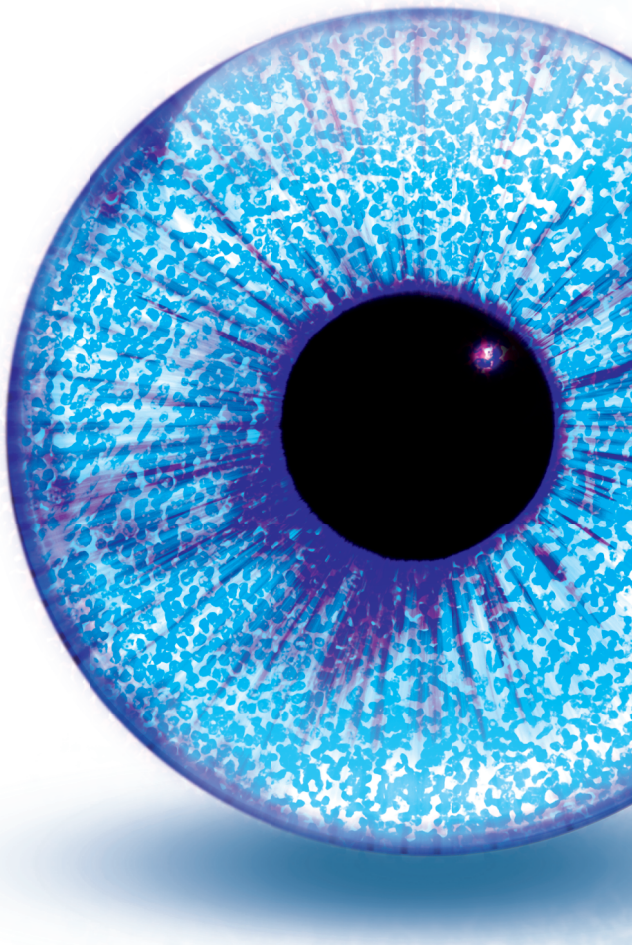
Health technology assessment of health care innovations in chronic lymphocytic leukaemia and glaucoma care

The value of mixed methods research



Kim M. Holtzer-Goor

Health Technology Assessment of Health Care Innovations in Chronic Lymphocytic Leukaemia and Glaucoma Care:

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gezondheidszorg innovaties bij
chronische lymfatische leukemie en glaucoom:
de waarde van mixed methods onderzoek

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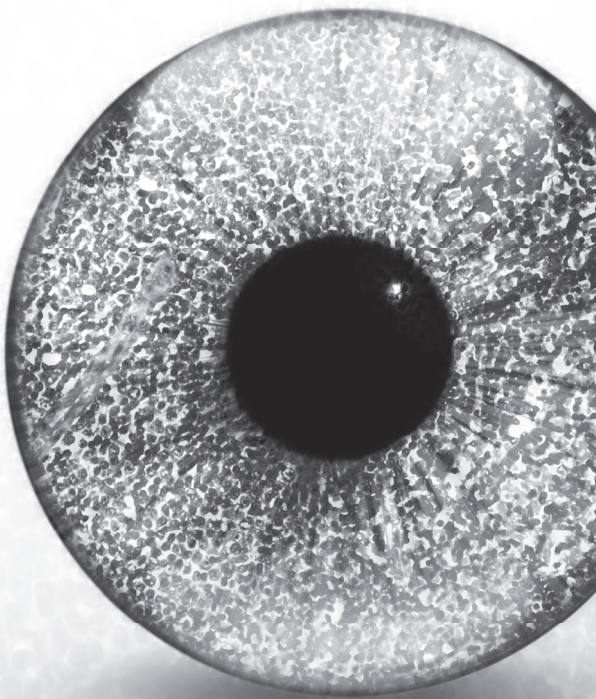
Introduction



1.1 GENERAL INTRODUCTION

Due to new diagnostic and treatment options, people live longer and are more likely to suffer from chronic diseases. Moreover, patients no longer behave passively and often pressure health care providers for access to drugs, diagnostics, services, and devices that they consider effective. This leads to an increasing demand for health care services and a raise in health care expenditures. Health care systems in many countries face the challenge of responding to this growing demand for health care.[1,2]

Health care innovations can be used to respond to this challenge, as they might help to make health care become more convenient, more effective and less expensive, so that more care can be provided with the same resources and health care can remain accessible to everyone.

Three kinds of health care innovations can be defined.[3] The first type of innovation changes the way *consumers* buy and use care. The second type uses *technology* to develop new products and treatments and improves care. The third type generates new *business models,* like the horizontal or vertical integration of separate health care organisations or activities.

This doctoral thesis addresses the implications of two health care innovations. One in glaucoma care and one in chronic lymphocytic leukaemia. The implications are expressed in terms of costs and health effects. Furthermore, in the case of one innovation, the implications of relations between professions are also discussed.

1.2 HEALTH TECHNOLOGY ASSESSMENT

Health Technology Assessment (HTA) is a multi-disciplinary analysis which can be used to obtain information about the economic and health implications as well as the social (e.g. accessibility) and organisational implications (e.g. feasibility and professionalism) of the development, diffusion, and use of health care innovations.[4]

The aim of HTA is to inform the formulation of safe, effective, health care policies that are patient focused and seek to achieve best value.[5]

An economic evaluation is commonly used to assess the economic impact within an HTA analysis. A distinction can be made between full and partial economic evaluations. Full economic evaluations are generally defined as the "comparative analysis of alternative courses of action in terms of their costs and consequences",[6] whereas partial economic evaluations focus on either costs and resource use or (health) effects. Examples of full economic evaluations are cost-effectiveness, cost-utility and cost-benefit analyses, and examples of partial economic evaluations are cost analyses, cost-description studies and cost-outcome descriptions. Although partial economic evaluations provide more

limited information about the cost and/or consequences of a health care innovation than full economic evaluations, they may nevertheless contribute useful evidence for an understanding of economic aspects of health care innovations. For instance, the description of costs related to chronic lymphocytic leukaemia (CLL) reveals for which treatment choices, chemo(immuno-)therapy proved to be the main cost driver. This gives insight into the consequences of future changes in the treatment of CLL with regard to the share of therapy costs in the total CLL related costs.

Economic evaluations can be based on different types of patient data sources. An economic evaluation can be performed alongside a (randomised) clinical trial, or be based on observational data (real world practice). A third option is to use published data on clinical trials or observational studies for an economic evaluation. Each method has its own potentials and methodological problems, which will be included in the general discussion.

The social, ethical and organisational implications within an HTA analysis cannot be fully assessed using an economic evaluation only. A qualitative approach is more suitable for obtaining this information. When an economic evaluation is combined with a qualitative study this is referred to as multi-method research or mixed method research. This combination has been applied in the assessment of the innovation in glaucoma care.

This thesis addresses the costs and consequences of two health care innovations using different types of economic evaluations and different data sources of two diseases. The first innovation is an example of a new business model in glaucoma care, the transfer of tasks from glaucoma specialists to optometrists and ophthalmic technicians. The second innovation is the development of a new treatment option (technology) for CLL: fludarabine. The next two paragraphs introduce the two diseases, their prevalence and burden.

1.3 GLAUCOMA

Glaucoma is a group of eye conditions characterised by damage to the optic nerve.[7] The optic nerve consists of numerous nerve fibres that carry images to the brain. When glaucoma damages the optic nerve fibres, blind spots develop. If it is left untreated, or when treatment cannot prevent further damage to the optic nerve, glaucoma may eventually lead to blindness.

In its early stages, glaucoma has no obvious signs in the majority of patients. As the disease progresses and more damage occurs, blank spots develop in the patient's peripheral (side) vision. These blank spots can, to a certain extent, be filled in by the brain with information from the surrounding area.[8] Blank spots might therefore not be noticed by

the patient until the optic nerve has become severely damaged and the spots become large. This underlines the importance of performing regular eye examinations when a patient is at high risk of developing glaucoma or once glaucoma has been diagnosed.

The damage to the optic nerve is usually, but not always, associated with an increased pressure within the eye (intraocular pressure). This pressure is due to a build-up of a fluid (aqueous humour) that flows in and out of the eye. In a healthy eye, this fluid exits the eye through a drainage system at the angle where the iris and the cornea meet. In the most prevalent type of glaucoma, the angle where the iris and the cornea meet remains open, but the drainage channels in the angle are partially blocked (open-angle glaucoma). This causes the fluid to drain out of the eye too slowly, building pressure within the eye. In the second main group of glaucoma, closed-angle glaucoma, the angle between the cornea and the iris is completely blocked. This results in a rapidly increasing eye pressure, requiring immediate treatment.

Obviously, patients with a high intraocular pressure are at risk of developing glaucoma. Other risk factors are a high age, an African-American background and a family history of glaucoma.

Prevalence and burden of glaucoma

The total number of patients with glaucoma in the Netherlands is estimated to be 162,500 of whom 96,200 patients have open-angle glaucoma. This represents approximately 1% and 0.6% of the total population, respectively.[9] In an extensive international review, a similar prevalence rate was found.[10] This rate increases with age, and varies according to ethnicity. The true number of people with glaucoma is probably much higher, since large screening studies found that more than half of the identified cases of glaucoma were previously undiagnosed.[11-14]

Even in early stage glaucoma, when the visual acuity has not been affected, glaucoma can have an impact on the health-related quality of life due to, for example, the loss of a driving licence.[10,14] The overall burden increases as glaucomatous damage and vision loss progresses.[14] The WHO estimates that due to impaired vision and blindness related to glaucoma, the disease is responsible for 1.3 million disability-adjusted life years (DALYs) among the 2.7 billion DALYs in the world in 2012 (WHO).

Most studies about the costs of glaucoma mainly focus on the direct medical cost of glaucoma. These studies show that the costs of glaucoma are considerable and are rising over the years. Indirect non-medical costs of glaucoma are, however, not negligible. Loss of productivity is less relevant in the largest part of this (older) patient group, but the costs of institutionalisation, care provision and home adaptations are relevant in patients with visual impairment.[15] The greater part of medical costs is spent on medication, with new, better, and more easily tolerated, but more expensive medication replacing

older and less expensive types. The economic burden of glaucoma is directly related to the severity of the disease.[10,14]

In the Netherlands, information on the costs of glaucoma is not readily available. The only information on direct medical costs of visual disorders is presented as aggregated costs. The costs of glaucoma, cataract, refraction errors, blindness, visual impairment and other eye disorders amounted to €2.8 million in 2011, which is 3.2% of the total health care expenditure.[16]

Treatment of glaucoma

Glaucoma cannot be cured, and damage to the optic nerve is irreversible, but treatment and regular monitoring can prevent a further loss of vision in people with glaucoma. Glaucoma treatment aims to lower the intraocular pressure. This can be achieved by medication (eye drops), laser treatment or surgery.

Glaucoma treatment often starts with medication. These medicines can work in two ways. They either aim to increase the outflow of fluid or to reduce the production of fluid, with both methods resulting in a lower intraocular pressure.

When medication is not tolerated or ineffective, laser treatment or another type of surgery may be performed. Laser trabeculoplasty uses high-energy laser beams to help fluid drain more easily from the eye. During a trabeculectomy, a small piece of eye tissue is removed at the base of the cornea through which fluid drains from the eye. This helps the fluid drain more easily. As a result, the eye pressure will be lowered. In some cases of advanced glaucoma, a drainage implant is placed in the eye to facilitate draining fluid from the eye.

When the treatment in patients with glaucoma has been effective, and the progression of the disease has come to a halt, patients are considered to be "stable glaucoma patients". Research in this thesis focuses on monitoring and treating patients with stable glaucoma and those at high risk of developing glaucoma.

1.4 CHRONIC LYMPHOCYTIC LEUKAEMIA

CLL is the most common type of leukaemia in the western world. It is a cancer of the lymphocytes (a type of white blood cells), characterised by their uncontrolled cell division that crowds out healthy blood cells. Due to a shortage of healthy white and red blood cells, a patient with CLL may develop infections and anaemia. Early symptoms of CLL are, however, usually minimal and diagnosis often follows a routine blood test that returns a high lymphocyte blood count. Some CLL patients present with enlarged lymph nodes.

The clinical course of CLL is highly variable.[17] Survival from the time of diagnosis ranges from several months to 20 or more years, depending on prognostic factors.[18,19]

Table 1.1. Classification of CLL patients by Rai and Binet

Rai classification	Binet classification
Stage 0. Lymphocytosis. No enlarged lymph nodes, spleen, or liver, and with near normal red blood cell and platelet counts.	Stage A. Fewer than 3 areas of lymphoid tissue are enlarged, with no anaemia or thrombocytopenia.
Stage I. Lymphocytosis plus enlarged lymph nodes. The spleen and liver are not enlarged, with near normal red blood cell and platelet counts.	
Stage II. Lymphocytosis and an enlarged spleen (and/or liver). The red blood cell and platelet counts are near normal.	Stage B. 3 or more areas of lymphoid tissue are enlarged, with no anaemia or thrombocytopenia.
Stage III. Lymphocytosis plus anaemia. Near normal platelet counts.	Stage C. Presence of anaemia and/or thrombocytopenia.
Stage IV. Lymphocytosis plus thrombocytopenia, with or without anaemia, enlarged lymph nodes, spleen, or liver.	

The first prognostic indices including lymphadenopathy, hepatomegaly, splenomegaly, anaemia and thrombocytopenia were developed by Rai and Binet[17,20] to define disease stages (see Table 1.1). Patients who are diagnosed at an early stage (Binet A, Rai 0) have a median estimated survival time of more than 10 years, intermediate stage patients (Binet B, Rai I/II) a survival time of 7 years and advanced patients (Binet C, Rai III/IV) have a median survival time of 1.5 years.[21] More recently, molecular based prognostic markers have been defined such as chromosomal abnormalities[22] and mutational status of the immunoglobulin genes.[23]

Prevalence and burden of Chronic Lymphocytic Leukaemia

CLL is primarily a disease of older adults, with a median age of 70 years at the time of diagnosis.[24] CLL affects roughly 3 to 6 people per 100,000 population.[25,26] In the Netherlands, 600 to 700 patients are diagnosed with CLL every year,[27] with twice as many males as females. As shown in Figure 1.1, the incidence of CLL increases with age and peaks at 60 to 80 years.[26,28,29] The real number of people with CLL is probably higher, because of the asymptomatic character of the disease at the start of the disease course.

Because of the prolonged survival, which was usually about ten years in past decades, but which can extend to a normal life expectancy,[30] the prevalence is much higher than the incidence.

Although CLL is often asymptomatic at the earliest stages, the awareness of living with an incurable disease can by itself have a profound impact on health related quality of life (HRQoL).[31] As the disease progresses, patients can also experience disease-related

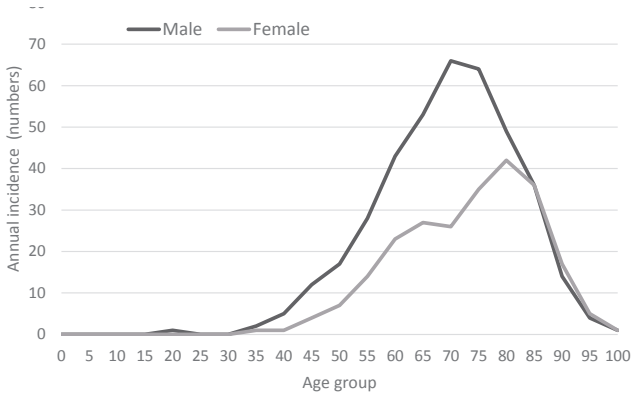


Figure 1.1 Annual incidence of chronic lymphocytic leukaemia in the Netherlands.

symptoms and the toxic effects of therapy like fatigue, weight loss, bleeding, and recurrent or persistent infections.[32,33] Despite these effects, little is known about the HRQoL of patients living with CLL.[31,34,35] The available information on HRQoL is often based on clinical trials, which represent only a small part of all CLL patients in clinical practice. Only a few studies were performed in the complete population of CLL patients. These studies conclude that CLL has a profound impact on HRQoL when compared to the general population[36,37] and that HRQoL differs between men and women.[38] The WHO estimates that CLL is responsible for 10.6 million DALYs per year which is 0.3% of the total number of annual DALYs.[39]

The three studies that present an overview of the longitudinal costs of CLL are all based on administrative claim data and show that the medical cost attributable to CLL ranges from €5000 to €1200 per year (2011 level) in Germany and are almost $68000 (€50320, 2011) through lifetime in the USA.[40-42] These studies concluded, contrary to an older review,[43] that it is not the therapy costs, but rather the usage of physicians and inpatient care that are the main cost drivers of CLL treatment.

Treatment of Chronic Lymphocytic Leukaemia

Although generally considered incurable, CLL can be treated and current standard chemotherapy regimens have been shown to prolong survival.

As randomised clinical trials[44,45,46] failed however to show a statistically significant difference in survival between early versus deferred treatment of patients with asymptomatic, low risk (Rai o/ Binet A) CLL, the majority of CLL patients are not treated immediately after diagnosis. They will first be monitored through a watch and wait approach. Around one third of patients never even require treatment.

Treatment is indicated only upon disease progression and/or the development of CLL related symptoms.[47] CLL treatment aims to control the disease and its symptoms.

Treatment possibilities are (a combination of) chemotherapy, radiation therapy, immunotherapy, and bone marrow transplantation. Symptoms are sometimes treated surgically (removal of enlarged spleen) or by radiation therapy ("de-bulking" swollen lymph nodes).

The management of CLL has changed in recent decades. The development of purine analogues like fludarabine was the first breakthrough in the 1980s. Before that time, treatment of CLL revolved around chlorambucil. At the turn of the century, almost all patients were treated with single chemotherapeutics like chlorambucil and fludarabine.[48] At that time there was no evidence claiming that drug combinations were preferable to monotherapy. Treatment combinations like CHOP (cyclophosphamide, doxorubicine, vincristine and prednisone) were used, but usually not in the first line.[48] Ten years later, especially after the introduction of monoclonal antibodies at the start of the twentieth century, multiple studies have shown improvement in progression-free survival with fludarabine based combinations.[49-52]

Although fludarabine was shown to give superior response rates to chlorambucil as primary therapy,[53,54] there is no evidence that early use of fludarabine monotherapy improves overall survival, and some clinicians therefore prefer to reserve fludarabine for relapsed disease.

The first time that the overall survival was improved by the choice of a first-line treatment, was in a large randomised trial comparing chemo-immunotherapy (fludarabine, cyclophosphamide, and rituximab - known as FCR) with chemotherapy (fludarabine and cyclophosphamide). Besides the overall survival, FCR also resulted in an improved response rate and progression-free survival in CLL patients selected for a good physical condition.[47]

1.5 THESIS AIMS

The overall aim of this thesis is to evaluate the health benefits and costs of health care innovations, illustrated in two different disease areas: glaucoma and CLL.

Population aging increases the number of glaucoma patients and already leads to higher workloads for glaucoma specialists. If stable glaucoma patients were monitored by optometrists and ophthalmic technicians in a glaucoma follow-up unit (GFU) rather than by glaucoma specialists, then the specialists' workloads and waiting lists might be reduced. We therefore compared costs and quality of care at the hospital-based GFU with those of the usual care by glaucoma specialists in the Rotterdam Eye Hospital in a randomised clinical trial. Furthermore we explored how stakeholders perceived the feasibility of transferring hospital-based monitoring of stable glaucoma patients to primary care optometrists.

In the past decades, the number of treatment options for CLL has increased rapidly. Since health care is under increasing pressure, cost-effectiveness data of new versus existing treatment options are urgently needed. That is especially true in countries like the Netherlands where expensive drugs are to be evaluated during the first years of temporary admittance in order to obtain unconditional reimbursement. In an observational study, we followed Dutch CLL patients for 6.4 years on average to get an overview of the management of CLL. A comprehensive cost calculation was performed to produce a transparent overview of different cost categories that would identify the main cost drivers during the complete course of CLL treatment, presented per treatment line and per type of treatment. Information about the longitudinal quality of life of CLL patients over time was collected during the prospective part of the same study.

Research questions

The aim of the research as described in the previous paragraphs has been translated into the following research questions:

Glaucoma

I. Is the quality of care delivered to stable glaucoma patients and to patients at risk of glaucoma by the hospital-based GFU similar to the quality of care delivered by glaucoma specialists in the Rotterdam Eye Hospital?
II. What are the costs of the care provided by the GFU in monitoring and treating stable glaucoma patients and patients at risk of glaucoma when compared with those of the usual care provided by glaucoma specialists in the Rotterdam Eye Hospital?
III. How do stakeholders perceive the feasibility of implementing substitution of person (from ophthalmologists to allied health professionals) and setting (from a hospital to primary care) for glaucoma care at the Rotterdam Eye Hospital, and what are their supporting and opposing arguments?

Chronic lymphocytic leukaemia

IV. How is CLL managed in the Netherlands and what is its clinical effectiveness in daily clinical practice?
V. What are the main cost drivers during the complete course of CLL treatment including the period before the start of treatment (watchful waiting)?
VI. What is the health related quality of life (HRQoL) of an unselected population of patients with chronic lymphocytic leukaemia (CLL) including untreated patients?

1.6 THESIS OUTLINE

The research conducted to address the questions listed above is described in the next six chapters of this thesis. Each chapter addresses a separate research question. Part 1, which comprises the first three chapters is concerned with the randomised clinical trial investigating optometrists to substitute for ophthalmologists in glaucoma care. It describes the clinical effects of this substitution within the hospital (Chapter 2), the cost-effectiveness (Chapter 3) and the feasibility of extending this substitution allowing primary care optometrists to substitute for ophthalmologists (Chapter 4).

The second part of this thesis, addresses the management (Chapter 5), resource use and costs of CLL (Chapter 6) and the long-term quality of life of patients with CLL (Chapter 7) based on an observational study conducted in 19 Dutch hospitals.

Chapter 8 of this thesis provides a discussion of the results and explores the implications of the findings for health care providers, managers and researchers. Implications for future research projects are summarised and discussed in this chapter as well.

Chapter 2

Shared care in monitoring stable glaucoma patients: a randomised controlled trial

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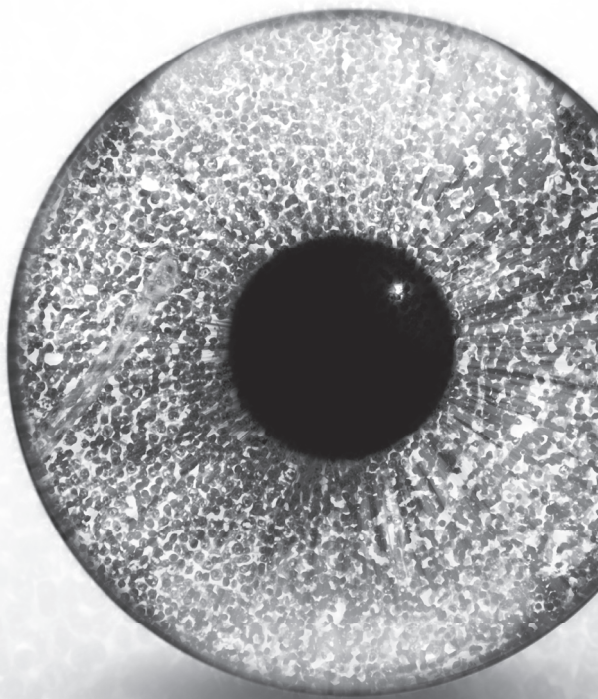

SUMMARY

Purpose. Comparing the quality of care provided by a hospital-based shared care glaucoma follow-up unit with care as usual.

Methods. This randomised controlled trial included stable glaucoma patients and patients at risk for developing glaucoma. Patients in the Usual Care group (n=410) were seen by glaucoma specialists. In the glaucoma follow-up unit group (n=405), patients visited the glaucoma follow-up unit twice followed by a visit to a glaucoma specialist. The main outcome measures were: compliance to the working protocol by glaucoma follow-up unit employees; difference in intraocular pressure between baseline and at ≥18 months; and patient satisfaction.

Results. Glaucoma follow-up unit employees closely adhered to the working protocol for the measurement of intraocular pressure, visual acuity and GDx (≥97.5% of all visits). Humphrey Field Analyser examinations were not performed as frequently as prescribed by the working protocol, but more often than in the Usual Care group. In a small minority of patients that required back-referral, the protocol was disregarded, notably when criteria were only slightly exceeded. There was no statistically significant difference in changes in intraocular pressure between the two treatment groups (p=0.854). Patients were slightly more satisfied with the glaucoma follow-up unit employees than with the glaucoma specialists (scores: 8.56 vs. 8.40; p=0.006).

Conclusions. In general, the hospital-based shared care glaucoma follow-up closely observed its working protocol and patients preferred it slightly over the usual care provided by medical doctors. The glaucoma follow-up unit operated satisfactorily and might serve as a model for shared care strategies elsewhere.

2.1 INTRODUCTION

Glaucoma is a progressive condition that requires lifelong observation and management. Quigley and Broman[55] predicted in 2006 an approximate 30% increase in the number of glaucoma patients worldwide by 2020, with the need for lifelong monitoring. This increase is caused by a longer life expectancy, enhanced societal expectations, and new diagnostic technologies.[56-59] It may thus be difficult for ophthalmologists worldwide to meet the growing demands of glaucoma patients.

One solution to manage the growing gap between the number of ophthalmologists and the demand for their services would be to increase the number of ophthalmologists; this appears unlikely because of limited resources.[2] Another possible solution might be to deliver care more efficiently through a transfer of tasks in glaucoma care.[60,61] In patients at a low risk of becoming significantly visually impaired during their lifetime, monitoring of the disease probably does not have to be performed entirely by an ophthalmologist but by (community) optometrists and ophthalmic technicians.[62-64] Suitable patients for such follow-up would be those in which the glaucoma is relatively mild, has stabilized or progresses at a relatively low rate or is not even apparent yet. In the latter group, follow-up would be merely required because the patients carried an increased risk of developing the disease, for instance in those with a positive family history. To meet the future demands of ophthalmic care, the shared care option merits consideration and study.

The Bristol Shared Care Glaucoma Study,[65-69] carried out over a decade ago, is to our knowledge the only study in which transfer of glaucoma care to community optometrists was studied and found to be successful. We believe that transferring glaucoma patients to community optometrists is not feasible in most countries, although there is little data available about shared care in the various countries. We showed earlier that the Rotterdam Eye Hospital (REH) in the Netherlands attempted to refer stable glaucoma patients in 2001 to community optometrists for some of their regular glaucoma follow-up visits.[70,71] In that particular project, the standard of care was substituted not only by health care provider (the glaucoma specialist by an optometrist) but also by setting (the hospital by the optic dispensary). It turned out that this substitution by both health care provider and setting was not successful. Both glaucoma specialists and patients were unfamiliar with the skills and knowledge of optometrists and questioned the quality of their care. As a result, few patients actually visited the optometrists. Unfortunately, the steady increase in glaucoma patients greatly exceeded the resources at the REH, so that it had to close its doors to new glaucoma patients in 2003.

To address this problem, the REH initiated an intermediate step of substitution of health care provider only. In a hospital-based Glaucoma Follow-up Unit (GFU), staffed by an optometrist and ophthalmic technicians, relatively low-risk glaucoma patients were

monitored by means of a standard protocol. These patients included those that had only mild or moderate glaucoma and were thought to be stable, as well as those patients who were glaucoma suspects without proven disease. The purpose of this substitution of care was that it would alleviate the burden of care by glaucoma specialists, allowing them to treat patients with more complicated or advanced glaucoma and also opening the hospital's doors to new patients. Because the GFU was located in the hospital (i.e., in a setting familiar to the patients), the patients were expected to have more confidence in the GFU, compared to community based optometrists. They were thought to be more willing to visit it. In the GFU, ophthalmic technicians and optometrists could become familiar with monitoring glaucoma. If necessary, supervision by glaucoma specialists would be relatively easy to obtain.

The aim of this randomised controlled trial (RCT) was to determine whether the quality of care in the in-hospital GFU was similar to that of glaucoma specialists.

2.2 MATERIALS AND METHODS

Study organisation

The GFU was located in the REH. The REH is the only independent eye hospital in the Netherlands and functions as a tertiary referral centre for ophthalmic care. The Ethics Review Committee of the Erasmus Medical Centre, Rotterdam, approved the study.

Inclusion criteria

The inclusion criteria used in this study have previously been described in detail.[72] In brief, eligible patients were at risk for glaucoma or had stable glaucoma in one or both eyes, had not undergone laser surgery for diabetic retinopathy and had no other clinically significant ocular disease. The best corrected distance visual acuity (BCVA) in each eye was ≥ 0.20 Snellen decimal equivalent, the refractive error was between +5 and –8 diopters (spherical equivalent) and the patient had no visual field loss within the central 10°.

Eyes were considered to be glaucomatous if they had typical thinning or notching of the neuroretinal rim of the optic nerve head, with or without disc haemorrhages, visual field defects, peripapillary atrophy and/or elevated IOP. Glaucoma was defined as stable if the glaucoma specialist scheduled the next appointment in 6 or more months.

Furthermore, the patient file had to contain information about the actual ophthalmic medication, the target pressure (TP) and the results of the examination of the optic disc, macula, and the peripheral fundus.

Patient selection and randomisation

Patients who had already been referred to the GFU before the start of this trial, as well as newly referred patients, were checked for eligibility. All eligible patients received oral and written information about the study during their next visit. All participants were randomly allocated to either the GFU group or the Usual Care group after giving their informed consent.

To avoid glaucoma specialists affecting the allocation of patients, central randomisation by the researchers was performed using stratification by 2 variables: the referring glaucoma specialist, and the time to the next scheduled visit, being either 6 months or more than 6 months. Patients were followed during a median period of 2 year.

Usual care vs. Glaucoma Follow-up Unit

In the Usual Care group, the patients were seen by glaucoma specialists. In the GFU group, every patient visited the GFU twice, followed by a visit to a glaucoma specialist.

Table 2.1. Provided care in the glaucoma specialist group and theg Glaucoma Follow-up Unit group with criteria for back referral to the glaucoma specialist

Activity	Glaucoma specialist	GFU	Criteria for back referral by GFU
Short history	Every visit	Every visit	
IOP [1]	Every visit	Every visit	IOP>TP
Medical prescriptions	Every visit	Every visit	
Optic disc assessment	Every visit	NA	
Snellen visual acuity	At least once yearly	Every visit	Decline in visual acuity of ≥ 2 lines
GDx ECC [2]	Approximately once yearly	Every visit	Suspicion of progression. In case of first GDx ECC: NFI > 35 and/or left/right asymmetry and/or local defect
HFA 24-2 [3]	Approximately once yearly	Yearly in moderate to advanced visual field damage[4]	Suspicion of progression
Overall judgment	Every visit	Every visit	
Timing next appointment	Every visit	Every visit	

[1] IOP by Goldmann applanation tonometry
[2] GDx ECC scanning laser polarimetry images
[3] Humphrey Field Analyzer, standard 24-2 test algorithm (HFA 24-2)
[4] Criteria moderate to advanced visual field damage: the mean deviation of the last performed visual field was < -5dB
GFU: glaucoma follow-up unit; IOP: intraocular pressure; NA: not applicable; NFI: nerve fiber indicator; TP: target pressure.

For the GFU, the next visit was always scheduled after the same time interval as before, as long as the glaucoma was considered to be stable.

The GFU employees observed a strict working protocol; they could call in the assistance of a glaucoma specialist whenever required. If specified criteria were exceeded, the GFU was supposed to refer the patients back to a glaucoma specialist, within a predetermined time-frame. The elements of 'care as usual' and of the working protocol in the GFU, including the criteria for back-referral to the glaucoma specialist, have been shown in Table 2.1. The most important reasons for referring the patients from the GFU back to the glaucoma specialists were loss of visual acuity, an IOP that was higher than the predetermined target pressure and/or any suspicion of glaucomatous progression on either visual fields or GDx.

Optic disc assessment was not carried out at the GFU, because ophthalmic technicians in the Netherlands are not trained to do so. As a surrogate for examining the optic disc, the GFU personnel carried out a GDx ECC or a Humphrey Field Analyzer (HFA; both devices manufactured and distributed by Carl Zeiss Meditec Inc., Dublin, CA, USA) exam.

Main outcome measures

For the definition of quality of care, we used the six aims of health care improvement as described by the Institute of Medicine: safe, patient-centered, timely, equitable, effective, and efficient care.[73]

The safety of care provided by the GFU was derived from the extent to which its employees followed the working protocol. We scored how often the obligatory examinations and ancillary tests (per protocol) were carried out and how often the patients were back-referred to the glaucoma specialists, as well as how often the glaucoma specialists were called upon for advice in case criteria were exceeded.

The patient-centeredness was measured by using the consumer quality index, an existing questionnaire for patient satisfaction, which had been tested previously in other patient populations for validity and reliability.[74] A translated version of the questionnaire has been provided as Appendix 2.1. The analysis focuses on five dimensions: 1) the overall mark given for the received care; 2) knowledge: the perceived knowledge of the health care provider; 3) information: how well the health care provider provided the patient with information; 4) courteousness: whether the patient was treated courteously; 5) the patient's opinion about the waiting area.

The effect in clinical productivity of glaucoma specialists was used as a measure for the timeliness and equity of care, since the establishment of the GFU was expected to decrease the workload of the glaucoma specialists, allowing the acceptance of new glaucoma patients. The effect in clinical productivity was expressed in the number of additional patients that could be accepted for treatment and was calculated as the difference in the average time spent per patient year by a glaucoma specialist in the

GFU group vs. the Usual care group. Visits to the glaucoma specialists were assumed to require 10 minutes, and giving advice 5 minutes. For patients in the GFU group who did not visit the glaucoma specialist yet -which they should, every third visit, one third of the visits was included in this calculation.

For the measurement of the effectiveness of care, several measures were used: a) the time till the next visit; it was thought that any reduction in that interval indicated that the patient required additional attention, indicating some form of additional concern over the clinical management of the disease; the time till the next scheduled visit reflected the overall clinical judgment of either the glaucoma specialist or the GFU employee, based on all available clinical information, such as history, IOP, appearance of the optic disc and/or of the GDx ECC scans, functional assessments (HFA visual fields) and tolerance of therapy b) mean difference in IOP (i.e., the IOP at baseline vs. the IOP at the last visit (if at least 18 months afterwards)), c) the results of the examinations and ancillary tests and, d) the number of treatment changes.

This manuscript does not present the results about the efficiency, since a cost-effectiveness analysis of our data has been reported separately.[72]

Visual field or GDx progression per se was not used as an outcome measure because we did not expect this patient population to progress in the relatively short time span of the study, since the patients either were assumed to be stable from its outset or only had a risk factor for glaucoma without any outright disease.

Data collection and quality assurance

To quantitatively assess the clinical outcomes and the provided care, Case Report Forms (CRF) were completed after each patient visit. The data were then checked independently by one of the researchers and subsequently entered into a database.

Patients' experiences were scored after each visit and were reported per treatment group (GFU group or Usual Care group) as well as per type of health care provider, since the GFU group was followed up by GFU employees as well as by glaucoma specialists (the latter every third visit or sooner whenever back referred).

The accuracy of the data was monitored regularly by selecting random samples of CRFs and patient questionnaires and then comparing the data in the database with the original forms.

Statistical analysis

SPSS 22.0 was used for the statistical analysis. Treatment groups were compared by using a t-test for independent samples in normally distributed variables. If the data were not normally distributed, a chi-square test was used. The change in IOP and target IOP over time were analysed with a paired sampled t-test. All statistical tests were performed two-sided and at a 5% significance level.

2.3 RESULTS

A total of 866 patients were enrolled. Patients who did not show up at any appointment (31 patients, 4%) and patients who moved their appointment to a date after the data collection period (13 patients, 2%) and 2 patients who underwent cataract surgery and had no glaucoma-related appointment during the study period were excluded from the analysis. Three others were excluded because they could not be monitored with the GDx and 2 patients withdrew their informed consent (see Figure 2.1).

There were no statistically significant demographic and clinical differences between the remaining 410 patients in the Usual Care group and 405 patients in the GFU group (Table 2.2). These 815 patients had a total of 2100 visits, of which 1832 regular visits. Table 2.3 presents all types of visits, their numbers in the two treatment groups and their inclusion in the various parts of the analysis. The average time between visits was 9.9 months (SD 3.4).

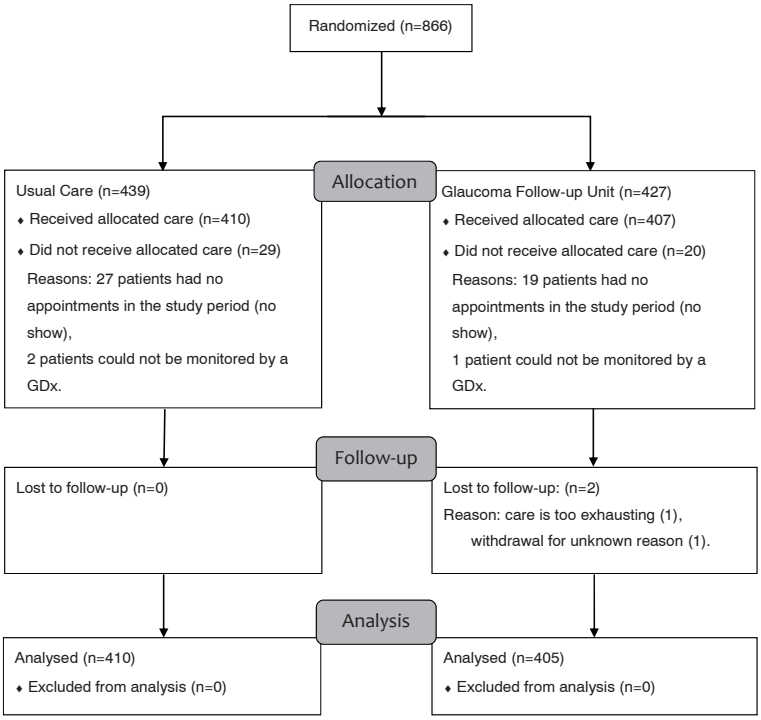

Figure 2.1 Patient flow chart. This figure depicts the patient flow from randomisation and allocation to analysis.

Table 2.2. Patient characteristics per treatment group at baseline and at end of study

	Usual Care Group n=410	GFU Group n=405	P-value
At baseline			
Age*	63.1 (11.9)	63.0 (12.1)	0.40 †
Men**	196 (47.8%)	187 (46.2%)	0.64 ‡
Diagnosis**			0.87 ‡
- Glaucoma	83 (20.2%)	73 (18.1%)	
- Increased IOP	133 (32.4%)	138 (34.2%)	
- Positive family history	15 (3.7%)	14 (3.5%)	
- Glaucoma suspect (≥ 1 other risk factor)	179 (43.7%)	179 (44.3%)	
IOP (mmHg)*	18.8 (4.0)	18.6 (3.9)	0.51 †
TP (mmHg)*	25.2 (5.3)	25.1 (5.1)	0.86 †
BCVA (logMAR value)*	0.05 (0.06)	0.05 (0.06)	0.59 †
Visual field loss (MD < –5 dB with HFA 24-2)**	56 (13.7%)	48 (11.9%)	0.50 ‡
At end of study (last visit at least after 18 M)			
IOP (mmHg)* n= 332 vs. 344	18.3 (3.8) §	18.2 (3.7) §	0.73 †
TP (mmHg)* n= 332 vs. 344	21.4 (4.0) §	21.4 (3.7) §	0.79 †
BCVA (logMAR value)** n= 249 vs. 294	0.05 (0.07) §	0.04 (0.08) §	0.29 †
$IOP+_{\geq 18m}$ - $IOP_{baseline}$	-0.33 (2.61)	-0.37 (3.33)	0.854 †

* Mean and standard deviation; ** Number and percentage

† Independent samples t-test, ‡ Chi-square test

§ *P*-value of paired samples t-test <0.05 for IOP and TP, and > 0.05 for BCVA.

BCVA: Best corrected distance visual acuity; dB: decibel; GFU: glaucoma follow-up unit; HFA: Humphrey Field Analyzer; IOP: intraocular pressure; M: months; MD: mean deviation; TP: target intraocular pressure.

Table 2.3. The type of visits per treatment group and their inclusion in parts of the analysis

	Usual Care group n=410	GFU group n=405	Included in analysis patient satisfaction	Included in analysis compliance with protocol / effectiveness
Total number of visits	919	1181		
Of which regular checks in GFU	40*	813	✓	✓
Of which regular checks with glaucoma specialist	785	194	✓	✓
Of which additional visits to glaucoma specialist	48	131	✓	✓
Of which additional visits for tonometry	42	37	✓	

* These visits were planned when the glaucoma specialist did not realized that the patient was randomised to the specialist group. He/she, therefore, accidentally referred the patient to the GFU.

A&E: Accident and Emergency; GFU: glaucoma follow-up unit.

Safety: compliance of the GFU employees

Table 2.4 shows to what extent the GFU employees followed the working protocol; it displays how often the various examinations and ancillary tests were carried out and also how often the GFU referred the patients back to the glaucoma specialists or called on them for advice, as required by the protocol.

The IOP and visual acuity should be measured at all visits to the GFU. During those visits, the required tests were performed almost every time (> 99%) (Table 2.4). The GDx imaging should be performed with every visit to the GFU, and yearly for every visit to

Table 2.4. Frequency and results of examinations and ancillary tests performed per group and per kind of health care provider

	Usual Care group		GFU group		P-value (between groups)
	Glaucoma specialist /resident n*=833	GFU employees n*=40	Glaucoma specialist / resident n*=325	GFU employees n*=813	
IOP					
Measurement and registration of IOP ODS	825 (99.0%)	40 (100%)	320 (98.5%)	810 (99.6%)	0.593 ‡
Of which IOP (OD and/or OS) > $TP_{baseline}$	86 (10.4%)	2 (5.0%)	69 (21.6%)	52 (6.4%)	0.699 ‡
Of which follow-up with glaucoma specialist	72 (86.7%)[1]	1 (50.0%)	44 (67.7%)[2]	37 (74.0%)[3]	
Of which advice of glaucoma specialist was called upon	0 (0.0%)	1 (50.0%)	0 (0.0%)	7 (13.5%)	
Of which change in medication	1 (1.2%)	0 (0.0%)	4 (5.8%)	0 (0.0%)	
Of which change of TP	6 (11.6%)	0 (0.0%)	6 (13.0%)	0 (0.0%)	
GFU referred to/consulted glaucoma specialist as per protocol	NA	40 (100%)	NA	805 (99.0%)	
Visual acuity					
Measurement and registration of VA ODS	579 (69.5%)	39 (97.5%)	181 (55.7%)	809 (99.5%)	<0.01 ‡
Of which decline in VA of ≥ 2 lines	37 (6.4%)	2 (5.1%)	17 (9.4%)	22 (2.7%)	0.032 ‡
Of which follow-up with glaucoma specialist	33 (91.7%)[4]	1 (100%)[4]	6 (50%)[5]	14 (66.7%)[4]	
Of which advice of glaucoma specialist	3 (8.1%)	0 (0.0%)	1 (5.9%)	1 (4.5%)	
GFU referred to/consulted glaucoma specialist as per protocol	NA	40 (100%)	NA	807 (99.3%)	

Table 2.4. Frequency and results of examinations and ancillary tests performed per group and per kind of health care provider (continued)

	Usual Care group		GFU group		P-value (between groups)
	Glaucoma specialist /resident n*=833	GFU employees n*=40	Glaucoma specialist / resident n*=325	GFU employees n*=813	
GDx ECC					
Number of visits that required a GDx ECC	569 (68.3%)	40 (100%)	325 (100%)	813 (100%)	<0.01 ‡
Of which GDx ECC was performed and documented	376 (66.1%)	40 (100%)	100 (30.8%)	792 (97.4%)	<0.01 ‡
Of which the result was: "suspicion of progression"	24 (6.4%)	2 (5.0%)	3 (0.3%)	37 (4.7%)	0.431 ‡
Of which follow-up with glaucoma specialist	20 (86.7%)[4]	2 (100%)	2 (100%)[4]	32 (86.5%)	
Of which advice of glaucoma specialist	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (13.5%)	
GFU referred to/consulted glaucoma specialist as per protocol	NA	40 (100%)	NA	813 (100%)	
HFA 24-2					
Number of yearly regular visits of patients with visual field loss (MD< –5 dB)	83 (61.0%)	6 (85.7%)	22 (41.5%)	71 (74.7%)	0.916 ‡
HFA 24-2 performed and documented	15 (18.1%)	0 (0.0%)	2 (9.1%)	18 (25.4%)	0.708 ‡
Of which the result was: "suspicion of progression"	4 (4.8%)	0 (0.0%)	0 (0.0%)	5 (7.0%)	0.784 ‡
Of which follow-up with glaucoma specialist	4 (100%)	0 (0.0%)	0 (0.0%)	5 (100%)	
GFU referred to/consulted glaucoma specialist as per protocol	NA	40 (100%)	NA	813 (100%)	

[1] Missing values: n=3
[2] Missing values: n=4
[3] Missing values: n=2
[4] Missing values: n=1
[5] Missing values: n=5
* indicates the number of visits;† independent-sample t-test; ‡ Chi-square test
dB: decibel; GFU: glaucoma follow-up unit; HFA: Humphrey Field Analyzer ; IOP: intraocular pressure; M: months; MD: mean deviation; NA: not applicable; TP: target intraocular pressure; VA: visual acuity

the glaucoma specialist. The GFU performed the GDx imaging in 97.5% of all visits. The HFA exam should be performed yearly in patients with moderate or severe vision loss in both treatment groups. In only 23.4% of all visits to the GFU that required an HFA exam per protocol, this test was performed. For the glaucoma specialist, this percentage was 16.2%.

For patients who fulfilled the criteria for back-referral, the GFU should in principle refer the patient back to the glaucoma specialist or else seek his advice. The GFU did this in all patients in whom there was suspected progressive glaucomatous damage on the GDx or HFA. In 84.6% of the visits that the IOP exceeded the TP, and in 68.2% of the visits that the visual acuity declined 2 or more lines, did the GFU comply with the working protocol. If the GFU employees did not follow the criteria for referral, the patients differed only slightly from these criteria (such as when the IOP exceeded the TP by no more than 2 mmHg).

Timeliness: clinical productivity of glaucoma specialists

The time invested by glaucoma specialists per patient per year was significantly lower in the GFU group than in the Usual Care group: 5.87 minutes vs. 13.71 minutes (Table 2.5). For every patient that could be transferred to the GFU, on average 0.57 extra stable glaucoma patients (1 - (5.87/13.71)) could be treated in the REH. In our study period, 815 patients were treated for glaucoma or their increased risk of developing glaucoma. If these patients were transferred to the GFU, an additional 464 extra stable glaucoma

Table 2.5. Clinical productivity of glaucoma specialists

	Usual Care group	GFU group	P-value
Number of visits per patient year*	1.39 (0.5)	1.37 (0.6)	0.561 †
- Follow-up consultations in GFU per year	0.05 (0.2)	0.97 (0.3)	
- Follow-up consultations with glaucoma specialist per year	1.28 (0.5)	0.35 (0.4)	
- Additional visits for tonometry after treatment change per year	0.06 (0.2)	0.04 (0.2)	
- Visit to A&E department per year	0.01 (0.1)	0.01 (0.1)	
Total amount of glaucoma specialist's time spent on consultation and supervision per patient year in minutes	13.71 (5.9)	5.87 (4.3)	<0.01 †
Clinical productivity (additional number of (stable) glaucoma patients that a glaucoma specialist could treat in the amount of time needed to treat one patient with usual care)	0.00 (0.5)	0.57 (0.3)	<0.01 †

* Mean and standard deviation

† Independent samples t-test

A&E: Accident and Emergency; GFU: glaucoma follow-up unit

patients could, in principle, be accepted for treatment in the REH. Since the management of new glaucoma patients will probably require more time than stable glaucoma patients, the number of extra glaucoma patients that could be accepted for treatment in the REH will be somewhat lower.

Effectiveness

Stability of (risk of developing) glaucoma

At the end of each visit, both the GFU employees and the glaucoma specialists determined whether the interval to the next visit could stay the same as before or should be shortened. Their decision was based on their overall judgment. Shortening of this interval was viewed as a sign that the patient required closer attention, either because of suspiciously unstable glaucoma, or because of an increased risk for that. The latter could for instance be the case when the IOP exceeded the target pressure or when a patient turned out to be intolerant to therapy, increasing the risk of noncompliance and subsequent progression of disease. The percentage of visits with a shortening in the interval to the next visit did not differ between the two groups. In the Usual Care group, this percentage was 15.1% and in the GFU group 16.0% (p=0.619). For the GFU group, this percentage was also 16.0% during the third visit to the glaucoma specialist, indicating that the GFU did not miss significantly more cases of suspected progression.

Difference in IOP

We analysed the IOPs of the 676 patients (83%) of which we had collected the IOP at baseline and at least 18 months later (344 patients of the GFU group and 332 of the Usual Care group). In case of any follow-up visits later than 18 months from baseline, the IOP measurement of the last visit was used. The average difference in IOP $(IOP_{\geq 18 \text{ months since baseline}} - IOP_{baseline})$ was -0.33 mmHg in the Usual Care group and -0.37 mmHg in the GFU group and did not differ statistically between treatment groups (p=0.854). In 40.3% vs. 39.3% of patients for whom the $IOP_{\geq 18 \text{ months since baseline}}$ was available, the last measurement of the IOP was higher than the IOP at baseline in the Usual Care group and GFU group respectively (p=0.619).

Results of the examinations and ancillary tests

Table 2.4 presents the frequency of the examinations and ancillary tests, as well as their results for the two treatment groups. Per treatment group, the results have been presented per type of health care provider (glaucoma specialists vs. GFU employees). The p-values reflect the statistical significance of the difference between the two treatment groups. The frequency of the tests and examinations has been described in the safety paragraph. Their results are presented here.

The results of the HFA and GDx were not different between the two treatment groups (see Table 2.4). The percentage of visits in which the IOP was higher than the TP was similar for the two treatment groups as well. However, the visual acuity declined with 2 or more lines in 6.3% vs. 3.9% of the examinations in the Usual Care group and GFU group, respectively (p=0.032; see Table 2.5).

Treatment changes

The glaucoma therapy was changed at least once during the study period in 14% of the patients in the GFU group and in 15% of the patients in the Usual Care group (p=0.603). The reasons for a change in therapy did not differ significantly between the two treatment groups as well. In half of the treatment changes, the IOP was the reason for changing the therapy. In approximately 20%, intolerance caused the change in medication, and in approximately 16% of cases, the therapy changed because of suspected progression in structure (by assessment of the optic nerve head or in the GDx images) or in function (HFA).

Patient centeredness: patient satisfaction

We received 1492 questionnaires from the patients (response rate 71%). Gender, diagnosis and time between visits did not differ between responders and non-responders, but the responders were significantly older than the non-responders (65.8 vs. 63.6 years of age, p<0.01).

Table 2.6 shows the results for most relevant items of the questionnaire. Since the patients in the GFU treatment group received care from GFU employees as well as

Table 2.6. Patient satisfaction per treatment group and per health care provider

	By treatment group			**By health care provider**		
	GFU N=806	Usual Care N=686	P-value	GFU N=627	Glaucoma specialist N=865	P-value
Overall mark (SD) Range: 1-10	8.50 (1.05)	8.42 (1.15)	0.147	8.56 (1.02)	8.40 (1.15)	0.006
N	*785*	*676*		*615*	*846*	
Knowledge (SD) Range: 1-4	3.84 (0.42)	3.83 (0.47)	0.749	3.82 (0.44)	3.84 (0.45)	0.319
N	*698*	*625*		*539*	*784*	
Information (SD) Range: 1-4	3.14 (0.76)	3.20 (0.70)	0.135	3.11 (0.75)	3.21 (0.72)	0.029
N	*655*	*577*		*511*	*721*	
Waiting area (SD) Range: 1-4	3.20 (0.62)	3.13 (0.67)	0.068	3.20 (0.59)	3.14 (0.67)	0.108
N	*621*	*584*		*486*	*719*	

from the glaucoma specialists, the results have been presented per treatment group (GFU group vs. Usual Care group) as well as per health care provider (GFU employees vs. glaucoma specialists). When the health care providers were compared, the overall score for the GFU employees was slightly, but significantly, higher than the score of the glaucoma specialists. The GFU employees were given a significantly lower score than the glaucoma specialists for the dimension 'information' indicating how well the patients were informed about the test or treatment and its possible alternatives.

The dimension 'courteousness' could only be analysed partly because the patients frequently answered "not applicable" to 6 of the 8 appropriate questions. The 2 items that remained (question b: taking sufficient time to talk to the patient, and question c: giving sufficient information about what was exactly going to happen) showed higher scores for the GFU group than for the Usual Care group (question b: means; 3.87 vs. 3.78, P= 0.000 / question c: means; 3.84 vs. 3.73, P= 0.000).

2.4 DISCUSSION

In the Netherlands, like in other countries, we expect increasing numbers of glaucoma patients, resulting from an aging population. Therefore, the Dutch College of Ophthalmologists (NOG) has stated that ophthalmologists should share their care with supporting personnel like optometrists and ophthalmic technicians.[75] In the Netherlands, substituting glaucoma care within hospitals is currently taking place, and our current report is the first to extensively evaluate this type of substitution.

In the 2-year follow-up of our study, we evaluated the transfer of monitoring stable glaucoma patients and those at risk of developing glaucoma to ophthalmic technicians and optometrists. Our study showed equivalence in clinical effectiveness regarding the (change in) IOP and ancillary tests when comparing the GFU group with the Usual Care group. Visual acuity declined in significantly more patients in the Usual Care group than in the GFU group. Since visual acuity was performed in fewer visits in the Usual Care group than in the GFU group, this difference in clinical outcome may have been caused by the selection of those patients who indicated to have difficulties with their sight.

Moreover, the patients were pleased with the functioning of the GFU. In the same study, we have demonstrated that the monitoring of patients in the GFU was less expensive than the care by glaucoma specialists. This financial aspect has been published elsewhere.[72] The GFU employees closely followed the working protocol. The only test that was not performed by the GFU and glaucoma specialists as frequently as prescribed by the working protocol was the visual field examination. A possible explanation for this might have been the logistics of ancillary testing. Since the HFA takes more time than the GDx, and it took place in another location, the GFU employees perhaps had

not scheduled sufficient time for the HFA and tried to catch up with their busy clinics by skipping this test altogether. Only in a small minority of patients requiring back-referral was the protocol disregarded, notably when criteria were only slightly exceeded.

Limitations of the study

One limitation of our study was that information about the provided care was extracted from the medical records. We adopted this approach, because we did not want to bother the glaucoma specialists with filling in case report forms during their already busy clinics, as an added burden to their usual administrative tasks. This method may have introduced errors. Therefore, the data entered in the database was checked by a research assistant. Nevertheless, we suspect that some provided care was left undocumented in the medical records. We did however get a good insight in whether the glaucoma specialists thought a patient showed any progression (by either the GDx, and/or HFA 24-2, and/or judgment of the optic nerve head), because virtually every treatment change (which happened in case of instability, defined as deemed progression, a too high IOP and/or tolerance to therapy) was explained in the medical records.

Another potential limitation of our study is that we incorporated the GDx in the GFU working protocol. We did this for several reasons. Firstly because it was already clinically used in the REH for glaucoma monitoring, and secondly because the GFU employees were already experienced in taking and assessing GDx images. In addition, the primary care optometrists, involved in the screening project that preceded the establishment of the GFU, had already access to and experience with this device. We thought this would be an advantage, if the monitoring of stable glaucoma patients were to be expanded to their optician shops in the future.[71] A downside of using the GDx for monitoring our patients was that there was no progression software available; any progression detection therefore was subjective. We thought this would not pose a significant problem in the relatively short follow-up period of our study, because we expected very little, if any, progression in this selected group of patients that were thought to be stable from the outset. Since progression software for the GDx became available after we closed our trial, we think that a more objective approach of detecting any (rapid) progression has become available. On the other hand, the manufacturer of the GDx has recently discontinued its production, which will eventually lead to the total disappearance of the GDx in clinical use. Other imaging devices, such as those that feature optical coherence tomography (OCT), which also offer progression detection software algorithms, may turn out to be more appropriate for follow-up of glaucoma.

A main question about our current study is whether we really assessed the quality of care in the two treatment groups. In general terms, it is almost impossible to attribute the observed outcome to the process of care, because outcome is often affected by a multitude of factors in the structure and process of care.[76] In our study, we did not use

glaucomatous progression as an outcome measure, for several reasons; (1) the GFU employees were, by law, not allowed to change the patients' treatment. Therefore, the role of the GFU employees was limited to referring patients back to the glaucoma specialists whenever specific criteria of visual acuity or IOP were exceeded or whenever progressive glaucomatous damage was suspected; (2) moreover, glaucoma typically runs a very slow course. As mentioned earlier, we did not expect to be able to detect any glaucomatous progression in our 2-year study period, especially since only patients that were deemed stable were included in our study.[77]

In our study, safety of care provided by the GFU employees was operationalized as the extent to which the working protocol was adhered to. The GFU should however, also be safe with regard to any other newly developed concomitant ocular disease. Although the GFU employees could potentially miss newly developed eye diseases, we thought the most common ones would be associated with a loss in visual acuity. That is why the assessment of the visual acuity was included in the working protocol of the GFU. In addition, any newly developed symptoms put forward in the history would prompt the GFU employees to ask the glaucoma specialists for advice. Having a GFU within the confines of a hospital offers the advantage of relatively easy communication with glaucoma specialists, which may be more difficult in external GFUs. In addition, we had every patient assigned to the GFU group pay every third visit to the glaucoma specialist, thereby again reducing the risk of any newly developed concomitant disease to pass undetected. The incidence of newly developed asymptomatic concomitant ocular disease turned out to be extremely low: only 1 case with a pseudo macular hole. It is therefore highly unlikely that significant newly developed concomitant disease would pass unnoticed in the GFU.

Suggestions for further research

The study design for the GFU group – with every third visit to the glaucoma specialist – was chosen because of clinical reasons mentioned above. This study design might have introduced bias with regard to patient satisfaction. Patients might be satisfied with the GFU only because they knew that they would visit a glaucoma specialist after 2 visits to the GFU. Moreover, the GFU had more time available for each patient (20 minutes vs. 9 minutes), which might have contributed to the higher satisfaction.[76] Whether this bias really affects patient satisfaction could be subject of further research.

Whether we could have the patients in the GFU group visit the glaucoma specialists less frequently, while maintaining the safety, remains to be determined. This will probably depend considerably on the way any glaucomatous progression may be detected reliably.

Comparison with previous studies

Little is known about the safety of shared glaucoma care. We were only able to compare our findings with those of the Bristol shared care study.[66] Patients in our study were less often referred back to a glaucoma specialist (19% vs. 55% back referrals). Possible reasons for this difference were the location of the GFU and the care structure. Contrary to Bristol, our GFU was situated in the hospital. The glaucoma specialists were only one floor away to answer any questions. In the GFU standard working protocol we also incorporated regular visits to the glaucoma specialist (every third visit), whereas no regular visits to glaucoma specialists were included Bristol.[66]

We believe that setting up a GFU inside a hospital is probably easier to do than referring patients to primary care optometrists in their retail stores, because of the advantage of convenient access to glaucoma specialists.

In medical specialties other than ophthalmology, there have been several studies into doctor-nurse substitution in the treatment of patients with chronic conditions. These studies into doctor-nurse substitution, as well as the Bristol study suggest that doctors and other health care providers generate similar health outcomes for patients.[66,78] The findings of these studies concur with ours.

Conclusion

We conclude that it is safe to refer glaucoma patients that are thought to be stable to a GFU staffed by optometrists and ophthalmic technicians that follow a strict protocol within a hospital. Our study showed equivalence in quality of care when comparing monitoring by the GFU with usual care provided by glaucoma specialists. Similar shared care programs might therefore be adopted safely elsewhere.

Acknowledgements

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The study and data accumulation were carried out with approval by the Rotterdam Eye Hospital Institutional Review Board. The Erasmus MC Medical Ethics Committee waived approval. We adhered to the Declaration of Helsinki and all laws in the Netherlands.

APPENDIX

Appendix 2.1. Patient questionnaire. Dimension: Waiting Area

The area where you were asked to wait had...

	No	Not really	I suppose so	Yes
a. a pleasant atmosphere	❑	❑	❑	❑
b. enough seating	❑	❑	❑	❑
c. comfortable chairs or benches	❑	❑	❑	❑
d. sufficient materials to help you relax and pass the time (e.g. TV, magazines)	❑	❑	❑	❑
e. sufficient facilities for you to get something to eat or drink	❑	❑	❑	❑

Dimension: Knowledge

The [ophthalmologist / GFU employee] who dealt with you during this visit...

	No	Not really	I suppose so	Yes
a. was well informed about your condition	❑	❑	❑	❑
b. was well informed about your treatment/tests	❑	❑	❑	❑

Dimension: Information

During this visit to the [ophthalmologist / GFU], did you know...

	No	Not really	I suppose so	Yes
a. why the particular test or treatment was necessary	❑	❑	❑	❑
b. what the particular test or treatment involved	❑	❑	❑	❑
c. how long the particular test or treatment would take	❑	❑	❑	❑
d. whether the particular test or treatment would be painful	❑	❑	❑	❑
e. what side effects or consequences the particular test or treatment might have	❑	❑	❑	❑
f. whether other tests or treatment were possible	❑	❑	❑	❑

Dimension: Courteousness

The [ophthalmologist / GFU employee] who dealt with you during this visit…

	No	Not really	I suppose so	Yes	N/A
a. allowed you to help decide about new tests or treatments	❑	❑	❑	❑	❑
b. took sufficient time to talk to you	❑	❑	❑	❑	
c. gave sufficient information about what exactly was going to happen	❑	❑	❑	❑	
d. took care that you were not interrupted by other people while you were talking or being examined/tested	❑	❑	❑	❑	❑
e. kept to the agreements that had been made	❑	❑	❑	❑	❑
f. ensured that the care you received was geared to the care from other care providers	❑	❑	❑	❑	❑
g. gave support or help if you felt uncertain or tense	❑	❑	❑	❑	❑
h. explained your glaucoma medication clearly and understandably	❑	❑	❑	❑	❑

Dimension: Overall Mark

We would like to know how you feel about the care given to you by the [ophthalmologist / GFU employee]. What score, from 0 to 10, where 0 is the worst possible care and 10 the best possible care, would you give for the care you received from the [ophthalmologist / GFU employee] who dealt with you? …….

Chapter 3

Cost-effectiveness of monitoring glaucoma patients in shared care: an economic evaluation alongside a randomised controlled trial

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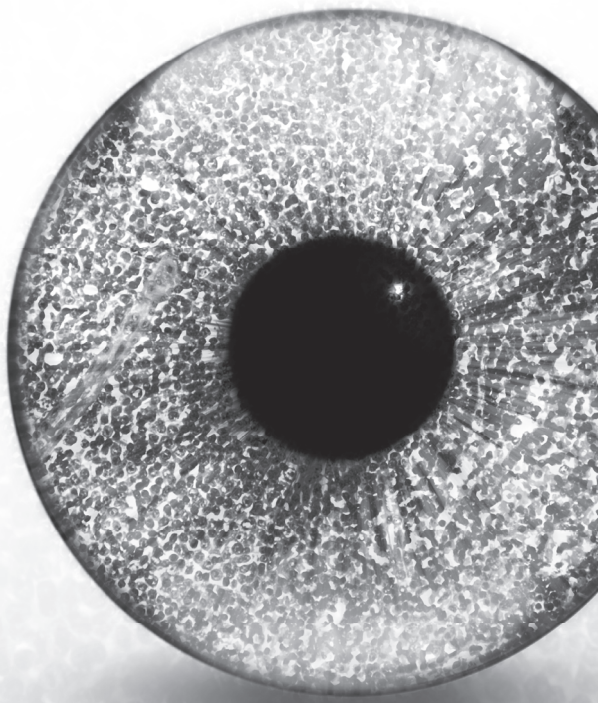

SUMMARY

Background. Population aging increases the number of glaucoma patients, which leads to higher workloads of glaucoma specialists. If stable glaucoma patients were monitored by optometrists and ophthalmic technicians in a glaucoma follow-up unit (GFU) rather than by glaucoma specialists, the specialists' workload and waiting lists might be reduced.

We compared costs and quality of care at the GFU with those of usual care by glaucoma specialists in the Rotterdam Eye Hospital (REH) in a 30-month randomised clinical trial. Because quality of care turned out to be similar, we focus here on the costs.

Methods. Stable glaucoma patients were randomised between the GFU and the glaucoma specialist group. Costs per patient year were calculated from four perspectives: patients, the Rotterdam Eye Hospital (REH), Dutch healthcare system, and society. The outcome measures were: compliance to the protocol; patient satisfaction; stability according to the practitioner; mean difference in IOP; results of the examinations; and number of treatment changes.

Results. Baseline characteristics (such as age, intraocular pressure and target pressure) were comparable between the GFU group (n=410) and the glaucoma specialist group (n=405).

Despite a higher number of visits per year, mean hospital costs per patient year were lower in the GFU group (€139 vs. €161). Patients' time and travel costs were similar. Healthcare costs were significantly lower for the GFU group (€230 vs. €251), as were societal costs (€310 vs. €339) ($p<0.01$). Bootstrap-, sensitivity- and scenario-analyses showed that the costs were robust when varying hospital policy and the duration of visits and tests.

Conclusion. We conclude that this GFU is cost-effective and deserves to be considered for implementation in other hospitals.

3.1 BACKGROUND

Glaucoma is a group of eye diseases characterized by damage to the optic nerve that causes gradual, irreversible visual field loss. It is often related to high intraocular pressure (IOP) and age. Usual care for glaucoma patients consists of diagnosis, lifelong monitoring and treatment, and in most countries is currently provided by glaucoma specialists.

Ophthalmic care in the Netherlands is currently being challenged by a high workload for glaucoma specialists and long waiting lists. Due to ageing of the population, the prevalence of glaucoma probably will increase strongly over time,[55] possibly endangering access to glaucoma care as currently provided. Task substitution may be one way to ease this problem.

Stable glaucoma patients and patients with a risk factor for developing glaucoma may not require care by a glaucoma specialist. Instead, monitoring by hospital optometrists or ophthalmic technicians may be sufficient. This would leave glaucoma specialists with more time for complex cases and new glaucoma patients, allocating their expertise more efficiently, and also reducing waiting lists. As optometrists and ophthalmic technicians are less expensive per hour than specialists, such task substitution might save costs.

To date, only one study[65,68,69,79,80] presented information about the efficiency of substitution in glaucoma care, and its consequences for both quality of care and cost-effectiveness. However, that study compared care by glaucoma specialists with that by community optometrists rather than hospital optometrists. It concluded that glaucoma monitoring by community optometrists is effective, but not cost-effective in most situations. The outcomes were similar to those in specialist care, and the patients were satisfied. However, because of a (standard) shorter follow-up interval than in specialist care, community monitoring was more expensive.[79]

We therefore conducted a randomised controlled trial (RCT) to determine the cost-effectiveness of shared care in stable glaucoma patients in a hospital setting. We compared usual care by glaucoma specialists and the care provided by optometrists and ophthalmic technicians within a glaucoma follow-up unit (GFU) in the Rotterdam Eye Hospital (REH) in terms of costs and quality of care.

Because this paper focuses on the costs of the glaucoma care related to important aspects of the quality of care, we also measured patient satisfaction, the number of treatment changes, the change in IOP and the compliance to the standard working protocol. The quality of care is described in more detail elsewhere.[81]

3.2 MATERIALS AND METHODS

Randomised Controlled Trial

Patients who visited a glaucoma specialist or the GFU between September 2005 and April 2006 were invited to participate. The RCT was explained and written information was provided to them. The study was approved by the Review Board of Erasmus MC.

To be eligible for the study, patients had to meet the following criteria:

(1) the patient was diagnosed with stable glaucoma in one or both eyes (the next visit scheduled in 6 months or more) or had a risk factor for glaucoma, i.e. high IOP and/or a positive family history. Eyes were considered to be glaucomatous if they had typical thinning or notching of the neuroretinal rim of the optic nerve head, with or without disc haemorrhages, visual field defects, peripapillary atrophy and/or and elevated IOP;
(2) a glaucoma specialist of the REH referred the patient to the GFU;
(3) the actual ophthalmic medication and the target pressure (TP) was recorded in the medical record. The target pressure was determined by the individual clinicians in all patients, where they took in consideration: the age of the patient, the appearance of the optic disc, the level of intraocular pressure, any co-morbidity and any other risk factors. For patients with a risk factor for glaucoma, the TP was by default 30 mmHg, unless other risk factors called for an explicitly lower TP;
(4) an examination of the optic disc, macula, and the fundus periphery was performed;
(5) the Snellen visual acuity in each eye was ≥ 20/100 and/or the patient had no visual field loss within the central 10°, as measured by a Humphrey Field Analyser, standard 24-2 test algorithm (HFA 24-2; Carl Zeiss Meditec, Dublin, CA, USA);
(6) the refractive error was between +5 and –8 dioptres (spherical equivalent);
(7) no other significant ocular disease was present;
(8) the patient had not undergone laser therapy for diabetic retinopathy.

Once the glaucoma specialist decided that the patient was suitable for the GFU, the patient was randomly allocated to a treatment group. In the glaucoma specialist group, the patients received care of glaucoma specialists and residents only. In the GFU group the patient visited the GFU twice followed by a visit to the glaucoma specialist or resident if the patient was stable. If necessary, the patient was seen by a glaucoma specialist earlier. The GFU employees (optometrist or ophthalmic technician level 1 or 2) provided care according to a standard working protocol (see Table 3.1) and under supervision of glaucoma specialists.

Table 3.1. Provided care and criteria for back referral to the glaucoma specialist

Activity	Usual care	GFU	Criteria for back referral
Short history	Every visit	Every visit	
IOP*	Every visit	Every visit	IOP>TP
Medical prescriptions	Every visit	Every visit	
Optic disc assessment	Every visit	Never	
GDx ECC**	At doctor's request (approx. once yearly)	Every visit	- Suspicion of progression - In case of first GDxECC: NFI > 35 and/or left/right asymmetry and/or local defect.
HFA 24-2***	At doctor's request (approx. once yearly)	Yearly in moderate to advanced visual field damage**** OR at doctor's request	Suspicion of progression
Snellen visual acuity	As required, at least once yearly	Every visit	Decline in visual acuity of ≥ 2 lines
Overall judgement	Every visit	Every visit	
Timing next appointment	Every visit	Every visit	

* IOP by Goldmann applanation tonometry
** GDx ECC (Carl Zeiss Meditec, Dublin, CA, USA) scanning laser polarimetric images
*** Humphrey Field Analyser, standard 24-2 test algorithm (HFA 24-2; Carl Zeiss Meditec, Dublin, CA, USA)
**** Criteria mild and moderate/severe visual field damage: the mean deviation (MD) of the last performed visual field was ≤ –5dB
GFU: glaucoma follow-up unit; IOP: intraocular pressure; NFI: nerve fiber indicator; TP: target pressure.

Identification and Randomisation

Glaucoma specialists were asked to provide information about this study to eligible patients. Eligible patients were also identified by searching the patient files of the patients that were already referred by the glaucoma specialists to the GFU in the months preceding the start of our study. They received information about the study during their next visit. All patients that were eligible and willing to participate were randomly allocated to a treatment group using a randomisation table. For the GFU patients that were allocated to the usual care group an appointment was made with the glaucoma specialist who referred them to the GFU.

To avoid glaucoma specialists influencing the allocation of patients, we used central randomisation by the researchers using stratification by 2 variables: the referring glaucoma specialist, and the time to the next scheduled visit, being either 6 months or more than 6 months.

Outcome measures

The outcome of the treatment was measured every visit. The outcome measures of the RCT were: 1) compliance of the GFU employees to the standard working protocol, 2) patient satisfaction with the following items: a) overall mark for the received care; b) social interaction with the health care provider**;** c) expectations about the visit; d) perceived knowledge of the health care provider; e) waiting area, 3) stability according to the practitioner (whether the time till next visit should be significantly shorter than the time from the previous visit), 4) mean difference of the IOP (IOP at baseline vs. IOP at the last visit (if at least 24 months afterwards))[1], 5) the results of the examinations and, 6) the number of treatment changes. We did not use glaucomatous progression as an outcome measure, because we did not expect this patient population (with a risk factor for glaucoma or with stable glaucoma) to progress during the study. The change in IOP during the study has been used as outcome measure instead.

Sample size and power analysis

We performed a post-hoc power analysis using our data to estimate the power (certainty) of our conclusion. We performed that analysis using two outcome parameters since quality of care has multiple dimensions: the stability of the patient according to the practitioner and the overall mark regarding patient satisfaction. The power of the study was >99% based on the stability outcome when using 5% as an acceptable difference, and >99% based on the overall mark when using a difference of 0.5 (on a 1-10 scale) as an acceptable difference between the treatment groups as well.

Patients and visits

From September 2005 to March 2006, 866 patients were included of which 46 patients did not visit the hospital during the study period. Three others could not be monitored with the GDx and 2 patients withdrew their informed consent (see Figure 2.1). The remaining 815 patients had a total of 2100 visits. The average time between visits was 8.8 months, SD ± 4.0. The mean age (63 years) and gender (53% women) was similar for the two treatment groups. There were no significant clinical imbalances between the groups as well (Table 3.2).

1 In a later stage of the analyses, it was decided to change this the definition of this measure into the difference in IOP from baseline until the last visit if at least 18 months later.

Table 3.2. Characteristics of included patients, by treatment group

	Glaucoma Follow-up Unit (n=405)		Usual Care (n=410)	
Gender, % of women	53.8		52.2	
Mean age (SD, standard deviation)	63.0 (12.1)		63.1 (11.9)	
Mean time till next visit in months (SD)	9.8 (2.9)		9.5 (2.9)	
	Right eye	Left eye	Right eye	Left eye
Mean intraocular pressure (SD)	18.7 (4.1)	18.5 (4.1)	18.8 (4.2)	18.8 (4.1)
Mean target intraocular pressure (SD)	25.1 (5.2)	25.2 (5.2)	25.2 (5.4)	25.1 (5.4)

SD: Standard Deviation

Study duration

The study duration depended on the allocated treatment group. Patients who were allocated to the usual care group on the day of their visit to the GFU, entered the study at their next visit (to the glaucoma specialist), whereas patients who were allocated to the GFU group, entered the study immediately. Therefore, the mean study duration was longer for the GFU group (1.81 year) than for the usual care group (1.43 year). This difference was statistically significant ($p<0.001$). Hence, for a better comparison, we will present the costs per patient year in most tables. The influence of this difference in study duration on the outcomes is probably minimal, because no major changes were made to the protocol.

Economic Evaluation

We conducted an RCT to measure the quality of care delivered by glaucoma specialists and by employees of the GFU. Alongside this RCT, we calculated the costs of glaucoma care from four perspectives. The perspectives used were those of the patient, the REH, the health care system and the society.

A difference in health outcomes between the GFU and the usual care group was not expected during this study, because of the slowly progressive nature of this disease. A literature review, searching for articles with glaucoma and co-management or shared care in the title or abstract, provided evidence of an equal quality of care by optometrists compared to ophthalmologists as well.[69,80,82-92] Only one of the articles reported a variation in individual performances of optometrists, which makes education and accreditation an essential prerequisite for co-management.[84] All other articles reported good quality of care by optometrists, high levels of agreement between optometrists and a research clinic reference or ophthalmologists or comparable inter- and intra-observer variability in optic disc assessments. Therefore we will not present a cost-effectiveness ratio, but we will discuss the costs in relation to the quality of care.

Identification cost items and measurement of the utilisation per cost item

We interviewed health care professionals and patients to identify relevant cost items in the field of medical consumption, implementation of GFU, and patient time and travel costs.

During the RCT, the medical procedures performed and the medication prescribed each visit were recorded in a case report form. The different types of hospital visits were a visit to: a glaucoma specialist, a resident, and three types of GFU visits, as there were three different types of personnel within the GFU (optometrist, ophthalmic technician level 1, and ophthalmic technician level 2). Per health care provider, the duration of 10 study related visits was measured. The duration of an HFA and GDx test were also measured in 10 patients.

Every visit, glaucoma patients were given a questionnaire to report their travelling distance, mode of transport, travelling time, waiting time and working status, in order to calculate the time and travelling costs. We also examined the fraction of visits in which the GFU employees asked a glaucoma specialist for advice over time. In addition, we performed a logistic regression to determine which variables influenced the probability of asking advice.

The substitution of care to the GFU required organisational changes and hence implementation costs (both initial and structural) within the hospital. To collect this information, health care providers were interviewed.

Valuation of the cost items

All costs were calculated (in Euros, price level 2007) according to the CVZ (The Health Care Insurance Board) costing guidelines and previous research in the REH.[93] Relevant items from the CVZ costing guidelines[94,95] were updated and used for the calculation of patient time costs per hour and travelling costs per kilometre.

Our cost calculation of hospital costs is based on data from the internal budget allocation provided by the REH financial administration. This information included location costs, costs of medical specialists and other personnel, administrative costs, costs of equipment, overhead costs and interest. Only for the costs of non-laser operations was the DBC rate (Diagnosis Treatment combination - a fixed reimbursement rate for a specific diagnosis related therapy) in 2007 used as estimate of the resource costs.

The direct personnel costs were calculated based on the mean duration for each type of visit. However, the indirect personnel and overhead costs were calculated top-down, based on the mean duration of a visit in the hospital as a whole.

The implementation costs, like internal preparatory meetings, visits to another Dutch hospital, writing the standard working protocol and the training of the employees of the GFU were dominated by personnel input. These costs were added to the costs of a GFU visit as implementation costs for the GFU. The initial implementation costs that

were only made before starting the GFU were spread over 5 years. The structural costs per year were added to the initial implementation costs per year. The implementation costs per visit were based on the total number of GFU visits in 2007 (1598 visits) as we expect this number of patients to be a representation of the number of patients in the near future.

We calculated the patient costs using the information of the patient questionnaires combined with the updated time and travelling costs per unit of time and per kilometre. The results will be expressed as average costs per patient per study year and average costs per patient.

Sensitivity / scenario analysis

To determine the influence of uncertainty regarding the duration of visits or tests on the costs per patient year, we performed the following uni-variate sensitivity analyses:

1. We varied the duration of the visits within the range we had measured in our study. This resulted in 4 scenarios:

a. We used the minimum duration for all visits;
b. We used the maximum duration for all visits;
c. We used the minimum duration of visits to the GFU and the maximum duration for the visits to the glaucoma specialist and resident;
d. We used the maximum duration of visits to the GFU and the minimum duration for the visits to the glaucoma specialist and resident.

2. We used the norm duration of the GDx and HFA as used by the financial department, instead of the duration of the GDx and HFA measured in our study.

Furthermore we performed scenario analyses to determine the effects of plausible policy changes in the (near) future on the costs. We considered the following scenarios:

3. No optometrists are working in the GFU. This actually happened during the course of the study. The direct personnel costs of visits to optometrists were replaced by those of the ophthalmic technicians.
4. In the study, the patients in the GFU group visited the glaucoma specialist (or resident) every third visit, or earlier if necessary. In this scenario, we calculated the visit costs if this routine was changed to every fifth visit (or earlier when necessary). In case of a non-stable patient, we distinguished two scenarios:
    a. The patient returned to the GFU as soon as he was judged as stable by the glaucoma specialist during a visit.
    b. The patient only returned to the GFU after he was judged as stable by the glaucoma specialist on two consecutive visits.

Uncertainty analysis

We performed a bootstrapping analysis on the costs per patient year and two quality of care parameters, to show the degree of uncertainty regarding the results. Since quality of care has different dimensions, we decided to use two outcome parameters. One clinical quality parameter: stability according to the practitioner (stability), and one patient satisfaction parameter: the overall mark given by the patient. By plotting all bootstrap replicates in a so-called cost-effectiveness plane (CE-plane), the uncertainty around the point estimates of the costs and effects was displayed. In this analysis individual observations of patients were randomly drawn from the distribution of patients in both groups in order to calculate the average costs and quality of care per treatment group. This was replicated for 2500 times. A CE-plane is an x-y-diagram with the x-axis representing the difference in quality of care between the GFU and usual care group and the y-axis representing the difference in costs.

Statistical analysis

We used Excel for the bootstrapping analysis. SPSS 15.0 was used for all other analyses. In normally distributed variables, we performed a t-test for independent samples. If not distributed normally, we performed the parametric Mann-Whitney U-test to compare the two treatment groups. We used bootstrapping for deriving the 95% confidence intervals around the utilisation and costs because of the non-normal distribution of those parameters.

For some visits (29%), information about one or more items related to patient costs was missing. The travelling distance could be calculated for every patient, based on the Zip code as known in the hospital information system. If appropriate, the remaining missing values were replaced by values known from other visits of the same patient. In all other cases (9%), the mean value of a comparable group of patients based on gender and age was imputed to the missing values.

3.3 RESULTS

Quality of care

The aspects of quality of care measured in our study were: compliance to the protocol, patient satisfaction, stability according to the practitioner, mean difference of the IOP, results of the examinations and the number of treatment changes. All these aspects of the quality of care turned out to be similar for the 2 groups[81] and the substitution of care to the GFU was successfully implemented.

1. The GFU employees performed the required tests in at least 98.8% of the visits and referred back to the glaucoma specialist in 84.4% of the remarkable cases.

2. The patient satisfaction was similar in both groups. The overall mark of the patient was 8.5 for the GFU group and 8.4 for the usual care group (p=0.147).
3. The percentage of visit that were considered "stable" was 16% in the usual care group and 17% in the GFU group (p=0.423)
4. No statistical difference was found between the two groups in the difference of the IOP during the study ($IOP_{(\geq 24 \text{ months since baseline})} - IOP_{(\text{at baseline})}$). The average difference in IOP OD was -0.2 mmHG in the usual care group and -0.6 mmHG in the GFU treatment group (p=0.207). The average difference in IOP OS was – 0.1 mmHg in both groups (p=0.915).
5. The number of treatment changes was 57 (14%) in the GFU group and 63 (15%) in the usual care group (p=0.603).
6. Patients as well as GFU employees and glaucoma specialists were pleased with the functioning of the GFU.

Therefore, the quality of care provided in the GFU was concluded to be equal to the care provided by the glaucoma specialists for these stable glaucoma patients.

Hospital perspective

The hospital costs covered hospital visits, diagnostic procedures and further treatment, but were mainly driven by the costs of the hospital visits to the glaucoma specialist, resident or GFU employee (approximately 80%). Table 3.3 shows the duration and composition of the unit costs per type of visit. The total annual implementation costs for starting up the GFU were €4917 for 1598 GFU visits. The implementation costs of the GFU were added to the GFU visits only.

Table 3.3 shows that despite their longer duration, GFU visits were less expensive than those to the glaucoma specialist. In the usual care group, most visits were paid to the glaucoma specialist or resident. Patients in the GFU group visited the glaucoma specialist every third visit or earlier when a patient was judged not stable. Therefore, the costs per visit could vary within one patient and between patients within one treatment group. The mean costs per hospital visit including GDx were €83.77 (SD=30.64) in the usual care group and €68.34 (SD=15.66) in the GFU group. This difference was statistically significant (t-test, p=0.000).

Table 3.4 describes the hospital care use per patient year for the two treatment groups. Although the number of visits per patient year was slightly higher in the GFU group (1.65 vs. 1.57), this difference was not statistically significant. In the GFU group, a significantly larger number of GDx images (1.28 vs. 0.77) and auto-refractions (0.20 vs. 0.08) was performed and more time was spent on asking advice (in 24% vs. 10% of the visits). On the other hand, glaucoma surgery, laser therapy, medication use and the number of HFA tests did not statistically differ between the two groups.

Table 3.3. Composition of the unit costs per type of hospital visit in € (2007)

	Visit glaucoma specialist	Visit resident	Visit GFU Optometrist*	Visit GFU TOA level 1 **	Visit GFU TOA level 2***
Costs per visit					
Total direct personnel costs	24.36	14.49	19.09	15.05	16.61
Total indirect personnel costs	5.46	5.46	6.59	6.59	6.59
Total overhead costs	29.76	29.76	35.90	35.90	35.90
Implementation costs GFU	0.00	0.00	3.08	3.08	3.08
Total costs excluding GDx	59.58	49.71	64.66	60.62	62.18
Costs GDx** **(fraction performed)**	25.00 (0.41)	22.25 (0.36)	3.05	3.05	3.05
Total costs including GDx	**84.58**	**71.96**	**67.71**	**63.67**	**65.23**
Mean visit duration (minutes)	9.06	11.00	20.40	20.40	20.40

* Visit to an optometrist or senior employee

** Visit to an ophthalmic technician level 1

*** Visit to an ophthalmic technician level 2

**** At the start of the Glaucoma Follow up unit (GFU), a Nerve Fiber Analyser (GDx) was purchased by the Rotterdam Eye Hospital. The costs of the GDx performed during GFU visits, consists only of the GDx imaging device. In the usual care group, the GDx was performed during an extra visit to the perimetry department. In that situation, the costs of a GDx image included personnel and overhead costs as well and were €61.61 based on a duration of 13.30 minutes.

TOA: ophthalmic technician; GDx: Nerve Fiber analyser.

Table 3.4. Average hospital care use per patient year for the two treatment groups

	GFU	Usual care	95%-CI of difference between 2 groups	P-value	Costs per unit (in €)
Hospital visits	1.65	1.57	-0.13 to +0.31	0.158	**See Table** 3.3
GDx ECC	1.28	0.77	+0.32 to +0.73	0.000	61.61
HFA	0.10	0.11	-0.11 to +0.07	0.266	158.44
Refractive Unit	0.01	0.05	-0.09 to +0.00	0.002	32.43
Auto-refraction	0.20	0.08	-0.03 to +0.21	0.000	4.64 - 6.59*
Pachymetry	0.02	0.04	-0.07 to +0.03	0.246	23.17
IOP diurnal curve	0.01	0.02	-0.04 to +0.01	0.109	92.66
Laser treatment	0.002	0.007	-0.02 to +0.01	0.267	78.38
Glaucoma surgery	0.002	0.001	-0.01 to +0.01	0.558	1251.70
Asking advice	0.24	0.10	+0.05 to +0.26	0.000	8.19 – 15.86**
Proportion patients using medication	0.57	0.59	-0.17 to +0.15	0.614	2.53 – 18.82***

* Depending on health care provider

** Costs per advice, depending on the health care providers involved

*** Costs per month

GFU: Glaucoma Follow-up Unit; CI: confidence interval; GDx ECC: Nerve Fiber Analyser Enhanced Corneal Compensation; HFA: Humphrey Field Analyser; IOP: Intra Ocular Pressure.

Table 3.5. Average costs in Euros per patient year per perspective used for the two treatment groups (SD)

	GFU	Usual Care	P-value
Hospital perspective			
Hospital visits (including GDx ECC)	111.93 (50.93)	133.17 (50.44)	0.000
Other tests (HFA, refraction, pachymetry, etc.)	20.66 (47.03)	24.18 (48.72)	0.001
Laser treatment related to glaucoma	0.18 (2.54)	0.57 (5.18)	0.258
Glaucoma surgery	2.84 (40.35)	1.72 (34.90)	0.558
Asking advice	3.24 (5.35)	1.78 (5.13)	0.000
Total hospital costs per patient year	**138.85 (89.30)**	**161.43 (86.88)**	**0.000**
Patient perspective			
Patient costs per visit			
Travelling costs of patient and accompaniment	8.26 (11.83)	8.19 (12.10)	0.966
Time costs of patient and accompaniment	40.58 (28.87)	47.51 (34.36)	0.000
Total patient costs per patient per visit	**48.83 (33.68)**	**55.70 (37.88)**	**0.000**
Patient costs per patient year			
Travelling costs of patient and accompaniment	13.04 (17.16)	12.70 (17.87)	0.488
Time costs of patient and accompaniment	66.62 (50.20)	75.17 (61.37)	0.088
Total patient costs per patient year	**79.66 (58.51)**	**87.87 (68.17)**	**0.143**
Health care perspective			
Hospital costs	138.85 (89.30)	161.43 (86.88)	0.000
Medication costs	91.54 (101.37)	89.82 (100.53)	0.867
Total health care costs per patient year	**230.39 (154.57)**	**251.26 (146.02)**	**0.004**
Societal perspective			
Hospital costs	138.85 (89.30)	161.43 (86.88)	0.000
Patient costs	79.66 (58.51)	87.87 (68.15)	0.143
Medication costs	91.54 (101.37)	89.82 (100.53)	0.867
Total societal costs per patient year	**310.05 (181.86)**	**339.13 (180.39)**	**0.009**

SD: Standard Deviation; GFU: Glaucoma Follow-up Unit; GDx ECC: Nerve Fiber Analyser Enhanced Corneal Compensation; HFA: Humphrey Field Analyser.

The hospital care use has been translated into costs per patient year for the two treatment groups in Table 3.5. The total hospital costs were significantly higher for the usual care group than for the GFU group, mainly because of the higher hospital visit costs. The costs of asking advice were modest, but significantly higher for the GFU group than for the usual care group, as was to be expected. The 95% confidence interval for the difference in total hospital costs as derived from the bootstrap analysis was €-59 to €-2. The probability that the GFU reduces hospital costs is 98%.

The proportion of visits by GFU employees needing advice increased initially from 15% to 20% in 2006 and then decreased (statistically significant) to 13% in 2007 and 7% in 2008. The proportion of visits requiring advice was not affected by the total number of visits per patient.

These findings were confirmed by a logistic regression. The year of the visit was the only variable that significantly influenced the probability of asking advice. The other variables in the regression analysis were: stable/not stable, visit number, gender, time till next visit and age. This indicates that the GFU employees got more experienced over time and therefore needed less advice.

Patient perspective

The patient costs consisted of time and travelling costs of patients and their accompaniment. Table 3.5 shows that the patient costs per visit were significantly higher in the usual care group, because of higher time costs (€80 vs. €88). This was mainly caused by a longer waiting time in the hospital in the usual care group. Patients in the GFU group spent, on average, 44.6 minutes in the hospital against 59.4 minutes for the patients in usual care group (p=0.000). However, because of a higher number of visits per patient year in the GFU arm, the patient costs per patient year were not statistically significantly higher anymore. The 95% confidence interval based on the bootstrapping analysis confirmed this (€-29 to €12). However, there is still a 78% probability to reduce patient costs.

Health care perspective

The health care costs consisted of the hospital costs as described above, and medication costs. Table 3.5 shows the health care costs per patient year. Because of the comparable medication costs and lower hospital costs in the GFU group, the total health care costs per patient year were nearly 10% lower for the GFU group (€230.39 vs. €251.26, p=0.04). The median cost differ statistically according to the Mann-Whitney U-test, but the confidence interval as provided through bootstrapping does not show a difference in the mean costs (€-76 to €21). However, the probability of cost reduction is considerable: 87%.

Societal perspective

In the societal perspective all costs were taken into account. It consisted of hospital costs, medication and patient costs, for 46%, 28% and 26% respectively. The total societal costs per patient year were almost 10% higher in the usual care group (Table 3.5: €339.13 vs. €310.05, p= 0.009). The mean difference in the total societal costs per patient year was €-36 (the GFU group was less expensive). The 95% confidence interval based on bootstrapping for this difference ranged from €-92 to €23. Thus, though the median costs per patient year differs between the two groups, the mean total costs are not statistically different. This is because the non-normal distribution of the societal costs. However, the probability that the GFU saves societal costs is 84% to 89% (see paragraph about the uncertainty analysis below).

Sensitivity / scenario analysis

Analysis 1: duration of visit

The mean duration of the visits to the glaucoma specialist was 9 minutes (ranging from 7 to 11 minutes), to the resident 11 minutes (ranging from 9 to 13 minutes) and to the GFU 20 minutes (ranging from 16 to 24 minutes).

In the base case – the situation as in our study –, the GFU group was less expensive than the usual care group. This conclusion only changed when the duration of a visit in the usual care group would be relatively short (7 minutes) and the duration of a visit in the GFU group would be relatively long (24 minutes, scenario 1d). In that unlikely situation the hospital costs per patient year were 10% higher for the GFU group (see Table 3.6).

Table 3.6. Total average hospital costs per patient year in Euros for all situations in the sensitivity/scenario analysis

	Hospital costs	
	GFU	Usual care
Base case	138.85	161.43
Scenario 1a	117.79	141.80
Scenario 1b	156.79	179.98
Scenario 1c	117.79	179.98
Scenario 1d	156.79	141.80
Scenario 2	153.78	173.18
Scenario 3	135.16	159.47

GFU: glaucoma follow-up unit

Analysis 2: duration HFA/GDX

The norm durations of GDx and HFA as used by the financial department, were 15 and 45 minutes respectively instead of 13.30 and 34.20 minutes. This longer duration of the HFA and GDx tests increased the hospital costs per patient year in the GFU group and usual care group with €15 and €12 respectively (Table 3.6).

Analysis 3: no optometrist in GFU

When the direct personnel costs of the optometrist were replaced by those of the ophthalmic technicians, the costs in both groups decreased, because incidentally a visit was paid to an optometrist in the usual care group as well (Table 3.6). Although the decrease in costs per patient year is small, it is almost twice as high in the GFU group (€3.69) as in the usual care group (€1.96). Thus, the costs remain lower for the GFU group.

Analysis 4: fewer specialist visits in GFU

a. In this scenario, the total savings were €2193 for five visits of 427 patients. Based on a mean number of 1.65 visits per year as measured in this study, the hospital costs could be reduced with €1.69 per patient year.
b. In the second scenario, the total savings in visit costs were €1882 for five visits of 427 patients, thereby reducing the hospital costs in the GFU group with €1.45 per patient year (=1%).

Uncertainty analysis

From a societal perspective, the incremental cost-effectiveness ratio of the GFU compared with usual care was €-27 per patient per decimal point increase of the patients' overall mark (on a 1-10 scale) per year. The CE-plane with overall mark as outcome showed that the majority of bootstrap replications (70%) fell within the lower-right quadrant, indicating that the GFU was dominant with lower costs and a higher overall mark (Figure 3.1a).

The incremental cost-effectiveness ratio for the GFU compared with usual care was + €19 per patient per year for one extra percent of visits that were considered to be stable by the practitioner. For the CE-plane with "stability" as outcome, the majority of bootstrap replications fell within the lower-left quadrant which reflects lower costs and fewer stable visits (Figure 3.1b). The probability that the GFU is cost saving is 89% using the overall mark and 84% using the "stability" outcome. Against this high probability of saving costs, the probability of inferiority of the GFU (being more expensive and less effective) is quite small: 2% using the overall mark and 14% using the "stability" outcome.

Using an acceptable difference of 0.5 point of the overall mark (range 1-10), and of 5% difference in the fraction of stable patients, the two groups have an equal quality of care in 99.5% and 80.5% of the bootstrap replications respectively. When including replica-

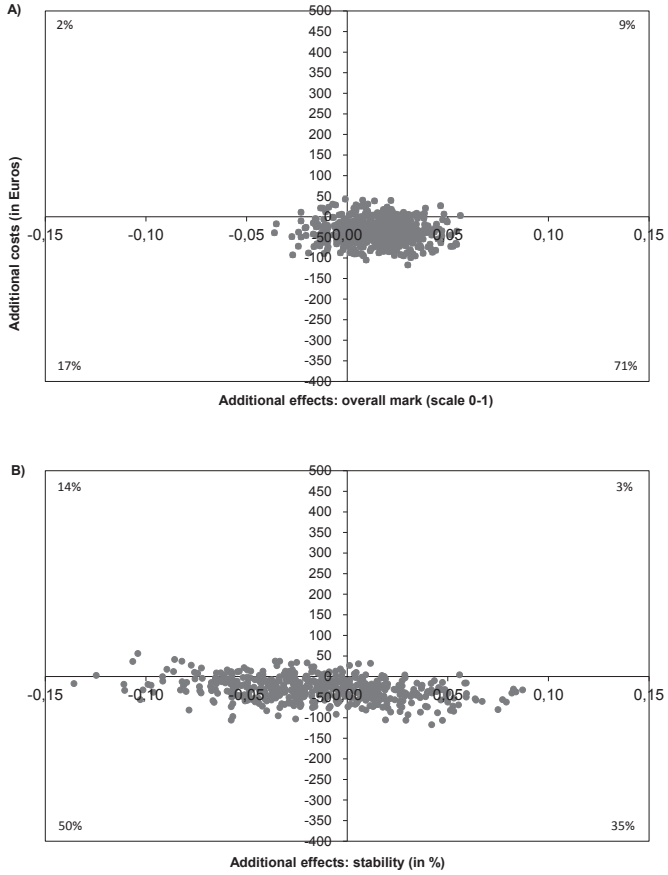

Figure 3.1 Cost-effectiveness plane.
A) yearly incremental costs per patient vs. change in the patients' overall mark
B) yearly incremental costs per patient vs. change in the percentage of stable visits

tions that result in a **better** quality of life for the GFU, the quality of care is acceptable (equal or better) in 100% and in 83.6% of the bootstrap replications.

3.4 DISCUSSION

Substitution of tasks that require less specialized skills is a possible solution for easing the increased workload of ophthalmologists and long waiting lists in ophthalmic care. It was hypothesized that task substitution reduces the costs as well. The monitoring of most stable glaucoma patients probably does not require specialized skills. In this study, we therefore compared the care as usual provided by glaucoma specialists with the care

provided by a GFU within the REH staffed by ophthalmic technicians and optometrists for stable glaucoma patients.

We found about 10% lower health care costs per patient year for the GFU group compared to the usual care group for three of the four perspectives used: the REH, the health care system and the society. Patient costs did not differ between the two treatment groups.

Scenario and sensitivity analyses confirmed that our results were robust. Only if the mean duration of a visit increased in the GFU (with 18% to the maximum duration measured in this study) and decreased for the glaucoma specialist (with 23% to the minimum duration measured in our study, scenario 1d), would the total societal costs not be significantly different any longer. However, this situation is not realistic. The bootstrap analysis showed that the equivalence of the two groups on quality of care is justified and that the GFU is cost saving in 89% of the bootstrap replications when using the overall mark as outcome parameter and in 84% of the replications when using the stability of the patient according to the practitioner.

We hypothesized that the establishment of the GFU would reduce the waiting list. This was confirmed by the increased number of patients (+23%) and patient visits (+16%) per year within the study period. The increased number of visits was largely caused by the establishment of the GFU, whereas the rise in the number of glaucoma patients was also influenced a little by a reduced follow-up interval for some glaucoma patients. However, the long term effect on the waiting list seems to be limited. Possible causes are: the chronic character of the disease which limits the patient outflow and the substantial increase in new glaucoma patients that outweighs the growth in capacity. Further research would be necessary to explore the true cause(s).

The hospital perspective was one of the perspectives used for the cost calculation. Although the probability that GFU is cost-effective from this perspective is 94-98%, we have to distinguish at least two stakeholders within the hospital; the hospital management and the glaucoma specialists. The interests of those two stakeholders are partially conflicting due to the current structure of financing care in the Netherlands. The physician part of the reimbursement is now paid to the specialist although the monitoring is partially transferred to the GFU. The distribution of this fee will therefore become subject of discussion between glaucoma specialists and the hospital management, especially when health care insurers insist on a lower fee in future negotiations, because of the lower costs of monitoring glaucoma patients by the GFU.

Our results could not be easily compared with results of other research. Even though substituting tasks within the hospital setting is taking place, a full cost calculation of this kind of substitution in the ophthalmic care has not been performed yet. In Bristol (UK), an economic evaluation alongside an RCT has been performed, comparing costs of monitoring stable glaucoma patients by ophthalmologists and community optometrists

(outside the hospital).[65,79] Contrary to ours, the UK study concluded that the substitution of care to community optometrists was not likely to save costs. The main reason for this was the larger number of referrals to the ophthalmologist in their study compared to ours (19% vs. 6%). An explanation for this difference might be the location of care. Community optometrists do not have the possibility to consult a specialist for quick advice and will therefore refer patients to the hospital relatively more often.

Furthermore, the frequency of visits to the community optometrist in Bristol was 66% higher than the visit frequency to the ophthalmologist, compared with a 5% higher frequency in our study. This difference is related to a difference in the protocol used. In our study, the time to the next visit was copied from the last visit to the glaucoma specialist instead of being pre-determined at 6 months.

A study about the trends in outpatient care provided by physicians and non-physician clinicians showed that substitution of care is not always a good strategy for containing health care costs.[96] The increase in the proportion of patients visiting a non-physician clinician is driven by the increase in patients visiting both a non-physician and a physician clinician. In our study however, the number of extra visits caused by referrals was relatively low as stated earlier.

A possible drawback of our study is the lack of information about disease progression. The progression rate of glaucoma depends on the intraocular pressure and the time to vision loss varies between 3 years for untreated patients with a high intraocular pressure to 38 years for well treated patients.[77,97] We therefore did not expect to detect any significant glaucomatous progression in the 30 month study period in these stable patients and performed a cost minimization study. This type of economic evaluation assumes an equal outcome for all patients. The results of the RCT[81] as well as many other studies[69,80,82-92] supported this assumption about the equal quality of care to glaucoma patients provided by different types of health care providers.

3.5 CONCLUSIONS

Considering the equal quality of care in both treatment groups, we conclude that monitoring of glaucoma patients by the GFU is cost-effective for a subset of glaucoma patients, i.e., those that were deemed stable in the Rotterdam Eye Hospital. Implementation of a similar GFU in other hospitals could therefore be considered.

3.6 ACKNOWLEDGEMENTS

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Chapter 4

Why a successful task substitution in glaucoma care could not be transferred from a hospital setting to a primary care setting: a qualitative study

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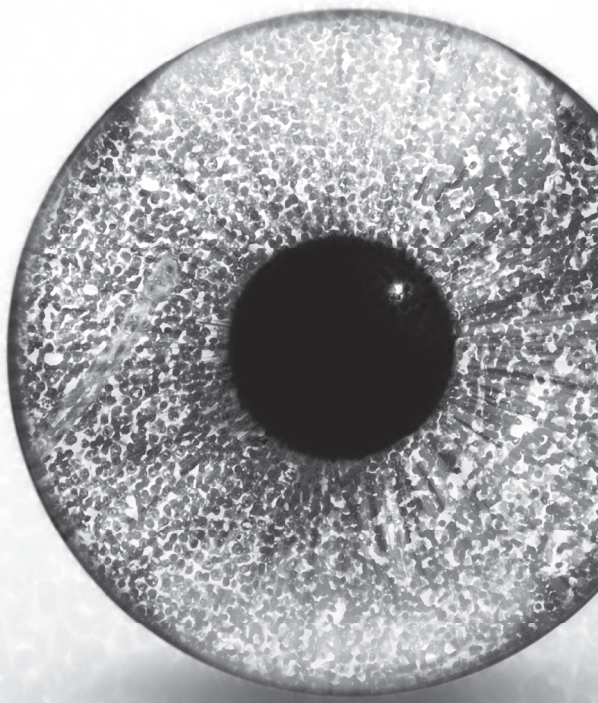

SUMMARY

Background. Healthcare systems are challenged by a demand that exceeds available resources. One policy to meet this challenge is task substitution/transferring tasks to other professions and settings. Our study aimed to explore stakeholders' perceived feasibility of transferring hospital-based monitoring of stable glaucoma patients to primary care optometrists.

Methods. A case study was undertaken in the Rotterdam Eye Hospital (REH) using semi-structured interviews and document reviews. They were inductively analysed using three implementation related theoretical perspectives: sociological theories on professionalism, management theories, and applied political analysis.

Results. Currently it is not feasible to use primary care optometrists as substitutes for optometrists and ophthalmic technicians working in a hospital-based glaucoma follow-up unit (GFU). Respondents' narratives revealed that: the glaucoma specialists' sense of urgency for task substitution outside the hospital diminished after establishing a GFU that satisfied their professionalisation needs; the return on investments were unclear; and reluctant key stakeholders with strong power positions blocked implementation. The window of opportunity that existed for task substitution in person and setting in 1999 closed with the institutionalisation of the GFU.

Conclusions. Transferring the monitoring of stable glaucoma patients to primary care optometrists in Rotterdam did not seem feasible. The main reasons were the lack of agreement on professional boundaries and work domains, the institutionalisation of the GFU in the REH, and the absence of an appropriate reimbursement system. Policy makers considering substituting tasks to other professionals should carefully think about the implementation process, especially in a two-step implementation process (substitution in person and in setting) such as this case. Involving the substituting professionals early on to ensure all stakeholders see the change as a normal step in the professionalisation of the substituting professionals is essential, as is implementing the task substitution within the window of opportunity.

4.1 BACKGROUND

Healthcare systems across many countries face a challenge in responding to growing demands for physicians' and nurses' care with increasing limitations on human and financial resources.[60,61] Extrapolations have shown that the number of physicians cannot keep pace with the growth in demand caused by ageing populations, enhanced societal expectations, and new diagnostic technologies.[56-59]

One option to cope with workforce shortages is task substitution, which can be defined as devolving clinical responsibilities to lesser or more narrowly-trained health professionals with or without supervision.[98] Task substitution can be realised with people (*e.g.*, a diabetes nurse practitioner substitutes for an internist of the same department), settings (*e.g.*, a primary care neurologist substitutes for a hospital-based neurologist), or both (*e.g.*, primary care midwives substitute for hospital-based gynaecologists). Research has shown that task substitution may improve the quality of care[66,67,78,82-86,88-92,99-101] and reduce costs because substitutes' fees are lower.[102] Strong evidence for cost savings is lacking however, perhaps because physician-substitutes perform additional tasks[96] or are less productive,[103] offsetting potential cost savings. Furthermore, the successful implementation of task substitution is at least partially influenced by contextual factors, such as local stakeholder interests,[104-107] power positions,[108,109] and the structure of the healthcare system, including its financing.[110] It therefore seems worthwhile to broaden the scope of evaluation and include the professional, organizational, financial, and political contexts within which task substitution is implemented.[111]

We explored a task-substitution project involving glaucoma care at the Rotterdam Eye Hospital (REH) in the Netherlands (see Appendix 4.1 for background information). Our research question was two-tiered: how do stakeholders perceive the feasibility of implementing task substitution of person (from ophthalmologists to allied health professionals) and setting (from a hospital to a primary care setting), and what are their supporting and opposing arguments?

Historical background

Our case study was not the first initiative of the REH to cooperate with primary care optometrists working in optical shops in the Rotterdam area (later united in a Collective of Optometrists in Rijnmond Region – OCR). The first initiative, started in 1997, led to the Transmural Glaucoma project (TG-project), a preliminary person and setting task substitution project in 1999. One part of the project consisted of primary care optometrists supplementing glaucoma specialists in monitoring glaucoma patients by means of GDx-technology (Carl Zeiss Meditec, Dublin, CA, USA), an imaging tool to assess (damage to) the nerve fibre layer. REH glaucoma patients were referred to a local primary care optometrist for three additional tests between two visits to the hospital-based glaucoma

specialist. It appeared difficult to convince patients to visit a primary care optometrist; only twelve of the twenty patients (60%) actually did so.[70,71] Nor were glaucoma specialists eager to participate because they could have referred more patients.

Given the results, the REH management suspended the project and initiated an intermediate step of task substitution of person only. The REH set up a Glaucoma Follow-up Unit (GFU) in the hospital and evaluated its impact through an RCT.[72] The GFU was staffed by a hospital optometrist and ophthalmic technicians who monitored the glaucoma patients according to a working protocol (see Table 2.1). Four years after the successful implementation of the GFU,[72] REH managers began the step of substituting primary care optometrists in optical shops for the GFU, as in the original plan (substitution of person and setting).

4.2 METHODS

An in-depth single case study evaluation was carried out from September 2007 to August 2008 using semi-structured face-to-face interviews and a document review to explore the feasibility of using primary care optometrists in optical shops as substitutes for in-hospital GFU employees.

Sampling and recruitment

Semi-structured interviews

We selected 27 participants based on role, profession, and organisation, thereby drawing on three sampling strategies. First, we included all four REH glaucoma specialists, five GFU employees, and the responsible hospital managers (CEO, CFO, manager of the Eye Care Network, and the advisor concerned with optometry relations). Second, we used convenience sampling to identify five primary care optometrists and two representatives of the major health insurers in the Rotterdam region. We contacted the Dutch Healthcare Authority to identify potential participants. Third, we randomly selected five patients who had participated in the GFU study, taking care that the sample included patients with only a risk factor for glaucoma as well as stable glaucoma patients and employed as well as unemployed patients. One patient was selected because of his function as chairman of the Dutch Glaucoma Patient Association. The sample is shown in Table 4.1.

Table 4.1. Interviewed stakeholders

Staff Rotterdam Eye Hospital

Respondent	*Position*	*Interviewers*
1	CEO Rotterdam Eye Hospital	ES & TP
2	CFO Rotterdam Eye Hospital	KHG & TP
3	Manager of the Eye Care Network	KHG & ES
4	Advisor concerned with optometry relations	ES
5	Glaucoma specialists, Rotterdam Eye Hospital	ES
6	Glaucoma specialists, Rotterdam Eye Hospital	ES & TP
7	Glaucoma specialists, Rotterdam Eye Hospital	KHG
8	Glaucoma specialists, Rotterdam Eye Hospital	KHG
9	Ophthalmic technician, Rotterdam Eye Hospital	KHG
10	Optometrist, Rotterdam Eye Hospital	ES
11	Ophthalmic technician, Rotterdam Eye Hospital	ES
12	Ophthalmic technician, Rotterdam Eye Hospital	KHG
13	Ophthalmic technician, Rotterdam Eye Hospital	KHG

Primary care optometrists

Respondent	*Self-employed / optical chain*	*Participant OCR*	*Interviewers*
14	Self-employed	Yes	KHG
15	Self-employed	Yes	KHG
16	Self-employed	Yes	ES
17	Optical chain	No	TP
18	Self-employed	Yes	TP
19	Optical chain	Yes	ES

Patients

Respondent	*Travelling distance to REH (in kilometres)*	*Working status*	*Severity of the disease*	*Interviewers*
20	21	Employed	Risk factor	TP
21	19	Unemployed	Glaucoma	ES
22*	75	Employed	Glaucoma	TP
23	14	Employed	Risk factor	KHG
24	18	Unemployed	Suspect	KHG

Health insurers / The Dutch Healthcare Authority

Respondent	*Position*	*Interviewers*
25	Health insurer (Health insurance only)	ES & MK
26	Health insurer (All kinds of insurances)	KHG & TP
27	Senior policy advisor of The Dutch Healthcare Authority	KHG

* chairman of the Dutch Glaucoma Patient Association; OCR: Collective of Optometrists in the Rijnmond region; REH: Rotterdam Eye Hospital.

Document review

Relevant policy and administrative documents were continually collected during the study period (2004 to 2009). Their sources were suggested by participants or found on the internet and websites of relevant stakeholders. EvS and KHG selected the documents when they considered any part of them relevant to the research question. Selected documents included public information, official policy reports, minutes of meetings, and working documents.

Procedure

Two researchers conducted the first six interviews together because it allowed them to give each other feedback on the interviewing process. The remaining interviews were done by one of four researchers (KHG, EvS, TP, MK). We developed a topic list (Appendix 4.2) based on the research question to guide the interviews, which contained open questions that left room for participants to expand and clarify their answers. Moreover, they had the opportunity to express their opinions and to share what was important to them concerning the feasibility of transferring glaucoma care to primary care optometrists. The interviews took approximately one hour each, were audio recorded, and later transcribed verbatim.

Analytic approach

The transcripts of interviews and documents were inductively analysed for the respondents' views regarding the feasibility of the task substitution. We thereby used an analytic approach, drawing on three theoretical perspectives.

First, we used sociological theories on professionalism to explore professionals' views and interprofessional dynamics. Professions are sociologically defined as groups of institutions that permit the members of an occupation to make a living while controlling their own work.[112] From such a sociological perspective, implementing task substitution is not a technical solution, but rather a social process affecting the professional status of those involved.[112-116] Key to our analysis was how hospital-based glaucoma specialists, primary care optometrists, and GFU employees viewed the feasibility of the desired task substitution, and how it related to opportunities for or threats to controlling their work.

Second, we applied management theories to explore managerial rationales and views underpinning the desired substitution of tasks. Research shows that evidence-based interventions to improve quality of care are not automatically implemented and returns on investments or so-called 'business cases for quality' are often absent or too small to be effective.[117] Moreover, an organizational infrastructure should be in place to support the innovation. Here, we explored how the respondents viewed the business case for the task substitution and whether they thought an appropriate infrastructure was in place.

Third, applied political analysis was used to map the interests and power positions of each stakeholder involved.[109] Their interests regarding the task substitution (supporting or opposing) together with their power positions and willingness to use them structure the political feasibility of successful implementation of task substitution.

Ensuring rigour

We used different strategies to monitor and enhance the rigour of data collection, analysis, and validity. First, we validated key findings by data triangulation. Data collected from different sources (semi-structured interviews, document analysis, and literature) and researchers were compared to verify specific findings. Second, we sought feedback from senior and other researchers (peer review; HL, MK, NK), who critically appraised the research process and earlier drafts of the article. Third, reflexivity of the main researchers (KHG, TP, and EvS) was applied to rule out threats to validity due to reactivity and researcher bias.

4.3 RESULTS

Our threefold data analysis showed that it is currently not feasible to implement task substitution in this particular case. Respondents' narratives revealed that the intermediate establishment of a suitable hospital setting (the GFU) in 2004 pre-empted the original sense of implementation urgency. Nor did the professionals (ophthalmologists and GFU employees) consider the shift to shop setting a positive step towards further professionalisation. An unclear return on investment did not help matters. Last, the power positions of reluctant key stakeholders were strong enough to block the implementation of task substitution from the hospital to the primary care setting. Table 4.2 contrasts the initial assumptions of the stakeholders with the perceived feasibility as expressed by the participants.

Closed window of opportunity

The analysis from the professionalisation perspective revealed that the window of opportunity for task substitution closed with an intermediate step, *i.e.*, establishing the GFU. In the late 1990s, waiting lists (demand pressures), new GDx technology, and competition from ophthalmologists working in private clinics all favoured the task substitution of both person (from ophthalmologists to optometrists) and setting (from hospital to primary care). Professional dynamics, however, impeded the twofold implementation strategy.

The first step (substitution within the hospital setting – the GFU) eased the pressures on the glaucoma specialists, and the GFU employees enjoyed their work. As a consequence,

Table 4.2. Stakeholder positions concerning the task substitution of person and setting before and after GFU establishment

		Theory 1: closed window	Theory 2: unclear returns on investments	Theory 3: power position - level interest
Before GFU establishment	Glaucoma Specialists	High workload, increasing demand for glaucoma care.	Workload release, decreasing the waiting list, more challenging work.	High power position and high interest for a successful task substitution.
	Management REH	Increased competition on volume.	Increase in volume of (new) patients.	Medium power position and high interest for a successful task substitution.
	Primary care optometrists	Competition with optical chains, chance to professionalize.	Increase in volume of (new) patients.	Low power position and high interest for a successful task substitution.
	Patients	Were not involved at the start.	More flexible appointments and more time per appointment.	Medium power position and medium interest for a successful task substitution.
	Dutch Health Care Authority / Health insurers	Were not involved at the start.	Care would possibly become less expensive	High power position and unclear interest for a successful task substitution.
	GFU employees	Were not involved at the start.		Low power position and low interest for a successful task substitution.
After GFU establishment§	Glaucoma Specialists	Release of workload due to GFU.	The establishment of the GFU already fulfilled their goals.	Reduction of interest for a successful task substitution.
	Management REH	Better alternative was found through cooperation with optical chain.	Disappointing increase in volume due to cooperation with OCR. Alternative was found.	Reduction of interest for a successful task substitution.
	Primary care optometrists	Cooperation remained on the same level.	Increase in new patients differed among optometrists.	Reduction of chance to strengthen relationship with glaucoma specialists
	Patients	GFU resulted in more time per patient, and care in a familiar setting.		Reduction of interest for a successful task substitution.
	Nza / Health insurers	Quality of care in GFU was good.		No changes in interest due to establishment of GFU.
	GFU employees	Improved relationship with glaucoma specialists and more satisfying work.	The consequences of starting task substitution for the GFU were unclear.	Increase of power position.

GFU: Glaucoma Follow-up Unit; Nza: Dutch Healthcare Authority; OCR: Collective of Optometrists in the Rijnmond region; REH: Rotterdam Eye Hospital.

the glaucoma specialists and GFU employees no longer supported the final step, which was implicitly reflected in the debate on the expertise of primary care optometrists.

Optometrists' subtle and constructive views confirmed that quality of care was perceived to be the most important factor for the feasibility of the task substitution. All six primary care optometrist-interviewees were convinced of their capability to monitor stable glaucoma patients (Table 4.3) because during the TG-project and the TOZ-project (transmural eye care for all indications) some participating OCR optometrists gained experience in screening patients and strengthened their relationships with REH ophthalmologists, and they were trained to detect pathological abnormalities of the eye.

Some primary care optometrists indicated, however, that they would like to have more routine monitoring of glaucoma patients to bolster their initial education (Table 4.3). In response, the REH organised training guided by glaucoma specialists for the optometrists participating in the TG-project. Optometrists interned for several days, studied a textbook, and were tested before they could participate. Despite this training, glaucoma specialists and GFU employees were, due to their experience during the TG-project in the late 1990s, not convinced of the primary care optometrists' expertise. The glaucoma

Table 4.3. Quotations 'closed window of task substitution'

Primary care optometrists
• As an optometrist you have done everything during your training, you have seen all the abnormalities, you have read and learned about them, and you graduated. (Respondent 14)
• Considering our experience in the TOZ project (transmural eye care), in my opinion, we are capable of providing, without any problems, part of the care for stable glaucoma patients and patients with a risk factor for glaucoma. (Respondent 15)
• We don't see enough glaucoma patients to monitor them. Even though it can occasionally occur, I do think that we need to get more practical experience of these patients on a daily basis. If we start monitoring patients, we have to know how the eye hospital wants it to be done, how they do it, and what they exactly want to know. This can only be achieved through training. By watching glaucoma specialists at work. (Respondent 19)
Glaucoma specialists and GFU employees
• To me, the GFU is a good system because I do have some idea of the quality being delivered. And I think that is essential to know. I am not in favour of transferring this care to optometrists who work outside of the REH, because then I'm not sure what the quality of their care will be. (Glaucoma specialist, respondent 7)
• Unfortunately, we have had quite some bad experiences with a number of primary care optometrists. A small number, but quite bad experiences. They were playing at being doctors, without having the knowledge. That's what I'm concerned about. (Glaucoma specialist, respondent 8)
• I still see the quality of care of these optometrists on a weekly basis (TG project), and I think that this group is not suitable for monitoring these patients. I still see too many assessments, where they say, there's nothing wrong, and where I think: well there is definitely something wrong. (GFU employee, respondent 9)

GFU: Glaucoma Follow-up Unit; REH: Rotterdam Eye Hospital.

specialists doubted whether the quality of care delivered by optometrists would be comparable to GFU employees despite the additional education. The glaucoma specialists were furthermore eager to check the GFU employees' quality of care in the hospital setting and feared losing control over their patients in an outpatient setting (Table 4.3).

Having the GFU staffed by hospital optometrists instead of primary care optometrists further reduced the likelihood that the task substitution to primary care optometrists would succeed. Besides eliminating the sense of urgency for task substitution of person and setting, establishment of the GFU strengthened the bond between the glaucoma specialists and GFU employees, closing the window of opportunity for task substitution of person and setting.

Unclear returns on investments

The stakeholders doubted whether the monitoring of stable glaucoma patients by primary care optometrists would still be financially interesting, *i.e.*, the return on investment was unclear (see Table 4.4). The high workload of the glaucoma specialists, which sparked the initiative, was significantly reduced by the establishment of the GFU in 2004. Increased capacity made it possible to lift the ban on accepting new glaucoma patients, which resulted in a 23% increase from 2004 to 2008. Two glaucoma specialists indicated that the increase in capacity eliminated the pressure to further pursue task substitution. Moreover, one underlying key assumption proved to be untrue. The REH management assumed that the task substitution would increase capacity and inflow of new patients. But in 2008 the primary care optometrists within REH's eye care network were responsible for only 1% of the new patient inflow. The collective OCR organisation was furthermore rudimentary: the optometrists were mostly self-employed, and could not be easily approached as a group. For both reasons, the REH started collaborating with a large optical chain to ensure a steady inflow of new patients.

This new collaboration put a strain on the REH-OCR collaboration. The optometrists had seen the monitoring of glaucoma patients as opportunity to compete with optical chains because they could not compete with them on the price of eyewear. On the other hand, some primary care optometrists were unsure about the competitive advantage of membership in the REH's eye care network. Despite their belief that monitoring glaucoma patients would provide work diversity, whether it would result in additional clients or income was unclear.

The combination of an unclear effect of eye care network membership with the absence of a separate reimbursement tariff for optometric examinations rendered the monitoring of glaucoma patients financially unattractive for primary care optometrists.

In the absence of a reimbursement tariff for an optometric examination, most patients did not choose primary care, because they would have to pay (directly or indirectly) for care that otherwise was reimbursable. Besides, some patients claimed that they relied

Table 4.4. Quotations 'Unclear returns on investments'

Glaucoma Specialists:

- I: But it is getting busier with glaucoma patients, and you cannot discharge everyone. R: That's why we created this system, the GFU. I: Do you think that is enough? R: I think so. (Respondent 6)
- If the pressure, the number of patients at the clinic increases, and we have to announce waiting lists again or limit the number of patients at some point, then it will not be beneficial to the quality of care. Then we'll have to do something like that [task substitution], we'll have to go down that road. (Respondent 8)

REH Management:

- What we do is, we move the chronic patients. Those patients are not financially attractive, not for the partnership either. So to make it financially attractive, we need to see new patients, we must get referrals. (Respondent 1)
- Primary care optometrists only send 1% of our referrals. So we need to arrange the other referral channels. (Respondent 3)

Primary Care Optometrists:

- But when an optical chain joins, it makes us less unique. And as an independent optical shop, we take optometry very seriously. (Respondent 16)
- Yes, there are customers who come to our shop, even if I do not know them personally… I have not seen them before, but they ask during their visit to the REH where they can buy spectacles, etc. Then they are referred to me, which is really great. (Respondent 16)
- I: As regards the fact that you are part of the Eye Care Network, do you use it, put a sign on the door: 'Optician, member of the Eye Care Network'? R: Um, good question. Hardly. I: Why not use it? R: Because it has no effect. I: How do you deduce that? R: Instinctive, advertising is purely instinctive. (Respondent 18)
- If you ask me what I think needs to be done, then I think health care insurers are keeping out of the way and do not take enough action in this matter. I think that when it comes to eye care, the health care insurers should accept their responsibility. (Respondent 18)

Dutch Healthcare Authority / Health care insurers:

- When it comes under the B segment (tariff becomes negotiable) the health care insurer will say: we no longer pay for the part of the DBC delivered by primary care optometrists, because we are already paying those optometrists directly. That is a possibility. Then the Dutch Healthcare Authority does not have to set a price. (The Dutch Healthcare Authority, respondent 27)
- If the reason for your question is: would we insurers be prepared to contract an optometrist, to agree on a tariff and let him be responsible for this care; that is something I would be prepared to consider. But on the condition that the quality of care is guaranteed, that the Health Care Inspectorate is confident about it, and above all that the referring glaucoma specialists have confidence in it. (Health care insurer, respondent 25)

Patients:

- I think it is a bit more reassuring when you stay under your doctor's care, of course. A specialist is probably a bit more knowledgeable. You're so used to it. (Respondent 24)
- In some ways, care by a local optometrist might be nicer. The ophthalmologist with his experience and knowledge might see certain things very quickly, though. But I have the impression that at the GFU they have a bit more time for you, they want to know things exactly and are more precise than the doctor.

  But still, if I have the choice between one and the other and they are both of good quality, then I would choose the one that doesn't cost me anything. (Respondent 23)

DBC: Diagnosis Treatment combination; GFU: Glaucoma Follow-up Unit.

more on the glaucoma specialists than the primary care optometrists. Such considerations outweighed the advantages of the optometrists' care, such as flexible appointments and proximity to patients' homes.

Health insurers could mediate between primary care optometrists and the REH to realize shared care and provide an appropriate reimbursement tariff, but were at the moment of evaluation in 2008 reluctant to initiate discussions. They claimed, however, that if the REH could guarantee the quality of care and if physicians supported the substitution, they would seriously consider recommending reimbursement of primary care optometric examinations to the Dutch Health Care Insurance Board.

The Dutch Healthcare Authority mentioned another problem in this regard: the realisation of a tariff for an optometric examination would result in additional costs for health insurers and their clients because such tasks (monitoring stable glaucoma patients) were also financed for hospital-based glaucoma specialists. This was, however, a temporary problem as the reimbursement of glaucoma monitoring by glaucoma specialists became negotiable in 2009.[118]

Power positions and level of interest

In Table 4.5 we summarised the stakeholder positions by mapping their willingness to participate in the task substitution and their power positions.

The REH management initially wanted to transfer visits of stable glaucoma patients to primary care optometrists with the conditional support of the Dutch Healthcare Authority, patients, and health insurers. The conditions of the Dutch Healthcare Authority included accessibility and affordability of care (Table 4.6). Although patients saw benefits of the task substitution, like faster and more flexible appointments and shorter travelling times, they were not likely to visit primary care optometrists if they had to pay for care that would have been otherwise reimbursed (Table 4.6). The reimbursement could be accelerated by the health insurers, but they stood with the patients, arguing that they were only willing to cooperate if glaucoma specialists and the Health Care Inspectorate were fully behind the task substitution.

Table 4.5. Summary of the stakeholder positions

Stakeholders	Support / opposition	Power-position
REH management	Moderate support	Medium
Glaucoma specialists	Strong opposition	High
GFU employees	Strong opposition	Low
Primary care optometrists	Strong support	Low
Patients	Neutral	Medium
Health insurers / Nza	Neutral	High

GFU: Glaucoma Follow-up Unit; Nza: Dutch Healthcare Authority; REH: Rotterdam Eye Hospital.

Table 4.6. Quotations 'Power positions and level of interest'

Management REH:
• With respect to glaucoma care, we have started to investigate whether apart of the activities that take place here could be substituted to optometrists who are closer to the patient's home. (Respondent 2)
• I: What is your opinion about substitution of eye care to other professionals? R: If we did not agree, we would not put so much energy into it. (Respondent 1)
The Dutch Healthcare Authority / Health care insurers:
• It looks like it would be more accessible than going to see a doctor. In that respect it seems to be in the interests of the patient. It seems like a good development. (The Dutch Healthcare Authority, respondent 27)
Patients:
• Yes, I thought it was safe, so I thought, well, if the doctor says so. I simply trust him, so you go along with it. (Respondent 21)
• I think it is a bit more reassuring when you stay under your doctor's care, of course. A specialist is probably a bit more knowledgeable. You're so used to it. (Respondent 24)
Primary care optometrists:
• Yes, there is a professional group, but I never hear anything about it. A great deal would have to be done there. So I'm afraid that that is also a factor. (Respondent 18)
Glaucoma specialists:
• So you need to move forward with small steps, take the lead yourself. Then you have to get clear results which you can show, and once you have these, you can gain the trust of others to do it. (Respondent 7)

REH: Rotterdam Eye Hospital.

Only one glaucoma specialist preferred the situation of having stable glaucoma patients monitored by primary care optometrists. The remaining three specialists and most GFU employees were not in favour.

The OCR optometrists supported the task substitution of monitoring stable glaucoma patients at their shops because the task substitution would improve their professional image and strengthen their competitive positions relative to other optometrists. Their power position, however, was relatively weak due to the OCR's low degree of organisation and the self-employed state of most of their optometrists, unlike, for example, large optical chains. The role of the primary care optometrists was therefore relatively passive (Table 4.6).

Stakeholders holding strong power positions were glaucoma specialists and health insurers. Although the health insurers supported the idea of task substitution, they did not intend to initiate discussions about the establishment of tariffs for primary care optometrists unless the REH could guarantee quality of care. Besides, insurers believed the active support of the glaucoma specialists important, as did most patients. Thus, the substitution of person and setting would not succeed in the short term. Even the most enthusiastic glaucoma specialist affirmed this (Table 4.6).

4.4 DISCUSSION

Transferring the monitoring of stable glaucoma patients to primary care optometrists did not seem feasible in the Rotterdam area in the period 2004 to 2011, despite other studies indicating that (primary care) optometrists can provide high-quality care.[66,67,72,82-86,88-92,99] The implementation turned out to be the stumbling block as the involved professionals quarrelled over professional boundaries and work domains, they disagreed on the capabilities of primary care optometrists, the assumed returns on investment were unclear after all, and power positions favoured the status quo.

The three theoretical perspectives used in our case study align very well with the implementation literature that broadly acknowledges that implementation of an innovation can be difficult and a well-designed implementation process is critical.[3,110,112,113,119-122]

Our results can be explained by classical theories on implementation, financial incentives, and stakeholder interests. From implementation theories, for example, it could be expected that ophthalmic examination by primary optometrists would be difficult without reimbursement, because the current situation (no reimbursement) differed from the desired situation (with reimbursement).[119] A second example is the failure to enhance ophthalmologists' perceived benefit of the innovation by staffing the GFU with primary optometrists at the outset, because that would have reduced the uncertainty about the future situation, which is very important to let the task substitution succeed.[110]

This study also taught us two theoretical lessons that might influence the implementation literature. First, the findings highlighted the merit of connecting the implementation literature with sociological theories on professionalism, which is also acknowledged by Adler *et al*. (2009). A key notion for understanding the feasibility of the task substitution was recognizing the path dependency of the professionalisation of the occupations involved. There was indeed a window of opportunity for the task substitution at the outset because ophthalmologists were pressured to make professional relationships and domains more fluid. The intermediate step of the GFU fixed the professionalisation processes, and the pressures were sufficiently relieved. Thus, being aware of (local) professionalisation processes combined with good timing seem crucial for successfully transferring tasks from one professional group to another. Combining implementation literature with sociological theories on professionalism,[112-115] we can say in general that it is crucial to involve the substituting professionals early on to ensure that stakeholders see the change as a normal step in the professionalisation of the substituting professionals.

Second, the study underscores the importance of time element; windows of opportunity may disappear over time. In Rotterdam, the accumulation of (local) dynamics proved the assumed benefits of the task substitution wrong in the end. The assumption that cooperation with primary care optometrists would increase the inflow of new pa-

tients appeared incorrect. Besides, the assumed financial benefits were unclear. Because only hospital visits were reimbursed, primary care optometrists had to monitor stable glaucoma patients for free, charge patients for the examination, or organise a payment by the REH, all of which reduced its benefits. The last possibility would be to create a separate tariff for monitoring glaucoma patients by primary care optometrists, but the power positions of key stakeholders did not support this. Implementation scientists thus should not underestimate (the effect of) changing aims and interests of the different stakeholders over time because they often do change. It is therefore crucial to make the right decisions at the right time to obtain the expected result.

4.5 CONCLUSIONS

National and local factors hamper transferring the responsibility to monitor stable glaucoma patients from the REH's GFU to primary care optometrists in an outpatient setting. Task substitution in person and in setting is therefore not feasible in the short term in the Rotterdam area.

Unlike the primary care optometrists, most hospital-based glaucoma specialists over time were unwilling to collaborate in the scheme. Moreover, the REH management's enthusiasm for the task substitution waned when its aim shifted from cooperating with primary care optometrists towards increasing the inflow of new patients, as the demand could be met with the newly established and successful hospital-based GFU.

Policy makers considering substituting tasks to lesser trained professionals as well as substituting the delivery of services from a hospital to a primary care setting should carefully think about the implementation process, especially when they decide to implement task substitution in separate steps. Our case study demonstrates that professional, financial, managerial, and political factors all play a role in rendering task substitution feasible and that consolidating task substitution within a hospital setting will freeze the opportunity to transfer to a primary care setting. Recognizing a restricted window of opportunity in the implementation of task substitution is critical.

4.6 ACKNOWLEDGEMENTS

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APPENDICES

Appendix 4.1. Background information about the hospital, glaucoma and GFU working procedure and protocol

The Rotterdam Eye Hospital is a Centre of Excellence that provides high level medical, paramedical and nursing care, and pays much attention to the transfer of knowledge. In 2009, the number of outpatient visits was 138,311 and the number of hospitalisations was 1048.

Glaucoma is a group of eye diseases characterised by damage to the optic nerve that causes gradual, irreversible visual field loss. It is often related to age and high intraocular pressure, and care is currently provided by general ophthalmologists and glaucoma specialists. It calls for a tailored approach for each individual patient to slow down or halt the natural course of the disease. Monitoring patients by optometrists or ophthalmic assistants might be sufficient for stable glaucoma patients who are regulated correctly by ophthalmologists or patients at risk for glaucoma.

Those patients were referred to the GFU by their treating ophthalmologist. As long as patients were stable according to specific criteria for back referral, they visited the GFU twice followed by a visit to the glaucoma specialist or resident. If the patient was not stable according to these criteria, the patient was seen by a glaucoma specialist earlier. The GFU employees performed the following activities: ask a short history, determine the IOP and Snellen visual acuity and make GDx images. In case of moderate to advanced visual field damage or at doctor's request, they performed an additional yearly HFA (Humphrey Field Analyser, standard 24-2 test algorithm; Carl Zeiss Meditec, Dublin, CA, USA).

Appendix 4.2 Topic list

Topic list

a. Introduction
b. Introduction of study, the interviewees and the participant

1. What is your attitude towards task substitution in general and more specifically in glaucoma care?
2. What are, according to you, the advantages and disadvantages of task substitution?
3. How would you define and picture the task substitution in glaucoma care in the ideal situation?
4. What basis criteria need to be fulfilled? To what extent have they already been fulfilled? And if applicable: how can you accomplish that?
5. For what reasons would you (not) cooperate to let primary care optometrists become substitutes for glaucoma specialists in monitoring stable glaucoma patients?

6. What would you (or your organisation) do to make sure that the task substitution will (not) be established or to increase or decrease the chance of its successful implementation?
7. Which adjustments to the current health care system are required to establish the proposed task substitution?
   Are there any other issues you would like to discuss?

Chapter 5

Management of chronic lymphocytic leukaemia in daily clinical practice

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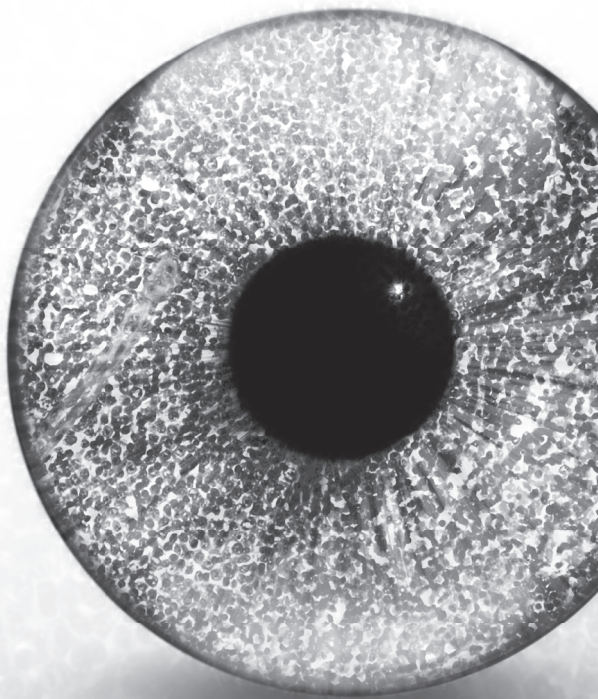

SUMMARY

Background. As the effectiveness and cost-effectiveness in daily clinical practice becomes more important in for example reimbursement decisions, observational studies also become increasingly important as these studies better reflect clinical practice in the complete patient population than randomised clinical trials.

Methods. In this observational study, we continually reviewed patient charts to assess daily clinical practice, treatment outcome and survival in 160 chronic lymphocytic leukaemia patients diagnosed between 1999 and 2003 in 19 Dutch hospitals. We also assessed whether daily clinical practice corresponded to the national guideline of 2004.

Results. Of the patients who received treatment (60.6%), 87% received chlorambucil in the first line. Fludarabine monotherapy (46%) and FC(R) (16%) were the most applied treatments in the second line. After the second treatment line, variation in treatment increases exponentially. The five-year overall survival was 89%.

Conclusions. The majority of Dutch CLL patients diagnosed between 1999 and 2003 were treated according to the national guideline that was formulated in 2004. However, since the management of CLL is heterogenic and has changed rapidly in the last decades, guidelines should be updated periodically.

For a disease like CLL, with a variety of and rapidly changing management strategies, capturing accurate and long-term observational data is necessary for quality assessment, but challenging.

5.1 INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia in the Western world, affecting roughly 3 to 6 people per 100,000 population.[123] Incidence increases with age, peaks at 60 to 80 years, and affects twice as many males as females.[123]

Early symptoms of CLL are usually minimal and diagnosis often follows a routine blood test that returns a high lymphocyte blood count. As the disease progresses, patients can experience fatigue, weight loss, bleeding, and recurrent or persistent infections.[124,125]

The clinical course of CLL is highly variable.[126] Survival from the time of diagnosis ranges from several months to 20 or more years, depending on prognostic factors.[127,128] The first prognostic indices including lymphadenopathy, hepatomegaly, splenomegaly, anaemia and thrombocytopenia were designed by Rai and Binet[126,129] to define disease stages. More recently molecular based prognostic markers have been defined like chromosomal abnormalities[130] and mutational status of the immunoglobulin genes.[131]

The CLL management changed in the last decades. At the onset of our study, alkylating agents (e.g. chlorambucil) and nucleoside analogues (e.g. fludarabine) were the only available effective agents for the treatment of CLL. At that time there was no evidence claiming that drug combinations were preferable to monotherapy but at the end of our study in 2009, multiple studies had shown improvement in progression-free survival with fludarabine based combinations.[132-135]

Observational research is becoming increasingly important, as policy makers are interested in disease management and its effectiveness in daily clinical practice for making reimbursement decisions. Results of observational studies may differ from results of clinical trials, as the latter frequently uses treatment protocols and concerns selected groups of patients with accrual depending on referral policies, and strict inclusion and exclusion criteria. Observational studies use minimal exclusion criteria leading to a more representative reflection of the total patient population.

As currently no observational study results are available, the aim of this study was to (1) obtain information about the management of CLL and its effectiveness in daily clinical practice in the Netherlands, (2) calculate actual costs of treatment of CLL, and (3) describe the quality of life of CLL patients.[136] In this paper, we describe the results of the first aim: CLL management in daily clinical practice and its effectiveness. We also compared these results with the Dutch guideline formulated in 2004.[137]

5.2 MATERIALS AND METHODS

Patient selection

Four university hospitals and 15 general hospitals in the Netherlands invited their CLL patients to participate in our observational study when they presented in clinical practice in 2004 and 2005. Any patient 18 years or older diagnosed with CLL between June 1999 and June 2003 could enter the study if he or she did not suffer from any other serious disease or previous malignancy, had a complete patient file, and gave informed consent. Patients who developed a non-CLL related malignancy were censored at the time of diagnosis of the second malignancy. The medical ethics committee of the Erasmus MC concluded that our study was exempted from the legal WMO criteria for scientific medical studies in humans due to its observational nature, and that there were no objections against conducting the study.

Data collection

Patient files and hospital databases were continually reviewed to assess (in- and outpatient) CLL treatment strategies from diagnosis till the end of the study. Patients were followed for at least five years for a sufficiently long observation time, since for a significant number of CLL patients, active treatment was not indicated directly after diagnosis.

Data were collected and entered in an internet database by trained study nurses under the supervision of the treating haematologists in 16 of the 19 centres. In the remaining three hospitals the data were collected by scientific personnel. In case of missing data on treatment outcome, treating haematologists were consulted to ensure a complete data set. Some patients had been partially treated in three hospitals outside the 19 participating centres; study personnel visited these hospitals to collect relevant data.

Data monitoring

For quality assurance, the data entered in the database were checked with the patient files and hospital databases continually. Basic characteristics (e.g., age, Binet stage at diagnosis and WHO score) and medical consumption related to the chemo(-immuno) therapy administration were checked for all patients. Other information (e.g. monitoring visits, adverse events, diagnostic procedures) was checked in over 75% of the patients.

Therapy description and outcomes

CLL management was reported for the first, second, and third or later treatment lines separately. The mean number of cycles has been calculated for each type of treatment separately, and information about the dose was reported for therapies used in 20 or more patients. A cycle of chlorambucil was defined as a period of treatment without breaks longer than one month.

Our main outcomes were 1) treatment outcome expressed as overall response (complete or partial response) and 2) time to next treatment: the time from the start of treatment until the start of the next treatment. Time to progression could not be measured appropriately, because of differences in hospitals' definitions of disease progression. Due to the variety in treatments, the treatment outcome has been presented per treatment group and was reported only for those treatment groups with 5 or more patients. The following treatment groups were used: chlorambucil (with or without prednisone), fludarabine monotherapy, fludarabine combinations, therapies including a monoclonal antibody, and other therapies. Other outcomes were overall and disease-specific survival, and the number of and reasons for hospitalisation.

Statistical analysis

CLL management was reported per treatment line. Survival rates were estimated using Kaplan Meier curves drawn in SPSS. A valid statistical comparison of different therapies per treatment line was not possible because patient sub-groups were too small.

5.3 RESULTS

Patients

Informed consent for participation was given by 173 patients. Of these, 13 patients (6%) were excluded from the analysis: eight did not meet the inclusion criteria, one patient file was not available, and one patient withdrew himself from the study. Additionally, one hospital discontinued participation during follow-up for technical reasons, resulting in the exclusion of three patients for incomplete data.

Table 5.1 shows that the majority of the patients was male (62.5%) with a mean age of 61.6 years (SD=10.2). The average age of the female patients was 66.3 (SD=10.7). The mean follow-up duration was 6.4 years (range=1.9-9.4, SD=1.4).

Table 5.1. Patients' characteristics at diagnosis

	Participating patients (n=160)
Hospital of inclusion:	
University	28 (17.5%)
General	132 (82.5%)
Age at diagnosis: Mean (SD)	63.4 (10.6)
Median	63
Range	30-86
Gender (% male)	62.5
Patients (%) with first or second degree relatives with leukaemia or lymphoma	8.1
Binet Stage (%):	
A	71.3
A progressive	1.9
B	15.0
C	11.3
Unknown	0.6
% of patients with ≥1 extra nodal sites	88.1
B-symptoms (yes %)	12.5
Involvement of spleen (yes %)	27.5
WHO-performance score (%):	
0	78.1
1	19.4
2	0.6

WHO: World Health Organization

Therapies per line

The treatment sequences informed us about the daily clinical practice in the period 1999–2009 for patients diagnosed between mid-1999 and mid-2003. The treatment sequence is presented schematically in Figure 5.1. Table 5.2 presents the number of cycles per line, time to next treatment and overall response rates per treatment group. Figure 5.2 shows the response rates for the treatment groups that contained 5 or more patients.

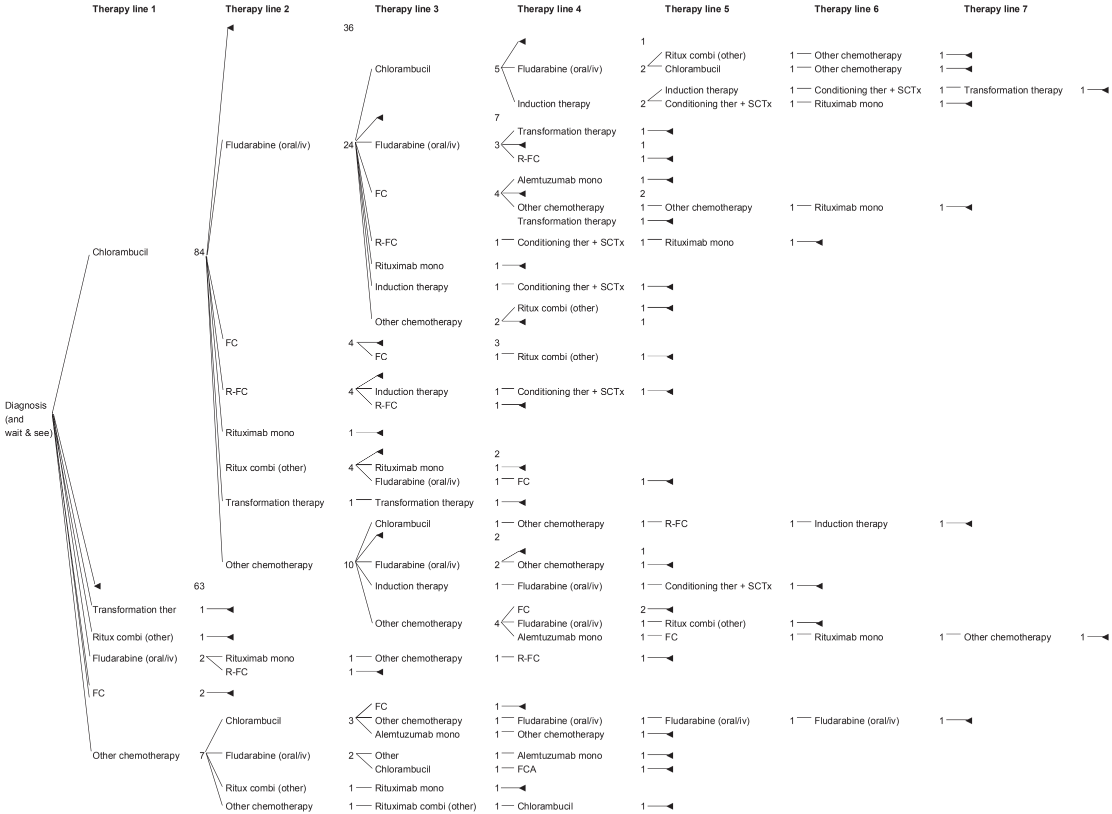

Figure 5.1 Flowchart management of CLL patients using twelve treatment groups: chlorambucil (+/-prednisone), fludarabine monotherapy, fludarabine plus cyclophosphamide (FC), rituximab monotherapy, F(C) plus rituximab, other rituximab combination (R-CHOP, R-CVP), alemtuzumab monotherapy, FC plus alemtuzumab, induction therapy, conditioning therapy plus stem cell transplantation, transformation therapy, other chemotherapy.

Table 5.2. Mean number of cycles and time to next treatment per treatment line

Line number	Treatment category	N	Mean number of cycles (SD)	Time to next treatment in days (SD)	Overall response (%)
1 (n=97)	Chlorambucil	84	2.4 (1.8)	1088 (831)	53.2
	Fludarabine monotherapy	2	5.0 (4.2)	Not presented	Not presented
	Fludarabine combination	2	4.0 (2.8)	Not presented	Not presented
	Therapy including monoclonal antibodies	1	14.0 (n.a.)	Not presented	Not presented
	Other therapies	8	7.3 (3.2)	857 (570)	1.0
2 (n=57)	Chlorambucil	3	3.3 (2.3)	Not presented	Not presented
	Fludarabine monotherapy	26	4.2 (2.6)	555 (530)	44.0
	Fludarabine combination	4	4.0 (2.4)	Not presented	Not presented
	Therapy including monoclonal antibodies	12	5.4 (2.6)	562 (393)	72.7
	Other therapies	12	5.3 (2.1)	507 (309)	75.0
3 (n=39)	Chlorambucil	7	1.6 (0.8)	424 (314)	16.7
	Fludarabine monotherapy	7	5.0 (1.2)	522 (365)	85.7
	Fludarabine combination	6	3.3 (1.8)	292 (184)	50.0
	Therapy including monoclonal antibodies	7	5.4 (2.4)	341 (225)	85.7
	Other therapies	12	5.3 (2.1)	294 (248)	50.0
>3 (n=50) Line 4: 28; Line 5: 11; Line 6: 9; Line 7: 2.	Chlorambucil	2	1.0 (0.0)	Not presented	Not presented
	Fludarabine monotherapy	7	2.9 (2.1)	255 (209)	66.7
	Fludarabine combination	4	3.0 (0.8)	Not presented	Not presented
	Therapy including monoclonal antibodies	19	4.0 (3.1)	181 (153)	56.3
	Other therapies	18	2.1 (1.7)	232 (350)	52.9

Watch and wait

During follow-up, 63 patients (39%) remained in 'watchful waiting' after diagnosis. One of these patients died during the study from a non-CLL related cause after 50.1 months of follow-up. The remaining 62 patients had an average follow-up period of 81.7 months (SD=13.8). The mean time between outpatient visits during the watchful waiting period was 3.1 months.

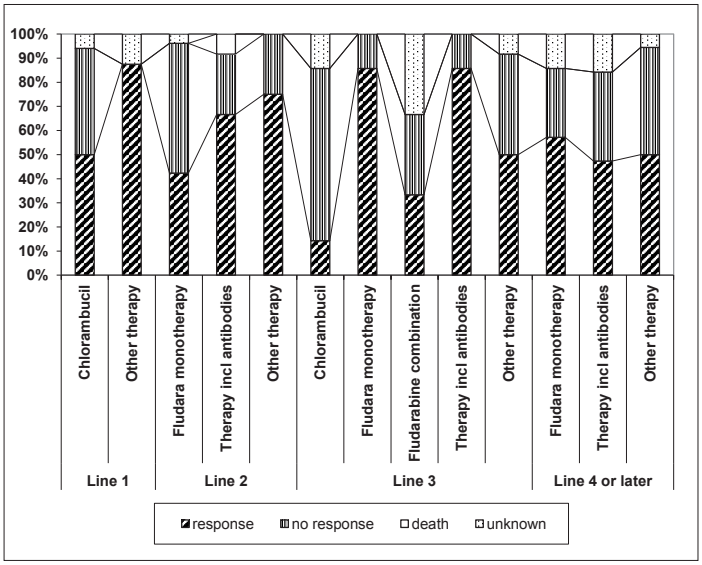

Figure 5.2 Overall response per treatment line per treatment group that included 5 or more patients.

First treatment line

Of the 97 patients (61%) who started treatment, 34 patients (35%) started with an active treatment within 28 days of their diagnosis. The remaining 63 patients started on average after 30.5 months of watchful waiting (median=24.3; range=1.2-93.9; SD=23.4).

In the first treatment line most patients were treated with chlorambucil (n=84; 87%). They received on average 2.4 cycles during an average period of 23.4 months. Treatment schemes varied: 78% received low dose chlorambucil continuously, 14% high dose in cycles, and 8% an intermediate scheme. In 56% of the patients, the daily dose varied from 0.5 mg to 6.0 mg. Compared to those treated with alternative therapies, patients receiving chlorambucil were on average older (63.4 vs. 58.8 years at diagnosis) and less frequently diagnosed with a Binet C stage (14.3% vs. 33.3%). Half of the patients (n=42) responded to chlorambucil, 3 of whom developed toxicity. Five additional patients (6%) had a toxic reaction to chlorambucil (response information not available). Eleven patients (13%) had no response, and 26 patients (31%) experienced progression during treatment. The mean time to next treatment for all patients receiving chlorambucil was 35.7 months.

The 13 patients (13%) who received another type of treatment, had a lower mean time to next treatment of 26.3 months but a higher mean overall response of 100% than patients who received chlorambucil. They and received the following therapies: cyclophosphamide, vincristine, and prednisone (CVP, 6.2%), rituximab-CVP (R-CVP, 1.0%),

fludarabine (2.1%), fludarabine and cyclophosphamide (FC, 2.1%), cyclophosphamide (1.0%) and treatment for a transformation (1.0%). The mean number of cycles was 8 for CVP, 14 for R-CVP, 5 for fludarabine, 4 for FC, 1 for cyclophosphamide and 9 for the treatment for a transformation.

Second treatment line

Table 5.2 shows that 57 patients (36%) required a second treatment line. Almost 50% of these patients (n=26), received fludarabine monotherapy. They received on average 4.2 cycles and their time to next treatment was 18.2 months. Nine of the eleven patients (82%) who completed their fludarabine treatment responded. Their mean dose was 37mg/m^2 per day during 6.6 cycles (range: 25 to 40mg/m^2). The 15 patients who did not complete treatment received 2.3 cycles on average with a mean dose of 30mg/m^2 per day. Two patients completed treatment early due to good response. The other patients ended treatment because of toxicity (6), anaemia (2), malaise (1), progression during treatment (2) or no response (2).

Alternative therapies and their average number of cycles in the second treatment line were: CVP (n=9; 5.8 cycles), fludarabine and rituximab with or without cyclophosphamide (FCR, n=5; 6.2 cycles), R-CVP (n=4; 4.3 cycles), FC (n=4; 4.0 cycles), chlorambucil (n=3; 3.3 cycles), rituximab (n=2; 4.0 cycles), cyclophosphamide, adriamycine, vincristine, and prednisone (CHOP, n=1; 4.0 cycles), rituximab combined with CHOP (R-CHOP, n=1; 9.0 cycles), cyclophosphamide, vinblastine, prednisone, and procarbazine (CVPP, n=1; 6.0 cycles) and a treatment for transformation (R-CHOP; n=1; 2.0 cycles).

Third and subsequent treatment lines

Table 5.2 shows the treatment outcomes per treatment group of the 39 patients (24%) who received three or more treatment lines. These lines included a variety of therapies for a small number of patients each. Table 5.2 presents the mean number of cycles per treatment category.

All patients in the treatment group 'fludarabine combinations' (6 in the third line and 4 in later lines) received FC in 3.2 cycles on average. The group of therapies including monoclonal antibodies comprised patients who received rituximab monotherapy (n=8; 3.8 cycles), R-CVP (n=6; 5.2 cycles), alemtuzumab monotherapy (n=4; 6.5 cycles), FCR (n=4; 3.8 cycles), R-CHOP (n=2; 4.0 cycles), FC combined with alemtuzumab (FCA, n=3; 1.0 cycle) and one treatment with fludarabine combined with rituximab (FR; 3.0 cycles).

The other chemotherapies were: CVP (n=13; 4.7 cycles), conditioning therapy (n=6; 1.0 cycle), CHOP (n=4; 5.0 cycles), treatment for transformation (n=4; 2.3 cycles), cyclophosphamide + prednisone (n=1; 1.0 cycle), vincristine (n=3; 6.0 cycles), daunorubicin and cytarabine (n=1; 1.0 cycle) and dexamethasone + cytarabine + cisplatin (n=1; 1.0 cycle).

Stem cell transplantations

A total of six patients were hospitalised for 17.5 days (range=8-25, SD=8.07) for allogeneic stem cell transplantation and conditioning chemotherapy. Conditioning chemotherapies were fludarabine, fludarabine combined with busulfan, FC, FC combined with methotrexate, cyclophosphamide and radiotherapy, and antithymocyte globulin with fludarabine and total body irradiation. Of the six patients, two achieved complete remission and three partial remission.

Transformations

A transformation of the CLL into an aggressive lymphoma occurred in seven patients (4.3%). In two patients the transformation was non-CLL-related and they were therefore censored at the time of transformation. The CLL of the five other patients transformed into diffuse large B-cell lymphoma. Four of these patients (80%) died during follow-up. One received two therapies for transformation during the second and third treatment line.

Hospital admissions

Table 5.3 presents the number of hospitalisations per patient and per patient year by cause. Within the mean study period of 6.4 years, 84 patients (48.6%) were hospitalised 731 times for reasons other than chemo(-immuno)therapy or stem cell transplantation. The two most common reasons were blood transfusions (66.4%) and fever/ infection/ pneumonia (22.3%).

Survival

Figure 5.3 displays the overall survival. The two- and five-year overall survival was 100% and 89%, respectively. A total of 39 patients (24.4%) died during follow-up: 29 deaths were CLL-related, 8 were non-CLL related, and in two patients cause of death was unknown. In general, the prognosis was better for patients with a Binet A stage than for patients with a Binet B or C stage.

The two-year CLL-specific survival was 100% and the five-year CLL specific survival was 91% (data not shown).

Table 5.3. Reasons of hospitalisations

Reason of hospitalisation	Number of patients	Number of hospitali-sations	Mean number of hospitalisations for all patients (n=160)	Mean number of hospitalisations per patient year
Blood transfusion	54	470	2.94	0.46
Fever/ Infection/ Pneumonia	47	158	0.99	0.15
Administration medication (excl. chemotherapy)	5	23	0.14	0.02
Malaise	15	15	0.09	0.01
Diagnostic procedures	13	15	0.09	0.01
Abdominal pain/ Constipation	8	11	0.07	0.01
Hemolysis/ ITP/ Pancytopenia	5	6	0.04	0.01
Heart problems	2	4	0.03	0.00
Graft versus Host disease	2	2	0.01	0.00
Dermatologic problems	2	2	0.01	0.00
Progression CLL	2	2	0.01	0.00
Thrombosis	1	2	0.01	0.00
Other reasons	14	18	0.11	0.02
Unknown	3	3	0.02	0.00

CLL: chronic lymphocytic leukaemia; ITP: immune thrombocytopenic purpura.

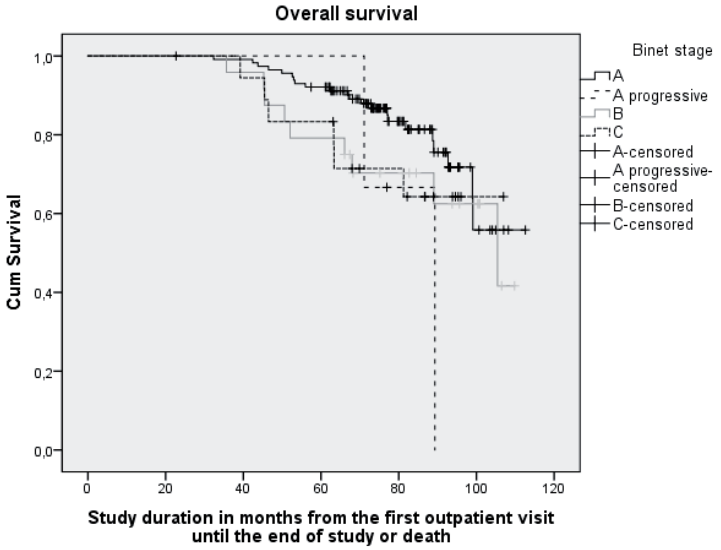

Figure 5.3 Kaplan Meier Curve for overall survival per Binet stage at diagnosis.

Guidelines in the Netherlands

At the start of the study there were no general guidelines available for the management of CLL patients. In the Netherlands the protocols of a few large academic hospitals were leading in the management of CLL. For many years chlorambucil has been the most important therapeutic drug for previously untreated CLL. With the introduction of fludarabine as a first-line treatment[138] a higher response rate was observed, but no prolonged overall survival when compared to chlorambucil as primary treatment. For this reason, in combination with the lower costs, chlorambucil was the treatment of choice for CLL patients in the Netherlands at the time of the present study. This contrasts with the management in the United States of America, where the higher response rate was reason enough to replace chlorambucil with fludarabine.

The first guideline for CLL from the Dutch-Belgian Cooperative Group for Haemato Oncology for Adults and the Dutch Institute for Healthcare Improvement CBO published in 2004 summarised the existing local protocols and current practices [137]. It advised chlorambucil as first-line treatment and fludarabine as second-line treatment in chlorambucil-resistant patients. The guideline advised against the use of total body irradiation as upfront treatment and against the use of interferon-α.[137]

With the introduction of FC and the monoclonal antibodies alemtuzumab and rituximab, more powerful treatment options came available in 2004. Although not proven to prolong survival at that time, these therapeutic modalities have been increasingly used as first- or second-line therapies in the last years of our study. More recent results show that alemtuzumab monotherapy and FCR improve the progression-free survival and that FCR improves the overall survival as well.[139,140]

Daily clinical practice versus guideline

Of the 97 CLL patients requiring treatment, 84 patients (87%) received chlorambucil, which corresponded with the guideline. Fludarabine was administered to 24 of the 48 patients (50%) who required treatment after they had received chlorambucil. Of the remaining 24 patients, 8 (33%) received a treatment combination containing fludarabine. As recommended in the guideline, none of the patients received total body irradiation as primary treatment nor did they receive interferon-α during their total follow-up period.

Recommendations in the Dutch guideline focused on the first treatment line, and the second treatment line of chlorambucil-resistant patients. Although the guideline did not exist at the time of the diagnosis of our patients, if we look at those 145 lines (97+48) in particular received by 97 patients, 74% of the lines administered to 62% of the patients complied with the guideline.

5.4 DISCUSSION

In this evaluation of daily clinical practice in the Netherlands, first line treatment reflected the guideline as formulated in 2004[137] in the 87% of the patients who received chlorambucil. However, our study also illustrated the wide variety of applied chemotherapy regimens and the frequent deviations from the guideline. As an example, 46% of the chlorambucil-resistant patients were treated with a combination treatment instead of fludarabine monotherapy as advised by the guideline. This was probably due to the release of evidence of the favourable result of combination therapies on progression-free survival[132-135] during our study, and can therefore be justified.

To obtain information on disease management and effectiveness in daily clinical practice, observational research is required. And although this type of research has its merits, it also has challenges. Dynamics in daily clinical practice due to continuous changes in insight and knowledge during the study could mean that study results are not up-to-date in the end. During our study period monoclonal antibodies like alemtuzumab and rituximab were introduced, and cytogenetic analysis to determine the most appropriate treatment became available. Another challenge relates to the comparison of treatment outcomes. CLL patients often receive multiple treatment lines, the outcome of which is influenced by the outcome of the preceding therapies. Consequently, the treatment history would have to be taken into account when comparing alternative strategies per treatment line. To achieve this, large numbers of patients are required. In combination with the relatively low incidence of CLL, treatment variation among physicians and patient (risk) groups, and rapid development of new therapies, it is clear that comparing alternative therapies in observational research is challenging. Considering the importance of observational research for health care policy, however, finding solutions is imperative. Towards this, long-term continuous registration has been started to keep records of daily clinical practice for all CLL patients in the Netherlands. Alternatively, a disease model could be developed to predict the impact of changes in the management on survival, quality of life and costs. Our study provides real world information which can be used for the development of such a model.

Although we prospectively collected the data during the last four years of follow-up, we had to collect data retrospectively for patients already diagnosed at the time of enrolment. Retrospective data collection complicates an objective measurement of treatment outcomes. Not all hospitals and specialists use the same response criteria and their assessments are not always reported in the patient files, which is why we could only report on overall response rates and survival.

The second limitation is that our study population may not be representative for all CLL patients in the Netherlands. Patients with a low disease activity who were monitored by their general practitioner were not included, as patients were asked for participation

by haematologists. The percentage of patients that did not require active treatment may therefore have been somewhat underestimated.

Such patients, however, would be referred to the haematologist or hospital when they needed active treatment, and thus our description of the CLL management is probably representative for the population that requires treatment. We could determine compliance with the guideline in daily clinical practice management. Seeing whether the updated national CLL guidelines of 2011[141] are reflected in the treatment of recently diagnosed patients would, however, be interesting.

Overall, the 2004 guideline recommendations are in line with daily clinical practice for most patients. Because of rapid developments in management strategies, however, continual assessment of the appropriateness of the guidelines is necessary. To accomplish this, observational research is worthwhile, but also very challenging in case of chronic diseases with rapidly changing management strategies.

5.5 ACKNOWLEDGEMENTS

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Chapter 6

Real-world costs of chronic lymphocytic leukaemia in the Netherlands

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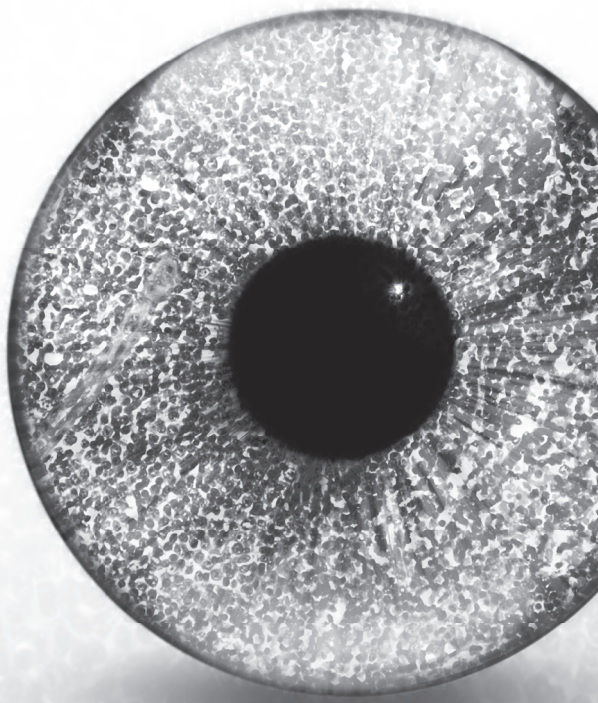

SUMMARY

We performed a comprehensive cost calculation identifying the main cost drivers of treatment of chronic lymphocytic leukaemia in daily practice. In our observational study 160 patient charts were reviewed repeatedly to assess the treatment strategies from diagnosis till the study end. Ninety-seven patients (61%) received ≥1 treatment lines during an average follow-up time of 6.4 years. The average total costs per patient were €41,417 (€539 per month). The costs varied considerably between treatment groups and between treatment lines. Although patients were treated with expensive chemo(immuno-)therapy, the main cost driver was inpatient days for other reasons than administration of chemo(immuno-)therapy.

6.1 INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia occurring in the Western world, affecting 3 to 6 people per 100,000 population,[142-144] but literature on its economic burden is scarce. Health care is under increasing pressure and cost-effectiveness data are urgently needed. That is especially true in countries like the Netherlands where expensive drugs are to be evaluated during the first years of temporary admittance in order to get unconditioned reimbursement.

Reviewing the existing literature on cost of CLL published between 1990 and July 2013, we identified 3 publications that presented an overview of the longitudinal (direct) medical costs of CLL treatment.[145-147] In these studies, administrative claim data were used to compare costs of CLL patients with those of patients without cancer to identify the main cost drivers. Administrative claim data give a quite complete overview of all medical costs of large patient populations in a short time frame from a third party payers perspective. They have however also drawbacks. Data from health insurers are not recorded to calculate the actual costs and moreover, these data are susceptible to upcoding in countries with casemix systems (like the USA, Germany and the Netherlands). Upcoding occurs when patients are miscoded or misclassified and leads to higher reimbursements for services provided, and therefore to higher health costs.[148,149] Besides, cost information subdivided by type of treatment or disease stage is often not available in these datasets.

In this observational study, we followed Dutch CLL patients for several years to get an overview of the management of CLL in clinical practice. A comprehensive cost calculation was performed to produce a transparent overview of different cost categories in order to identify the main cost drivers during the complete course of CLL treatment. To evaluate most CLL related costs, we followed the patients for 6.4 years on average. This long follow-up period was deemed necessary due to the chronic character of CLL in the majority of patients. Although treatment strategies for CLL, and therefore costs, are evolving over time, our calculations seem to remain relevant for two reasons. Due to the long follow up period, nearly all currently available treatments are included in our analysis. Besides, and more importantly, in contrast to the currently available data, we also reported costs per treatment line and per type of treatment.

6.2 PATIENTS AND METHODS

Study design

An observational study design was chosen to calculate the costs of CLL, to reflect daily clinical practise.

Inclusion and exclusion criteria

In 2004 and 2005, 19 hospitals in the Netherlands invited CLL patients for participation in the study. Patients aged 18 years or older diagnosed with CLL between June 1999 and June 2003 could enter the study if they did not suffer from another active malignant disease or another serious previous malignancy, had a complete patient record, and gave written informed consent. Patients who developed a non-CLL related malignancy were censored at the time of that diagnosis.

Data collection and monitoring

Patient charts were reviewed repeatedly to assess the treatment strategies for CLL in daily practice from diagnosis till the end of the study. All CLL-related medical resources consumed within the hospital or in the outpatient setting (i.e. medication prescribed by a haematologist) were derived from patient charts and hospital databases by trained research nurses under supervision of the treating haematologists or by scientific personnel. To ensure a complete data set, treating haematologists were asked to provide any missing information.

Data were entered in an electronic data file which was accessible through the Internet, and checked yearly for quality assessment. Baseline characteristics (e.g. age, Binet stage, and WHO score) and resources related to the chemo(immuno-)therapy administration were obtained for all patients. The remaining information about e.g. outpatient / day ward visits, adverse events, and diagnostic procedures (X thorax, CT scans) was obtained for all patients and checked in over 75% of them.

Cost calculations

Total costs for individual patients were calculated by multiplying the resource use and unit costs. The analysis was based on the resource use of all patients including patients still treated at the end of data collection. Costs were based on the year 2012 (when necessary adjusted using general price index figures from the CBS Statistics Netherlands).

The unit costs for hospital days, outpatient visits, and day care treatment include direct and indirect labour costs, hotel and nutritional costs, overhead and capital costs and were derived from different resources using a micro costing method.[150-152] These unit costs were calculated for university and general hospitals separately.

For the calculation of laboratory costs, we recorded the number of days per treatment line on which laboratory tests were performed. In general we assumed that one blood sample was taken per day, during hospitalisations we assumed two blood samples per day. The unit costs of laboratory tests per withdrawal were based on our data in a cohort of multiple myeloma patients.[153]

Costs of diagnostic procedures were based on national tariffs derived from the Dutch Healthcare Authority (NZa) which are assumed to reflect the actual costs reasonably.[154]

For the costs of allogeneic stem cell transplantation (AlloSCT) we combined our data with results of an earlier study,[150] as not all components of SCT could be identified in the patient file. We distinguished AlloSCT from related donors and from matched unrelated donors. The donor costs for unrelated donor transplants were based on published costs of stem cell transplantation in the Netherlands.[150]

Costs of medication were acquired from the national pharmaceutical formulary drafted by the Dutch Healthcare Insurance Board.[155] Wasting was taken into account for the cost calculation of intravenous medication.

6.3 RESULTS

Patient characteristics

Informed consent for participation was given by 173 patients. Of these patients, 13 patients (6%) were excluded from the analysis. Eight patients did not meet the inclusion criteria; one patient chart was missing; and one patient withdrew himself from the study. Additionally, one university hospital refused further participation during follow-up, resulting in three patients with incomplete follow-up data.

Table 6.1 presents patients' characteristics at diagnosis of the 160 evaluable patients. The majority of the patients were male (62.5%). Male patients had a mean age at diagnosis of 61.6 years (median=63, SD=10.2). The average age at diagnosis of female patients was 66.3 years (median=69.5, SD=10.7). The mean follow-up duration was 6.4 years (median=6.4 years, range=1.9-9.4, SD=1.4). Furthermore, Table 6.1 presents the characteristics of patients who remained in the wait and see stage (n=63) and of patients who were solely treated with chlorambucil monotherapy (n=36). These patients were significantly older than the average age of the other patients (64.3 and 66.2 years vs. 60.7 years) and were diagnosed more often with Binet A stage disease.

Unit costs and resource use

Table 6.2 presents the unit costs and the average resource use per patient during the study period for all types of hospital visits, (diagnostic) tests, and treatment regimens.

Patients visited the internal/haematology outpatient clinic on average 5.6 times per year, and other departments 0.2 times a year (outpatient visits). Additionally, they had on average 0.2 telephone contacts per year. The therapy costs are the highest in the allogeneic transplantations and the monoclonal antibody containing regimens like rituximab monotherapy, FCR (fludarabine, cyclophosphamide, and rituximab), and FCA (fludarabine, cyclophosphamide, and alemtuzumab).

Appendix 6.1 describes the unit costs of AlloSCT in more detail, resulting in a unit price of €55,966 for an AlloSCT of a related donor and €111,913 for an AlloSCT of an unrelated

Table 6.1. Patients' characteristics at diagnosis

	All patients (n=160)	Patients without treatment (n=63)	Patients treated with CLB only (n=36)	Other patients (n=61)
Age at diagnosis:				
Mean (SD)	63.4 (10.6)	64.3 (9.4)	66.2 (11.9)	60.7
Median	63	64	67	61
Range	30-86	34-83	30-86	38-85
Gender (% male)	62.5	57.1	55.6	72.1
Patients (%) with first or second degree relatives with leukaemia or lymphoma	8.1	6.3	8.3	9.8
Binet Stage (%):				
A	71.9	95.2	72.2	47.5
A progressive	1.9	0	0	4.9
B	15.0	1.6	16.6	27. 9
C	11.3	3.2	11.1	19.7
B-symptoms (yes %)	12.5	6.3	11.1	19.7
Involvement of spleen (yes %)	27.5	11.1	38.9	37.7
WHO-performance score (%):				
0	78.1	84.1	75.0	73.8
1	19.4	15.9	22.2	21.3
2	0.6	0	0	1.6
4	1.3	0	2.8	1.6
n.a.	0.6	0	0	1.6

N.a.: not available; CLB: chlorambucil; WHO: World Health Organization.

Table 6.2. Unit costs and average resource use per patient for the complete study duration of on average 6.4 years (in €, year 2012)

Unit	**Unit costs**		**Average resource use**
	General hospital	University hospital	
Hospital visits			
Inpatient hospital day	441	749	17.30
Outpatient visit	95	156	37.85
Visit to nurse (practitioner)	58	58	0.15
Telephone contact	14	14	1.52
Day care visit	194	336	7.91
ICU per day	2137	2137	0.41
Emergency room visit	227	227	0.23
Inpatient hospital isolation day	n.a.	980	0.66
Revalidation clinic	392	392	Not separately reported

Table 6.2. Unit costs and average resource use per patient for the complete study duration of on average 6.4 years (in €, year 2012) (continued)

Unit	Unit costs		Average resource use
	General hospital	University hospital	
Diagnostic tests			
Laboratory test (per withdrawal)	58	58	83.23
X-ray	57	57	Not separately reported
CT scan	260	260	Not separately reported
Echo (ultrasound)	95	95	Not separately reported
Haemoculture	35	35	Not separately reported
Other culture	22	22	Not separately reported
Puncture bone marrow and cytology testing	69	69	Not separately reported
Blood: erythrocytes	221	221	Not separately reported
Blood: thrombocytes	534	534	Not separately reported
ECG	21	21	Not separately reported
Bone biopsy	227	227	Not separately reported
Immunophenotyping	279	279	Not separately reported
Bone marrow biopsy	326	326	Not separately reported
Therapy costs			
Chlorambucil	198 per cycle		2.3 cycles*
Fludarabine (oral/i.v.)	1134 per cycle		4.1 cycles
Fludarabine, cyclophosphamide (FC)	911 per cycle		3.5 cycles
FC plus Rituximab (FCR)	3131 per cycle		4.9 cycles
Other rituximab combination	2454 per cycle		5.6 cycles
Rituximab monotherapy	3350 per cycle		3.8 cycles
Alemtuzumab monotherapy	2119 per cycle		6.5 cycles
Induction therapy	2068 per cycle		4.1 cycles
Transformation therapy	2022 per cycle		3.3 cycles
FC + Alemtuzumab (FCA)	2957 per cycle		1.0 cycles
Other chemotherapy	132 per cycle		5.4 cycles
SCT of related donor (excluding laboratory costs)**	55,966 per procedure		0.03 procedures
SCT of unrelated donor (excluding laboratory costs)**	111,913 per procedure		0.01 procedures

* In the treatment with chlorambucil, treatment periods were considered to be two separate lines when the period between them was more than 365 days.

** See Appendix 6.1 for more details.

ECG: Electrocardiography; ICU: intensive care unit; SCT: stem cell transplantation.

donor. The components marked with *** were directly derived from our study and are the average of 5 transplantations of a related donor and one transplantation with an unrelated donor. The other components could not be extracted from the patient files in most cases. To calculate the costs of these components, we used the data from another study.[150]

Costs and cost categories

Table 6.3 shows how the total costs related to (the treatment of) CLL of €41,417 per patient for the average total follow-up period of 6.4 years break down into different cost categories. The following categories were distinguished: monitoring visits (day ward or outpatient visits), chemo(immuno-)therapy in in- or outpatient setting including stem

Table 6.3. Breakdown of the total direct medical costs related to chronic lymphocytic leukaemia

Totals (N = 160)		
Total costs (SD)		41,417 (65,983)
Treatment line duration in months (SD)		76.9 (18)
Total monthly costs		539
Monitoring visits	**43.1%**	
Laboratory tests		11.7%
Outpatient visits		9.6%
Day ward visits		1.1%
Procedures		10.7%
Medication (in periods without treatment)		9.9%
Chemo(immuno-)therapy	**28.1%**	
Chemo(immuno-)therapeutics		13.9%
Administration of therapy (day ward/outpatient)		3.5%
Blood products		1.3%
Procedures		3.9%
(Prophylactic) medication (during treatment periods)		3.9%
Inpatient days (stem cell transplantation)		1.6%
Hospitalisation due to other reasons	**28.8%**	
Inpatient days (normal care)		18.5%
Inpatient days (intensive care unit)		2.1%
Other contacts (outpatient visits, ICC, dietician)		0.7%
Emergency room visit		0.1%
Procedures		6.2%
Medication		1.3%

cell transplantation, hospitalisation due to other causes than administration of therapy. Stem cell transplantation counted for 5.9% of all costs (€2444).

The main cost driver was inpatient days/day ward treatment (23% of the total costs), followed by costs of chemo(immuno-)therapy (13.9% of the total costs). Patients were hospitalised most frequently for a blood transfusion, pneumonia, other infections, or fever of unknown origin.

The majority of the costs were made during the monitoring visits (43% of the total costs, but this also includes outpatient medication and procedures over the complete course of CLL (including during treatment periods).

Table 6.4 presents the costs differentiated per treatment line and per treatment group. In most treatment lines the main cost driver was inpatient days. Only in the wait and see stage, the outpatient visits (and procedures, not presented) were the main cost driver.

When looking at the different types of treatments, costs were mainly driven by inpatient days as well. Only in the 38 patients (24%) who received the following treatments, chemo(immuno-)therapy was the main cost driver: FCR, rituximab monotherapy, therapy for a (Richter's) transformation, induction therapy preceding AlloSCT, or conditioning therapy plus AlloSCT. In patients who received other rituximab combinations or alemtuzumab monotherapy the costs of chemo(immuno-)therapy did not exceed the total costs made during the monitoring visits, but did exceed the costs of the outpatient visits.

The mean monthly costs of €539, ranged from €116 to €5,801 per patient when differentiated per treatment line and from €116 to €22,132 when differentiated per treatment group. Although the latter maximum is not representative as it concerned one patient who died within a month after treatment, the exclusion of this patient still resulted in a very broad range of the monthly costs per treatment group (€116 to €7,932) indicating that costs in CLL treatment vary enormously.

The mean total costs per treatment line increased by the number of lines up to the fifth line. The costs in the sixth and seventh line were lower, but as only very few patients had that advanced disease nothing can be said about the trend in costs in these lines.

Table 6.4. Breakdown of the costs related to chronic lymphocytic leukaemia per treatment line and per treatment group

	N	Total costs (SD)	Mean line duration in months (SD)	Total monthly costs	Monitoring visits		Chemo(immuno-) therapy		Hospitalisation for other reasons**	
					Total	Outpatient visits	**Total**	Chemo (immuno-) therapeutics	**Total**	Inpatient days
Total	160	41,417 (65,983)	76.9 (18)	539	**43.1%**	9.6%	**28.1%**	13.7%	**28.8%**	20.6%
Per subsequent treatment line										
Wait and see	160	5,138 (12,204)	44.2 (36)	116	**72.6%**	25.9%	**0.0%**	0.0%	**27.4%**	21.5%
First line	97	16,516 (24,210)	34.5 (26)	479	**54.5%**	13.5%	**18.1%**	7.5%	**27.4%**	17.1%
Second line	57	26,197 (30,290)	18.3 (15)	1432	**37.5%**	6.3%	**31.3%**	20.9%	**31.3%**	21.7%
Third line	39	27,704 (24,327)	12.0 (9)	2306	**35.5%**	4.2%	**30.1%**	17.6%	**34.4%**	24.3%
Fourth line	28	32,166 (34,478)	8.1 (10)	3983	**28.1%**	3.3%	**52.3%**	21.30%	**19.6%**	14.5%
Fifth line	11	37,852 (45,028)	6.5 (6)	5801	**24.4%**	4.1%	**43.1%**	13.5%	**32.6%**	25.8%
Sixth line	9	24,294 (26,610)	5.3 (5)	4558	**29.1%**	6.1%	**53.1%**	19.9%	**17.8%**	15.9%
Seventh line	2	46,643 (44,715)	13.6 (13)	3442	**23.4%**	4.7%	**14.3%**	9.4%	**62.4%**	57.8%

Table 6.4. Breakdown of the costs related to chronic lymphocytic leukaemia per treatment line and per treatment group (continued)

	N	Total costs (SD)	Mean line duration in months (SD)	Total monthly costs	Monitoring visits		Chemo(immuno-) therapy		Hospitalisation for other reasons**	
					Total	Outpatient visits	**Total**	Chemo (immuno-) therapeutics	**Total**	Inpatient days
Total	160	41,417 (65,983)	76.9 (18)	539	**43.1%**	9.6%	**28.1%**	13.7%	**28.8%**	20.6%
Per treatment group										
Wait and see	160	5,138 (12,204)	44.2 (36)	116	**72.6%**	25.9%	**0.0%**	0.0%	**27.4%**	21.5%
Chlorambucil	96	17,067 (24,483)	33.6 (27)	508	**58.3%**	13.3%	**11.3%**	2.7%	**30.4%**	18.9%
Fludarabine (o/i.v.)	41	26,977 (33,452)	16.3 (15)	1654	**32.1%**	5.8%	**28.6%**	17.2%	**39.3%**	28.8%
Fludarabine, cyclophosphamide (FC)	16	23,304 (22,210)	10.2 (6)	2280	**32.3%**	4.8%	**25.9%**	13.7%	**41.8%**	31.1%
FCR (FC plus Rituximab)	10	37,282 (17,710)	14.8 (14)	2512	**27.3%**	3.9%	**51.8%**	41.1%	**20.9%**	10.5%
Other rituximab combination	12	38,423 (28,006)	14.3 (11)	2694	**42.6%**	3.2%	**42.0%**	35.8%	**15.3%**	12.1%
Rituximab monotherapy	9	25,111 (15,135)	8.3 (6)	3042	**27.1%**	5.0%	**59.5%**	50.7%	**13.4%**	11.5%
Alemtuzumab monotherapy	4	59,086 (2,3722)	14.1 (3)	4205	**39.9%**	2.5%	**36.5%**	23.3%	**23.6%**	22.0%
Induction therapy	7	22,428 (16,466)	7.4 (13)	3013	**18.4%**	4.4%	**50.6%**	37.8%	**31.0%**	19.6%
Conditioning therapy + AlloSCT	6	109,090 (33,789)	13.8 (16)	7932	**21.2%**	3.2%	**59.8%***	3.3%	**18.9%**	13.1%
Transformation therapy	6	25,218 (26,183)	13.4 (28)	1877	**19.4%**	5.1%	**45.1%**	26.5%	**35.5%**	33.0%
FCA (FC + Alemtuzumab)	1#	21,810 (n.a.)	1.0 (n.a.)	22132	**15.0%**	0.0%	**13.6%**	13.6%	**71.5%**	34.3%
Other chemotherapy	35	11,609 (10,217)	14.3 (10)	809	**42.4%**	9.7%	**27.9%**	6.1%	**29.7%**	23.7%

AlloSCT: allogeneic stem cell transplantation; i.v.: intravenous; O: oral. # This concerns one patient who died after one month; * This concerns the costs of conditioning chemotherapy; ** Hospital admission for other CLL-related reasons than administration of chemo(immuno-)therapy.

6.4 DISCUSSION

We presented a detailed cost analysis for CLL outlining the costs of CLL in daily practice as realistic as possible by choosing for an observational design. Our patient characteristics seem to be reasonably representative for the entire Dutch CLL population since the percentage of men and the average age at diagnosis agree reasonably well with those of the national registration of CLL and indolent lymphomas (62% vs. 56% males and 63 vs. 66 years of age).[29] The slightly lower mean age at diagnosis may be caused by the tendency of haematologists not to bother older patients with the study. The distribution of the disease stages, however, also corresponds with the published distribution in the Netherlands: Binet stage A: 74% vs. 60%, Binet stage B: 15% vs. 30% and Binet stage C: 11% vs. 10%.[21]

Our AlloSCT costs, were quite comparable with those from a recent study in multiple myeloma, leukaemia and lymphoma patients. After correction for differences in cost calculation methodology (exclusion of the laboratory costs and costs during the first year of follow-up), the costs were €55,966 vs. €53,420 for an AlloSCT of a related donor and €111,913 vs. €94,450 for an unrelated donor AlloSCT (price year 2012).[156]

Costs of CLL vary greatly over the course of the disease and per treatment type. For most treatment choices, costs were mainly driven by inpatient hospital days. This finding is consistent with the conclusions of previous publications of costs of CLL by Lafeuille[146] and Blankart[147] who conclude that -in contrary to the study of Stephens et al.[43]- the main cost drivers were not the costs of chemotherapy, bone marrow or stem cell transplantation but the usage of physicians[146] and inpatient care.[146,147]

In treatment lines with newer combination regimens, including immunotherapy (i.e. FCR, rituximab monotherapy or AlloSCT), however, chemo(immuno-)therapy proved to be the main cost driver. It may be expected that the cost of CLL will further increase in the future as recently diagnosed patients are treated more frequently with these expensive treatments, which will also increase the share of therapy costs on the total costs. Development of other new treatment modalities that improves the overall survival compared with a wait and see approach will even further increase the share of therapy costs.

Previous publications focus either on one treatment or diagnostic technology within the course of CLL, or use administrative data from health insurers to calculate the cost of illness of CLL. Compared to the latter studies, the monthly direct medical costs in our study are significantly lower.

The first possible explanation for this difference is the phenomenon of upcoding which may occur when using data from health insurers. Upcoding leads to higher health costs because of miscoded or misclassified patients.[148,149]

The second explanation for the changing costs of immuno- or chemotherapy is provided by Reis et al.[145] Their study included all costs during one year, but was prevalence-based instead of incidence-based. A prevalence based study does not necessarily reflect the mean costs per year over the complete course of the disease and may lead to an under or overestimation of costs.

A third explanation is the difference in prices between countries. This may apply to the study of Lafeuille[146] since the medical costs in the USA are known to be much higher than those in the Netherlands.[157]

But also within a given country, costs increase over time due to changes in management and the development and implementation of (more expensive) novel therapies. This can be well demonstrated by comparing the two German studies.[145,147] The treatment costs reported in 2013 by Blankart et al had doubled when compared to those reported in 2006 by Reis et al.[145] That is the reason why we reported the price of chemotherapeutics separately enabling readers to easily adjust the disease management strategy and unit prices.

The possibility in these observational data to adjust the cost calculation according to differences in disease management and unit costs makes a cost calculation based on patient record data valuable for modelling studies that are used for economic evaluations. However, using observational data has limitations as well. Observational studies optimally reflect the situation in clinical practice when patients are followed from diagnosis till their cure or death. During our study 39 patients died (24%). In the remaining patients the costs made due to CLL are not complete as their treatment continued. Because the costs per treatment line vary enormously, the estimation of costs for these survivors cannot be done easily, but require modelling. The results of our study may however be used as source for the model's input parameters due to the relatively long follow-up period and the report of the results per treatment line and type of treatment.

A second limitation is the underrepresentation of patients with a low disease activity who were referred back to their general practitioner. Due to our inclusion strategy, these patients were probably missed. This may have led to an overestimation of the costs of CLL per patient and of CLL overall. On the other hand, as already described, the costs of CLL are likely to increase in the future when new (more) expensive treatment options will be applied more frequently in clinical practice.

In conclusion, cost of illness of CLL varied greatly over the course of the disease and was driven mainly by hospital admissions and hospital visits when considering the complete course of the disease. During treatment lines of FCR, rituximab and AlloSCT, costs of chemo(immuno-)therapy were the main cost driver. In this era of high health care costs, it is important to know how the costs of CLL are structured. That information is

valuable especially when the economic impact of changes in the current (international) guidelines – based on the quick developments in the management of CLL – is high.

APPENDIX

Appendix 6.1. Costs of Allogeneic Stem Cell Transplantation (excluding laboratory costs)

	SCT of related donor	SCT of unrelated donor
HLA typing patient	1,385	1,385
HLA typing donor	3,971*	58,276**
Stem cell harvesting	1,637	n.a.
Stem cell selection	6,301	6,301
Donor Lymphocyte Infusion	1,388	4,667
Personnel cost	16,025	16,025
Conditioning therapy	3,555***	3,555***
Prophylactic medication	1,478***	1,478***
Blood transfusions	985***	985***
Diagnostic procedures	1,869***	1,869***
Inpatient stay	17,316***	17,316***
Other contacts during stem cell trans-plantation (day ward, outpatient visits)	57***	57***
Total costs	**55,966**	**111,913**

* On average HLA-typings of four relatives were performed in order to choose one donor

** Including stem cell harvesting, transport and medication of Europdonor

*** Mean costs of all allogeneic stem cell transplantations (5 related, 1 unrelated) based on the data collected during our study

HLA: human leukocyte antigen; SCT: stem cell transplantation.

Chapter 7

Quality of life of patients with chronic lymphocytic leukaemia in The Netherlands: results of a longitudinal multicentre study

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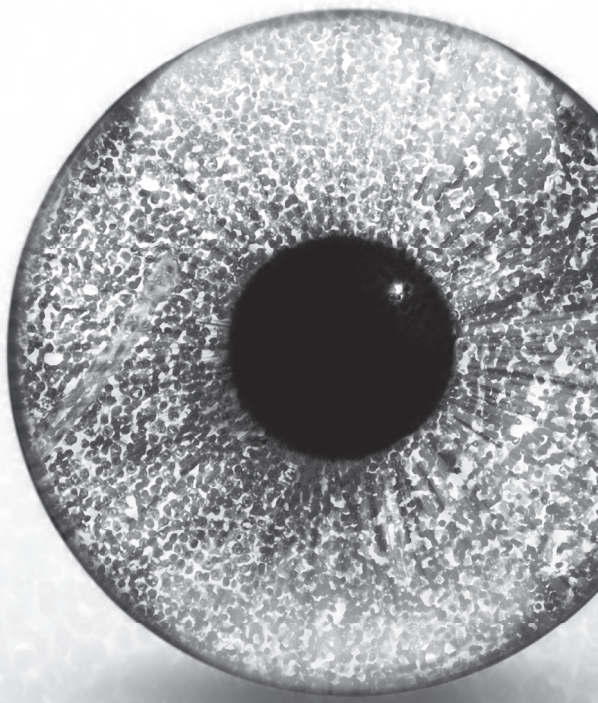


SUMMARY

Purpose. To describe the health related quality of life (HRQoL) of an unselected population of patients with chronic lymphocytic leukaemia (CLL) including untreated patients.

Methods. HRQoL was measured by the EORTC QLQ-C30 including the CLL16 module, EQ-5D, and VAS in an observational study over multiple years. All HRQoL measurements per patient were connected and analysed using area under the curve analysis over the entire study duration. The total patient group was compared with the general population, and three groups of CLL patients were described separately, i.e. patients without any active treatment ("watch and wait"), chlorambucil treatment only, and patients with other treatment(s).

Results. HRQoL in the total group of CLL patients was compromised when compared with age- and gender-matched norm scores of the general population. CLL patients scored statistically worse on the VAS and utility score of the EQ-$5D_5$, all functioning scales of the EORTC-QLQ-C30, and the symptoms of fatigue, dyspnoea, sleeping disturbance, appetite loss, and financial difficulties.
In untreated patients, the HRQoL was slightly reduced. In all treatment stages, HRQoL was compromised considerably. Patients treated with chlorambucil only, scored worse on the EORTC-QLQ-C30 than patients who were treated with other treatments with regard to emotional functioning, cognitive functioning, bruises, uncomfortable stomach, and apathy.

Conclusions. CLL patients differ most from the general population on role functioning, fatigue, concerns about future health, and having not enough energy. Once treatment is indicated, HRQoL becomes considerably compromised. This applies to all treatments, including chlorambucil, which is considered to be a mild treatment.

7.1 INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia occurring in the Western world, affecting around 3 to 6 people per 100,000 persons.[143,144,158] Early symptoms of CLL are minimal and diagnosis often follows the incidental finding of a high lymphocyte blood count or lymph node swelling. Unlike most types of cancer, the majority of CLL patients will not be treated immediately after diagnosis but will be monitored through a 'watch and wait' approach.[159] Only upon disease progression and/or the development of CLL-related symptoms such as fatigue, weight loss, malaise, bleeding, and recurrent or persistent infections,[124,125] treatment is indicated.

Disease-related symptoms, toxic effects of therapy, and the awareness of living with an incurable disease[31] can have a profound impact on health related quality of life (HRQoL). Despite these effects, little is known about the HRQoL of patients living with CLL.[31,35,160] Currently, nearly all available information is obtained during clinical trials which also studied the influence of treatment with chemotherapy on HRQoL.[132,161-163] However, the generalisability of these studies is limited because these studies only enrol patients in need of treatment. In addition, they use strict inclusion and strict exclusion criteria, e.g. often excluding patients over the age of 65.

The measurement of HRQoL in clinical trials which enrol mostly younger patients in need of treatment is valuable for comparison of treatments with regard to their effect on HRQoL and the course of these effects over time, i.e. from the start of treatment till the start of next treatment. From the available studies, we know that the HRQoL of patients during and after treatment with fludarabine plus cyclophosphamide (FC) does not differ from that of patients treated with fludarabine monotherapy on global health score, physical and emotional functioning and fatigue. Patients treated with FC score worse on nausea and vomiting during treatment, and better (but not significantly better) after treatment than patients treated with fludarabine monotherapy.[132,161] However, these clinical trials do not allow a conclusion with regard to the HRQoL in patients who are not in need of treatment yet.

That information would be valuable since one-third of all CLL patients,[164] will not progress to treatment even over decades. Current study provides an indication of the type of symptoms treatment naïve patients experience and the limitations in daily functioning that occur. The comparison of the HRQoL in untreated patients versus those who just started treatment might give some indication of the impact of starting first line treatment on HRQoL. When the HRQoL of untreated patients is already severely compromised, the impact of expected side effects during treatment on HRQoL is not likely to have a decisive role in the decision whether to start treatment. In the opposite situation, the expected impact of starting treatment on HRQoL should be seriously considered in the decision whether to start treatment or not.

None of the available studies that address HRQoL in the whole CLL population,[36-38] measured the HRQoL over a period longer than 1 year. In order to fill this gap, we conducted a longitudinal, multicentre observational study including a HRQoL study.

7.2 PATIENTS AND METHODS

Inclusion and exclusion criteria

Nineteen hospitals in the Netherlands invited patients with CLL for participation in an observational study addressing the management of CLL, costs, and HRQoL.[165] Patients aged 18 years or older diagnosed with CLL could enter the study if they did not suffer from another serious malignant disease or previous malignancy, had a complete record, and gave informed consent. Patients who developed a non-CLL related malignancy were censored at the time of its diagnosis.

Quality of life

Patients who participated in the HRQoL study received a HRQoL questionnaire at the start, halfway through, and at the end of therapy from their treating specialists. Additional questionnaires were sent every 6 months in the periods without treatment to get information about the HRQoL in the period before treatment and between treatments. Since chlorambucil was frequently administered continuously for a long and not predetermined period of time, we choose to send questionnaires during this treatment every 6 months as well, to get more information about the HRQoL during the whole period of treatment.

The instruments employed in the HRQoL assessment were the EORTC QLQ-C30 with the accompanying CLL specific module[166] and a modified version of the EQ-5D in which 5 response levels replaced the original 3 levels[167] as suggested and investigated by Kind and Macran.[168]

EORTC QLQ-C30

The EORTC QLQ-C30, has been developed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Study Group to assess the HRQoL of patients with cancer.[166] The core instrument includes 30 questions covering many HRQoL issues related to cancer patients in general and can be supplemented by a diagnosis-specific module.[169]

The questionnaire EORTC QLQ-C30 incorporates five functional scales, three symptom scales, a global quality of life scale (2 items), and six single items. The functional scales are physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. The symptom scales are fatigue, nausea and vomiting, and pain.

Dyspnoea (shortness of breath), sleeping (disturbance), appetite loss, constipation, diarrhoea, and financial difficulties are the six single items. According to the EORTC scoring manual, scores were linearly transformed to a 0–100 scale.[170] A higher score on the functional scales and global quality of life scales meant better functioning and quality of life, whereas a higher score on the symptom scales meant more complaints. Differences in scale scores of 10 points or more were considered clinically meaningful.[171]

In this study the core questionnaire EORTC QLQ-C30 was supplemented by the CLL specific module.[171] The module is used to describe aspects of CLL that are not included in the core questionnaire and provides information about several domains. There are three multi-item scales, i.e. fatigue, treatment side effects and disease symptoms, infections, and two single item scales on social activities and future health worries. However the module is not yet officially published, and the score on the scales cannot be calculated,[172] the average score - ranging from 1 (not at all) to 4 (very much) - on the items can be described.

Modified version of the EQ-5D

The EQ-5D measures the general HRQoL and is therefore not influenced by CLL only. At the time of start of the study, a 5-level EQ-5D had been developed since the original 3 level EQ-5D was not sensitive enough for smaller changes in HRQoL. Since patients with CLL in general experience a high level of HRQoL,[36] at least until they reach the advanced stages, it was hypothesised that this expanded 5-level classification might provide a more sensitive measure of change in health status than the original 3 level EQ-5D (EQ-$5D_3$).

The modified version of the EQ-5D (EQ-$5D_5$)[168] comprised the same two items as the EQ-$5D_3$: a visual analogue scale (VAS) providing a single overall summary score of HRQoL and descriptive classification with five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). However, the descriptive classification of the EQ-$5D_5$ contained five levels, rather than the standard 3 levels. The two additional levels were unlabelled.[168] It can be seen as the predecessor of the labeled 5-level version of the EQ-5D,[173] which did not exist at the start of our study yet.

The responses on the descriptive classification can be translated to a utility score, which is a value that reflect an individual's preference for a certain health outcome with zero reflecting states of health equivalent to death and one reflecting perfect health. Utility values for the EQ-$5D_5$ states have never been determined, as this instrument has been replaced by a 5-level labelled version. We calculated utility values following the suggestion of the creator of the EQ-$5D_5$.[168] The known utility values for the levels 1, 2 and 3 of the EQ-$5D_3$ were used for the levels 1, 3 and 5 of the EQ-$5D_5$ and the additional 2 levels were generated assuming the midpoint value between the standard 2 tariff values using an adaptation of the Dutch 3 level tariff.[174]

Statistical analysis

The HRQoL of a CLL patient over time was calculated by connecting all measurements per patient using area under the curve analysis over the entire study duration. To enable the comparison of patients, we presented area under the curve values corrected for the follow-up duration per patient. For each patient, an individual norm score was derived from age- and gender-matched scores of the general population on the EQ-5D[175] and EORTC QLQ-C30.[176] Both studies used a panel consisting of more than 2000 Dutch households, representative of the Dutch-speaking non-institutionalised population in the Netherlands.[175,176]

Patient scores were compared with norm scores using t-test or nonparametric test for related samples (significant when $p < 0.05$). Patient scores of three patient groups (patients without any active treatment, patients treated with chlorambucil only, and other patients) were compared using the Kruskal Wallis test.

Subsequently, we chose to focus on the HRQoL during two treatment phases. First, we focused on the questionnaires completed during the watch and wait phase since data on this subject is scarce, and second on the questionnaires filled in during chlorambucil treatment because this was the most frequently administered treatment in our study. The results of both phases were described in a separate section and compared using Kruskal Wallis test or t-test depending on the variable distribution.

7.3 RESULTS

Patient characteristics

Informed consent for participation was given by 173 CLL patients. Of these patients, 13 patients (6%) were excluded from the analysis for the following reasons: eight patients did not meet the inclusion criteria after all; one patient chart was missing; and one patient withdrew himself from the study. Additionally, one hospital dropped out of the study, leaving three patients with incomplete follow-up data.

Of the 160 evaluable patients, 144 patients (90%) participated in the HRQoL study. For 25 patients we did not have information during the complete follow-up duration of the study (see Figure 7.1). Table 7.1 presents patient characteristics of these 144 patients as a whole and per patient group: patients who did not receive any active treatment during the study period, patients who only received chlorambucil and patients with other or more treatments. It also presents the characteristics of the patients who did not participate in the HRQol part of the study.

The mean age at diagnosis of all patients was 62.6 years (SD=10.5) of whom the majority were male (63%). On average, male patients were younger at diagnosis (60.8

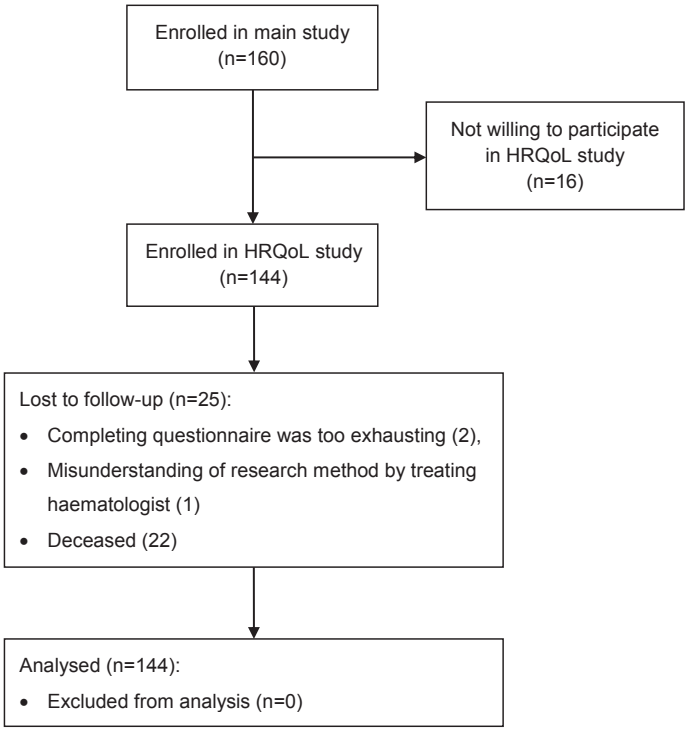


Figure 7.1 Patient flow chart.

years, SD=10.1) than female patients (65.5 year, SD=10.5). Age at diagnosis did not differ significantly between the patient groups.

From diagnosis until the end of the HRQoL study, 85 patients received active treatment (59%). Seventy-three patients started treatment before the start of the HRQoL study and 12 patients started their first line treatment during the study period. Eighty-five percent of all patients who received active treatment, were treated initially with chlorambucil with or without prednisone. Other initial treatments were: chlorambucil-vincristine-prednisone (CVP) (7%), fludarabine (2%), fludarabine-cyclophosphamide (FC, 2%), rituximab plus CVP (R-CVP, 1%), cyclophosphamide (1%) and cyclophosphamide-doxorubicin-teniposide-prednisone with bleomycin-vincristine + radiotherapy (1%). Fifty-three patients also received subsequent line(s) of treatment. Second line treatment was fludarabine monotherapy in most patients (23 patients, 43%). Other second line treatments were: CVP (17%), FC (8%), FCR (8%), R-CVP (8%), chlorambucil plus prednisone (6%), rituximab (4%), R-CHOP (4%), CVPP (2%) and fludarabine-rituximab (FR, 2%).

Patients were diagnosed for on average 3.9 years at the time of their first questionnaire. Their last questionnaire was on average completed 2.6 years later, at 6.5 years since diagnosis. The mean number of questionnaires was 5.7 per patient and 127 patients

Table 7.1. Patient characteristics

	All participants (n=144)	Patients without any active treatment (n=59)	Patients treated with CLB only (n=28)	Other patients (n=57)	Non-participants in HRQoL study (n=16)
Age at diagnosis:	62.6 (10.5)	64.1 (9.3)	63.6 (12.1)	60.5 (10.6)	71.0 (8.6)
Mean (SD)	63	64	66	61	69
Median	30-86	34-82	30-86	38-85	56-84
Range					
Gender (% male)	62.5	59.3	50.0	71.9	62.5
Patients (%) with first or second degree relatives with leukaemia or lymphoma	9.0	6.8	10.7	10.5	0.0
Binet Stage (%):					
A	70.8	94.9	67.9	47.4	81.2
A progressive	2.1	0	0	5.3	6.3
B	16.0	1.7	21.4	28.1	12.5
C	11.1	3.4	10.7	19.3	
B-symptoms (yes %)	12.5	5.1	10.7	21.1	13.3
Involvement of spleen (yes %)	27.8	10.2	42.9	38.6	26.7
Co-morbidities (yes %)	27.8	20.3	39.3	29.8	43.7
WHO-performance score (%):					
0	78.5	84.7	71.4	75.4	75.0
1	19.4	15.3	25.0	21.1	18.8
2	0	0	0	0	6.3
n.a.	2.1	0	3.6	3.5	0

N.a.: not available; CLB: chlorambucil; HRQoL: health related quality of life; WHO: World Health Organization.

(88.2%) completed 3 or more questionnaires. For 25 patients we did not have information during the complete follow-up duration of the study (see Figure 7.1).

Quality of life during total study

Table 7.2 summarizes the results on all instruments used for the total CLL population and for the three patient groups that were described before.

Taken into account the total group of CLL patients, the score on both the EQ-5D and the VAS was lower than the norm score corrected for age and gender.[175,176] This also applies for the subgroups of patients treated with chlorambucil only or with more /other

Table 7.2. Average patient and norm scores on EQ-5D$_5$, EORTC QLQ-C30 and EORTC QLQ-CLL16 (SD) of the total CLL population, and the three patient groups

	Total group of CLL patients		Patient groups		
	Total group (n=144)	Age-and gender matched norm score	Patients without any active treatment (n=59)	Patients with (watch & wait +) chlorambucil only (n=28)	Other patients (n=57)
EQ-5D$_5$					
Utility	0.85 (0.1)†	0.89 (0.0)	0.89 (0.1)	0.82 (0.2)*	0.85 (0.1)†
VAS	73.5 (12.9)‡	83.1 (3.7)	77.6 (12.8)†	71.3 (12.0)‡	70.3 (12.4)‡
EORTC-QLQ-C30 – functioning scales					
Physical functioning	79.15 (18.1)‡	87.18 (5.9)	83.95 (16.2)	75.89 (22.3)*	75.79 (17.8)‡
Role functioning	75.44 (22.9)‡	86.57 (4.2)	81.99 (20.9)	71.30 (23.9)†	70.68 (24.8)‡
Emotional functioning	85.31 (15.3)‡	89.89 (2.0)	87.29 (13.4)	77.52 (18.3)†	87.09 (16.3)
Cognitive functioning	84.98 (16.1)‡	90.81 (2.9)	85.59 (16.3)*	76.50 (18.2)‡	88.53 (16.6)
Social functioning	85.61 (18.3)‡	93.44 (2.4)	90.60 (14.5)	82.76 (22.0)*	81.85 (21.5)‡
Global health	75.36 (13.8)	77.06 (2.7)	78.68 (13.1)	73.86 (14.7)	72.66 (14.8)*
EORTC-QLQ-C30 – symptoms					
Fatigue	31. 17 (21.0)‡	17.51 (3.8)	24.96 (21.4)†	36.48 (21.1)‡	34.97 (20.6)‡
Nausea vomiting	3.77 (7.7)	2.50 (1.8)	2.31 (5.0)	5.96 (9.9)	4.20 (9.3)
Pain	15.06 (17.9)	17.26 (5.6)	14.48 (18.2)	19.58 (23.0)	13.45 (15.6)
Dyspnoea	18.15 (21.7)‡	9.30 (3.1)	12.12 (17.9)	19.02 (21.4)*	23.96 (23.0)‡
Sleeping	22.07 (23.6)‡	15.18 (4.9)	20.86 (25.0)	28.85 (20.9)†	20.00 (25.4)
Appetite loss	8.36 (15.8)‡	3.48 (1.7)	3.94 (9.6)	16.92 (24.9)*	8.73 (13.9)†
Constipation	4.77 (10.5)	5.98 (2.9)	4.41 (9.6)	4.87 (9.9)	5.09 (12.3)
Diarrhoea	4.75 (9.8)	3.96 (0.9)	4.52 (11.2)	5.76 (11.3)	4.50 (7.1)
Financial difficulties	5.78 (13.8)*	3.33 (1.35)	4.77 (11.5)	5.38 (16.5)	7.03 (20.1)
EORTC-QLQ-CLL16					
Weight loss	1.15 (0.5)	n.a.	1.06 (0.4)	1.34 (0.6)	1.15 (0.6)
Dry mouth	1.38 (0.8)	n.a.	1.35 (0.7)	1.61 (0.9)	1.31 (0.7)
Bruises	1.06 (0.5)	n.a.	1.05 (0.4)	1.24 (0.7)	0.98 (0.4)
Uncomfortable stomach	1.27 (0.7)	n.a.	1.24 (0.6)	1.49 (0.7)	1.20 (0.6)
Changes in temperature	1.14 (0.6)	n.a.	1.03 (0.4)	1.30 (0.7)	1.17 (0.7)
Night sweats	1.55 (0.9)	n.a.	1.42 (0.8)	1.76 (0.9)	1.58 (0.9)
Feeling sick or unwell	0.78 (0.5)	n.a.	0.68 (0.4)	0.99 (0.7)	0.79 (0.5)
Feeling apathetic	1.41 (0.7)	n.a.	1.30 (0.7)	1.71 (0.7)	1.37 (0.7)
Not enough energy	1.49 (0.8)	n.a.	1.36 (0.7)	1.79 (0.8)	1.47 (0.8)
Planning activities	1.45 (0.8)	n.a.	1.29 (0.7)	1.73 (0.9)	1.46 (0.8)
Future health concern	1.62 (0.8)	n.a.	1.50 (0.8)	1.93 (1.0)	1.59 (0.9)
Respiratory infection	1.42 (0.8)	n.a.	1.26 (0.5)	1.42 (0.7)	1.58 (0.9)
Other infection	1.26 (0.6)	n.a.	1.19 (0.6)	1.25 (0.6)	1.33 (0.8)
Repeated use antibiotics	1.26 (0.7)	n.a.	1.10 (0.5)	1.17 (0.5)	1.48 (0.9)
Worries for infection risk	1.32 (0.7)	n.a.	1.10 (0.5)	1.47 (0.8)	1.48 (0.8)

Patient scores were based on an Area Under the Curve analysis. CLL: chronic lymphocytic leukaemia; n.a.: not available.

*P < 0.05, † p < 0.01, ‡ p < 0.001 for comparisons with age- and gender-matched norm scores

treatments than chlorambucil. Patients who received no active treatment at all, scored lower on the VAS than the general population, but not on the utility score of the EQ-$5D_5$.

The patients' mean score and the mean norm scores per EORTC QLQ-C30 item/scale are also shown in Table 7.2. It identifies the significant differences of $p<0.05$ from the norm score. Statistically significant differences are however, not always clinically meaningful. Meaningful differences (of more than 10 points[171]) between the norm score and patients' score were observed for role functioning and fatigue in the total group of CLL patients. This was also applicable to the subgroups of patients treated with chlorambucil only or with more / other treatments than chlorambucil. Other differences were observed for emotional and cognitive functioning, appetite loss, and sleeping in patients who only received chlorambucil and for physical and social functioning, and dyspnoea in patients who received more or other treatments than chlorambucil. None of the significant differences for patients who did not receive any active treatment were clinically meaningful.

When looking at the total population of CLL patients that reported "a little", "quite a bit", or "very much" problems on the EORTC QLQ-CLL16 questionnaire, most patients reported problems on future health concern (62% of the questionnaires), feeling to have not enough energy (50%), and having night sweats (48%). For all patient groups, most problems were reported on future health concern and night sweats. The subgroup with patients who were treated with more or different therapies than chlorambucil also reported many problems with respiratory infections and worries about getting infections. The subgroup with patients who only received chlorambucil had the highest (worst) total mean score over all items.

Figure 7.2 shows that on almost all single-items and scales, the group without any active treatment (watch and wait approach only), scored best of all patient groups. Patients who were treated with chlorambucil only scored worse on HRQoL than patients who were treated with more or different treatments with regard to emotional functioning, cognitive functioning, bruises, uncomfortable stomach, and apathy (data not shown).

Being currently treated or not did influence the HRQoL. The 41 patients who filled in questionnaires during treatment and before/after treatment had a significantly lower utility score during treatment (data not shown). This pattern was also observed in the total study sample as presented elsewhere when the data was analysed per treatment line.[136]

In the total population of CLL patients, scores on the VAS and EQ-$5D_5$ differed significantly between the categories of WHO performance status and the presence/absence of co-morbidities (See Appendix 7.1).

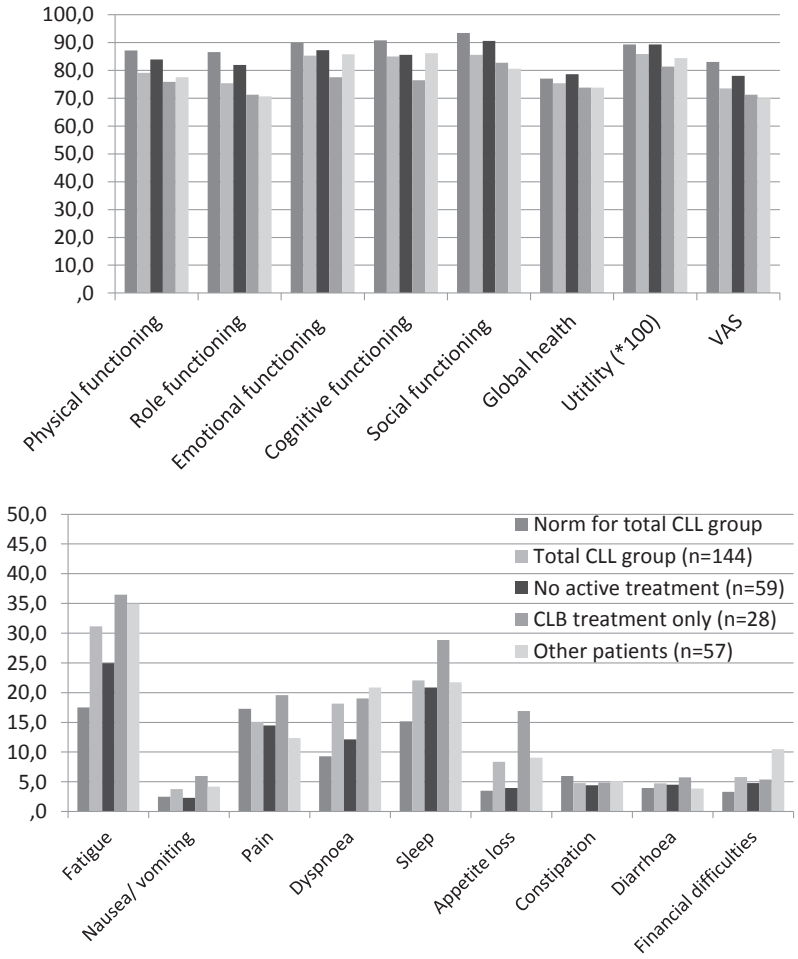


Figure 7.2 Norm scores and patient scores on the EORTC QLQ-C30 and EQ-$5D_5$.
Patient scores *on the EORTC QLQ-C30 and EQ-$5D_5$* are reported for the general population (norm score),[175,176] the total CLL group and for the three patient groups separately. The norm scores present the mean norm score of all CLL patients in our study. Patient scores were based on an Area Under the Curve analysis.
Upper figure: results of the functioning scales of the EORTC QLQ-C30 and the EQ-5D. The higher the score, the higher the quality of life (range 0-100).
Lower figure: results of the symptom scales of the EORTC QLQ-C30. The higher the score, the lower the quality of life (range 0-100).
CLB: chlorambucil

Quality of life during watch and wait phase and during treatment with chlorambucil vs. general population

HRQoL results during the watch and wait phase are based on all questionnaires completed before the start of active treatment. This covers not only patients who did not receive any active treatment at all, but also the patients who received a treatment after being in the watch and wait phase. During the watch and wait phase, HRQoL can be compromised due to the illness and its related insecurity as well as by other causes like comorbidities or life events.

The HRQoL during treatment with chlorambucil covers only those questionnaires which were filled in during active treatment with chlorambucil.

Both patients in the watch and wait phase and those during treatment with chlorambucil scored lower on the VAS than the general population corrected for age and gender distribution (Table 7.3). The difference in utility was only significant for patients treated with chlorambucil (0.81 vs. 0.90).

Supplemental Table 7.1 shows that scores on the EQ-$5D_5$ were significantly different between the categories of gender, age at diagnosis, WHO performance status, and the presence/absence of co-morbidities for patients during the watch and wait phase. During treatment with chlorambucil, none of the collected patient characteristics influenced the score on the EQ-5D and VAS significantly (e.g. males vs. females).

When comparing the individual patient scores on the EORTC QLQ-C30 with the individual age and gender adjusted norms scores, the patients' scores were meaningfully different from the norm score on emotional and role functioning and on sleeping and dyspnoea during treatment with chlorambucil. Differences were also found for physical, cognitive, and social functioning and sleeping scales but although statistically significant, they were not clinically meaningful. In the watch and wait phase, differences from the norm score for cognitive, role and physical functioning, fatigue and sleeping were statistically significant, but not clinically meaningful.

With regard to the items of EORTC QLQ-CLL16 module, patients in the watch and wait phase suffered most from worries about their future health (55% of the questionnaires), night sweats (44%), and having not enough energy (40%). Patients during treatment with chlorambucil suffered most from worries about their future health (78% of the questionnaires), having not enough energy (61%) and infection risk (56%).

With regard to the items of EORTC QLQ-CLL16 module, patients in the watch and wait phase suffered most from worries about their future health (55% of the questionnaires), night sweats (44%), and having not enough energy (40%). Patients during treatment with chlorambucil suffered most from worries about their future health (78% of the questionnaires), having not enough energy (61%) and infection risk (56%).

Table 7.3. Average patient and norm scores on EQ-5D$_5$ and EORTC QLQ-C30 (SD) during watch and wait phase and during treatment with chlorambucil

	During watch & wait phase (n=71)	Norm score watch & wait phase	p-value	During treatment with CLB (n=42)	Norm score during treatment with CLB	p-value ***
EQ-5D$_5$						
Utility	0.88 (0.1)	0.89 (0.0)	0. 052	0.81 (0.2)**	0.90 (0.0)	*0.003*
VAS	77.4 (12.4)	82.8 (3.9)	*0.000*	69.1 (14.5)**	82.7 (3.7)	*0.000*
EORTC-QLQ-C30 – functioning scales						
Physical functioning	83.2 (15.9)	86.8 (6.1)	*0.030*	79.0 (18.2)	86.2 (5.3)	*0.011*
Role functioning	79.8 (21.2)	86.3 (4.4)	*0.009*	73.3 (22.5)	85.5 (3.5)	*0.001*
Emotional functioning	86.6 (13.7)	89.7 (2.1)	0.055	78.0 (18.0)**	89.7 (2.1)	*0.000*
Cognitive functioning	85.2 (16.9)	90.9 (2.9)	*0.038*	82.6 (19.3)	90.2 (3.0)	*0.011*
Social functioning	89.9 (15.0)	93.3 (2.5)	0.051	83.5 (20.0)*	92.7 (2.2)	*0.004*
Global health	78.0 (13.6)	76.9 (2.8)	0.474	72.9 (15.4)	76.4 (2.1)	0.147
EORTC-QLQ-C30 – symptoms						
Fatigue	25.5 (20.5)	17.7 (4.0)	*0.002*	22.99 (17.8)*	18.6 (3.1)	*0.000*
Nausea vomiting	2.9 (5.9)	2.7 (1.9)	0.766	4.49 (15.6)	2.6 (1.8)	0.435
Pain	15.5 (17.6)	17.8 (5.9)	0.254	15.38 (18.3)	18.4 (4.9)	0.279
Dyspnoea	12.1 (18.6)	9.4 (3.2)	0.225	24.28 (26.1)**	9.6 (3.0)	*0.001*
Sleeping	21.6 (24.6)	15.6 (5.1)	*0.032*	26.75 (26.3)	16.1 (4.7)	*0.012*
Appetite loss	5.5 (12.4)	3.6 (1.7)	0.191	9.98 (21.9)	3.7 (1.6)	0.067
Constipation	4.3 (9.4)	6.2 (3.0)	0.085	3.48 (8.6)	6.5 (2.7)	*0.025*
Diarrhoea	4.4 (10.3)	3.9 (1.0)	0.720	3.62 (8.6)	4.2 (0.8)	0.686
Financial difficulties	5.6 (14.0)	3.4 (1.4)	0.195	5.00 (16.7)	3.5 (1.5)	0.561
EORTC-QLQ-CLL16						
Weight loss	1.2 (0.3)	n.a.		1.48 (0.3)*	n.a.	
Dry mouth	1.5 (0.7)	n.a.		1.70 (0.7)	n.a.	
Bruises	1.1 (0.3)	n.a.		1.20 (0.3)	n.a.	
Uncomfortable stomach	1.4 (0.5)	n.a.		1.53 (0.6)	n.a.	
Changes in temperature	1.1 (0.3)	n.a.		1.43 (0.3)**	n.a.	
Night sweats	1.7 (0.7)	n.a.		1.95 (0.7)	n.a.	
Feeling sick or unwell	1.3 (0.4)	n.a.		1.45 (0.4)	n.a.	
Feeling apathetic	1.5 (0.5)	n.a.		1.79 (0.6)**	n.a.	
Not enough energy	1.5 (0.6)	n.a.		1.88 (0.6)*	n.a.	
Planning activities	1.4 (0.6)	n.a.		1.74 (0.6)	n.a.	
Future health concern	1.7 (0.7)	n.a.		2.10 (0.7)	n.a.	
Respiratory infection	1.4 (0.5)	n.a.		1.78 (0.5)*	n.a.	
Other infection	1.3 (0.5)	n.a.		1.38 (0.5)	n.a.	
Repeated use antibiotics	1.3 (0.5)	n.a.		1.40 (0.5)	n.a.	
Worries for infection risk	1.3 (0.4)	n.a.		1.78 (0.4)**	n.a.	

Patient scores were based on an Area Under the Curve analysis. N.a.: not available.

* a significant difference between the watch and wait phase and treatment with chlorambucil (p-value <0.05)

** a significant difference between the watch and wait phase and treatment with chlorambucil (p-value < 0.01)

*** A value in italics indicates a significant difference between the patient score and norm score (p value < 0.05)

Quality of life during watch and wait phase versus during treatment with chlorambucil

Patient characteristics of the patients who completed questionnaires during the watch and wait phase were comparable with those of the patients who completed questionnaires during treatment with chlorambucil. Age at diagnosis was 68.7 vs. 67.2 years (p=0.426), WHO performance status was 0 in 83.1% vs. 82.9% of the patients (p=0.981) and co-morbidity was present in 26.8% vs. 37.2% of the patients (p=0.195) respectively.

The HRQoL was significantly worse during treatment with chlorambucil than during the watch and wait phase for the following outcomes: utility, VAS, emotional functioning, social functioning, fatigue, dyspnoea, losing weight, changes in temperature, feeling apathetic, lack of energy, respiratory infections, and risk of infections.

Norm scores were available for the EQ-5D[175,176] and the EORTC QLQ-C30.[176] The mean difference between the patients' score and the norm score for that patient was significantly higher during treatment with chlorambucil than during the watch and wait phase for the following scales and items: emotional functioning (p=0.004), fatigue (p=0.021), dyspnoea (p=0.003), VAS (p=0.002) and utility (p=0.004).

7.4 DISCUSSION

This longitudinal observational study showed that the HRQoL in CLL patients is compromised when compared with age- and gender-matched norm scores of the general population. Patients with CLL differed from the general population on the VAS and utility score of the EQ-$5D_5$, all functioning scales of the EORTC QLQ-C30, and the symptoms of fatigue, dyspnoea, sleeping, appetite loss, and financial difficulties.

The HRQoL in untreated CLL patients is already compromised with regard to physical, role and cognitive functioning, VAS score, fatigue and sleeping. During treatment with the most frequently administered therapy in our study (chlorambucil), patients also had dyspnoea and constipation and were compromised in their emotional and social functioning. Although, we are aware that treatment is initiated only when there is a treatment indication and clinical benefits are to be expected, we conclude that starting treatment will probably further reduce the already slightly compromised HRQoL during the watch and wait phase - at least temporarily. That applies to the relatively mild agent chlorambucil, and that decrease might be even bigger for the more effective, but also more intensive therapies that are (coming) available. The expected impact of starting treatment on HRQoL should therefore be considered in the decision whether to start treatment.

It is remarkable that the HRQoL is already compromised in untreated patients since in general treatment is started when the patients experience B-symptoms or disease

progression. None of the three previous studies that reported the HRQoL in CLL patients in a non-trial setting, reported the scale scores of HRQoL in untreated patients. We are therefore not able to compare our results in untreated patients with other studies.

When looking at the total group of CLL patients, our results compare very well with those of Holzner et al.,[37] who found a lower HRQoL in CLL patients compared with the age- and gender-matched healthy population on 8 of the 15 items/scales of the EORTC QLQ-C30 at baseline. We came to the same conclusion, but we found more statistically significant differences (10 of 15 items/scales) compared with the general population. However, our patient scores on the EORTC QLQ-C30 were better than those reported by Holzner et al.[37] This is probably due to the lower age of the patients in our study, and the earlier disease stage at diagnosis.

A recent article by Pashos et al.[38] reported the baseline results of the HRQoL study using the Brief Fatigue Inventory, EQ-5D, and Functional Assessment of Cancer Therapy-Leukemia. Our results on the EQ-$5D_5$ are comparable to those reported by Pashos et al.[38]

In the study by Shanafelt et al.,[36] CLL patients scored worse than the general population on the emotional scale of the FACT-G questionnaire only. Just like the results of the study by Shanafelt et al., we found a significant difference from the norm score on emotional functioning for the total group of CLL patients, but in contrary to their study, we found many other differences as well.

Fatigue is one of the most frequently reported symptoms among patients with CLL. Our study showed that even untreated patients report significantly more symptoms of fatigue than the general population, and during or after treatment the symptoms were worse. It is a common symptom even many years after diagnosis. More attention should be given to this symptom during and after treatment, but also during the watch and wait phase. Interventions may help to reduce fatigue, but since the precise underlying pathophysiology is largely unknown,[177] further studies are necessary.

Limitations of the study

Since new treatments tend to prolong the overall survival of CLL patients,[139] the quality of life during and after treatment becomes more important. Although our study provides insight into the problems that patients with CLL are likely to have, the relatively small number of patients did not allow for comparisons between therapies. This would be very informative for clinicians, but to enable these comparisons in a real world setting, many patients need to be enrolled, given the high number of available treatments. Due to a low incidence rate of CLL, this would require a long inclusion period, or an international approach. Changes in management of CLL over time makes it difficult to interpret results of a study with a long inclusion period and an international study also carries difficulties to the interpretation of the results. Fortunately, the HRQoL results of clinical trials can provide important information on this issue.

A second limitation of our study was that due to the observational character of the study, we were dependent on the health practitioners involved in the study for the timely administration of questionnaires, specifically the questionnaire at the start of a new treatment. Despite our efforts to remind them, they forgot to hand over the questionnaire to the patients before the start of the treatment in the majority of the patients who started a new treatment during our study period. We did not have sufficient information about the HRQoL at the start of treatment to compare the HRQoL before and after treatment.

Another limitation is the uncertainty around the utility scores of the EQ-$5D_5$ instrument. To decrease this uncertainty, we also calculated the mean utility over the study period using two other methods to generate utility values. The first additional method used a predictive model which was developed in multiple myeloma and validated in non-Hodgkin lymphoma patients. The predicted values appeared to follow a similar pattern to the observed EQ-5D values.[178] The second additional method used the "crosswalk" obtained from an international study of the EuroQol group that administered both the 3-level and 5-level versions of the EQ-5D (see their website: www.euroqol.org).

The mean utility score of the midpoint estimation and the two additional methods for the total CLL group – based on only those questionnaires without missing values necessary to derive all three estimations- give the following utility scores: 0.854, 0.847, and 0.844. Since these three methods give quite similar results, we can conclude that our calculation is quite reliable.

Since HRQoL is influenced by the WHO performance status and the presence of comorbidities, they are potential confounders in our study. We were not able to correct for these potential confounders due to the heterogeneity in treatment patterns resulting in too small patient groups to apply for example propensity score matching. These patient characteristics were, however, not statistically different for the patients with measurement during the watch and wait phase versus those with measurements during treatment with chlorambucil.

Generalisability

The patient characteristics in our study seem to be reasonably representative for the entire Dutch CLL population since the distribution of gender and the average age at diagnosis agree reasonably well with those of the national registration of CLL and indolent lymphomas (63% vs. 56% males and 63 vs. 66 years of age).[179] The slightly lower mean age at diagnosis may be caused by the tendency of haematologists not to bother older patients with the study, or the higher refusal rate to participate by the older patients. The distribution of the disease stages, however, also corresponds with the published distribution in The Netherlands: Binet stage A: 71% vs. 60%, Binet stage B: 16% vs. 30%, and Binet stage C: 11% vs. 10%.[21]

In contrast to most RCTs, we also included patients with severe co-morbidity. Co-morbidity (severe heart failure, severe pulmonary disease, severe neurologic disease, severe metabolic disease, inadequate liver function, inadequate renal function, or other co-morbidity) was present in 28% of the patients. RCTs which aim to study the efficacy of treatments and their influence on HRQoL, often exclude these patients. The outcome of treatments in daily practice could therefore differ from the results found in the RCT. We showed that HRQoL is indeed negatively influenced by having co-morbidities and the WHO stage at diagnosis. In our study, the patient group "chlorambucil only" had the highest percentage of patients with co-morbidity. This may explain the relatively worse HRQoL of the patients in this group compared with the patients receiving other treatments.

The percentage of patients with comorbidities was even higher in the group with non-participants. They were also significantly older at diagnosis than participants. This might be related to their choice not to participate in the quality of life study. The percentage of patients willing to participate in the HRQoL study was, however, very high (90%) so that we do not expect that inclusion of these patients would significantly affect the results.

Since the group of patients with co-morbidity is growing steadily due to an ageing population and an improved overall survival, future research should also focus on the effectiveness of treatments in these patients and the effect of treatments on their HRQoL.

Conclusion

We concluded that chronic lymphocytic leukaemia has a profound impact on HRQoL. The HRQoL in CLL patients is compromised when compared with age- and gender-matched norm scores of the general population. Patients with CLL differ most from the general population with regard to the level of role functioning, symptoms of fatigue, concerns about future health, and lacking energy. For patients in the watch and wait phase, the impact of their disease was limited, but larger than generally assumed. Especially with regard to symptoms of sleeping problems and fatigue more attention should be given to these patients. Once treatment was indicated, HRQoL became considerably compromised. This applied to all treatments, including chlorambucil, which is considered to be a mild treatment. The impact of starting a treatment on the HRQoL should therefore be weighted in the decision whether to start therapy, especially since more effective, but also more intensive therapies are coming available.

7.5 ACKNOWLEDGEMENTS

We would like to thank all investigators for including patients. We also thank the (research) nurses and research assistants who entered data for this study.

APPENDIX

Appendix 7.1. Utility and VAS scores per category of the included patient characteristics

	During Watch and wait phase (N=71)		During treatment with Chlorambucil (N=42)		Total group of patients (N=144)	
	Utility (SD)	VAS (SD)	Utility (SD)	VAS (SD)	Utility (SD)	VAS (SD)
Total score	0.88 (0.13)	77.37 (12.4)	0.81 (19.3)	69.1 (14.5)	0.85 (0.14)	73.5 (12.9)
Gender (p-value)	**p=0.025**	p=0.132	p=0.595	p=0.843	p=0.068	p=0.102
Male	0.91 (0.12)	79.26 (12.1)	0.79 (0.23)	69.5 (16.5)	0.88 (0.13)	75.1 (12.9)
Female	0.84 (0.14)	74.77 (12.4)	0.82 (0.13)	68.6 (12.3)	0.82 (0.14)	70.9 (12.7)
Ageclass (p-value)	**p=0.046**	p=0.290	p=0.242	p=0.836	p=0.721	p=0.888
<59	0.91	78.76 (12.6)	0.83 (0.15)	71.2 (10.0)	0.88 (0.10)	74.1 (12.2)
60-69	0.91 (0.10)	79.66 (11.1)	0.78 (0.10)	67.5 (12.1)	0.86 (0.14)	73.7 (13.5)
>69	0.81	74.22 (13.0)	0.79 (0.29)	67.6 (20.2)	0.83 (0.17)	72.7 (13.4)
WHO status at diagnosis (p-value)	**p=0.021**	**p=0.004**	p=0.730	p=0.826	**p=0.041**	p=0.146
WHO 0	0.90 (0.12)	79.22 (11.4)	0.81 (0.20)	69.8 (15.8)	0.87 (0.13)	74.8 (12.8)
WHO 1	0.80 (0.17)	68.24 (13.5)	0.78 (0.17)	68.4 (16.4)	0.81 (0.15)	70.6 (11.9)
WHO not known	-	-	0.73 (0.24)*	59.5 (13.4)*	0.68 (0.19)	56.2 (13.7)
Binet stage at diagnosis (p-value)	p=0.259	p=0.742	p=0.795	p=0.789	p=0.375	p=0.265
Stage A	0.88 (0.13)	77.58 (12.5)	0.79 (0.23)	67.2 (17.6)	0.87 (0.14)	75.1 (13.2)
Stage A pr.	-	-	0.90 (n.a.)*	75.0 (n.a.)*	0.87 (0.06)	70.1 (15.1)
Stage B	1.00 (0.00)*	71.20 (10.4)*	0.81 (0.15)	72.0 (11.3)	0.82 (0.15)	68.1 (11.9)
Stage C	0.86 (0.20)*	76.23 (15.0)*	0.84 (0.06)	69.5 (2.5)	0.85 (0.10)	72.4 (10.7)
B-symptoms at diagnosis (p-value)	p=0.551	p=0.543	p=0.302	p=0.333	p=0.447	p=0.276
No	0.88 (0.13)	77.18 (12.2)	0.79 (0.21)	68.1 (15.2)	0.86 (0.14)	73.9 (12.8)
Yes	0.93 (0.11)	81.67 (18.6)	0.87 (0.08)	74.0 (9.7)	0.84 (0.12)	71.0 (13.5)
Involvement spleen (p-value)	p=0.391	p=0.551	p=0.070	p=0.495	p=0.876	p=0.068
No	0.88 (0.14)	77.72 (12.9)	0.74 (0.26)	67.0 (17.4)	0.86 (0.15)	74.9 (13.0)
Yes	0.92 (0.08)	75.18 (8.7)	0.86 (0.08)	70.1 (10.5)	0.85 (0.11)	69.6 (11.8)
Unknown	-	-	0.90 (n.a.)*	91.6 (n.a.)*	0.89 (n.a.)*	90.8 (n.a.)*

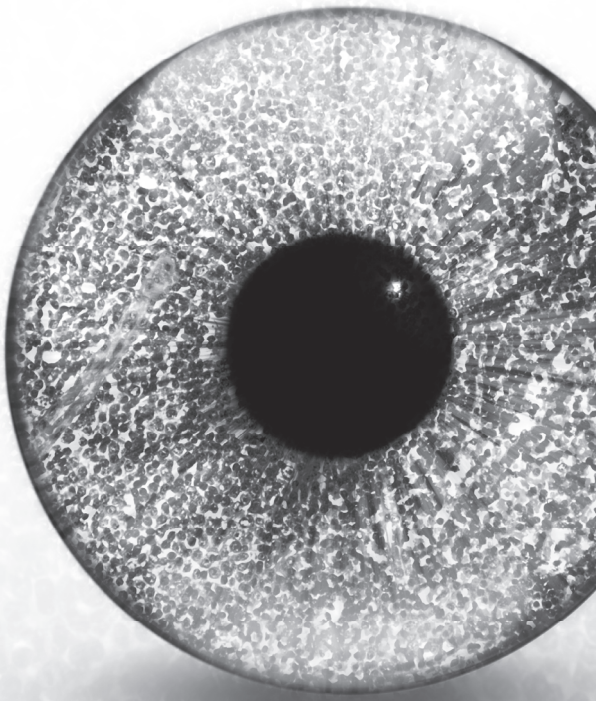
Appendix 7.1. Utility and VAS scores per category of the included patient characteristics (continued)

	During Watch and wait phase (N=71)		During treatment with Chlorambucil (N=42)		Total group of patients (N=144)	
	Utility (SD)	VAS (SD)	Utility (SD)	VAS (SD)	Utility (SD)	VAS (SD)
Total score	0.88 (0.13)	77.37 (12.4)	0.81 (19.3)	69.1 (14.5)	0.85 (0.14)	73.5 (12.9)
Involvement bone marrow (p-value)	p=0.320	p=0.357	p=0.371	p=0.741	p=0.148	p=0.322
No	0.85 (0.15)	79.88 (12.5)	0.65 (0.44)	65.3 (29.2)	0.82 (0.18)	76.8 (14.2)
Yes	0.89 (0.13)	76.61 (12.3)	0.85 (0.11)	69.5 (8.6)	0.88 (0.11)	73.9 (11.7)
Unknown	0.89 (0.10)	76.38 (13.2)	0.79 (0.16)	70.1 (15.8)	0.81 (0.16)	69.2 (15.5)
Co-morbidities (p-value)	**p=0.028**	**p=0.041**	p=0.702	p=0.719	**p=0.024**	**p=0.026**
No	0.90 (0.11)	79.18 (12.1)	0.81 (0.14)	69.7 (11.2)	0.88 (0.12)	74.8 (13.2)
Yes	0.81 (0.17)	72.41 (12.0)	0.79 (0.27)	68.0 (19.3)	0.81 (0.17)	70.3 (11.6)
Education after 16 years (p-value)	p=0.069	p=0.807	p=0.197	p=0.143	p=0.077	**p=0.031**
No	0.82 (0.19)	76.67 (12.1)	0.76 (0.26)	65.03 (17.9)	0.81 (0.18)	69.29 (13.8)
Yes	0.90 (0.11)	77.57 (12.7)	0.84 (0.12)	71.70 (11.5)	0.87 (0.12)	74.79 (12.5)
N.A.	0.93 (0.04)	77.26 (12.4)			0.92 (0.04)	77.92 (11.0)
Smoking status at diagnosis (p-value)	p=0.482	p=0.423	p=0.494	p=0.885	p=0.305	p=0.434
Current smoker	0.91 (0.13)	79.37 (14.0)	0.82 (0.07)	69.59 (12.2)	0.89 (0.14)	75.99 (11.8)
Ex smoker	0.89 (0.12)	78.65 (12.2)	0.75 (0.26)	68.63 (17.3)	0.85 (0.14)	73.62 (13.7)
Non smoker	0.85 (0.15)	74.96 (12.4)	0.86 (0.10)	69.44 (11.1)	0.85 (0.14)	72.03 (12.7)
N.A.	0.92 (0.03)	75.86 (10.5)			0.93 (0.04)	76.44 (9.45)

* Less than 3 patients within the subgroup. P-values indicate statistical significance between the categories of the patient characteristics (e.g. between age classes). WHO: World Health Organization

Chapter 8

General discussion



8.1 BACKGROUND

Health care innovations can be used to respond to the challenge presented by the growing demand for health care. Such innovations can contribute to making health care more convenient, more effective and to reducing costs. This would make more health care available with the same resources and thus continuing to be accessible to everyone.

Three types of health care innovations can be defined.[3] The first are changes to the way *consumers* purchase and use health care. The second uses *technology* to develop new products and treatments to improve health care. The third generates new *business models,* such as integration of health care organisations.

This thesis compares the cost implications and consequences of two health care innovations, using different types of economic evaluation and different data sources in two diseases. The first innovation is an example of a new business model in glaucoma care, in which some tasks undertaken by glaucoma specialists are carried out by optometrists and ophthalmic technicians. The second innovation is a new treatment option (technology) for chronic lymphocytic leukaemia (CLL): fludarabine.

8.2 GLAUCOMA

Currently, glaucoma is mainly managed by glaucoma specialists. The sustainability of this practice is questionable because the rapidly growing demand for glaucoma care cannot be met by the current number of glaucoma specialists (in training). In a subgroup of patients (those deemed stable and those at risk of developing glaucoma), glaucoma care could well be provided by optometrists or ophthalmic technicians.

In this subgroup of patients, care by glaucoma specialists was compared with the care by a Glaucoma Follow-up Unit (GFU) in the Rotterdam Eye Hospital (REH) that is staffed by ophthalmic technicians and optometrists. The proposition was that task substitution would be a solution to the increasing workload of ophthalmologists and long waiting lists for ophthalmic care, would result in the same quality of care and would reduce costs.

The GFU staff adhered to their work protocol for almost all patients, patient satisfaction in both treatment groups was comparable and the difference in intraocular pressure (IOP) over time did not differ statistically between the two treatment groups. The average time spent per patient per year, and the increased number of patients and patient visits confirmed our hypothesis that the GFU reduced the waiting list (Chapter 2).

Health care costs were about 10% lower for the GFU group compared to the usual care group (Chapter 3). The bootstrap analysis showed that the equivalence of the two

groups on quality of care is justified and that the GFU is cost saving from a societal perspective in 84% to 89% of the bootstrap replications.

However, despite the evidence indicating that (primary care) optometrists can provide high-quality care, this health care innovation could not be transferred to primary care optometrists in the Rotterdam area in the period 2004 to 2011 (see Chapter 4). Implementation was the stumbling block, because glaucoma specialists disagreed with the primary optometrists about professional boundaries and work domains. They disagreed on the capabilities of primary care optometrists, and the assumed returns on investment were unclear. Power positions favoured the status quo, because the establishment of the GFU in the hospital sufficiently relieved the workload of glaucoma specialists. This situation might have been different if the primary care optometrists had been involved in the first step of the task substitution, the establishment of the GFU. Then all stakeholders could have seen the second step (transfer to the primary care setting) as a progressive step in the professionalisation of the primary care optometrists.

8.3 CHRONIC LYMPHOCYTIC LEUKAEMIA

Management of chronic lymphocytic leukaemia (CLL) has changed in the last few decades. At the start of our study in 2003, multiple studies showed that fludarabine mono-therapy, which was given market authorisation in the European Union in 1994, was more effective than chlorambucil.[180,181] However, there were still no studies on its cost-effectiveness in daily clinical practice.

The observational study in patients with CLL showed little treatment variation in the first treatment line, but variation increased exponentially with the second and later treatment lines. The cost of CLL varied greatly over the course of the disease and per treatment type. Although patients were treated with expensive chemo(immuno-) therapy, costs were mainly driven by hospital admissions and hospital visits in most treatment choices. Chemo(immuno-)therapy was the main cost driver during treatment lines of 'rituximab', 'therapy for a (Richter's) transformation', 'induction therapy preceding allogeneic stem cell transplantation' and 'fludarabine plus cyclophosphamide and rituximab'. The cost of CLL may be expected to rise further as more patients receive expensive treatments, which will also increase the proportion of therapy costs of the total costs.

Although the two- and five-year overall survival was good (100% and 89%, respectively), CLL had a profound impact on health related quality of life (HRQoL) of the patients. The HRQoL in CLL patients was compromised compared to age- and gender-matched norm scores of the general population. For patients in the watch and wait phase, the impact of their disease was limited, but larger than generally assumed. Once treatment

was indicated, HRQoL was considerably compromised. This applied to all treatments, including chlorambucil, which is considered to be a mild treatment.

8.4 OVERALL TOPICS

Difficulties in implementing innovations in health care

In health technology assessment (HTA), economic evaluation is used to provide information about the relative cost-effectiveness of a health care innovation compared to usual care or another relevant alternative. Although a favourable outcome may be sufficient to obtain or maintain reimbursement, it does not necessarily mean successful implementation and uptake in daily practice.

As shown in Chapter 4, implementation of the hospital-based GFU, an effective and cost saving innovation, was not feasible in a primary care setting. Glaucoma specialists were unwilling to refer stable glaucoma patients to primary care optometrists, yet the intermediate step to transfer the monitoring task in the hospital was a workable compromise that sufficiently relieved their workload.

In case of the introduction of a new drug, the implementation process may appear easier, but in practice, it often takes a long time before effective medications are used as frequently as expected based on the results of the clinical trials.[182,183]

The question is why implementation of health care innovations is so difficult. The first reason can be found in the differences in the agendas of stakeholders involved. Even an innovation that has been proven to be effective and efficient is only quickly adopted when the majority of the powerful stakeholders benefit from its implementation. These benefits may be financially, but also benefits in terms of technical advances, status or ease can facilitate the implementation.

The chance of successful implementation may be affected by the payment scheme to health care practitioners. In the case of the shared glaucoma care, glaucoma specialists were paid a fixed amount per glaucoma patient. Thus, there was no incentive to refer stable and 'easy' patients to other health care professionals, because they would be left to treat the more severe patients while not receiving more payment to do so. However, primary care optometrists welcomed glaucoma patients, because monitoring these patients was expected to generate additional income. The fact that no reimbursement protocol for monitoring stable glaucoma patients (in a primary care setting) was in place led some primary care optometrists to doubt the feasibility and financial benefits of shared glaucoma care. These reservations by glaucoma specialists and some optometrists hampered implementation of shared glaucoma care in the primary care setting.

In line with this, the insurer responsible for purchasing most of the health care did not always see the link between reduction in labour costs and the additional cost of the new

care. This is more obvious in preventive care, because the health gains and possible cost reduction occur later than the investment in the innovation.

Furthermore, patients are generally committed to the opinion of their treating physician, which empowers the physician as a stakeholder in a health care innovation. Often, patients have limited information about the relevant and best alternatives from sources other than their own physician. In the last decade, health care insurers have endeavoured to become an independent information source, but as yet are little used by patients for this purpose. The success of an innovation relies on the health care provider and innovations need to appeal to physicians, who are in a position to recommend care products to their patients.

In addition to recommending new care to their patients, physicians must be convinced that the new care does not threaten their power position. Thus, a key factor in implementing new care is structured and long-term dialogue between physicians and the party that threaten their power position because fear for the unknown is the greatest of all fears.[184]

There is also a limited time frame for implementation. If adoption of an innovation starts too early, the supporting infrastructure may not yet be in place, while starting late reduces the competitive advantage. Equivalent or even better alternatives may be developed in the meantime, or the sense of urgency for change has disappeared.

The value of mixed method research in HTA

As stated above, users of a health care innovation need to be convinced of the value. An economic evaluation can contribute to convincing them of the effectiveness and cost-effectiveness of the health care innovation.

Most economic evaluations are conducted for pharmaceuticals because a requirement for a significant part of the new pharmaceutical products is to demonstrate its cost-effectiveness to obtain and/or maintain reimbursement. In these evaluations, the relationship between the administration of a medicine in a trial setting and its effect on the outcome measures is in general quite clear. The evaluations and the interpretation of the results are thus rather straightforward.

As described in Chapters 5 to 7, calculation of the cost-effectiveness of a new treatment option is more problematic in a real world setting, especially for a disease with large treatment variation and rapidly changing management strategies, such as CLL. Disease management changes with the introduction of each new treatment option. Existing treatments are prescribed for fewer or other patients, also affecting the effectiveness and marginal cost-effectiveness of that treatment option. This dynamic process impedes calculation of the cost-effectiveness, and may make the results of a multi-year observational study out dated before the analysis is performed. However, it can provide

information about trends in management of a disease in clinical practice and budget impact.

CLL patients often receive multiple treatment lines, the outcome of which is influenced by the outcome of the preceding therapies. Consequently, treatment history has to be taken into account in comparing alternative strategies per treatment line. This requires large numbers of patients. Comparing alternative therapies in observational studies is challenging in CLL, which has a relatively low incidence. A solution might be long-term continuous registration or development of a disease model.

Interpretation of the results of an economic evaluation is even more difficult if the effects of a health care innovation cannot be seen directly. The results may be partially influenced by contextual factors, such as stakeholder interest,[104-107] power positions,[108,109] and the structure of the health care system, including its financing,[110] as discussed in the organisational intervention (see Chapters 2 to 4).

Quantitative measurement of these factors is difficult. Real insight into the cost-effectiveness of a health care programme, organisational change or implementation method can be obtained only by supplementing the economic evaluation with a qualitative study of these less tangible factors, using a mixed methods approach.

As shown in Chapter 4, although the quality of care of an innovation (for instance, a hospital-based GFU) was equal to that of the usual care and provided a cost saving from a societal perspective in 84% to 89% of the bootstrap replications, the glaucoma specialists were not willing to refer patients to a GFU-like construction in primary care. They argued that the capabilities of primary care optometrists were insufficient. The primary care optometrists disagreed, and believed they were capable – in some cases after a short period of training – of monitoring these stable glaucoma patients. The return on investment for the primary care optometrists and the REH were unclear and reluctant key stakeholders with strong power positions blocked implementation. In addition, the glaucoma specialists' sense of urgency for task substitution outside the hospital diminished after a hospital-based GFU was established that satisfied their professionalisation needs. The window of opportunity for task substitution in person and setting in 1999 closed with the institutionalisation of the GFU.

The combination of qualitative research and a quantitative economic evaluation yields valuable information (see Chapter 4). The question is whether this is a coincidence, or whether this benefit can be expected in many HTA analyses. To answer this question, the potential value of qualitative research in the observational study described in Chapters 5 to 7 was explored.

In an observational study, a qualitative approach might contribute to identifying possible confounding by indication, which occurs frequently in observational studies (see Section 8.4.3). By asking physicians to explain treatment choices made in the recent past,

insight can be obtained in the presence of confounding by indication, and more easily taken into account in the analysis.

Interviews may also reveal the role of high treatment costs, or other potential prescription barriers in treatment decisions. The combination of quantitative and qualitative research methods has already been shown to be valuable in oncology.[185]

Furthermore, qualitative research can give insight into the difference between the expected and observed place of the new treatment for a specific group of patients, when carried out at the start of the observational study. The latter happens regularly in modelling HTA studies in the form of an expert panel.

The value of qualitative research in addition to the economic evaluation depends on the situation and is influenced by the data source for the economic evaluation.

The values and pitfalls of observational research

An economic evaluation can be based on different types of data sources. It can be performed alongside a (randomised) clinical trial, or based on observational data (real world practice). The third option is to use published data on clinical trials or observational studies.

An economic evaluation piggy-backed on a randomised clinical trial was considered to be the preferred method because randomisation ensures a good internal validity. Randomisation spreads patients evenly over the treatments when sufficient patients are included, and when patients are treated precisely according treatment protocol. However, this method has some drawbacks. Firstly, a randomised controlled trial often compares the new treatment with only one relevant alternative. Secondly, a trial does not always provide all information required for a complete economic evaluation. Thirdly, often a trial protocol does not reflect the treatment in daily clinical practice, which leads to a limited external validity.

Due to the lack of strict inclusion and exclusion criteria in clinical practice, more and/or other patients are treated with the new treatment than in a clinical trial. Furthermore, the dose, treatment duration, and follow-up intensity can differ considerably from that of the trial protocol. For these reasons, the treatment effect and costs and thus also the cost-effectiveness of the new treatment in daily practice can differ considerably from its cost-effectiveness in the trial.

Use of observational data overcomes the problem of limited external validity, because it can provide an indication of differences in management patterns and clinical effectiveness between patients in clinical trials and those in clinical practice. This is essential information in calculating marginal cost-effectiveness which reflects results in clinical practice. Moreover, information about management in daily clinical practice can be used by medical practitioners to reflect on their own treatment choices.

However, observational data also have methodological challenges. The first challenge that impedes comparison of treatments in clinical practice is the variation with regard to the type of treatment, dose, treatment duration and sequence of subsequent treatments. This variation is useful because it enables comparison of the new treatment with several alternatives, as an extensive economic evaluation aims to do. However, this requires a large number of participating patients, which is not always feasible, as shown in Chapter 5.

The second methodological challenge is the correlation between aspects that affect the choice of treatment (patient characteristics such as age, disease symptoms, physical condition, and patient preferences regarding route of administration) and the expected treatment effect. This correlation, also referred to as confounding by indication, might lead to an uneven spread of patients over the treatments.

Confounding by indication can be identified using qualitative research and corrected for using statistical methods such as multivariable regression modelling, propensity score matching, and data synthesis. Multivariable regression models require information on patient and disease characteristics such as disease classification that is not always available in a retrospective observational study. Propensity score matching requires larger numbers of patients, because all subgroups distinguished need sufficient patients. The extent to which this correction can be made depends on the heterogeneity of the study population with regard to treatment variation and sequence, the natural course of disease and the number of patients. This method is less attractive for comparison of multiple treatment options.

When statistical methods to correct for confounders cannot be applied, the solution might be data synthesis to model incremental outcomes, combining efficacy data from a randomised clinical trial and effectiveness data from daily clinical practice might be a solution. Development of the model requires data from reliable studies in a relevant group of patients to provide reliable outcomes. However, availability of these data can be problematic for several reasons. A first reason is publication bias. Studies with disappointing results have less chance of being published, and this can lead to a biased picture. A second reason is that when the model is to provide information about the cost-effectiveness of a new treatment in daily clinical practice, the input parameters should also be based on observational studies or patient registrations. These sources are subject to the same problems as described above.[185]

The role of economic evaluation in clinical guidelines for Chronic Lymphocytic Leukaemia

Recommendations on CLL diagnosis and treatment in the Netherlands by the Dutch-Belgian Cooperative Group for Haemato Oncology for Adults (HOVON) are based on the

recommendations of the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) for the management of CLL in clinical trials and general practice in 2008.[186]

Many new treatment options for CLL, such as idelalisib, ofatumumab and ibrutinib, have become available in the last few decades, which are in general more expensive than the older treatments. However, the role of economic considerations is currently not explicit in the CLL guidelines. The development of innovative but expensive treatment options will probably continue in the near future. As is common in oncology, these expensive drugs are often combined putting further pressure to incorporate economic considerations in the clinical CLL guidelines. Whether this is necessary, depends on the structure and main cost drivers in the CLL treatment.

In the period 1999 to 2008, the cost of CLL was mainly driven by the cost of outpatient visits and hospital admissions (see Chapter 6). The cost of hospital admissions could be reduced if treatments become available that do not require hospitalisation and/or result in fewer adverse events related to treatment.

In treatment lines with some newer combination regimens, the cost of chemo(immuno)-therapy has been the main cost driver. Since currently more CLL patients receive these treatment options, the proportion of therapy costs of the total costs will increase. The proportion of treatment costs will further increase with the development of other new treatment modalities that improve overall survival compared with a wait and see approach. Thus, it might become inevitable to reflect on the marginal cost-effectiveness in addition to the clinical effectiveness of treatment options.

The Dutch Government seems to have difficulties in denying reimbursement of very expensive treatments, such as aglicosidase alfa for Pompe's disease and agalsidase alfa or agalsidase bèta for Fabry's disease.[187] In these cases, the medical profession could play a role in the decision making process by incorporating considerations on the economic consequences of treatment choices when updating clinical guidelines. HTA analysis as part of this reflection is challenging when disease management is continually changed by successive introduction of new treatment options. The marginal cost-effectiveness is difficult to calculate because the most appropriate comparator is changing rapidly. Results of an observational study over multiple years are likely to be out dated by the time the analysis is performed.

The update of the CLL guideline should give attention to the following considerations with regard to the HRQoL. Based on the findings set out in Chapter 7, more attention needs to be given to sleep problems and fatigue since this affects all CLL patients, including treatment naïve patients when compared to the general population of the same age.

Furthermore, the study showed that HRQoL is significantly reduced after the start of treatment compared to treatment naive CLL patients, also for the relatively mild treatment with chlorambucil. It should be stressed that the negative impact of starting a

treatment on patient HRQoL should be weighted in the decision when to start therapy, especially as more effective but also more intensive therapies are coming available.

8.5 LIMITATIONS AND SUGGESTIONS FOR FURTHER RESEARCH

The main limitation of the economic evaluation alongside the RCT in shared glaucoma care is the relatively short period of follow-up, which was up to 44 months. The progression rate of glaucoma depends on the intraocular pressure and the time to vision loss varies between 3 years for untreated patients with a high intraocular pressure to 38 years for well-treated patients.[77,97] For this reason, we could not use glaucomatous progression as an appropriate outcome measure. Our alternative outcome measure, the mean difference in intraocular pressure over the study period, did not differ between the usual care group and GFU group. Further research into the effect of shared on glaucomatous progression would be valuable, because the safety of a shared care scheme should be equal to the care by glaucoma specialists on this measure as well.

A second limitation is the study design for the GFU group with every third visit to the glaucoma specialist. This study design was chosen for clinical reasons, but may have introduced bias with regard to patient satisfaction. Patients might have been satisfied with the GFU because they knew that they would visit a glaucoma specialist after two visits to the GFU. Moreover, the GFU had more time available for each patient, which might have contributed to the higher satisfaction.[76] Whether this bias affects patient satisfaction should be subject of further research.

The main limitation of the study in CLL patients was data collection on resource use and effectiveness based on retrospective chart review. Although this method provided detailed information about the treatment type, dose, duration and sequence, the reason for the choice of one treatment over another was not clear. Moreover, the difference between partial and complete response could not be traced in a significant number of the patients (Chapter 5).

A second limitation of this study was the dependency on the health practitioners for the timely administration of questionnaires, specifically the questionnaire at the start of a new treatment. Despite our efforts to remind the health practitioners, patients often did not receive the questionnaire before the start of the treatment. Thus, HRQoL before and after treatment could not be effectively compared.

HRQoL was shown to be negatively influenced by having co-morbidities and a high WHO stage at diagnosis. In our study, the treatment group 'chlorambucil only' had the highest percentage of patients with co-morbidity. This may explain the relatively lower HRQoL of patients in this group compared with the patients receiving other treatments. Since the patient group with co-morbidities is increasing steadily due to an ageing

population and an improved overall survival, future research needs to focus on the effectiveness of treatments in these patients and the effect of treatments on their HRQoL.

A third limitation is the limited follow-up duration of the observational study. Observational studies optimally reflect the situation in clinical practice when patients are followed from diagnosis until cure or death. In the case of an incurable disease with a long overall survival for all or a proportion of patients (such as CLL), it is both expensive and time consuming to collect these data. In the CLL study, complete data were collected for 39 patients (24%) who died during the study period. The CLL-related costs for survivors could not be estimated easily because the costs per treatment line varied enormously.

This challenge and the difficulties in comparing treatments may be solved using information from the observational study on the management, treatment cost and treatment effects in clinical practice as input to a mathematical model, when other relevant sources of information are available.

8.6 LESSONS LEARNED

First and foremost, a HTA is very challenging in a real world setting in which the disease management strategy is rapidly changing because of the introduction of new treatment options. In such a dynamic process, the most appropriate comparator is changing rapidly. This impedes calculation of the marginal cost-effectiveness because the new treatment option has to be compared with multiple (older and newer) treatments to ensure the results are not outdated. This will often result in an insufficient number of comparable patients per treatment option.

Secondly, mixed methods research appeared to be valuable in the glaucoma study. Chances of implementation of an organisational innovation and thus the cost-effectiveness and budget impact on a macro level are partially influenced by contextual factors, such as local stakeholder interests, and the structure of the healthcare system. This makes it worthwhile to broaden the scope of evaluation to include these contexts in the analysis.

The first lesson from this study is that policy makers considering substituting tasks to lesser trained professionals and transferring services from a hospital to a primary care setting need to consider carefully the implementation process, especially when deciding to implement task substitution in separate steps. An intermediate step might diminish the sense of urgency for task substitution if it satisfies the professionalisation needs of the professionals involved. Recognising a restricted window of opportunity in the implementation of task substitution is thus critical.

The second lesson from this mixed methods study is that it is crucial to involve the substituting professionals early to ensure that all stakeholders see the change as a normal step in the professionalisation of the substituting professionals.

Third, the combination of methods is also expected to be valuable in the HTA of drugs. Like the implementation of an organisational innovation, the uptake of a new drug depends on contextual factors, such as the criteria for reimbursement, the division of the hospital budget for expensive drugs over all departments, the opinion of the treating specialist and patient preferences. The addition of qualitative research methods to an HTA analysis to reveal the influence of stakeholder interests, power positions and the financial structure of the health care system might result in a more accurate calculation of the marginal cost-effectiveness of a new medicine.

Chapter 9

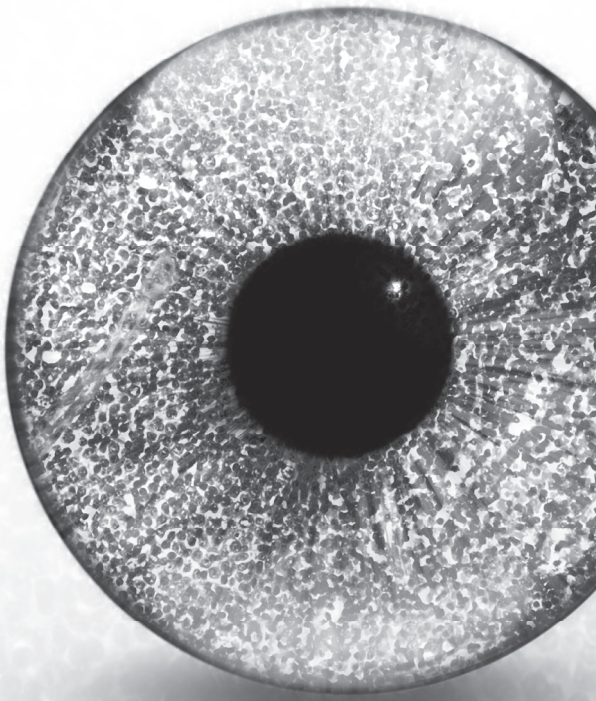
Summary

Samenvatting

Dankwoord

PhD portfolio

Curriculum vitae



SUMMARY

This thesis addresses the costs and effects of health innovations in two diseases: glaucoma and chronic lymphatic leukaemia.

Glaucoma is a group of eye conditions characterised by damage to the optic nerve, which may lead to blank spots in the patient's peripheral (side) vision and eventually lead to blindness if left untreated. Increased intraocular pressure is an important risk factor for the development of glaucoma. Glaucoma treatment aims to lower the intraocular pressure. This can be achieved by medication (eye drops), laser treatment or surgery. When the treatment in patients with glaucoma has been effective, and the progression of the disease has come to a halt, patients are considered to be "stable glaucoma patients". These patients and those with a risk factor for developing glaucoma are currently treated by glaucoma specialists, although lower educated staff such as optometrists or ophthalmic technicians are also capable of monitoring these patients.

Because of the high workload of the glaucoma specialists, the Rotterdam Eye Hospital (REH) attempted to refer stable glaucoma patients and patients with a risk factor for developing glaucoma to community optometrists for some of their regular glaucoma follow-up visits. It turned out that this attempt was not successful, because it took more time and effort of the glaucoma specialists to convince patients to visit the primary optometrist, and not all glaucoma specialists were willing to do that. The REH then decided to set up a Glaucoma Follow-up Unit (GFU) within the hospital staffed by an optometrist and ophthalmic technicians. Care provided by the GFU has been compared with the care as usual by glaucoma specialists and residents in a randomised controlled trial.

In the GFU group, every patient visited the GFU twice, followed by a visit to a glaucoma specialist. If necessary, the patient was seen by a glaucoma specialist earlier. Medical resource use and clinical outcomes were reported for the 815 participating patients with glaucoma or a risk factor for developing glaucoma. After every visit to the REH, the patients completed a questionnaire about their satisfaction with the received care, time and travelling costs of themselves and their accompaniment (if applicable).

Chapter two describes the quality of care delivered by the GFU and glaucoma specialists. GFU employees closely followed the working protocol regarding the measurement of intraocular pressure, visual acuity and GDx images. They performed fewer Humphrey Field Analyser assessments than prescribed by the protocol, but more than in the Usual Care group. Only in a small minority of patients requiring back-referral was the protocol disregarded, notably when criteria were only slightly exceeded. The clinical effectiveness, measured as the change in intraocular pressure over time, was equal for the two treatment groups and the overall mark for the GFU was slightly higher than that of the

glaucoma specialists. The GFU functioned well, patients were satisfied and no differences in clinical effectiveness could be observed.

Chapter three compared the costs of the GFU group with those of the Usual Care group. The GFU was about 10% less expensive than usual care for 3 of the 4 perspectives used: the REH, the health care system, and societal perspective. Patient costs did not differ between the two patient groups. Bootstrap analysis showed that the overall mark given by the patient, as well as the percentage of 'stable' patients was equal and that the GFU was cost saving in 84 to 89% of the bootstrap replications. Scenario- and sensitivity analyses confirmed that the results were robust. Only in unlikely situation that the duration of a visit to the GFU would have been underestimated ánd the duration of a visit to a glaucoma specialist would have been overestimated, was the GFU not cost saving any longer.

After having obtained the results of the randomised clinical trial, all glaucoma specialists working in the REH as well as the GFU employees and the responsible hospital managers were interviewed to reassess the feasibility to transfer stable glaucoma patients to community optometrists. We also interviewed a sample of other stakeholders such as patients, community optometrists, the Dutch Healthcare Authority and healthcare insurers using semi-structured interviews. **Chapter four** describes the results of this case study using three implementation related theoretical perspectives: sociological theory of professionalism, management theory and applied political analysis. At that moment, task substitution by community optometrists turned out to be impossible, because of the following reasons: the establishment of the hospital-based GFU diminished the originally felt sense of urgency for task substitution; the returns on investments were unclear; and the glaucoma specialists and GFU employees did not expect that the task substitution would improve the professionalism of these optometrists. Finally, the power position of the stakeholders who did not support the task substitution was strong enough to block the implementation. The 'window of opportunity' closed with the establishment of the GFU. For this reason, it is necessary that policy makers considering substituting tasks to lesser trained professionals and transferring services from a hospital to a primary care setting consider the implementation process carefully, especially when deciding to implement it in separate steps.

Chronic Lymphatic Leukaemia (CLL) is the most prevalent type of leukaemia among adults in western countries. Early symptoms of CLL are often minimal and the diagnosis often follows a routine blood test that returns a high lymphocyte blood count.

Since randomised studies failed to a significant difference in survival between early versus deferred treatment of patients with asymptomatic, low risk CLL, the majority of CLL patients are not treated immediately after diagnosis. They will first be monitored through a watch and wait approach. Treatment is indicated only upon disease progres-

sion and/or the development of CLL related symptoms. It aims to control the disease and its symptoms. Treatment options are (a combination of) chemotherapy, radiation therapy, immunotherapy, and bone marrow transplantation.

In the past decades, the number of treatment options for CLL has increased rapidly. Since health care is under increasing pressure, cost-effectiveness data of new versus existing treatment options are urgently needed. That is especially true in countries like the Netherlands where expensive drugs are to be evaluated during the first years of temporary admittance in order to obtain unconditional reimbursement. In an observational study, we followed Dutch CLL patients for 6.4 years on average to get an overview of the management of CLL and the patients' quality of life in clinical practice.

Chapter five describes little treatment variation in the first treatment line. After the second treatment line, variation in treatment increases exponentially. A large proportion of patients (39%) did not receive active treatment for their disease. Twenty five percent received one active treatment, 12% received two active treatments and 24% received three or more treatments. The two- and five-years survival was 100% and 89% respectively and the CLL specific survival was 91% after five years.

A comprehensive cost calculation was performed to produce a transparent overview of the different cost categories. **Chapter six** presents the most important cost categories per treatment line and per type of treatment. The average total CLL related costs per patient were €41,417 (€539 per month) and varied considerably between treatment groups. The costs increased by the number of treatment lines. Although patients were treated with expensive chemo(immuno-)therapy, the main cost driver was inpatient days for other reasons than administration of chemo(immuno-)therapy, such as the administration of blood products.

Information about the longitudinal quality of life of an unselected group of CLL patients over time was collected during the same study. **Chapter seven** describes the health related quality of life which was measured over multiple years by the EuroQol-5D, Visual Analogue Scale (VAS) and the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 including the CLL16 module. Patients received the questionnaires every 6 months in periods without active treatment, as well as at the start in the middle and at the end of each treatment line. All HRQoL measurements per patient were connected and analysed using area under the curve analysis over the entire study duration.

The total patient group was compared with age- and gender-matched norm scores of the general population. CLL patients scored statistically worse on the VAS and utility score of the EQ-$5D_5$, all functioning scales of the EORTC-QLQ-C30, and the symptoms of fatigue, dyspnoea, sleeping disturbance, appetite loss, and financial difficulties. The results were described separately for CLL patients without any active treatment, for patients with chlorambucil treatment only, and patients with other treatment(s).

In untreated patients, the HRQoL was slightly reduced. In all treatment stages, HRQoL was compromised considerably. Patients treated with chlorambucil only scored worse on the EORTC-QLQ-C30 than patients who were treated with other treatments. This difference can probably be explained by the relatively high percentage of patients with co-morbidity in the group of CLL patients treated with chlorambucil only.

The studies described in this thesis show that health technology assessment in daily clinical practice is challenging when disease management of the disease of interest is continually changed by successive introduction of new treatment options (**Chapter eight**). In such a dynamic process, the most appropriate comparator is changing rapidly. This impedes calculation of the marginal cost-effectiveness because the new treatment option has to be compared with multiple (older and newer) treatments to ensure the results are not outdated. This will often result in an insufficient number of comparable patients per treatment option for a reliable comparison.

The glaucoma study shows the value of mixed methods research in HTA analyses. Chances of implementation of an organisational innovation and thus the cost-effectiveness and budget impact on a macro level are partially influenced by contextual factors, such as local stakeholder interests, and the structure of the healthcare system.

This study teaches us that policy makers considering substituting tasks to lesser trained professionals and transferring services from a hospital to a primary care setting need to consider carefully the implementation process, especially when deciding to implement task substitution in separate steps. An intermediate step might diminish the sense of urgency for task substitution if it satisfies the professionalisation needs of the professionals involved. Recognising a restricted window of opportunity in the implementation of task substitution is thus critical.

The second lesson is that it is crucial to involve the substituting professionals (in this case the community optometrists) early to ensure that all stakeholders see the change as a normal step in the professionalisation of the substituting professionals.

Third, the combination of methods is also expected to be valuable in the HTA of drugs. Like the implementation of an organisational innovation, the uptake of a new drug depends on contextual factors, such as the criteria for reimbursement, the division of the hospital budget for expensive drugs over all departments, the opinion of the treating specialist and patient preferences. The addition of qualitative research methods to an HTA analysis might result in a more accurate calculation of the marginal cost-effectiveness of a new medicine.

SAMENVATTING

Dit proefschrift behandelt de kosten en effecten van gezondheidszorg innovaties binnen twee ziektegebieden: glaucoom en chronisch lymfatische leukemie.

Glaucoom is een verzamelnaam voor een groep oogaandoeningen die gekenmerkt wordt door schade aan de oogzenuw en daarmee samenhangende uitval in het gezichtsveld. Een verhoogde oogdruk is een belangrijke risicofactor voor het ontstaan van glaucoom. De behandeling richt zich daarom op het verlagen van de oogdruk, wat mogelijk is door middel van medicatie, laserbehandeling of een operatie. Wanneer de oogdruk goed kan worden gereguleerd is er sprake van stabiele ziekte. Patiënten die stabiel glaucoom hebben of een risicofactor hebben voor het ontwikkelen van glaucoom worden nu veelal behandeld door glaucoom specialisten, terwijl dit ook door lager opgeleid personeel zoals optometristen of technisch oogheelkundig assistenten kan worden gedaan. De hoge werkdruk van glaucoom specialisten heeft ertoe geleid dat in Het Oogziekenhuis Rotterdam is getracht stabiele glaucoompatiënten en patiënten met een risicofactor voor het ontwikkelen van glaucoom te verwijzen naar eerstelijns optometristen. Toen dit niet bleek te lukken, omdat het glaucoom specialisten veel tijd kostte om patiënten ervan te overtuigen dat de optometristen deze zorg evengoed konden leveren en niet alle glaucoom specialisten hiertoe bereid waren, is er besloten een glaucoompost op te richten binnen het ziekenhuis. De glaucoompost werd bemand door een ziekenhuis-optometrist en technisch oogheelkundig assistenten.

Met behulp van een gerandomiseerd onderzoek is de zorg die werd geleverd door de glaucoompost vergeleken met de gebruikelijke zorg door glaucoom specialisten of arts assistenten. Daarbij brachten patiënten die in de arm glaucoompost zaten, twee bezoeken aan de glaucoompost en daarna één bezoek aan de glaucoom specialist. Wanneer daar aanleiding toe was, werd de patiënt eerder door een glaucoom specialist gezien. Bij 815 patiënten met stabiel glaucoom of een risicofactor voor het ontwikkelen van glaucoom werd het zorggebruik en de uitkomst ervan vastgelegd. Daarnaast werden alle deelnemende patiënten gevraagd om bij ieder bezoek aan Het Oogziekenhuis Rotterdam een vragenlijst in te vullen over hun tevredenheid over de geleverde zorg, en de gemaakte reis- en tijdkosten door de patiënt en eventuele begeleiders.

Hoofdstuk twee beschrijft de kwaliteit van de geleverde zorg door de glaucoompost en glaucoom specialisten. Medewerkers van de glaucoompost bleken het opgestelde protocol nauwgezet te volgen voor het meten van de oogdruk, gezichtsscherpte en GDx metingen. Humphey Field Analyser beoordelingen werden minder vaak uitgevoerd dan voorgeschreven door het protocol, maar vaker dan in de arm 'glaucoom specialist'. In een klein deel van de patiënten dat de glaucoompost had moeten terugverwijzen naar de glaucoom specialist, gebeurde dat niet. Bij deze patiënten was de overschrijding

van de norm die was beschreven in het protocol echter beperkt. De uitkomst van de zorg, gemeten als de verandering in oogdruk over de duur van de studie, bleek niet te verschillen tussen de twee armen en patiënten gaven een iets hoger rapportcijfer aan de medewerkers van de glaucoompost dan aan de glaucoom specialisten. De glaucoompost bleek goed en naar tevredenheid van de patiënten te functioneren en er konden geen verschillen worden waargenomen in de klinische uitkomst van de zorg.

Hoofdstuk drie vergeleek de kosten van de glaucoompost met die van de glaucoom specialisten. De kosten van de glaucoompost waren ongeveer 10% lager dan die van de gebruikelijke zorg voor 3 van de 4 gebruikte perspectieven: Het Oogziekenhuis Rotterdam, het zorgsysteem en de maatschappij. De kosten voor de patiënt verschilden niet tussen de twee groepen patiënten. Bootstrap analyses toonden aan dat zowel het rapportcijfer gegeven door de patiënt als het percentage patiënten dat werd beoordeeld als 'stabiel' in de twee armen gelijkwaardig was en dat de glaucoompost kostenbesparend was in 84 tot 89% van de bootstrap herhalingen. Scenario- en sensitiviteitsanalyses bevestigden dat de resultaten robuust waren. Alleen in het onwaarschijnlijke geval dat de gemiddelde duur van een bezoek aan de glaucoompost zou zijn onderschat én de duur van een bezoek aan de glaucoom specialist zou zijn overschat, zou de glaucoompost niet langer kostenbesparend zijn.

Om na te gaan of de betrokkenen het haalbaar achtten om alsnog, na het uitvoeren van het gerandomiseerde onderzoek en het daaruit verkregen bewijs, een deel van de glaucoom patiënten over te dragen aan de eerstelijns optometristen, is er een casestudie uitgevoerd. Met alle betrokkenen vanuit Het Oogziekenhuis Rotterdam en een gerichte steekproef van externe betrokkenen werd een semigestructureerd interview gehouden. **Hoofdstuk vier** beschrijft de resultaten hiervan in het licht van drie implementatie gerelateerde theoretische perspectieven: sociologische theorie over professionalisme, management theorie en toegepaste politieke analyse. Hieruit bleek dat het op dat moment niet mogelijk was om de zorg te verplaatsen naar de eerste lijn. Dit kwam enerzijds door de oprichting van de glaucoompost binnen het ziekenhuis, die de oorspronkelijke gevoelde noodzaak tot verandering sterk verminderde en anderzijds doordat de opbrengsten van de investering onduidelijk waren. Daarnaast zagen de glaucoom specialisten en glaucoompost medewerkers de verplaatsing van de zorg naar de optiekzaken niet als een positieve ontwikkeling richting verdere professionalisering van de eerstelijns optometristen. Tenslotte bleek de machtspositie van de betrokken partijen die niet achter de verplaatsing van de zorg stonden sterk genoeg om deze tegen te houden. De 'window of opportunity' voor de verplaatsing van zorg naar de eerste lijn verdween door de oprichting van de glaucoompost binnen het ziekenhuis. Om die reden is het essentieel dat het ontwerp van het implementatie proces goed is doordacht, zeker wanneer beleidsmakers overwegen om taaksubstitutie stapsgewijs te implementeren.

Chronische Lymfatische Leukemie (CLL) is de meest voorkomende vorm van leukemie onder volwassenen in westerse landen. Vroege symptomen van CLL zijn echter meestal minimaal en diagnose volgt vaak na een routine bloedonderzoek, waarbij een te hoge waarde voor lymfocyten wordt gevonden.

Aangezien gerandomiseerde studies aantonen dat vroegtijdige behandeling niet leidt tot een betere overleving dan uitgestelde behandeling van patiënten met asymptomatisch, laag risico CLL, worden de meeste CLL patiënten niet onmiddellijk na het stellen van de diagnose behandeld. Bij hen wordt eerst alleen de ziektevoortgang goed gemonitord door middel van lichamelijk en bloedonderzoek. Bij ziekte progressie of de ontwikkeling van CLL gerelateerde symptomen wordt een behandeling in de vorm chemotherapie, radiotherapie, immunotherapie, beenmergtransplantatie of een combinatie daarvan gestart met het doel om de ziekte en de symptomen onder controle houden.

In de afgelopen decennia is het aantal behandelopties voor CLL snel toegenomen. Aangezien de gezondheidszorg onder toenemende druk staat, is informatie over de kosteneffectiviteit van nieuwe versus bestaande behandelingsmogelijkheden dringend nodig. Dat is vooral het geval in landen als Nederland, waar het gebruik (de kosten) en de effectiviteit van dure medicijnen tijdens de eerste jaren van de tijdelijke toelating worden geëvalueerd om definitieve vergoeding te kunnen verkrijgen. In een observationele studie, werden 160 CLL patiënten gedurende gemiddeld 6,4 jaar gevolgd om inzicht te krijgen in de behandeling van CLL in Nederland en de kwaliteit van leven van CLL patiënten in de dagelijkse praktijk. In **Hoofdstuk vijf** wordt beschreven dat de behandeling van CLL sterk varieert, met name na de tweede behandellijn. Een groot deel van de patiënten (39%) ontving geen enkele actieve behandeling voor de ziekte. Vijfentwintig procent ontving 1 actieve behandeling, 12% ontving 2 actieve behandelingen en 24% ontving drie of meer behandelingen. De twee- en vijfjaars overleving was respectievelijk 100% en 89% en de CLL-specifieke overleving was 91% na 5 jaar.

Een uitgebreide kostenberekening werd uitgevoerd om een transparant overzicht te verkrijgen van de omvang van de verschillende kostencategorieën. Per behandellijn en per type behandeling zijn de belangrijkste kostencategorieën beschreven in **Hoofdstuk zes**. De totale gemiddelde kosten gerelateerd aan CLL bedroegen €41.417 per patiënt (€539 per maand) en varieerden sterk per type behandeling. Bovendien namen de kosten toe met iedere behandellijn. Ondanks dat de behandeling met (dure) chemo(immuno-) therapie was meegenomen in de kostenberekening, kwamen de meeste kosten voort uit de opnamedagen voor een andere reden dan de toediening van chemo(immuno-) therapie, zoals de toediening van bloedproducten.

In hetzelfde onderzoek is informatie verkregen over de longitudinale kwaliteit van leven van een ongeselecteerde populatie van CLL-patiënten. **Hoofdstuk zeven** beschrijft de kwaliteit van leven die gedurende meerdere jaren werd gemeten door middel van

een samengestelde vragenlijst bestaande uit de EuroQol-5D, Visual Analogue Scale (VAS) en de European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 inclusief de CLL16 module. Patiënten ontvingen de vragenlijsten iedere 6 maanden in periodes zonder behandeling en daarnaast bij de start, halverwege en aan het einde van iedere behandellijn. De uitkomsten per patiënt over de tijd zijn met elkaar verbonden en uitgedrukt als het oppervlakte onder de curve.

De totale groep CLL patiënten is vergeleken met de voor geslacht en leeftijd gewogen norm scores voor de algehele bevolking. CLL patiënten scoorden slechter op de VAS en de utiliteitsscore van de EQ-5D, alle functionele schalen van de EORTC-QLQ-C30 en de volgende symptomen: vermoeidheid, kortademigheid, moeite met slapen, gebrek aan eetlust, en financiële moeilijkheden. De resultaten zijn apart beschreven voor patiënten die nog geen actieve behandeling hadden ontvangen, voor patiënten die alleen met chloorambucil waren behandeld en patiënten die waren behandeld met andere of meerdere behandelingen. Voor patiënten die nog niet waren behandeld bleek de kwaliteit van leven enigszins beperkt te zijn. In andere fases van de behandeling was die beperking aanzienlijk. Patiënten die waren behandeld met alleen chloorambucil, een relatief milde behandeling, bleken nog iets slechter te scoren dan patiënten die meer of andere behandelingen hadden gekregen. Waarschijnlijk is dit verschil voor een deel te verklaren doordat de groep patiënten die alleen met chloorambucil was behandeld vaker last had van comorbiditeiten dan de groep die meer of andere behandelingen hadden gekregen.

Uit de onderzoeken beschreven in dit proefschrift blijkt dat health technology assessment in de dagelijkse klinische praktijk een uitdaging vormt wanneer het een technologie betreft voor een aandoening met een snel veranderende behandelingsstrategie doordat er in een korte tijd veel nieuwe behandeling beschikbaar (zijn ge)komen (**Hoofdstuk acht**). In een dergelijke dynamische omgeving, wisselt de behandeling waarmee de interventie zou moeten worden vergeleken ook snel. Dit bemoeilijkt de berekening van de marginale kosteneffectiviteit, omdat de interventie met meerdere (oudere en nieuwere) behandelingen moet worden vergeleken om ervoor te zorgen dat de resultaten in achterhaald zullen zijn. Het gebruik van meerdere behandelingen maakt het vaak lastiger om genoeg vergelijkbare patiënten per groep te vinden voor een betrouwbare vergelijking.

Daarnaast blijkt uit de glaucoom studie, dat mixed methods onderzoek waardevol is in HTA onderzoek. Kans op implementatie van een organisatorische innovatie en daarmee zijn relatieve kosteneffectiviteit en budget impact op macro niveau worden mede bepaald door omgevingsfactoren, zoals de belangen van stakeholders, en de structuur van het gezondheidszorgsysteem.

Dit onderzoek leert dat beleidsmakers die overwegen taken te verschuiven naar minder hoog opgeleid personeel, en van een ziekenhuisomgeving naar de eerste lijn, het implementatie proces zorgvuldig moeten vormgeven, zeker wanneer de verplaatsing van zorg in meerdere stappen plaats vindt. Een tussenstap kan de gevoelde noodzaak voor verandering wegnemen, als deze tussenstap voldoet in de behoeften op het professionele vlak. De 'window for opportunity' is daarom beperkt. Het hebben van aandacht voor dit feit is cruciaal. Daarnaast bleek het essentieel om de beoogde zorgverleners (in dit geval de eerstelijns optometristen) al vroeg in het proces van verplaatsing van zorg te betrekken, zodat alle stakeholders de verandering zouden zien als een normale stap in de professionalisering van de optometristen.

Mixed methods onderzoek is wellicht ook waardevol in de HTA van geneesmiddelen. Net als bij de implementatie van een organisatorische innovatie, hangt het gebruik van het nieuwe geneesmiddel namelijk af van omgevingsfactoren, zoals de vergoedingscriteria, de verdeling van het ziekenhuisbudget voor dure geneesmiddelen over de verschillende afdelingen, de mening van de behandelend specialist en patiëntvoorkeuren. De toevoeging van kwalitatief onderzoek aan de HTA analyse, kan de berekening van de marginale kosteneffectiviteit van een nieuw geneesmiddel daarom betrouwbaarder maken.

DANKWOORD

Het einde van mijn avontuur dat promoveren heet, is in zicht. Dit avontuur heeft hoogte en dieptepunten gekend, en een eindsprint waarin ik veel avonden en weekenden heb doorgewerkt. Maar nu is het boekje klaar! Deze afronding was niet mogelijk geweest zonder de hulp, steun, bijdrage en ideeën van vele anderen, waarvoor veel dank! Het is onmogelijk om iedereen hiervoor persoonlijk te bedanken, maar toch wil ik een aantal mensen bij naam noemen.

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PHD PORTFOLIO

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Training

2005 Clinical Trial Statistics for Non-Statisticians, European Organisation for Research and Treatment of Cancer, Brussels, Belgium

2007 Regression-analysis, Netherlands Institute for Health Sciences, Erasmus Medical Center, Rotterdam, The Netherlands

2007 Discrete choice analysis and choice experiment design, Erasmus University Rotterdam, Rotterdam, The Netherlands

2007 Write it right, Netherlands Organisation for Scientific Research, Den Haag

2009 Writing biomedical articles, Erasmus Medical Center, Rotterdam, The Netherlands

2010 Public health research, Netherlands Institute for Health Sciences, Erasmus Medical Center, Rotterdam, The Netherlands

2011 Tutortraining Probleemgestuurd Onderwijs, institute for Psychology, Erasmus University Rotterdam, Rotterdam, The Netherlands

2013 Short media training, Erasmus University Rotterdam, Rotterdam, The Netherlands

Teaching

2006-2014 Supervisor and co-evaluator for bachelor and master theses, institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands

2010 Quality management - lecture efficiency in healthcare, premaster program, institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands

2010-2014 Quality and efficiency in healthcare, tutor in bachelor program Health Sciences, institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands

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2013	Internship 'blik op zorg', practicum, bachelor program, institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands
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2013-2014	Writing and research skills for premaster students, practicum, premaster program, institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands
2010	The cost-effectiveness of monitoring stable glaucoma patients in shared care: an economic evaluation alongside a randomized controlled trial, at the 7th Health Technology Assessment international annual meeting, Dublin.
2011	Management, costs and quality of life of CLL in the real world, at the 5th Dutch Hematology Congress, Arnhem.
2014	Cost-effectiveness of computer training for people with visual impairments, at the national meeting InZicht, Huizen.

Poster presentations

2006	Use of a 5-level EQ-5D in patients with chronic lymphocytic leukaemia, at the 10th Annual European International Society for Pharmacoeconomics and Outcomes, Dublin.
2008	Innovation of glaucoma care delivery: transferring the monitoring of stable glaucoma patients out of the hospital to primary care optometrists, at the 25th International Society for Quality in Healthcare International Conference, Copenhagen.
2010	Cost-effectiveness of Chronic Lymphocytic Leukaemia in the real world, at the 7th Health Technology Assessment international Annual Meeting, Dublin.
2010	Is it useful to screen institutionalized people for vision problems? at the 7th Health Technology Assessment international Annual Meeting, Dublin.

2011 Value of outcomes research to inform reimbursement decisions; A case study in Chronic Lymphocytic Leukaemia, at the 14th Annual European International Society for Pharmacoeconomics and Outcomes, Madrid.

2011 Is it useful to screen institutionalized people for vision problems? at the Annual Congress of the Optometrists Association of the Netherlands, Ede.

2012 Modelling the 10-year cost-effectiveness of bendamustine as first line treatment for Chronic Lymphocytic Leukaemia in the Netherlands, at the European Hematology Association Annual Congress, Amsterdam.

2012 Cost effectiveness analysis of bendamustine as first line treatment for Chronic Lymphocytic Leukaemia in The Netherlands at the 15th Annual European International Society for Pharmacoeconomics and Outcomes, Berlin.

2015 Validation of an algorithm to predict the risk of sight threatening retinopathy in a multi-ethnic patient group treated in a Dutch hospital, at the European Association for the Study of Diabetes annual meeting, Stockholm.

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Kim Marleine Holtzer-Goor was born on July 27, 1980 in Rotterdam, the Netherlands. In 1998, she graduated from secondary school (Athenaeum) at the Comenius College in Capelle aan den IJssel. She then attended the Erasmus University Rotterdam, where she graduated with a master's degree in Health Policy and Management in 2002. From 1999 to 2002, she was a student research assistant at the institute for Medical Technology Assessment (iMTA); she contributed to a cost-effectiveness study in multiple myeloma. At the same institute, she completed her master's thesis on the cost-effectiveness of CO_2-laser decortications versus radiotherapy in glottic carcinomas. After her graduation, she worked as a policy advisor in the mental health sector, supporting project teams and drafting protocols and policy documents. In 2004, she returned to iMTA as a researcher. Her first project at iMTA was the observational study in chronic lymphocytic leukaemia as described in this thesis. During her time at iMTA, she has been working on several health technology assessments such as screening in nursing homes for elderly with low vision, the substitution of care to glaucoma patients, visual revalidation and the personalization of the screening interval for diabetic retinopathy. She is currently finishing the project in diabetic retinopathy at the VU University Medical Centre Amsterdam.

She lives in Nieuwerkerk aan den IIssel with her husband Paul and their two children Lars (2009) and Vera (2012).

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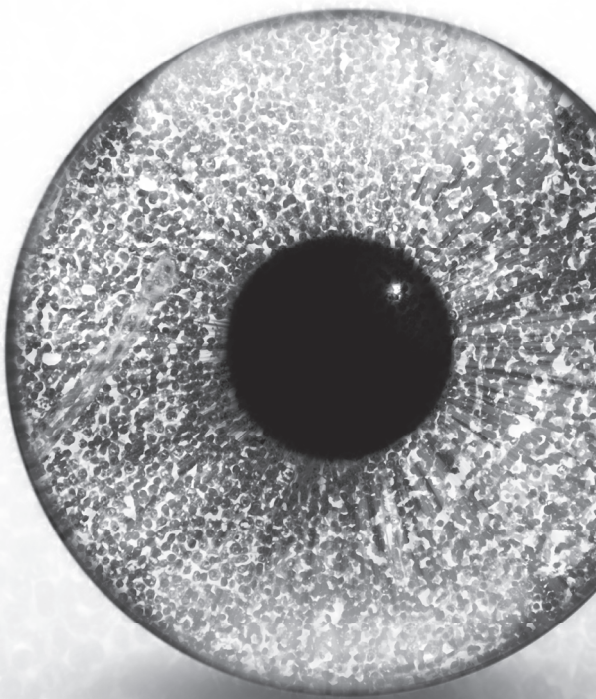

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