507-515
[47] European Medicines Agency (EMA) guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis, London, January 20, 2010.
[48] Lockwood W Osteoarthritis (Degenerative Joint Disease), Available from: http://www.rn.org/courses/coursematerial-247.pdf [Accessed: November 15, 2016]
[49] Fernandes L, Hagen KB, Bijlsma JWJ et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis Ann. Rheum. Dis. 2013; 0: 1-11
[50] National Institute for Health and Care Excellence (NICE) Rheumatoid arthritis in adults: management, Available from: https://www.nice.org.uk/guidance/ng100 [Accessed: October 24, 2018]
[51] National Institute for Health and Care Excellence (NICE) Osteoporosis All NICE products on osteoporosis. Includes any guidance, advice, NICE Pathways and quality standards. Available from: https://www.nice.org.uk/guidance/conditions-and-diseases/diabetes-and-other-endocrinal--nutritional-and-metabolic-conditions/osteoporosis#panel-pathways [Accessed: October 24, 2018]

[52] National Institute for Health and Care Excellence (NICE) Osteoarthritis: care and management, Available from: https://www.nice.org.uk/guidance/cg177 [Accessed: December 15, 2016]
[53] Veronese N. Adherence to mediterranean diet is associated with lower incidence of frailty: DATA from the osteoarthritis initiative, World Congress on Osteoporosis Osteoarhritis and Musculoskeletal disorders, Florence Italy, 23-26 March 2017
[54] KSH: http://www.ksh.hu/thm/2/indi2_8_1.html Egészségi állapot (2003–2016)
[55] Diabétesz.hu: https://www.diabetes.hu/cikkek/diabetes/1602/a-diabeteszprevalenciaja-no-a-ferfiak-es-stagnal-a-nok-koreben&nofb=true
[56] Magyar Diabétesz Társoság oldal: http://www.diabet.hu/betegtajekoztato.aspx
[57] Nayak, K., Misra, M., A review on recent drug delivery systems for posterior segment of eye. Biomed. Pharmacother. 2018.107, 1564–1582. https://doi.org/10.1016/j.biopha.2018.08.138
[58] Patel, A., Ocular drug delivery systems: An overview. World. J. Pharmacol. 2013.2, 47. https://doi.org/10.5497/wjp.v2.i2.47
[59] Bíró, T., Horvát, G., Budai-Szűcs, M., Csányi, E., Urbán, E., Facskó, A., Szabó-Révész, P., Csóka, I., Aigner, Z., Development of prednisolone-containing eye drop formulations by cyclodextrin complexation and antimicrobial, mucoadhesive biopolymer. Drug. Des. Devel. Ther. 2018.12, 2529–2537. https://doi.org/10.2147/DDDT.S165693
[60] Ilka, R., Mohseni, M., Kianirad, M., Naseripour, M., Ashtari, K., Mehravi, B., Nanogel-based natural polymers as smart carriers for the controlled delivery of Timolol Maleate through the cornea for glaucoma. Int. J. Biol. Macromol. 2018.109, 955–962. https://doi.org/10.1016/j.ijbiomac.2017.11.090
[61] Johannsdottir, S., Jansook, P., Stefansson, E., Kristinsdottir, I.M., Fulop, Z., Asgrimsdottir, G.M., Thorsteindsottir, M., Eiriksson, F.F., Loftsson, T., Topical drug delivery to the posterior segment of the eye: Dexamethasone concentrations in various eye tissues after topical administration for up to 15 days to rabbits. J. Drug. Deliv. Sci. Tec. 2018.45, 449–454. https://doi.org/10.1016/j.jddst.2018.04.007
[62] Lee, V.H.L., Robinson, J.R., Topical Ocular Drug Delivery: Recent Developments and Future Challenges. J. Ocul. Pharmacol. Ther. 1986.2, 67–108. https://doi.org/10.1089/jop.1986.2.67
[63] Salzillo, R., Schiraldi, C., Corsuto, L., D'Agostino, A., Filosa, R., De Rosa, M., La Gatta, A., Optimization of hyaluronan-based eye drop formulations. Carbohydr. Polym. 2016.153, 275–283. https://doi.org/10.1016/j.carbpol.2016.07.106
[64] WHO – Cardiovascular Disease, 17 May 2020, https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
[65] Goldhaber SZ. Venous thromboembolism: epidemiology and magnitude of the problem. Best Pract Res Clin Haematol. 2012;25(3):235–42.
[66] Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update the global burden of ischaemic and hemorrhagic stroke in 1990–2013: the GBD 2013 study. Neuroepidemiology. 2015;45(3):161–76.
[67] Bajorek B, Magin PJ, Hilmer S, Krass I. Utilization of antithrombotic therapy for stoke prevention in atrial fibrillation: a crosssectional baseline analysis in general practice. J Clin Pharm Ther. 2016;41(4):432–40.
[68] Hanemaaijer S, Sodihardjo F, Horikx A, Wensing M, De Smet PA, Bouvy ML, et al. Trends in antithrombotic drug use and adherence to non-vitamin K oral anticoagulants in the Netherlands. Int J Clin Pharm. 2015;37(6):1128–35.

[69] Hernandez Madrid A, Potpara TS, Dagres N, Chen J, Larsen TB, Estner H, et al. Diffrences in attitude, education, and knowledge about oral anticoagulation therapy among patients with atrial fibrillation in Europe: result of a self-assessment patient survey conducted by the European Heart Rhythm Association. Europace. 2016;18(3):463–7.
[70] Rodriguez RA, Carrier M, Wells PS. Non-adherence to new oral anticoagulants: a reason for concern during long-term anticoagulation? J Thromb Haemost. 2013;11(2):390–4.
[71] Yao X, Abraham NS, Alexander GC, Crown W, Montori V, Sangaralingham LR, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. J Am Heart Assoc. 2016;5(2):e003074.
[72] Kagansky N, Knobler H, Rimon E, Ozer Z, Levy S. Safety of anticoagulation therapy in well-informed older patients. Arch Intern Med. 2004;164(18):2044–50.
[73] Ewen S, Rettig-Ewen V, Mahfoud F, Boehm M, Laufs U. Drug adherence in patients taking oral anticoagulation therapy. Clin Res Cardiol. 2014;103(3):173–82.
[74] Wang Y, Kong MC, Lee LH, Ng HJ, Ko Y. Knowledge, satisfaction, and concerns regarding warfarin therapy and their association with warfarin adherence and anticoagulation control. Thromb Res. 2014;133(4):550–4.
[75] Borg Xuereb C, Shaw RL, Lane DA. Patients' and health professionals' views and experiences of atrial fibrillation and oralanticoagulant therapy. A qualitative meta-synthesis. Patient Educ Couns. 2012;88(2):330–7.
[76] Kneeland PP, Fang MC. Current issues in patient adherence and persistence. Focus on anticoagulants for the treatment and prevention of thromboembolism. Patient Prefer Adherence. 2010;4:51–60.
[77] Hedegaard U, Kjeldsen LJ, Pottegard A, Bak S, Hallas J. Multifaceted intervention including motivational interviewing to support medication adherence after stroke/transient ischemic attack: a randomized trial. Cerebrovasc Dis Extra. 2014;4(3):221–34.
[78] Varnai R, Vegh M, Poto L, Nagy L. Level of knowledge among patients treated with oral anticoagulant. Orv Hetil. 2008;149(43):2047–51.
[79] Patrick DL, Deyo RA Generic and Disease-Specific Measures in Assessing Health Status and Quality of Life Medical Care 1989;21: 217-232.
[80] Norman R, Cronin P, Viney R, King M, Street D, Ratcliffe J. International Comparisons in Valuing EQ-5D Health States: Value Heal. 2009;12(8):1194-1200. doi:10.1111/j.1524-4733.2009.00581.x
[81] EuroQoL Group. EuroQol * - a new facility for the measurement of health-related quality of life. Health Policy (New York). 1990;16:199-206.
[82] Brooks R, Group E. EuroQol : the current state of play *. Health Policy (New York). 1996;37:53-72.
[83] Hoyle CK, Tabberer M, Brooks J. Mapping the COPD Assessment Test onto EQ-5D. Value Heal. 2016;19(4):469-477. doi:10.1016/j.jval.2016.01.005
[84] Devlin NJ, Brooks R EQ-5D and the EuroQol Group: Past, Present and Future, Appl Health Econ Health Policy (2017) 15:127–137.
[85] Dolan, P.: Modeling valuations for EuroQol health states. Med.Care, 1997, 35(11), 1095–1108.
[86] Zrubka Z et all., A comparison of European, Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases, The European Journal of Health Economics (2019) 20 (Suppl 1):S119–S132).

[87] Kullmann L, Harangozó, J - Hungarian Adaptation of the WHO Method for Measuring Quality of Life, Orv.Hetil, 1999 Aug 29;140(35):1947-52.
[88] WHOQoL Group The World Health Organization Quality of Life Assessment (Whoqol): Position Paper From The World Health Organization Soc Sci Med 1995;41:1403-1409.
[89] WHOQoL Group Development of the World Health Organization WHOQOL-BREF Quality of Life Assessment Psychol Med 1998;28:551-558.
[90] Skevington SM, Lotfy M, O'Connell KA The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial A Report from the WHOQOL Group Qual Life Res 2004;13:299–310.
[91] Paulik E, Belec B, Molnar R, Müller A, Belicza E, Kullmann L et al. Applicability of the abbreviated version of the World Health Organization's quality of life questionnaire in Hungary [Hungarian] Orvosi Hetilap 2007;148:155-160.

[92] Rat AC, Coste J, Pouchot J, Baumann M, Spitz E, Retel-Rude N et al. OAKHQOL: A new instrument to measure quality of life in knee and hip osteoarthritis J Clin Epidemiol 2005;58:47–55.
[93] Rat AC, Pouchot J, Coste J, Baumann C, Spitz E, Retel-Rude N et al. Development and testing of a specific quality-of-life questionnaire for knee and hip osteoarthritis: OAKHQOL (OsteoArthritis of Knee Hip Quality Of Life) Joint Bone Spine 2006;73:697-704.
[94] Rat AC, Guillemin F, Pouchot J Mapping the osteoarthritis knee and hip quality of life (OAKHQOL) instrument to the international classification of functioning, disability and health and comparison to five health status instruments used in osteoarthritis Rheumatology 2008;47:1719–1725.
[95] Goetz C, Ecosse E, Rat AC Measurement properties of the osteoarthritis of knee and hip quality of life OAKHQOL questionnaire: an item response theory analysis Rheumatology 2011;50:500–505.
[96] Gonzalez Sáenz De Tejada MGS, Escobar A Herdman M, Herrera C, García L, Sarasqueta C Adaptation and validation of the Osteoarthritis Knee and Hip Quality of Life (OAKHQOL) questionnaire for use in patients with osteoarthritis in Spain Clin Rheumatol 2011;30:1563-1575.
[97] Serhier Z, Harzy T, ELfakir S, Diouny S, El Rhazi K, Bennani Othmani M et al. Cross-cultural adaptation and validation of the knee and hip health-related quality of life (OAKHQoL) in a Moroccan Arabic-speaking population Rheumatol Int. 2012;32:1015-1023.
[98] Duruöz MT, Duruöz E, Uçar Ü, Topçu E SAT0338 Adaptation and Validation of the Osteoarthritis Knee and Hip Quality of Life (Oakhqol) Questionnaire in Turkish Population [abstract] Ann Rheum Dis 2013;72(Suppl 3): P:697
[99] Ouédraogo DD, Zabsonré JT, Kenagnon ADS, Kaboré F, Compaoré C, Drabo YJ et al. Quality of Life of Patients with Knee Osteoarthritis with Questionnaire OAKHQOL (OsteoArthritis of Knee Hip Quality of Life) in Rheumatology Consultation in Burkina Faso (West Africa) Open J Rheumatol Autoimmune Dis 2014;4:219-225.
[100] Wang W, He CR, Zheng W, Li J, Xu WD Development of a valid simplified Chinese version of the Osteoarthritis of Knee and Hip Quality of Life (OAKHQOL) in patients with knee or hip osteoarthritis J Eval Clin Pract 2016;22:53-61.
[101] Ben Slama I, Rkain H, Traki L, Bouaddi I, Bouazzaoui L, Allal F et al. AB0975 Quality of life in women suffering from knee osteoarthritis [abstract] Ann Rheum Dis 2013;71(Suppl 3) A:694

[102] Ayhan FF, Gümrük S, Ceceli E The Predictor for Disease Specific-Quality of Life in Patients with HIP and Knee Osteoarthritis: Mental Health [abstract] Ann Rheum Dis 2015;74(Suppl 2) A:375
[103] Ken Watkins, Cathleen M. Connell, Measurement of health-related QOL in diabetes mellitus, *PharmacoEconomics* volume 22, pages1109–1126(2004)
[104] Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R, The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL, *Qual Life Res*, 1999;8(1-2):79-91. doi: 10.1023/a:1026485130100.

[105] Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, et al. Understanding Pharmaceutical Quality by Design. AAPS J [Internet]. 2014;16(4):771–83. Available from: http://link.springer.com/10.1208/s12248-014-9598-3
[106] ICH. Pharmaceutical Development Q8. ICH Harmon Tripart Guidel. 2009;8(August):1–28.
[107] ICH. Quality Risk Management Q9. ICH Harmon Tripart Guidel [Internet]. 2005;1–23. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/%5CnGuidelines/Quality/Q9/Step4/Q9_Guideline.pdf
[108] ICH. ICH Q10 Pharmaceutical Quality Systems. EPT-The Electron Newsl Pharm Tech Jun. 2009;(May):21.
[109] Csóka I, Pallagi E, Paál TL. Extension of quality-by-design concept to the early development phase of pharmaceutical R&D processes. Drug Discov Today [Internet]. 2018; Available from: https://doi.org/10.1016/j.drudis.2018.03.012
[110] World Health Organisation. Adherence to Long-Term Therapies. 2003. 1–211 p.
[111] Stegemann S, Ternik RL, Onder G, Khan MA, Riet-nales DA Van. White Paper Defining Patient Centric Pharmaceutical Drug Product Design. AAPS J. 2016;18(5).
[112] Huynh TK, Østergaard A, Egsmose C, Madsen OR. Preferences of patients and health professionals for route and frequency of administration of biologic agents in the treatment of rheumatoid arthritis. Patient Prefer Adherence. 2014;8:93–9.
[113] Hudon C, Fortin M, Haggerty JL, Lambert M, Poitras M. Patient-Centered Care : A Systematic Review of Tools for Family Medicine. Ann Fam Med. 2011;9:155–64.
[114] International Alliance of Patients' Organizations. What is Patient-Centered Healthcare-A review of definitions and principles. 2007;1–37.
[115] Clarke S, Ells C, Thombs BD, Clarke D. Defining elements of patient-centered care for therapeutic relationships : a literature review of common themes. Eur J Pers Centered Healthc. 2017;5(3):362–72.
[116] Williams K, Sansoni J, Morris D, Grootemaat P. Patient-reported outcome measures Literature review. 2016. 1–91 p.
[117] Beaton DE, Bombardier C, Guillemin F et al. Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures Spine 2000;25:3186-3191.
[118] Epstein J, Santo RM, Guillemin F A review of guidelines for cross-cultural adaptation of questionnaires could not bring out a consensus J Clin Epidemiol 2015;68:435-441.
[119] Guillemin F, Bombardier C, Beaton DE Cross-cultural adaptation of health-related quality of life measures: Literature review and proposed guidelines J Clin Epidemiol 1993;46:1417–1432.

[120] Mokkinka LB, Terweea CB, Patrick DL, Alonso J, Stratford PW, Knol DL et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of

measurement properties for health-related patient-reported outcomes J Clin Epidemiol 2010;63:737-745.
[121] Terwee CB, Mokkink LB, Knol DL, Ostelo RW, Bouter LM, de Vet HC Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist Qual Life Res 2012;21:651-657.
[122] Terweea CB, Bota SDM, de Boer MR, van der Windt DAWM, Knol DL, Dekker J et al. Quality criteria were proposed for measurement properties of health status questionnaires J Clin Epidemiol 2007;60:34–42.
[123] Terwee CB, Mokkink LB, Steultjens MPM, Dekker J Performance-based methods for measuring the physical function of patients with osteoarthritis of the hip or knee: a systematic review of measurement properties *Rheumatology* 2006;45:890–902.
[124] Mann HB, Whitney DR On a Test of Whether one of Two Random Variables is Stochastically Larger than the Other, *Ann. Math. Statist*., Vol. 18, Number 1 (1947), 50-60.
[125] Fay MP, Proschan MA Wilcoxon-Mann-Whitney or t-test? On assumptions for hypothesis tests and multiple interpretations of decision rules, *Stat Surv*. 2010; 4: 1–39.

[126] Koo TK, Li MY, A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research, *Journal of Chiropractic Medicine* 2016;15,155-163.
[127] C. Bradley, The Audit of Diabetes-Dependent Quality of Life (ADDQoL) *USER GUIDELINES*, 2006
[128] C. Bradley, J. Speight, Patient perceptions of diabetes and diabetes therapy: assessing quality of life - Diabetes/Metabolism Research And Reviews, 2002; 18: S64–S69
[129] Abetz, L., Rajagopalan, K., Mertzanis, P., Begley, C., Barnes, R., Chalmers, R., Impact of Dry Eye on Everyday Life (IDEEL) Study Group. Development and validation of the impact of dry eye on everyday life (IDEEL) questionnaire, a patient-reported outcomes (PRO) measure for the assessment of the burden of dry eye on patients. Health Qual Life Outcomes. 2011.8,9,111 https://doi.org/10.1186/1477-7525-9-111
[130] De Boer, M.R., Moll, A.C., De Vet, H.C.W., Terwee, C.B., Völker-Dieben, H.J.M., Van Rens, G.H.M.B., Psychometric properties of vision-related quality of life questionnaires: a systematic review. Ophthal. Physiol. Opt. 2004. 24, 257-273. https://doi.org/10.1111/j.1475-1313.2004.00187.x
[131] Denniston, A.K., Kyte, D., Calvert, M., Burr, J.M. An introduction to patient-reported outcome measures in ophthalmic research. Eye (Lond). 2014. 28,637-45. https://doi.org/10.1038/eye.2014.41
[132] Grubbs, J.R., Tolleson-Rinehart, S., Huynh, K., Davis, R.M., A Review of Quality of Life Measures in Dry Eye Questionnaires. Cornea. 2014.33,215–218. https://doi.org/10.1097/ICO.0000000000000038
[133] Khadka, J., McAlinden, C., Pesudovs, K.. Quality assessment of ophthalmic questionnaires: review and recommendations. Optom Vis Sci. 2013.90,720-44. https://doi.org/10.1097/OPX.0000000000000001.
[134] Li, M., Gong, L., Chapin, W.J., Zhu, M.. Assessment of vision-related quality of life in dry eye patients. Invest. Ophthalmol. Vis. Sci. 2012.53,5722-7. https://doi.org/10.1167/iovs.11-9094
[135] Mukherjee, A.M., Lapré, M.A., Van Wassenhove, L.N., Knowledge Driven Quality Improvement Manage. Sci. 1998.44, 11. https://doi.org/10.1287/mnsc.44.11.S35
[136] Nordmann, J.P., Denis, P., Vigneux, M., Trudeau, E., Guillemin, I., Berdeaux, G., Development of the conceptual framework for the Eye-Drop Satisfaction Questionnaire (EDSQ)

in glaucoma using a qualitative study. BMC Health Serv Res. 2007.6,124. https://doi.org/10.1186/1472-6963-7-124
[137] Regnault, A., Viala-Danten, M., Gilet, H., Berdeaux, G., Scoring and psychometric properties of the Eye-Drop Satisfaction Questionnaire (EDSQ), an instrument to assess satisfaction and compliance with glaucoma treatment. BMC Ophthalmol. 2010.10,1. https://doi.org/10.1186/1471-2415-10-1
[138] Vandenbroeck, S., De Geest, S., Zeyen, T., Stalmans, I., Dobbels, F., Patient-reported outcomes (PRO's) in glaucoma: a systematic review. Eye (Lond). 2011.25,555 577. https://doi.org/10.1038/eye.2011.45
[139] Alphonsa A, Sharma K, Sharma G, Bhatia R. Knowledge regarding oral anticoagulation therapy among patients with stroke and those at high risk of thromboembolic events. J Stroke Cerebrovasc Dis. 2015;24(3):668–72.
[140] Zeolla MM, Brodeur MR, Dominelli A, Haines ST, Allie ND. Development and validation of an instrument to determine patient knowledge. The oral anticoagulation knowledge test. Ann Pharmacother. 2006;40(4):633–8.
[141] Briggs AL, Jackson TR, Bruce S, Shapiro NL. The development and performance validation of a tool to assess patient anticoagulation knowledge. Res Soc Adm Pharm. 2005;1(1):40–59.
[142] Chenot JF, Hua TC, Abed A, Schnider-Rudt H, Friede T, Schnider S, Vomfelde SV. Safety relevant knowledge of orally anticoagulated patients without self-monitoring: a baseline survey in primary care. BMC Fam Pract. 2014;25(15):104.
[143] Ishikawa K. What Is Total Quality Control, The Japanese Way.; 1985.
[144] Tague NR. Fishbone Diagram (Ishikawa) - Cause & Effect Diagram. Qual Toolbox. 2005:247–249. http://asq.org/learn-about-quality/cause-analysis-tools/overview/fishbone.html.
[145] Best, M., Neuhauser, D., Kaoru Ishikawa: from fishbones to world peace. BMJ Quality & Safety. 2007. 17,82-82 http://dx.doi.org/10.1136/qshc.2007.025692)