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Summary of PhD thesis

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

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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.

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 (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 (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 (WHO) health definition is: „*a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity*”. 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 (EMA) and Food and Drug Administration (FDA), the term ***Patient Reported Outcome*** (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. In addition, PROs evaluate all the subjective perceptions of the patients obtained directly from them. 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. Patient Reported Outcome Measurements (PROMs) are performed mostly via self-reported questionnaires. Generic and disease specific questionnaires are used for detecting PROs. 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. 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 (OA), type 2 diabetes mellitus, in other words non-insulin dependent diabetes (NIDDM), chronic ophthalmic disorders, and cardiovascular diseases (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 (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* (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.

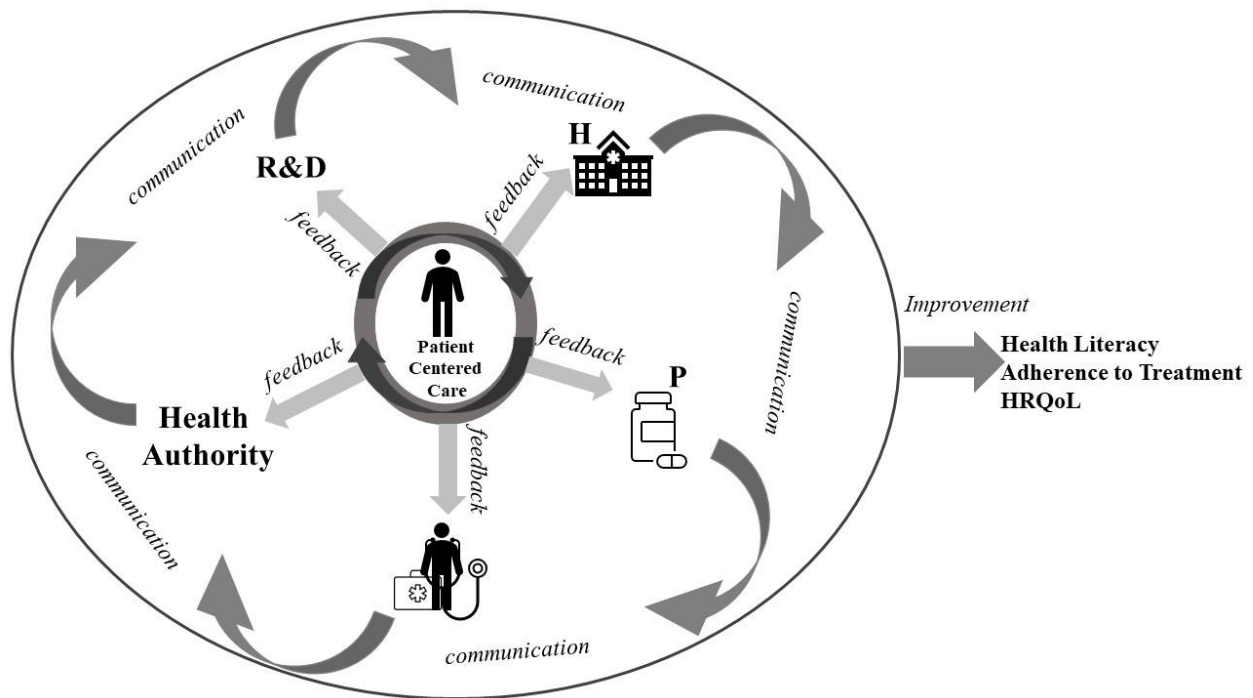


Figure 1. – Intervention points for Patient Centered Care improvement

2. Methods

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. As general tools the WHOQoL – BREF and EQ-5D-3L questionnaires were used. As disease specific tools Osteoarthritis Knee and Hip Quality of Life Questionnaire (OAKHQoL), Audit of Diabetes Dependent Quality of Life questionnaire (ADDQoL) were used. In order to fulfill the aim of the PhD work several disease specific questionnaires were analyzed and used as a support in case of Chronic Ophthalmic disorders and Oral Anticoagulant Treatment. At least, generally in the field of pharmaceutical industry used, QbD based model development was performed.

2.1 Adaptation and validation of OAKHQoL for the Hungarian population

The process was conducted according to the published guidelines, based on the instructions and cooperation with the researchers of the original French questionnaire. 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). The adapted Hungarian questionnaire was tested among patients diagnosed with OA of the lower limb, in six hospitals situated in six different geographical regions of Hungary

2.2 Not-Insulin Dependent Diabetes Mellitus - study design

The evaluation was performed in 3 Hungarian pharmacies. ADDQoL was used as a disease specific tool and the EQ-5D – 3L was used as a generic HRQoL questionnaire.

2.3 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. These factors were classified according to the WHO dimensions of HRQoL. The factors were analyzed with using Quality by Design approach.

2.4 Cardiovascular Disease - Oral Anticoagulant Treatment survey methods and materials

A cross-sectional study was carried out including patients in OAT, who visited one of the seven out-patient pharmacies in Hungary selected for participation. A self-developed structured questionnaire was used to assess the patients' knowledge on OAT.

2.5 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. In the method development process, the following quality management tools were applied: (a) Ishikawa diagram for 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 flowchart 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 (REM) was applied as a quality management tool during Risk Assessment (RA) in the interdependence rating step. (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). 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. Results and discussion

3.1 Osteoarthritis Knee and Hip Quality of Life survey results

The team successfully performed the adaptation and validation process. As per expert panel's suggestion some changes were implemented in the content of the items and in the line of the items. The adapted questionnaire was completed by 99 patients, suffering from OA. OAKHQoL items are divided into five domains, covering different parts of HRQoL: (1) Physical activity, (2) Mental health, (3) Pain, (4) Social support, (5) Social activities, and 3 independent questions referring to patients' private life. In total 43 items between a 0-10 response scale. 0 is referring to the worst HRQoL status and 10 for the best status. The standardized scores (0–100) were calculated in case of each dimension based on the scoring sheet. Reliability was accessed by determining internal consistency – by calculation of Cronbach's alpha – and validity (construct and known-group) was calculated as well. In this way, the OAKHQoL-HUN 5 domains were compared to two generic quality of life questionnaires' domains (WHOQoL-BREF and EQ-5D). The determination of the correlation was calculated by using Pearson's correlation coefficients (r). The main results are summarized in Table 1. and Table 2. As the most important results, the lowest value belongs to the domain "Physical activity", (38.39). 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. Based on Cronbach's α values, the questionnaire has good or excellent internal consistency in the case of Physical activity (0.93), Mental health (0.91), and Pain (0.89). 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).

Table 1. – 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 ⁱⁱ (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)

Table 2. summarizes the results of Construct validity assessment. 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 ($r=0.621^{**}$).

Table 2. - Construct validity of the OAKHQoL-HUN with correlation of WHOQoL-BREF and EQ-5D-3L generic quality of life questionnaires

	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

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.

3.2 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. 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 and the two introductory items (general HRQoL and DM dependent HRQoL) were compared to the demographic characteristics which predicted significance difference in HRQoL. Based on results, middle-aged patients (56-65) rated their QoL with the highest value. Except from the two introductory items ADDQoL contains 19 diabetes specific items. As per responses for these items, the highest number of the impact score was observed regarding “freedom to drink” and “freedom to eat”. The results perfectly reflect how much patients’ everyday life is influenced by taking care what to drink and what to eat.

3.3 Chronic Ophthalmic Study main results

Based on the reviewed questionnaires, influencing factors of patients’ HRQoL were categorized based on EQ-5D-3L 5 dimensions and the analyzation of this factors were performed by using QbD approach (Figure 2.) As the most important result, the team determined the Quality Target Product Profile (QTPPs), the Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs). The selected QTPPs, CQAs and CPPs were applied in the initial RA process. The presented method helps to systemize the available information on a risk-based manner.

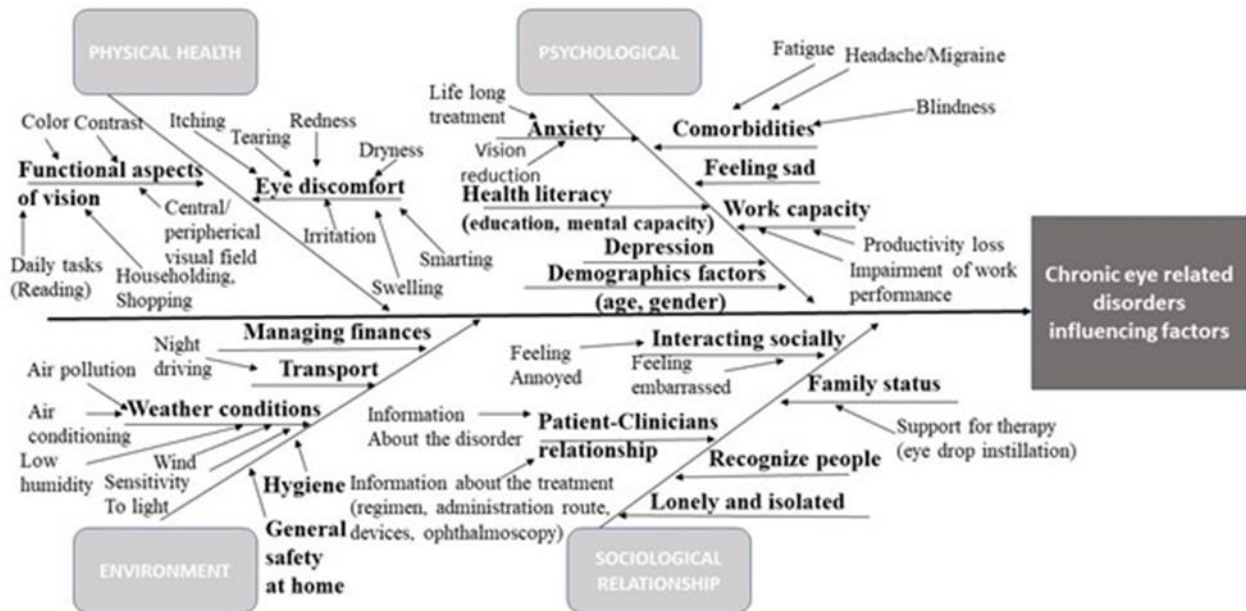


Figure 2: Ishikawa diagram of influencing factors related to the chronic eye disorders

3.4 Cardiovascular Disease - Oral Anticoagulant Therapy survey main results

40 patients in total, completed the test questionnaire. The final version developed for patients on Vitamin K Antagonist therapy consisted of 17 multiple choice questions. Patients on NOAC therapy were given a shorter version of the knowledge assessment questionnaire (10 questions). 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. Most of the patients were treated with acenocumarol (68.6%) and the indication of OAT was mostly atrial fibrillation (63.2%). 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.

3.5 QbD-TOM model development main results

Based on the results and conclusions of the previously performed research works, the team decided to develop a QbD based model, which could be use in case of all chronic disorders and could provide feedback to all relevant parties (academia, doctors, pharmacists, competent authorities etc.). 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" (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 (DoI) in the therapy. DoI replaces the original Design of Experiments (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 logical line of the designed method is summarized in Figure 3.

Flowchart of the newly developed QbD and RA based Quality of Life improvement process: the QbD-TOM method

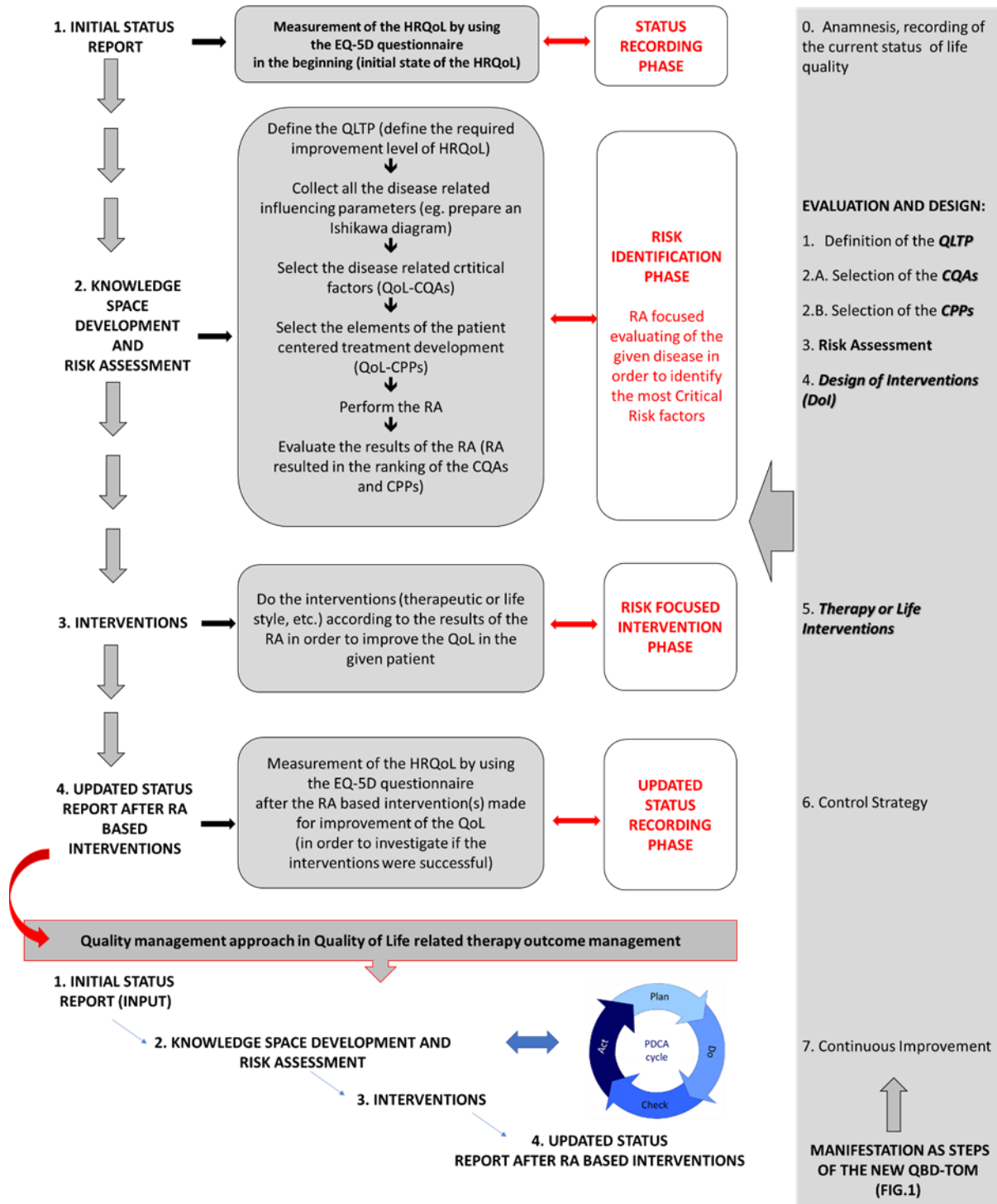


Figure 3. Flowchart of the adaptation of the classic QbD into the therapy outcome management for quality-of-life improvement process

4. Conclusion

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. In case of the different pilot studies the team was cooperating with different involved parties and provided feedback to these specific parties. In each study the patient and the patient centered care was in the focus.

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

IF: 5.043

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

IF: 1.616

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

IF: 0.070

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

IF: 0.070

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

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

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

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-1of 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

1. 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 arthrosisokkal diagnosztizált betegeknek életminőségét, együttműködését befolyásoló tényezők, rizikó faktorok és általános betegségterhek” A rehabilitációs osztály 10 éves fennállásának 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.

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