Ph.D. Programme in Business Administration

THESES OF PH.D. DISSERTATION

Márk Péter Molnár MD, MSc

Rationale, Effectiveness and Economy of Therapy Management Programmes

Ph.D. thesis

Thesis Supervisor:

Viktória Bodnár, PhD
associate professor

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Institute of Management

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1. Antecedents and choice of subject matter

1.1Choice of subject matter

My dissertation is a scientific investigation of the justification, effectiveness and economy of activities aimed at supporting patients in order to ensure that they want to and are able to perform the steps required for regaining their health in a maximally active and medically appropriate fashion. The thesis shows why there is – or at least, why there may be – a need for such activities in modern healthcare systems, details the possible types, participants and forms of those activities, and attempts to furnish an answer to the question of which stakeholders may derive a benefit from those activities in an economic sense. Theoretically speaking, it is certainly clear that all the stakeholders of healthcare systems – or more narrowly, the supply chain of pharmaceuticals – may derive a profit from improvements in the cooperation of patients; my dissertation seeks to answer the question whether that is a sufficient basis for the stronger claim that therapy management programmes themselves are of actual benefit for all the stakeholders in the supply chain of pharmaceuticals.

There are innumerable objective as well as personal, subjective arguments for my choice of subject. Among objective arguments, I would emphasise the fact that modern healthcare systems, which aim for maximum efficiency and operate in an evidence-based fashion, aided by scientific results are gradually losing the ability to retain the human face of healing, with the result that so-called conventional healthcare is becoming mechanistic, inhuman. Within that increasingly sterile framework, the patient's person, their personality get lost, and we are forced to admit with increasing frequency that while we provide ever more costly and innovative medical technologies and medications, their actual, real-life effect decreases and eventually vanishes because patients do not cooperate with the specialists that treat them and they do not get involved in the therapeutic process. They do not cooperate – that is to say, they do not comply with instructions, or they do not comply with them accurately, either on purpose or possibly despite their best intentions (WHO [2003] p. 3; ABC Project Team [2012] p. 5). There may be a number of factors that explain the phenomenon – as we will see later – including, to mention a few, lack of knowledge, simple forgetfulness, or conscious and wilful refusal to cooperate. In the pharmaceutical supply systems of developed countries, which consume significant financial resources, it has become an everyday occurrence that a course of medications costing five thousand dollars a month fails to bring the expected results because nobody has taught the patient that if they don't take the medicine during a meal, the acidity of the stomach will neutralise the active ingredient. In another, equally absurd and common scenario, the most modern pharmaceutical product ends up in the waste bin because the colour of the pill has bad connotations attached in the culture where it was prescribed, leading to the patient refusing to take it due to his superstitious beliefs.

As, in recent decades, healthcare systems have been consuming increasingly significant funds and modern medical technologies have become increasingly costly, considerations of economy have come increasingly to the forefront of attention. Also as a result of that, the cooperation – or non-cooperation – of patients has also become more important both for specialists in the field and theoreticians. In the medical literature of recent years, patient adherence has become an increasingly significant issue, and most recently, the economic aspects of that theme have also been the subject of an increasing number of research papers (ABC Project Team [2012] p. 5). So the subject sits well with the research trends of recent years.

In addition to the objective argument for selecting this subject that the issue of patient adherence has become a focal point of scientific research in the fields of medical science, pharmacology as well as

economics, I must also mention a number of personal motivations. It was primarily on account of those personal motivations that I decided, as a researcher, to achieve as good an understanding as possible of the complex and almost inscrutable process that leads a patient to cooperate with healthcare professionals, or, as the case may be, to not cooperate with them. My personal motivations primarily spring from the fact that over the last 10 years, as a practising specialist, I have worked in four different roles that all made the harmful impacts of the lack of patient adherence palpable to me. Firstly, as a practising physician prescribing courses of treatment, secondly, for an insurance company responsible for the financing of medical treatment, thirdly as a consultant to pharmaceutical companies for whom treatments generate sales revenue, and fourthly as an inventor and leader for a company developing therapy management solutions using telecommunications equipment.

1.2 Antecedents of the research

Over the recent years I have been exposed to the issue of patient adherence from a number of perspectives, and I used those experiences in a number of specific pieces of research. The research I have conducted over the last few years had a stable logical framework and progression, as it is demonstrated in the 1st Figure. Fundamentally, the research aimed to create an accurate scientific assessment of the international and domestic situation as the first step, followed by an investigation of the explanatory factors and finally the formulation of specific guidelines for practising doctors. The figure below (see Figure 1) is ample demonstration that my scientific work was planned to improve the knowledge of healthcare professionals – primarily doctors and pharmacists – working in Hungary of the significance of patient adherence and the allow them the turn patients into allies with maximum efficiency, so as to achieve the best possible results in their day-to-day work. In the interest of achieving those objectives, our research team cooperated continuously with representatives of the various social sciences, fellow universities, medical professional bodies and the leading medical specialists of the specialist areas involved.

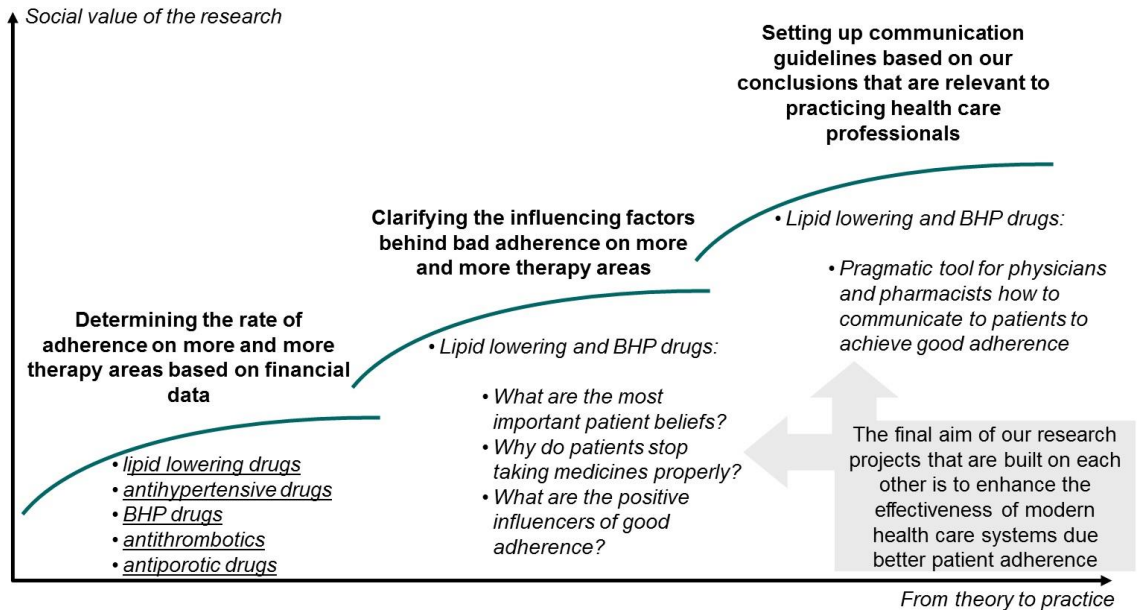

Figure 1: The system of objectives of the research effort (my own figure, used at a meeting of the Hungarian Health Communication Society on 26 January 2011)

2. Methodological considerations

2.1Structure of the dissertation

The logical progression of my work leads from the general towards the specific. Having underlined the reasons behind the choice of the matter, I will attempt to explicate the problem itself, its theoretical background and significance. This includes not only a description of the theories of patient adherence, but also a presentation of international and Hungarian measurement results. I wish to go beyond pure theory and present the specific, palpable medical and economic impact of patient nonadherence, and to justify the necessity and utility of therapy management programmes improving and supporting patient adherence in modern healthcare systems first on a theoretical basis and then also using specific measurements.

As I have shown above, the theoretical background of patient adherence involves a number of scientific disciplines, but today it has become a specialist field in its own right, with its own extensive international and Hungarian literature.

In my dissertation, I will present the core definitions, theories and influencing factors of patient adherence stratum by stratum, based on the literature. In relation to patient adherence, it is necessary to introduce a number of fundamental concepts that are indispensable for a comprehensive exploration of the phenomenon. We are faced with a special situation in which the evolution of the definitions themselves provides a fascinating glimpse of the developmental paths, philosophically and in terms of attitudes, that have transformed the assessment of patients and the system of relationships between doctors and patients in recent decades. After reviewing the definitions, I will present and review the basic literature related to patient adherence and describe our current scientific understanding of the most important factors that determine whether a patient cooperates with his doctor during therapy, and I will also outline the points of intervention at which the situation may be improved. Those theoretical considerations shall provide justification for the therapy management programmes whose effectiveness I will measure in the empirical part of my study.

Illustrating the magnitude of the problem is also part of the theoretical background, so I shall use the examples of a few major chronic diseases to present the measured levels of patient inherence based on international research and, where possible, also Hungarian research, in particular my own research results.

In the last part of the dissertation I will present the objectives, foundations and results of my empirical research. During that research, my fundamental hypothesis was that therapy management programmes improve patient adherence significantly. In addition to providing evidence for that hypothesis, I also investigate a number of secondary hypotheses concerning the economy of therapy management programmes. Is a therapy management programme economical for society? Is a therapy management programme economical for a player in the pharmaceutical market?

2.2 Theoretical background of patient adherence

In the second half of the 20th century, with the development of societies, the creation of modern healthcare systems and general improvement in welfare, the composition of diseases shifted towards chronic conditions. While in previous periods, infectious diseases were the leading causes of death, by today the situation has been transformed completely. In parallel with that, healthcare systems are increasingly devote most of their resources to treating chronic – usually life-long and non-infectious –

diseases. Those diseases require long-term pharmaceutical (and non-pharmaceutical) treatment, in contrast with the treatment of rapidly progressing infections, where the cure is also rapid, if there exists one at all. Long-term treatment requires a great deal more from patients in terms of active participation, agreement and attention, so the effect of the lack of those things on the ultimate objective of treatment is much stronger. With chronic diseases, accurate and persistent adherence to the therapy plays an essential role. Adopting a sensationalist approach, we could say that while the epidemics of the 19th century were caused by bacteria and viruses, the epidemic of the 21st century is caused by patient nonadherence. Although we have effective and generally available treatments for most diseases, we do not have the ability to get our patients to actually use them appropriately, and as a result, we eventually lose those patients (McMullen et al [2015]). The healthcare system of the 21st century need to achieve multidisciplinary cooperation and the support of the companies that deliver practical solutions in order to "cure" non-adherent patients, i.e. to secure their cooperation.

As regards the patient adherence data measured in various countries, the literature shows a highly varied picture. Very generally – i.e. without selecting a specific disease, a specific therapy or a specific country of patient demographic – approximately a half of all patients adhere to the prescribed course of medication. It is important to emphasise that without considering the specific factors listed above, we can only establish very general findings, as many publications have reached the conclusion that, along with other factors, patient adherence is highly linked to the level of development of countries, the specific therapeutic area, the specific treatment and a number of other parameters that I will discuss in detail later. The value of around 50% is valid in the developed world, the level of patient adherence can be significantly worse in developing countries, although we have significantly less information about them. (WHO [2003] p. 7)

In view of the highly unfavourable data the question arises as to the factors that prevent appropriate patient adherence. Most of the factors that can be established are directly related to the character of the cooperation between patients and their doctors, i.e. they are independent of the pharmacological features of the medication used (Hankó [2006]). The scenarios below, and there various combinations, can all be included in the definition of nonadherence (Molnár [2010] p. 4-5):

- "The patient doesn't necessarily get the medication prescribed at the pharmacy. This can be caused by forgetfulness, the lack of awareness of illness, or the "overwriting" of the doctor's instruction for some other reason.
- The patient gets the prescription filled, but doesn't take the medicine, for similar reasons.
- The patient does take the medicine, but not with the prescribed frequency, or at the prescribed times or doses, or not using the method specified in the patient information leaflet.
- The patient stops or interrupts taking the medicine before the prescribed time, which may be caused by feeling better, regaining a psychological sense of security, a reduced awareness of illness, or experiencing unpleasant side-effects, or it may be simply because the patient is "too busy" for some reason to obtain the next subscription or to get it filled (e.g. holiday, accident resulting in being bedridden, a personal crisis, etc.).
- The pharmaceutical therapy doesn't follow a clear treatment strategy, so the patient switches active substances without justification, begins a parallel auxiliary therapy with a different active substance, changes the dose, etc."

As explained above, the level of patient adherence cannot be characterised in general, exact data can only be produced about specific diseases and specific patient populations. The indicative value of 50% specified by the WHO (World Health Organisation) is a rough estimate and it is primarily suitable for illustrating the magnitude of the problem. The great variations that actually exist are characterised well by an analysis performed in 2004 by DiMatteo, which drew its conclusions based on a meta-analysis

of 569 previous studies (DiMatteo [2004]). DiMatteo's analysis obtained an average adherence level of 75.2%, ranging from 65.5% to 88.3% in the therapeutic areas reviewed. So that publication reported a more favourable average patient adherence level than the previously published 50%, which may have been partly due to the fact that the fundamental data came from studies before 1998. In Chapter 3 I will provide a detailed description of the likelihood of patients suffering from various diseases discontinuing their medication, but let us look at a few examples from the international literature just to outline the situation.

In the case of asthma, the literature indicates that less than half the patients adhere to the prescribed therapy (Bender [2002]). According to Lerman, the situation doesn't appear to be any better with diabetes, either, the ratio of adherent patients is below 50% there as well (Lerman [2005]). According to the studies performed by Wogen and colleagues, after a year, 63% of patients were taking the prescribed doses of valsartan, while the same figure was 53% for amlodipine and 50% for lisinopril (Wogen et al [2003]). According to another study, 1 year after commencing the therapy, 62% of patients were still taking the prescribed ACE inhibitors, 54% were still taking their calcium channel blockers and 42% were still taking their diuretics (Colin et al [2001]). Data from the United States indicates that in the case of both primary and secondary prevention, 60% of patients discontinue their life-saving anti-cholesterol drugs (Joanne et al [2008]).

2.3 Direct and indirect clinical impacts

The conditions outlined above indicate that therapies that should be life-long are in reality not continued indefinitely, because there is some "defect in the machine", and the therapeutic process is interrupted. It is also evident that about half of all cases and patients fall in that problematic group, i.e. half the patients do not exhibit appropriate adherence. The meaning of that observation, the significance of that fact is a highly important question. To answer it, we need to understand the causal relationship between the end-result of therapy and appropriate patient adherence.

We have clear scientific evidence that the most frequent cause of a poorly adjusted blood pressure is poor patient adherence (Borghi et al [1999]). Some doctors say there is no such thing as a poorly adjusted blood pressure, only patients who fail to adhere to the prescribed treatment. We also have some studies that indicate that among non-adherent patients, only 18% actually achieve the target blood pressure, while the same ratio was 96% for adherent patients (Waeber et al [2000]). We also know from the work of several authors that appropriate patient adherence improves the effectiveness of the therapy, for instance it reduces the frequency of the complications of high blood pressure and hence the probability of stroke (Marmot et al [2002]) and heart disease (Heller et al [1978]). All of this shows that in the case of cardiovascular disease – where the effects of medication are quite discernible already in the short term – the link between patient adherence and final effectiveness. A 2006 publication used a statistical approach to study exactly that question, and it reached the same results: the authors investigated the relationship between the mortality and the adherence of ischemia and diabetes sufferers. (Ho [2006]) It is quite clear in the figure below that the life prospects of patients not receiving treatment were essentially identical to those of patients who did receive treatment but failed to adhere to the therapy. It is important to note here that the authors treated mortality as a hard limit, so in essence the results say that non-adherent patients dies with the same probability as those who didn't get treatment at all. That is a good illustration of the real stakes involved in improving or achieving patient adherence in modern healthcare systems. The figure below makes it quite clear that, though this may be a slight exaggeration, no matter what new instruments we add to the arsenal of modern medicine if we are unable to get more than half our patients to actually use them as intended. Perhaps the day has come when a unit of the resources of modern healthcare would be more profitably spent on improving patient adherence than on developing a new active substance.

2.4 Direct and indirect economic impacts

Poor adherence causes significant extra costs for patients, healthcare systems – which are equivalent to payers, insurance companies or the state – and for pharmaceutical manufacturers both directly and indirectly, through the resulting failure of therapies. In most cases, all three of these three so-called stakeholders share the financial loss caused by patient nonadherence in varying shares, so these three stakeholders are also the ones who can benefit from appropriate patient adherence.

Poor adherence leads directly to a loss of economic efficiency if the patient used partly her own funds and partly those of some payer to purchase the medication but doesn't use it, doesn't take it, or uses it in a manner whose effect is significantly below the intended effect. Let's assume a simple and extreme case: the medicine costs 100 units of money, of which the patient herself pays 50 units as a co-payment, while the payer pays 50 units as a subsidy. If the patient decides not to take the tablets because after reading the information leaflet she is scared of the potential side-effects, the direct financial loss incurred by the patient is 50 units, and that of the payer is the same. If the drug in question has to be taken specifically during a meal because otherwise stomach acidity prevents appropriate absorption, the result is the same if the patient does take the pills, but does so before eating. It is clear that those two scenarios do not have an economic impact on the pharmaceutical manufacturers, as the product is purchased. Another way to put it is to say that once drugs are purchased, only the patient and the payer have an interest in appropriate use, the manufacturer of the drug no longer has little direct economic interest at that point. The situation is rendered somewhat more complex, however, by the fact that the payer's endeavours do make the manufacturer interested in ensuring that its products do have a real effect. Once that is taken into account, the pharmaceutical manufacturer is also seen to have an interest in the patient's adherence to the therapy.

It is obvious that the economic impacts of the above scenario can be considered in the short term and in the longer term as well. While the above reasoning primarily concerned the short-term, direct effects, we should not forget the consequence that a drug bought but not taken is not going to have its desired effect, which will result in indirect costs. If, in the above example, if the pills not taken or not taken in accordance with instructions are an antihypertensive, and, as a result, on the day after her failure to take the drug the patient in question suffers a stroke in the early hours of the day, when blood pressure usually exhibits a peak in its normal daily variation, this event, and the costs resulting from that event will also be indirectly attributable to poor patient adherence. In such a case, we can quantify the total cost of treating the stroke for the patient as well as the healthcare system, i.e. the payer. Naturally, the patient's "costs" need to be understood in a wide sense, as the costs of a stroke even include all the actual costs of treatment and rehabilitation, but they may also be considered to include all the lost income due to the incapacitation of the patient and her family. It is exactly those long-term costs that Dankó illustrated in her 2011 article, in which he reached the conclusion that in the case of antihypertensives, the extra cost of drugs resulting from an adherence programme amount to 10.8 million forints in total, the cost of the hospital treatment of just three strokes thus averted could come to 21 million forints. (Dankó [2011])

Naturally, such an analysis of indirect costs is not limited to cardiovascular disease. The same type of analysis can also be applied to respiratory illness, and indeed this has been done by Balkrishnan and his team, who followed 1,595 patients over the age of 65 with chronic lung complaints for two years in a retrospective study. They found that poor patient adherence increased the annual number of registered specialist-patient appointments by 5%, while better patient adherence was able to reduce the number of hospitalisation events by 20%. (Balkrishnan et al [2000])

In summary, we can conclude that if patients get their prescriptions filled but do not actually take the medication or use it incorrectly, there is primary economic damage largely for the patients themselves and the payer, that kind of nonadherence is economically indifferent for pharmaceutical manufacturers. However, it must be noted that due to the provisions of more recent agreements concluded between payers and pharmaceutical manufacturers, and the spread of conditional listing systems, manufacturers also increasingly shoulder a part of the loss.

The economic costs at the level of society have been quantified in several countries, and extremely shocking results were obtained, particularly as regards the economic impact of the complications and expensive hospital treatments attributable to nonadherence. In the United States, the costs attributable to nonadherence and improper drug selection were estimated in 1995 and in 2000, furnishing a view of the trends in those costs and the dynamics of change. According to a 2001 study by Ernst and Grizzle, in 1995, the drug related problems they described cost 76.6 billion dollars in the United States of America, while calculations using the same model yielded a figure of 177.4 billion dollars for the year 2000. 70% of the 177.4 billion dollars were contributed by hospitalisation costs that would have been unnecessary in case of proper drug selection and appropriate patient adherence. (Ernst-Grizzle [2001]) In 2011, a more recent calculation has been estimated the yearly economic damage caused by nonadherence at 310 billion dollars (Capgemini Consulting [2011], p. 9).

The literature also furnishes and answer to the question of the relationship between the greater expenditure on drugs caused by better adherence and long-term savings for the payer. A number of studies reached the conclusion that programmes aimed at improving adherence are profitable for the payer even in the short term. Some authors monitoring such programmes report that the ratio of costs to savings is 1:10, i.e. the savings available through the regular taking of drugs are ten times the cost of improving adherence. In the manner described above, Holman and colleagues studied the effects of a complex educational programme, and their highly favourable results were primarily due to the very significant savings resulting from the hospitalisation events that were thereby avoided. They found that members of the control group, who did not participate in the programme, cost 820 dollars more for the US healthcare system than those who did participate in the programme, whose per capita cost was only 70 dollars, of which the cost of trainers was 26 dollars per patient (Holman et al [1997]; [1999]).

2.5 Therapy management programmes and patient education

Improving patient adherence is a highly complex task. As many as possible of the five groups of factors defined by WHO should be targeted for intervention if we wish to achieve really good results (WHO [2003]). It is not sufficient to simply adjust the therapy – for instance by switching from three daily doses to just one tablet a day – it is expedient to exert an influence on other factors, too, for example by giving the patient a printed package of educational material at the time of the switch, or starting a patient log in cooperation with the patient. That is how the complex therapy management programmes that modern healthcare systems truly need are built up. (Molnár [2011] p. 5.)

On the basis of the foregoing, an ideal therapy management programme would be a comprehensive initiative that targets all five of the groups of factors defined by the WHO. Obviously, an individual stakeholder in the healthcare system can rarely exert an activity that is able to influence all five groups of factors, so we can consider any solution that targets at least two of the groups of factors at the same time in order to improve patient adherence to be a therapy management programme.

At present, the only stakeholders that are willing to finance such therapy management programmes are the pharmaceutical manufacturers, but due to the benefits for society and for the payer, the participation of the social insurance system in the operation of such programmes is not out of the

question. In developed countries, especially where the payers have complex, long-term interests, the insurance institutions already participate regularly in the organisation of therapy management programmes, in a manner similar to prevention programmes. There are many such examples among German insurance companies (Stock et al [2010]), but American managed care organisations (MCOs) and health maintenance organisations (HMOs) have also been operating such initiatives professionally and monitoring them scientifically for decades. (Wilson-Pessaro et al [1987]; Bachman et al [2007])

The operation and financing of therapy management programmes by pharmaceutical manufacturers is increasingly common around the world. This statement might be partly contradict the research, where only four pharmaceutical companies out of the interviewed nine indicated that improving adherence is their key strategic objective, and only four indicated that they are actively engaged in such activities. (ABC Project Team [2012] pp. 184-190) As I explained above, a number of background factors can be identified to explain the phenomenon. Firstly, increasingly stringent drug promotion regulations have transformed the attitudes of pharmaceutical manufacturers, and the emphasis has shifted from getting new patients to retaining the existing ones. Although that process is forced on the manufacturers, in recent years the pharmaceutical industry has voluntarily taken steps, towards the concept of "health companies", and increasingly away from just selling pills towards supplying complex healthcare solutions, including the monitoring of treatment, patient education, and the development and supply of intelligent devices and IT solutions. The third pillar of the process is also a factor forced onto the players in the pharmaceutical market: payers are less and less interested in paying for medications that do not actually work in the real world. As a result of that, pharmaceutical companies increasingly need to assume shared risks with the payers as regards real-world effectiveness, and patient adherence is one of the main factors involved there.

2.6 Research aims, hypothesis

With my empirical research, I will try to establish how to assess the effectiveness of a comprehensive therapy management programme using objective, scientific methods, that is to say I will try to measure how the implementation of such a programme impacts the levels of patient adherence. In the course of my research, I will endeavour to apply the theories presented in my dissertation in practice, i.e. I will measure the effectiveness of a therapy management programme that influences as many different factors driving therapy adherence as possible, as explained in Chapter 4. In addition, I will use the methodologies presented in the chapter on the measurement of adherence during the measurement of the effectiveness of the programme, and I will try to establish the relationship of the 3, 6 and 12-month persistence values of the patients that participate in the therapy management programme with those of the control group.

So my fundamental research question concerns the effectiveness, the impact on adherence of the therapy management programme investigated. In addition, I also want to determine the economy of the programme as seen from the perspective of the pharmaceutical manufacturer that finances the programme and the insurance fund that finances the medications themselves.

My hypothesis is that the complex therapy management programme examined has a beneficial effect on the level of patients' adherence, i.e. the 3, 6 and 12-month persistence of the patient population participating in the programme will exceed the values characteristic of the population that does not participate in the programme. If I am able to confirm my hypothesis with the results of my study, I will be able to conclude that programmes similar to the one examined are effective in improving adherence.

As an auxiliary hypothesis, I will also posit that the costs of the programme will be below the increase in the turnover of the drug therapy that the programme focuses on, so the initiative is highly likely to result in a financial profit for the pharmaceutical manufacturer that finances the programme.

Finally, my third hypothesis shall be that the unfavourable effect of the increase in drug consumption resulting from the therapy management programme on social insurance expenditure will be below the savings made by the payer by not having to finance the hospitalisation events and the treatment of other consequences that it would have incurred if the programme had not been implemented.

2.7 The therapeutic area selected

I wish to conduct my research in a therapeutic area about which there are is plenty of international and Hungarian evidence, preferably including the results of my own previous research. The figure shown in Chapter 1 about the research strategy was most applicable to lipid-lowering therapy and the treatment of prostate disorders, as it was in relation to those disorders that in recent years, international and Hungarian persistence conditions were the most fully mapped out, and those were also the treatment areas in which patient attitude studies were also conducted. Of those two areas, cholesterol-reducing treatments are already in the focus of a number of studies in progress, so I decided to perform a detailed analysis of a complex therapy management programme in the therapeutic area of prostate disorders.

2.8 The structure of the therapy management programme

In the course of my research, I studied the drug consumption habits of patients treated with benign prostatic hyperplasia (BPH) who had participated in a complex therapy management programme aimed at increasing adherence. The complexity of the programme was a theoretical advantage in terms of expected results, however, this fact is a significant limitation on the other hand to extrapolate the findings for other therapy management activities, or use the research outcomes as general rules. The structure of the therapy management programme reflected the requirements detailed in a previous chapter, i.e. it attempted to improve as many underlying factors of adherence as possible at the same time. The programme was implemented within the framework of the PraxisPlatform™ patient education system, and it concerned a pharmaceutical product containing a fixed dose combination of dutasteride and tamsulosin, i.e. it was available to patients using that medication for the treatment of BPH, and their doctors. This fact is a limitation of my study, which was linked to an existing therapy management programme linked to a specific pharmaceutical product.

In every instance, the patient was introduced to the therapy management programme by the doctor, i.e. the doctor and the patient made the mutual decision about enrolling the patient in the programme. This act was legally implemented by having the patient sign a consent form authorising his doctor to initiate the programme for him, and authorising our research group to submit the Social Insurance Number (hereinafter the SIN) that identifies the patient to the NHIFA in order to obtain aggregate data about medication consumption habits. I have to emphasise that my study method has a limitation related to the selection of physicians and patients and the positive bias of this selection process. Firstly, the requested and cooperative physicians who took part in the initiative were apparently more open and more sensitive to issues of adherence, which in itself raises the possibility that their patients were already more adherent to therapies. The second level of positive selection was on the level of patients, who had the opportunity to participate in the intervention voluntarily, thus it can be assumed that due to the openness to participate these population might have had already better adherence before the programme.

The programme itself contained the following main components in order to achieve the desired effect on patient adherence:

1. Educational opportunity for the patients' doctors
2. Surveying individual patient needs using a questionnaire
3. Educational opportunity for the patients

2.9 Measuring the effectiveness of the therapy management programme

I intended to follow and analyse the drug consumption of the total Hungarian population taking the specific pharmaceutical product in the relevant timeframe to determine the effectiveness of the therapy management programme. To do this, the SINs of the patients participating in the therapy management programme were submitted to the specialists of the NHIFA (in compliance with data protection rules; see section "Data privacy aspects" later in this chapter), who filtered out those patients who had been still alive at the end of the study period and had at least one package of the product studied dispensed to them during that time. Using those filters, the NHIFA established a specific range of patients, and that became my test population. The difference between the two sets of the SINs consisted of the patients who died during the study period, and those who, despite the doctor's instructions, never had a single prescription filled. At my request, based on the SINs I submitted and the set of patients who had the drug dispensed to them at least once during the study period, the NHIFA also determined the complete population who had the drug studied dispensed to them but definitely didn't take part on the therapy management programme. That set of patients became the control group of my study.

In the course of the measurement, I analysed the itemised drug-dispensing data of the population participating in the education (experimental group), and the control group, i.e., using a 60-day grace period, I determined the proportion of patients that maintained the treatment as a function of the days elapsed from the commencement of treatment. By producing a graph representation of the results, I obtained the persistence curves of the experimental group and the control group.

2.10 Determining economy from the perspective of the pharmaceutical manufacturer

In the course of my study, I obtained an accurate view of the content of the therapy management programme, its costs of development and operation, and the medication consumption habits of the patients participating and not participating in the programme. Based on that, I was able to establish accurately the overall incremental costs of the programme for the financing pharmaceutical manufacturer relative to the "do nothing" scenario, and also the incremental revenues realised specifically as the result of improved adherence. The comparison the expenditure and the palpable positive effects of the programme allowed me to determine the economy of the programme from the perspective of the pharmaceutical company. The calculations did obviously not include any potential additional effects of the programme that did not influence the turnover of the drug through the improvement of adherence but in some other way (for example: better company image).

2.11 Economy from the perspective of the social insurance fund

The third – and the most uncertain – research question of my study was the question of economy from the perspective of the payer. As the aggregate result of the complex network of short-term and long-term effects outlined in the previous chapters, the therapy management programme is certainly

economical (that is to say, dominantly cost-efficient or cost-effective) for the payer if the total of the extra reimbursements resulting from increased consumption of the drug is less than the saving the payer realises from avoiding medium-term costs. As my study will gave me a completely accurate view of drug consumption, it was possible to calculate the incremental reimbursement outflow caused by the programme. Determining the costs avoided was a much more difficult task, and I certainly had to use some estimates:

- As a first step, I used the available clinical studies to establish the basic cost events that the combination drug therapy can prevent, and the prevalence of those events in the experimental and the control groups.
- Afterwards, based on the different proportions of patients receiving those treatments in the two groups, I modelled the number of cost events that occurred, and I attached specific costs to them based on Hungarian reimbursement data.
- Based on my calculations, finally I was able to compare the cost savings resulting from the therapy management programme with the extra reimbursement outflow caused by the increased consumption of the medication.

3. Results

3.1 The effectiveness of the therapy management programme

All together 1,358 pieces of various SINs were handed over to the NHIFA. This patient population entered the therapy management programme sometime between 31 November 2011 and 2 December 2012. I asked the NHIFA to filter out those patients who were alive during the entire study period from 1 July 2011 until 31 December 2013 and started the therapy at any time – bought at least one unit from the study medicine. The data analysis resulted 934 SINs, which determined the relevant study population. The following factors were responsible for the difference between the two groups; the patients passed away during the study period, patients recorded by doctors with invalid SINs, and patients participating in the programme but not buying even one single dosage from the study drug. It is not possible to gather credible information on the composition of the three subgroups. Based on our former research related to cholesterol lowering drugs (Csóka et al [2012]) I assumed that the rate of primary nonadherence might have been low, therefore the main reason behind the difference might have been the administrative error or death of patients. Based on the patients participating in the programme and the patients buying the study pill, NHIF was able to determine the total population that certainly did not take part in therapy management programme, but indeed consumed the tablets. NHIF identified 9,403 persons in this group respectively.

In the course of the measurement, I analysed the itemised drug-dispensing data of the 934 patients participating in the education and taking the study drug (experimental group), and the control group, i.e., using a 60-day grace period, I determined the proportion of patients from each group that maintained the treatment, and obtained the persistence curves of the experimental group and the control group.

Based on international studies I showed that the 12-month persistence of BPH is a wide range, the average rate is between 20% and 30%. I also pointed out that based on our research the Hungarian patients have similar measures with 12-month persistence of 22.3% (Dankó-Molnár-Piróth [2011]). The therapy management programme in my research was linked to a fixed dose combination medicinal product, so this factor had obviously a significant positive effect on patient cooperation, and baseline 12-month persistency. The tamsulosin and dutasteride fixed dose combination has 12-month

persistence of 31.9%, which is far better than the baseline from the literature. This data is valid for the total population taking tamsulosin and dutasteride fixed dose combination in the study period, which means 10,337 patients in total (9,403 patients left out of the programme, 934 patients taking part in the programme). The co-operation level of the patient group (9,403 patients) certainly left out from the therapy management programme was lower, 31.0% respectively. The 12-month persistence of the 934 patients taking tamsulosin and dutasteride fixed dose combination and in parallel certainly taking part in the therapy management programme was 41.2%

Thus, I arrived at the persistence curve of the total population taking the study drug and participating in the therapy management programme, as I had the discontinuation rate of treated patients who did not participate in the programme as well. I used the simplifying assumption that the only decisive difference between these two groups is whether the patients did or did not take part in the investigated programme. In this way, I built up research on the assumption that the different persistence of the two populations is due to the effect of the therapy management programme. I needed to use this assumption, but its simplistic nature is a limitation of my research methodology, which is pointed out in detail later on. The figure below shows the measured difference in term of persistence between the control and the examination group.

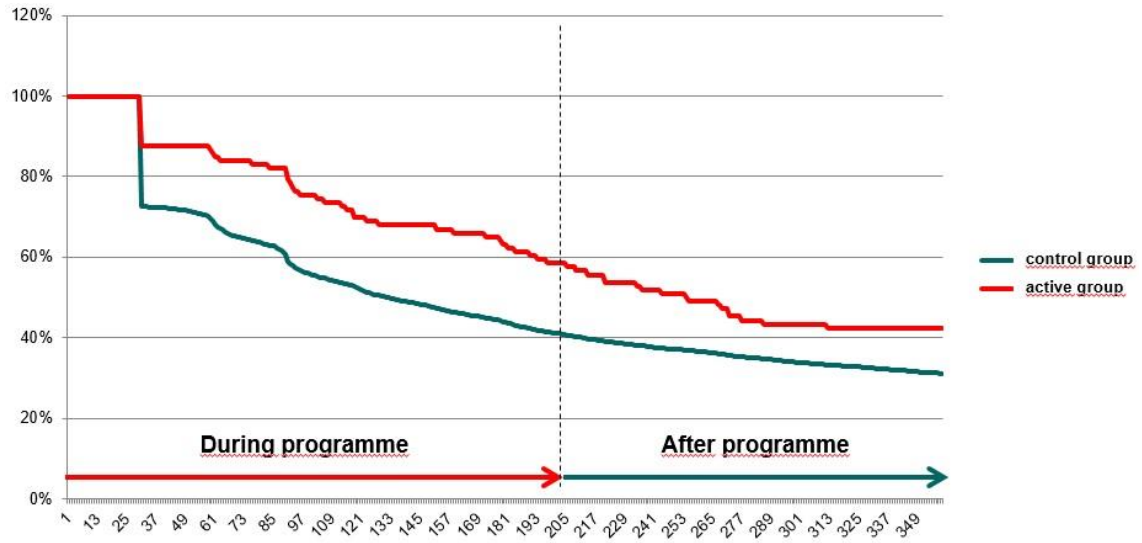

Figure 2: Comparison of persistence curves from the control and the examination groups (own illustration)

I quantified the visible difference on the graph above between the two patient groups. As the graph shows the advantage of the educated group in terms of persistence remained stable all the way long, and the difference in percentage points ranged from 10.0 to 14.7. I was not able to justify any clear trend in the extent of the difference, though in the first 120 days it showed an increase, then a decrease could be observed. The last third of the curve showed a stable difference at around 10 percentage point. It is worth to underline that the therapy management programme lasted only six months, so its effect on persistence seemed to last longer than the intervention itself. The characteristics of the curves allow us to extrapolate, that the programme has a long term effect on persistence, which is maintained well beyond the period.

Based on the results I confirmed my first research hypothesis, therefore I proved that the investigated therapy management programme was able to improve patient adherence significantly in long term period, the intervention was effective.

3.2 Effectiveness from the pharmaceutical manufacturer's perspective

Determining the economic effectiveness of the programme from the perspective of the financing pharmaceutical company I used the results of programme effectiveness analysis from the previous chapter. In parallel I used the drug prices of the studied fixed dose combination and programme cost of PraxisPlatformTM that were publicly available. Thus, the cost of therapy management programme was calculated as 5,000 Hungarian forint (hereinafter HUF) per enrolled patient, and the cost of the drug was 5,832 HUF on the basis of ex-factory price per box which contained medicine sufficient for 30 days. The reimbursement amount for the box was 1,125 HUF, respectively.

Along the outlined conditions the 12-month revenue of the pharmaceutical company from the 934 patients assuming the adherence measured for the non-educated group would be 33.9 million HUF. With the therapy management programme, the dropout rate would be lower, at 12 months the manufacturer would realize 41.5 million HUF as net income, however it should finance the programme itself. The total programme cost for educating the 934 patients would be 4.67 million HUF.

To fully determine the economics of the intervention I missed the data related to manufacturing costs of the drug, therefore I was not able to clarify the specific additional margin due to the programme. All I could conclude from the model calculation was that if the drug with 5,832 HUF ex-factory price has a lower than 2,264.3 HUF manufacturing cost per box, the therapy management programme's favourable impact on revenue certainly offsets the expenses. According to my assumptions there is a very high degree of certainty that my second hypothesis is also been supported by hard evidence, therefore we can conclude, that it is worth to run, initiate or support a therapy management programme by a pharmaceutical company, because it certainly may realize economic benefits as a result of the intervention. The statement is valid even regardless the fact, that the pharmaceutical company supporting such a programme may gain other, intangible benefits also – like better company image – which are hard to quantify.

3.3 Effectiveness from the payer's perspective

To analyse the effectiveness from payer perspective I had to determine two main financial factors; the cost saving due to avoided events and the extra cost of additional drug consumption. First I estimated the frequency of avoided costly events due to the therapy management programme. To do so, I used a double-blind, long follow-up study analysis published by McDonnell et al, which was investigated 3,047 patients treated with BPH. The study demonstrated that on the placebo arm 5% of patients had to be treated with invasive interventions due to BPH, on the active arm with oral combination therapy this probability was only 1% during the 4-year follow-up. (McDonnell et al [2003], p. 2391)

I had the assumption that the costly adverse events occurred with the frequency published by McDonnell et al and that these events show equable distribution within the 4-year period. I weighted the probability of having invasive treatment events within 12 months to the dropout rate from the persistence curve. My calculation was based on the fact that chance of having invasive treatment of patients discontinued the drug treatment is equal to the probability of patients without treatment in the McDonnell study. As clinical data from the study referred to a 4-year period I extrapolated the difference between the two discovered persistence curves and considered the gap constant from the 12th month till the end of the 4-year period.

According to my model calculations in the control group assuming baseline persistence from my research 32.7677 invasive procedures is needed over a period of 4 full calendar years due to BPH, while for patients taking part in the therapy management programme, this value is 28.8575

respectively assuming the measured better persistence. This means that over a period of 4 years the 934 patients involved in the programme avoid nearly four full-invasive intervention thanks to the participants' better adherence.

In the next section I defined which official costs can be associated with events avoided. I took the official DRG and German Point values as reference to calculate the payer's expenditures related to one invasive treatment event.

I estimated the cost of an invasive urological treatment based on the DRG value of a urological surgical event and on the other hand 5 urological out-patient visits. Based on these expenditures the cost of 3.9 hospital treatment avoided turned out to be 1,940,783 HUF all together. In parallel the payer has to face additional drug consumption in form of additional reimbursement cost due to better adherence for the total 4-year period. This reimbursement amount is 5,265,283 HUF for the whole period.

The result of my calculations concluded that a total of 3,324,500 HUF additional expenditure might arise on the payer side due to the programme as a balance. Approximately four hospital treatments can be avoided in exchange for this expenditure. It is clear that however my research could not underline that the therapy management programme is a budget saving tool, but the costs and benefits seem to be in line with the cost-effectiveness parameters of modern pharmaceutical treatments. Based on my model is can be stated, that the cost-effectiveness of such interventions primarily determined by cost of the investigated drug, cost the programme and the cost and frequency of the avoided events. In the field of BPH I have to point out that these main factors do not drive into to direction of cost-effectiveness, so it is very difficult to set up a budget saving adherence improving intervention from payer perspective in the Hungarian context. In Hungary the reimbursement level of hospital interventions is very low, therefore the avoided cost due to such an intervention is lower than in most Western-European setting they would be. The higher hospitalization cost we assume, the more certain the intervention will be cost-effective.

4. Summary of conclusions

My results showed that the investigated therapy management programme was effective to improve patient adherence in the field of BPH, it was economically rational investment from the financing pharmaceutical company, however from payer's perspective the programme did not turn out to be predominantly cost-effective, because I could not prove its budget saving nature. Nevertheless, it should be noted that the programme was able to avoid complications, adverse events and hospitalizations, therefore it could avoid additional expenditures and improve the patients' quality of life. Due to methodological limitations I could not quantify all the avoided costs, and determine the degree of improvement in quality of life. To be able to measure the cost-effectiveness more precisely, further researches are needed. These further investigations might focus on measuring avoided costs more properly and calculating the quality of life improvement due to therapy management programmes. My measurement methodology seems to be appropriate in field of other chronic diseases not only in BPH. In further researches applying this methodology for other diseases might help to detect how treatment- and disease specific attributes may influence the results. Based on my model calculations it has become clear that there is conceptual correspondence among drug costs, programme costs, avoided costs of complications and the cost-effectiveness of therapy management programme. Lower drug and programme costs, and more expensive avoided complications lead to more cost-effective therapy management programmes in the field of chronic conditions.

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