Part II

The
TOM and OMA
projects
This chapter describes the development of the methodology of two intervention studies, TOM and OMA. Both studies are designed to prove the effect of the provision of pharmaceutical care. TOM studies the effects of pharmaceutical care in asthma patients, OMA studies the effects of pharmaceutical care in the elderly, using 4 or more different medicines.

The hypothesis that pharmaceutical care improves patients’ Health Related Quality of Life (HRQL) can in principle only be proven by providing the first and measuring the latter in a controlled trial. The effects of the provision of pharmaceutical care by the pharmacist are best measured in patients receiving chronic medication, since care is a process over time and more drug related problems can evolve. This does not mean that a concept like pharmaceutical care has no place in over the counter (OTC)-medication or short-term use of prescription drugs e.g. courses of antibiotics or pain-relieving medication. But it is more likely that the benefits of pharmaceutical care can be proven in those patients who have a more or less steady medication-regime, since they visit pharmacies frequently and their medication gives the pharmacists different angles to apply their care, skills and knowledge.

The contents of pharmaceutical care can be such that many different approaches are possible (see Chapter 1). A basic pharmaceutical care circle can be applied, with an emphasis on therapeutic outcome monitoring (TOM) like Heplers’ concept of pharmaceutical care. This type of pharmaceutical care is suitable to be applied to patients with specific, drug sensitive diseases like asthma and diabetes. The medication can then adapted to the actual disease state of the patient. In those cases it must be possible to prove that the intervention results in a short time better control of the disease. But one can also imagine a more diffuse process in which the pharmacist performs drug use evaluations, keeping an eye on specific patient characteristics, interactions, other adverse drug related problems including compliance, where counselling is an almost continuous process like described by Cipolle, Strand and Morley in 1998. In such comprehensive pharmaceutical care many pharmaceutical care circles may be present at the same time and influence each other. Preventive actions by the pharmacist will not directly be recognised by the patient or reflected in a better short-term disease control, for instance in hypertension. Such a type of pharmaceutical care can be applied in patients with some equal characteristics (e.g. age, gender) or multiple or complex diseases. In those cases the link between medication and effect is less clear but the same benefits may evolve like increased compliance, less side effects, better coping and presumably a better HRQL.
In both types the increased professional attention by the pharmacist in itself may already have an improving effect on several outcomes, or as Louis Nizer said:

‘Words of comfort, skilfully administered, are the oldest therapy known to man’.

The first part of this chapter gives general information about the drug use and possible drug related problems in both populations. The second part outlines the study design, data-collection and the interventions, followed by some additional considerations and a table with an overview of the design.

3.1 Introduction

3.1.1 Asthma and drug use

According to the Nederlands Astma Fonds, about 5% of the Dutch population have asthma, i.e. 700,000 people. Another 5% have chronic bronchitis or emphysema. The mortality rate as a result of asthma in The Netherlands is rather low in the age group 5-34 year: 0.3 per 100,000. This means that measuring changes in mortality as a result of an intervention will not render useful information, unless the sample size and duration of the project are very large. Obstructive airway diseases in The Netherlands are mainly treated by the general practitioner (80%), the rest by medical specialists. Inhalation therapy is the most common treatment method (86%).

In several projects it has been proven that many patients with asthma feel insecurity, fear, depression and anger. Part of these feelings probably originates from insufficient information and knowledge about the disease. It can be expected that more knowledge, better guidance of the treatment and improved pharmacotherapy will influence these feelings.

Many asthma and COPD patients still have questions about their disease and its treatment. As a result of a Dutch television program ‘Het leven gaat door’ (‘Life continues’) in May 1997, a telephone team received 146 questions. Most questions (47%) were related to the aetiology of the diseases and drug use and 29% were related to drugs and drug use. Findings from van Ganse et al. show a suboptimal education and health status in a random sample of asthma patients and most patients expressed a negative attitude towards the use of inhaled corticosteroids, which is the cornerstone of the treatment.

It has been postulated that the measures of emotions are sometimes better predictors of the course of asthma than some medical parameters like PEF-values. But measuring these emotions is too complex for the purpose of a large-scale study. On the other hand, measuring HRQL, as will be performed in the TOM study, includes the emotional aspects of the disease. More practical and measurable parameters are frequency of awaking at night, presence of morning dip in peak expiratory flow rate (PEFR) and frequency of use of beta-agonists.

The perception of symptoms in COPD and asthma-patients is poor in general, but in asthma this perception is better than in COPD. Usually it is found that in asthma there is

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Throughout this paragraph data and statements are also used from: Maillé AR, Kaptein AA. Omgaan met CARA. Sociaal wetenschappelijk CARA-onderzoek op weg naar de toekomst. Leusden, Astma Fonds, 1993. ISBN 90 668 014 0.
only a discrepancy between objective and subjective obstruction in 15% of the cases. Self-measurement of the peak-flow improves the signalling of bronchial obstruction, although keeping a symptom-diary might sometimes serve the same purpose. In the publication of Kendrick et al., a high frequency of poor symptom perception of 60% was found in patients treated for asthma in general practice, however, in this study no proper difference between asthma and COPD was made.

In The Netherlands in 1993, when this study was designed, no self-management scheme was advised by the Dutch organisation of general practitioners (NHG), nor by the patient-organisation or the Dutch Asthma Foundation. Glaxo introduced a self-management program in March 1993, but it was not widely distributed at that time. In some regions lung-specialists started to introduce self-management in 1995 (i.e. Enschede). Although no well-designed controlled study has been published to date on the positive effects of self-management and self-treatment, results of other studies indicate that self-management improves asthma control.

According to a study published in 1989 only approximately 13% of the asthma patients show full compliance. Better coaching of asthma patient therefore seems desirable, not only to prevent acute exacerbations of asthma but also to improve persistent pulmonary morbidity and prevent emphysema, of which the first is closely linked with the quality of life. It is to be expected that application of pharmaceutical care will improve compliance. Improving communication and implementing self-management have positive effects on compliance. Some general practitioners as well as lung specialists and paediatricians in The Netherlands are becoming more aware of the improvements achieved in self-managed asthmatics, but the patient’s lack of knowledge proves to be a barrier. Occasionally special asthma-nurses and clinics are put in place. The TOM study uses these strategies, but originated and implemented by the community pharmacist. Self-management plans in themselves are known to significantly reduce the number of doctor consultations and the use of oral steroids/inhaled beta-mimetic agents, if properly implemented.

Asthma is a reversible obstructive airway-disease. The causes of the obstruction can be manyfold, ranging from emotions or effort to allergens or smoke. If obstruction occurs, there is always some form of inflammation process present in the airways, which can be treated with drugs in several ways. The acute treatment with short acting beta-agonist agents usually is the first step. The actual inflammation is not being treated by this class of drugs, but the dilatation of the airway by itself should last long enough for the cause to subside. What the next step should be, if occasional treatment with a beta-agonist agent by inhalation does not treat the condition sufficiently, depends on the protocol followed by the physician, but in general chronic use of inhaled corticosteroids is advised.

Protocols or critical pathways for the treatment of asthma differ over the world. Currently most protocols adhere to two international consensus reports on the treatment of asthma. The older one is very clear but does not include long acting beta-sympaticomimetic agents in the treatment schedule. The newer one is more diffuse but allows for long acting beta mimetic agents to be used. The Dutch standardised protocols differ only slightly from the international consensus documents. Since the start of the project a new Dutch standard has appeared with a slightly different approach, in which long acting beta-mimetic agents...
are introduced into the treatment, but this standard has not been used as a basis for the study. Anti-leukotriene drugs are not yet included in any treatment-standard.

3.1.2 Drug use in the elderly

The use of drugs in the elderly has been subject of many research projects. Several forms of problems may occur when elderly people use different drugs, e.g. compliance problems, increased risk of adverse drug reactions and drug interactions, and drug misuse. In general the researchers have found a significant overuse of drugs, estimated to be 25% by Lamy. The use of drugs in the elderly is high. From a study in a group of independently living older people in a rural area in The Netherlands it was concluded that over 90% had used drugs in the four weeks previous to the interview, 87.4% on prescription and 12.6% over the counter (OTC). In a Swedish population of patients over 80 years old around 1995, Giron et al. even found that 94.1% had used drugs, during the period of 2 weeks before the interview. Using a certain drug for a period longer than originally intended (55%, 'once a drug, always a drug'), appeared to be a major problem followed by incompatible combinations of drugs (22%). In an American study published in 1992, an average number of 5.6 drug-related problems per patient was found in the elderly over 60, who were responsible for taking their own medication. From the results of these research projects it can be concluded that several factors are responsible for the high and/or incorrect use of medicines in the elderly. Firstly women tend to use drugs incorrectly more often than men do. The chance of incorrect use increases with the frequency of visits of the GP, the amount of help people need in handling their medication, the amount of information they have and the positive attitude towards the use of drugs in general. In general patients are quite satisfied with the provision of information but from the result of the first study it is surprising that people who read the information leaflets and get more oral information, also tend to show incorrect use more often. The latter findings might be due to a misinterpretation of information, or a bad quality of the information leaflets.

The principal groups of drugs being used in the elderly in The Netherlands are cardiovascular drugs, analgesics, sedatives, antacids and hypoglycaemic agents. According to a Dutch publication in 1993, drug use decreases from 2.5 to 2.1 drugs on average, when older people are admitted into a psychogeriatric ward. This indicates that drug-use can decrease if it is properly monitored.

Data from the AFTO-database show that in 1996 benzodiazepine hypnotics and sedatives are used by 33% of the Dutch population over 65 years (calculated on 10,334 patients of whom the date of birth was known). In the general population this figure is only 14.5% (calculated on 65,702 patients of which for 1.78% the date of birth is unknown). This enormous overuse of benzodiazepines (they use 127% more then the average population) has to be taken into consideration when developing a pharmaceutical care project in the elderly, because this class of drugs has many unwanted effects in this population especially in higher dosages.
ones found by van Hulten in his rural population in the North of The Netherlands (131.2% and 145.3% in 1992 and 1990 respectively)

The pattern in the USA is somewhat different and therefore not comparable in detail. In a study published in 1992, using the database of the Established Populations for Epidemiologic Studies of the Elderly, 60-68% of the men and 68-78% of the women older than 65 use drugs on a doctors’ prescription. According to the results of the same project 52-58% of the men and 64-76% of the women used OTC-drugs. Users of drugs were especially found in the elderly with symptoms of depression. Also handicapped people, elderly people who were in hospital more often than average and people with little insight into their own health used more drugs than average. It is probable that this difference between the countries is a result of differences in insurance-systems.

3.2 TOM and OMA, the study design

It was decided to study the effects of pharmaceutical care in asthma patients, where Therapeutic Outcomes Monitoring can be applied and self-management can be put in place. This study is called TOM of Holland. In this patient group improved drug-use should result in better control of the disease, better coping behaviour and through these effects, a better HRQL. In spite of the relative clear-cut model of Therapeutic Outcome Monitoring, it was nevertheless expected that several pharmaceutical care circles would be present at the same time. Parts of the basics of the Dutch study are described by Jansman et al. Similar studies are under way in Austria, Belgium, Florida (US), Iceland, N. Ireland, Norway, Germany, and Canada. A TOM-asthma study was completed in Denmark in 1995, but to date the results have not been published in the international literature.

It was also decided to study the effect of pharmaceutical care in the elderly over 65, using 4 or more different drugs and living independently. This study is called OMA (which stands for ‘Ouderen Medicatie Analyse’) or Elderly Medication Analysis. In this patient group the increased rationality of the treatment and better control over side effects, together with the increased attention by the pharmacist should result in a better HRQL. Similar studies, based upon our protocol, are now under way in Denmark, Germany, Ireland, Northern Ireland, Portugal and Sweden, co-ordinated through a Biomed grant.

3.2.1 The hypothesis

The hypothesis for both the TOM and OMA study was: A specified process of pharmaceutical care does improve the HRQL of the patients involved, the satisfaction of patients, pharmacists and GPs involved, the knowledge on drugs and diseases, the drug use and the use of medical resources of the patient. Derived from this hypothesis, the outcomes to be monitored in the studies are the following.

- Health Related Quality of Life of patients;
- Satisfaction on the provided care of the patients;
- Satisfaction on the provided care of the GPs;
- Satisfaction on the provision of care of the pharmacists;
- Disease state;
- Patients’ knowledge of disease state and medications;
Drug use (including compliance);
- Use of medical resources.

### 3.2.2 Reference groups

Both studies are designed as controlled (cohort) studies, because pharmaceutical care is in a rapid development (see Chapter 1 and 2) in The Netherlands. External reference groups for both studies were selected from randomly chosen pharmacies.

**Crossed design, internal reference groups**

What happens if a pharmacist starts providing pharmaceutical care to a specific group of patients? Would there also be a general influence on the way other patients, with other characteristics than the intervention group, are treated in this pharmacy? Would there possibly be an influence on the attitude of the pharmacist at the counter or the provision of information? To study these effects it was decided to include a second reference group, the internal reference group. Table 3-1 outlines the connection between the TOM and OMA-study. The reference patients were all selected in the same manner as the intervention patients.

N.B. In the TOM-pharmacies, the elderly were the internal-reference group; in the OMA-pharmacies the asthma patients were the internal-reference group.

<table>
<thead>
<tr>
<th>Table 3-1 Cross links between TOM and OMA-study</th>
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<tbody>
<tr>
<td><strong>Intervention patients</strong></td>
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<tr>
<td>TOM pharmacies (n=18)</td>
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<tr>
<td>OMA pharmacies (n=21)</td>
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<td>Ext. Reference pharmacies (n=15)</td>
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### 3.2.3 Patient selection

The TOM project

To be able to measure the changes in all domains of HRQL with one of the selected instruments, the SF-36, a minimum of approximately 300 patients was required (see section 3.6). Therefore an attempt was made to find 20 pharmacists all over The Netherlands, who would each recruit 25 patients, to allow for a dropout rate of 40%.

The intervention pharmacies for the TOM study were directly requested to co-operate by the research team, on the basis of a shown interest for the research. The pharmacists of those pharmacies were already active in the field of providing information and actively involved in medication surveillance. Patients were selected by means of the automated prescription database in each participating pharmacy. To be able to have a population with mild to moderate asthma, the pharmacists were asked to provide a list of all patients who had...
received both beta-mimetic agents and corticosteroids per inhalation in the previous 6 months‡. Excluded were:

- patients younger than 20 (less likely to co-operate);
- patients over 45 (more likely to suffer from COPD);
- patients using continuous oral prednisolone or more than 3 courses of oral antibiotics or prednisolone per year (more likely to have chronic bronchitis or severe asthma);
- patients using ipratropium bromide (more likely to suffer from COPD).

These selection criteria later proved to resemble those of Osborne et al. and are more elaborate than those mentioned by van der Molen. The selection criteria were tested in one pharmacy by checking with the GP if the selected patients indeed had asthma. In 95% of the cases this proved to be the case, according to the GP. When the same therapeutic selection criteria in this pharmacy were applied to 45-50 year old patients, 73% of this group had COPD according to the GP.

After the initial selection in the pharmacies, the research team randomly assigned a new sequence to the list and the pharmacists were asked to ask the patients in the given sequence by telephone if they would like to co-operate. Then an information leaflet was provided through the pharmacist and a preliminary registration form. This form was sent back to the research team. Pharmacists continued until they had 30 positive responses and 30 registration forms were received. Informed consent forms were signed at intake. Control patients were recruited in the same way, in randomly chosen control pharmacies and the pharmacies participating in the OMA project.

**The OMA project**

In the elderly group a higher dropout rate was expected than in the TOM-group. To be able to measure the expected changes in most domains of HRQL with one of the selected instruments, the SF-36, a minimum of approximately 300 patients was required (see section 3.6). Twenty pharmacists throughout the Netherlands were needed who would each recruit 30 patients, thus allowing for a dropout rate of 50%.

The intervention pharmacies were recruited by means of an article in the weekly Dutch pharmacist journal the *Pharmaceutisch Weekblad*. Most of the pharmacies included were already active in the field of providing information and actively involved in medication surveillance. Patients were selected by means of the automated prescription database of each participating pharmacy. Pharmacists were asked to provide a list of all patients who were 65 or older and used 4 or more different drugs on prescription. Patients living in nursing homes were excluded from the study. The research team then randomly assigned a new sequence to the list and the pharmacists were asked to ask the patients by telephone if they would like to co-operate. The research team then provided an information leaflet via the pharmacist and a preliminary registration form. This form was sent to the research team. Pharmacists continued till they had 30 positive responses. Informed consent forms were signed at the intake.

‡ The possible number of patients per pharmacy was estimated by a small test-run in 5 pharmacies, in which all users of corticosteroids and beta-mimetics were listed per age-group of 5 years. This usually generated between 50 and 60 patients in the age group between 25 and 40.
When people are filling in a HRQL questionnaire, they are supposed to be able to express their opinions and feelings and have a reasonable possession of perceptual functions. In the case of the elderly this might not always be the case and therefore it was decided to include an instrument for measuring the mental state, the Mini-Mental State Examination (MMSE) into the OMA study. This instrument is a brief screening test that quantitatively assesses the severity of cognitive impairment. The MMSE seemed the most appropriate because its contents are highly verbal, which suits research purposes in the field of care. It has been well validated and used all over the world. It has been translated into Dutch. Although the Dutch MMSE is not fully validated, it has been in use for a long time. Some authors state that the MMSE scores are also sensitive to changes in drug use, especially CNS drugs. This was, however, not confirmed in a recent study by Janzing et al. The cut off point (19-23) depends on age, education and social status. After the intake a final selection by the research team excluded all patients with a MMSE score < 20. The MMSE was administered face to face. In the elderly intervention group the pharmacists administered the MMSE while in the reference group it was administered by paid volunteers or the staff of reference pharmacies. The research team trained all interviewers.

Control patients for the OMA study were recruited in the same way, in randomly chosen control pharmacies and the pharmacies participating in the TOM project.

3.2.4 Length of the studies and time schedule

Pharmaceutical care was expected to be a lengthy process. To allow for the process and the outcomes to be studied as completely as possible it was decided to design two-year studies. Because it was also known that changes in HRQL have the tendency to return to the original value, intermediate assessments were planned.

The selection procedures started in September 1994 and were completed in November 1994. Both studies therefore started around December 1994. The time-schedule for the collection of the different data can be found in table 3-2. In the same table it is recorded who was responsible for the collection of the data and where the data should be collected. Data collection was concluded relatively late in May 1997, due to the fact that some intervention pharmacies experienced delays in performing the intakes and that there was a delay in getting the data to the research centre.

3.2.5 Training of the pharmacists

To enable the pharmacist to provide pharmaceutical care optimally, three one-day education sessions were organised before the start of the projects. During the projects one-day education and evaluation sessions were organised every 6 months (see section 3.5).

3.3 Data Collection

Three sources were used for collecting data: the patient, the pharmacists and general practitioners. Information from pharmacists and GPs was obtained by mailed questionnaires. Information from the patients was obtained in two ways.

We obtained the Dutch version in September 1994 from Prof. Dr. T.J. Heeren, H.C. Rümke groep, Zeist, The Netherlands
Through pharmacists, at the intake and the half-year consultations;

Through mailed questionnaires, telephone assisted and directly sent back to the research team (e.g. HRQL, satisfaction).

Answers to questions in our questionnaires could in general be given in either a 2 point (yes/no) scale or a 5-point Likert scale (global frequencies, opinions). Validated instruments were not altered and the appropriate scales were used. Since similar projects are now being or have been conducted in other countries, the use of international instruments for measurements of final outcomes, if available, was preferred to be able to compare results. This applies especially to the field of HRQL assessment.

In the table 3-2 the main items on which data were collected, when they were collected and by whom, are summarised.

| Table 3-2  Time schedule TOM / OMA incl. sources of data |
|-------------|--------------|------------|----------------|
| Demographics | 0  | 6  | 12 | 18 | 24 | Patient | Pharmacist | GPs |
| HRQL | R,P | R | |
| Satisfaction with care provision | R | R | R | R | R |
| Drug use | R,P | R | |
| Use of medical resources | R | |
| Severity of symptoms* | R,P | |
| Peak flow data* | R | |
| Knowledge about diseases and | + | R | |
| Compliance with drug use | R,P | R | |
| Time investment of pharmacist | R | R | |
| Opinion on PhC | R | R | R | |
| Contents of consultations | R | R | |

* Only in TOM project
# P=Data collected by pharmacist. R=Data collected by research team directly
+ During the studies it was decided to omit the 12 months knowledge assessment

3.3.1 Dealing with Bias

If data were sensitive to bias as a result of the relationships between the pharmacists and other parties, those data were asked for in the mailed questionnaires that should be sent back to the research centre directly. Some items were to be double-measured because self-reported data sometimes differ from data reported by others (e.g. compliance, health status, the contents of consultations, time investment).
3.3.2 Collection of demographic data
To be able to interpret the results, demographic data were collected from the patient (age, gender, life-style, etc.) by questionnaires and patient interviews by the pharmacists. Basic data about the pharmacists and his/her pharmacy (size and location of the pharmacy, age and interests of the pharmacist, number of workers, computer systems) were collected through interviews by the research team.

3.3.3 Collection of data on process, intermediate and final outcomes
Although Health Related Quality of Life is by definition the final outcome of pharmaceutical care (see Chapter 1 and 2), not only this outcome was measured but also other possible effects of pharmaceutical care, for instance on the use of health service and drug use. In the field of HRQL it was decided to use the SF-36 as generic instrument and the Asthma Quality of Life instrument devised by Juniper and Guyatt (see also section 3.6). To avoid possible bias when the intervening or other pharmacists administer those questionnaires, it was decided to use mail versions to be returned to the research team. It was also decided to provide the patients with independent telephone assistance for filling in questionnaires because HRQL instruments (and our questionnaires) are lengthy and sometimes complex.

The patient’s satisfaction with the care provided is of course of paramount importance. According to Robert satisfied patients get well more quickly. This satisfaction was measured by straightforward questions in the questionnaires, but also by asking opinions on the role and skills of the pharmacist and other health care professionals. Satisfaction-questions were always asked directly to the patient by the research team.

In view of current and future developments also the satisfaction of pharmacists and general practitioners can not be neglected. The professional satisfaction of the pharmacists, with the provided care, and of the GPs involved, about the provided care, was also asked directly in a self-reported questionnaire.

The data on drug use were collected, 6 months before the intervention as well as during the intervention. The analysis was concentrated on the use of beta-agonists, inhaled and oral corticosteroids and the antibiotic use in the TOM patients. In the OMA project the use of benzodiazepines and diuretics was concentrated upon. The latter group can be used as a parameter for compliance.

The use of medical resources was measured in the patient completed questionnaires, to be able to get an impression of the possible financial benefits involved in the provision of pharmaceutical care.

Questions on the severity of symptoms and peak flow data were only applicable in TOM-patients. During the intake questions were asked by the pharmacist to estimate the severity of asthma. Some questions concerning asthma symptoms were also asked directly to the patient. In the TOM-project the pharmacist were asked to collect 3-day peak-flow data from all TOM-patients at intake and at each consultation. Peak-flow meters were centrally distributed, including diaries and instructions for use.

—- Peak flow meters for the project were provided by Pharmachemie, Haarlem.
Since increased knowledge also plays a role in coping capability (certainly in asthma it helps with the illness adaptation\textsuperscript{41}), it was decided also to measure the development of knowledge in the patients. The knowledge questions were asked via the pharmacists about either asthma-related subjects (TOM) or heart disease related subjects (OMA). Currently no validated Dutch instrument to measure knowledge exists. Therefore it was tried to develop a sensitive instrument that would both measure actual knowledge as recalled knowledge. A sample of the questionnaire can be found as Appendix 6 to this dissertation.

Changes in compliance with the medication were also expected, but measuring the concept of compliance is a complicated matter, because compliance has different meanings depending on the interpreter\textsuperscript{42,43,44,45}. Sometimes the term ‘adherence’ is used, meaning adherence to professional advice. Improving compliance is also a complicated activity. From the 13 randomised clinical trials evaluated by Haynes through the Cochrane collaboration, only one showed significant improvements as a result of counselling and written information. Six studies showed an improvement in treatment outcomes\textsuperscript{46}. Usually the patients’ viewpoint is not taken into account and therefore the term ‘concordance’ has been used, meaning that there should be a concordance in the intentions of patient and physician as to the way a treatment should be implemented\textsuperscript{47}. Hippocrates, who gives his opinion very much from the physicians’ viewpoint, best describes the dilemma:

‘Keep watch also on the fault of patients which often make them lie about the taking of things prescribed\textsuperscript{48}.

Nevertheless, compliance may influence outcomes. There are different ways of measuring compliance\textsuperscript{49,50}, and for these projects it was decided to use two indirect methods because of their relative simplicity. Firstly to ask the patients if they ever skip a dose or take a dose extra. And secondly to study the computer medication-data for delays or overlap in getting the refills for certain drugs. But there may still be a difference in information from the pharmacists automated prescription data and the actual advice received by patients from professionals who are treating them.

Data on time investment were mainly asked to the pharmacists. Some questions concerning the length of the consultations were also asked to the patients, as a control. Of course these data were not yet available at the intake. Time investment data can be used for the economical evaluation. Pharmacists were therefore also asked how much time they spent on other matters concerning the provided care (preparation, performing drug use evaluations). The opinion on pharmaceutical care could of course only be asked at people with experience, meaning the intervention patients, the intervention pharmacists and the GPs of the intervention patients. Such data may help to explain the satisfaction data.

The contents of the consultations were assessed as a process outcome, to be able to analyse if the proposed intervention had taken place.

3.4 The content of the offered care
In both studies only pharmacists would provide the full scope of pharmaceutical care and the assistant pharmacists would only play a marginal role. However, in the OMA-study
assistant-pharmacists were allowed to conduct a small part of the protocol. The contents of the care offered was as follows (see also table 4-4):

- An intake to get to know the patient and initiate data collection for the study and pharmacist’s documentation;
- Frequent pharmacist-patient contact, every time a prescription is dispensed. These frequent contacts should establish a relationship based on mutual trust and thus enable patients to access the pharmacist more easily whenever they have medication related problems or just want to discuss their pharmacotherapy;
- Every half-year a consultation with the pharmacist, in which extra attention will be paid to medication related problems, a drug use evaluation will be performed according to the guidelines as described in Appendix 1 to this dissertation;
- An intervention of the pharmacist regarding the patients’ medication, whenever there is a reason. These interventions will always be discussed with the patient, before contacting the GP if necessary.

3.4.1 Additional care in the TOM study

Additionally in the TOM study the pharmacists were asked to provide following:

- Installation of a self-management program in co-operation with the GP and regular evaluation of the PEF-measurement results, at least once every 6 months;
- Regular inhaler instruction based upon an article by van Mil et al.

The self-management protocol

In the British Thoracic Society Asthma Self Management Protocol, dating from 1990, an action by the patient is required if the PEF-value is less than 75% of their maximum consistent PEF-value, i.e. doubling the steroid dose over a certain period with no change in bronchodilator-therapy. If the PEF is less than 50% of the maximum consistent PEF-value, contact with the physician is required. Under 25% the patient must go to hospital without delay. Charlton and others have described a similar project in general practice in which the limits were 70%, 50% and 30%. That study was carried out in a nurse-run asthma-clinic. Collins et al. have adapted that study to a set of instructions of their own, which were used within the Australian Asthma Management Plan. They used limits of 80%, 70% and 60%.

In the international consensus the limits are 80 and 60%. Between 80% and 100% (the green zone) no action has to be taken. Between 60 and 80% (orange zone) doubling the inhaled corticosteroid dosage is required until the peak flow has returned to its 80% value and then one week more, possibly without consulting a doctor. Below 60% (red zone) medical intervention is necessary, and the patient is advised to contact his physician immediately.

As the pharmaceutical industry is handing out PEF-meters more or less freely, portable peak-flow meters can be obtained. Use of the same brand of meter for all participating patients has to be ensured. Charlton selected the cheap and accurate Mini-Wright peak flow

†† This protocol has been used in a study in 300 patients, by Dr. K. Jones, Department of Primary health Care of the Medical School in Newcastle upon Tyne. The follow-up period was 6-9 months. In July 1993 the study was in its evaluative phase.
meter as has the Dutch Asthma-Fonds. It is the most popular PEF-meter to date certainly for use in adults and its accuracy has been properly evaluated.

Although Miller has doubts about the error-profiles of the different meters available (and advises the development of a self-management scheme on the basis of the PEF-meter that is going to be used) he also used the Mini-Wright instrument.

On basis of the international consensus it was therefore decided to use the 60-80% limits in the TOM study and because of its proven accurateness, the Mini-Wright PEF-meter.

3.4.2 Additional care in the OMA study

In the OMA study, pharmacists were asked to additionally provide the following:
- House visits when the patient was unable to come to the pharmacy for the six monthly consultations or whenever necessary;
- An effort to decrease the use of benzodiazepines in the target group.

Influencing benzodiazepine use

Influencing the use of benzodiazepines is not an easy task for pharmacists. Support from the GP, and support of the GP by the pharmacist is certainly necessary. Several studies indicated that reducing benzodiazepine use in the elderly in general is a difficult, but not impossible task.

The withdrawal from benzodiazepines is a complex procedure. On top of the dependency, which must be broken, there is also a high probability of recurring anxiety-related symptoms and frequent sleep-disturbance. Success rates of gradual withdrawal programs vary between 50 and 70%, but no specific data in large populations of elderly are available. Ashton reports that in younger patients the success rates of her program were better than they were in the elderly. She reported a success rate of 70% in the younger population in the UK. All patients in the program were referred to a clinical pharmacologist. Schweizer et al. found almost the opposite. Their elderly patients (over 60) showed significantly less severe withdrawal symptoms during gradual tapering than younger (under 55) patients, and did as well regarding outcomes. Both groups were rather small, however, (19 and 22 patients respectively) and were outpatients under psychiatric surveillance. Reasons for these conflicting results might be found in the programs used in the population studied. Schweizer’s study was performed in a university psychiatry unit and his success rate was, after 4 weeks, only 50% in both the elderly and younger group. Ashton’s population was not primarily a clinical psychiatric one.

Most withdrawal or detoxification programs describe a gradual dose reduction, but the rate at which the withdrawal is obtained and the dosage schedules used, differ substantially. The usual withdrawal period is 1-3 months. Ashton, an experienced worker in this field, suggests leaving the control over the rate of dosage tapering to the individual patient, an idea very much supported in view of the desired outcome. Swantek et al. described the use of carbamazepine to treat benzodiazepine withdrawal symptoms in only 4 elderly patients. The results are vague and are not likely to be reproducible in a non-hospital setting. It

‡‡ Because of unforeseen circumstances the selected peak-flow meter was changed during the study.
should be questioned whether the approach of replacing one drug by a drug from another class, with its own side effects and interactions, is such a good idea.

Holton studied a population of 41 patients and has been looking into factors, which may predict the long-term success of a benzodiazepine-withdrawal program\textsuperscript{63}. Unemployed men, under the age of 50 with little or no premorbid personality disturbances will usually do very well. Conversely older women with considerable anxiety related symptoms, even when taking benzodiazepines and with personal disturbances, are unlikely to do well.

According to a panel of GPs, stopping the use of benzodiazepines was indicated in 43\% of the chronic users in their practice\textsuperscript{64}. Only in 10\% of those 100 users the GPs actually managed to let the patients stop. A recent article by Hijzeldoorn et al. described a 19\% reduction in chronic benzodiazepine use through a pharmacist supported GP intervention. The only intervention was that the GP informed the patient of the dangers of benzodiazepine use when writing a repeat prescription. During the study the use of this class of drugs in a reference group increased with 19\%\textsuperscript{65}. Coolen and Sitters describe a new project and different examples of reducing the use of benzodiazepines in co-operation with GPs in The Netherlands in 1998\textsuperscript{66}. The results of this project will be available in 2001.

In the OMA study the pharmacists were advised to try to gradually decrease the dosage by 10\% in one-week steps, after consultation with the patient’s GP.

### 3.5 The education of the pharmacists

Although pharmacists are academic professionals, this does not necessarily mean that they have all knowledge, attitudes and skills to provide pharmaceutical care ready to use. The pharmacists also needed to have some insight in the research method. Therefore the TOM and OMA pharmacists received four half-day training sessions on different topics before the projects started. During the projects additional half-day training sessions were provided, each dealing with specific topics they had come across while providing care.

Topics for the pre-intervention training for TOM pharmacists included asthma and pharmaceutical care, the treatment of asthma, asthma treatment standards and self-management, communication with GPs and patients, the content of the protocol, and the selection of patients. During the project, every six months, half-day training sessions were given on performing medication analysis, giving inhaler instructions, the relationships and communication with patients and physicians, the mechanisms and treatment of asthma, self-management, and the patient’s view on the meaning of suffering from asthma.

Topics for the pre-intervention training for OMA pharmacists included the elderly and pharmaceutical care, medication problems and the elderly, communication with GPs and patients, the content of the protocol, and the selection of patients.

During the project, every six months, additional half-day training was given on drug use evaluation and medication analysis, relationships and communication, benzodiazepine use and withdrawal, and heart diseases and their medications.
3.6 Research and documentation tools and their use in Pharmaceutical Care

During the TOM and OMA study a number of instruments were used or developed for documenting the care. The main problems of pharmacy practice research and thus pharmaceutical care research in the field of strategy are the facts that experimental conditions can hardly be influenced by the researchers and that there is a large possible variety in outcomes. It is therefore essential that the intervention is described in detail and that the process be monitored well. Odedina and Segal have developed an instrument to measure the pharmacists’ activities, but this instrument was not yet available at the beginning of the TOM and OMA study. The outcomes of care are partially subjective and include a large array of human variables. This implies that many instruments should be used to measure outcomes, or a limited number should be chosen in the knowledge that not all results of the application of pharmaceutical care, or the fulfilment of all pharmaceutical needs of patients, will be measured.

During our studies the Problem-Assessment-Solution (PAS®) system was developed, to document elements of the consultation process. The system can also be used to analyse the occurring drug related problems using statistical methods and has been added as Appendix 2 to this dissertation. In 1999 the Pharmaceutical Care Network Europe started the development of a new documentation system, which is partially based upon the PAS® concept.

The ICPC-code, a documentation tool to register diseases and complaints, was adapted to the needs of pharmacists providing pharmaceutical care. The results of that adaptation were published.

For documenting and analysing the patients’ drug use, the ATC and DDD coding was used, not only because it is a good system for pharmacoepidemiology, but also because Dutch drug files for pharmacy computer software includes the ATC-codes of drugs.

The choice of quality of life instruments

Health related quality of life is the main outcome of all forms of care. In pharmacy the concept became important with the definition of pharmaceutical care. Health related quality of life (HRQL) as a research subject in relation to medicines became important as a marketing tool for the pharmaceutical industry in the beginning of 1990. Today most registration-authorities demand HRQL evaluations within the registration files to be submitted.

A simple survey in Medline-advanced on the keywords ‘Pharmaceutical Care’ or on ‘Quality of Life’ and ‘Pharmaceutical Care’ (see Figure 3-3) shows an increasing number of hits for pharmaceutical care, starting in 1991. This simple fact is a good indication of the increasing importance of the pharmaceutical care concept in biomedical literature, although not much has been published yet about pharmaceutical care and health related quality of life combined.

§§ Remark of Prof Ingela Wiklund, Astra Sweden during the 2nd Symposium on Pharmaceutical Care, November 1996, Utrecht
Figure 3-3  Hits in Medline for HRQL and pharmaceutical care

The selection of a quality of life instrument has been described frequently in literature. Both Guyatt and König-Zahn have written excellent articles about this topic. Based upon their criteria it was decided to use the SF-36 as the generic instrument in the TOM and OMA study. Additionally in the TOM study it was decided to use the Asthma Quality of Life Questionnaire, based upon the criteria mentioned in the articles by Mallié et al. and Juniper.

3.7 Power calculation for the TOM and OMA study

Since Quality of Life is the major outcome of pharmaceutical care, the power calculations for both studies were based upon the two least sensitive domains of the SF-36, the major HRQL instrument. These domains are Physical Role and Emotional Role, and when the instrument is applied to detect a 5-point difference over time within one group, 300 patients are needed. The number of patients calculated per group would also be sufficient to measure a 5-point difference in the 6 other domains (Physical Functioning, Bodily Pain, General Health, Vitality, Social Functioning and Mental Health), when applying this instrument to measure differences over time between two experimental groups in a repeated measure design. A 5-point difference is clinically and socially relevant. For showing a 10-point difference (moderate differences) the maximum sample sizes is only 118, but such differences were not to be expected in this study.

3.8 Summary of the intervention

The interventions in the TOM and OMA study were developed based upon a number of considerations, described in this chapter. Although the interventions were complex, and difficult to monitor, they reflect the situation in everyday pharmacy practice in Dutch community pharmacies. The interventions find a firm base in the standard experience of the almost all Dutch pharmacists, who give drug-information to their clients and in the general presence of automated prescription databases, including medication surveillance.

Based upon the considerations and discussions in this chapter the following table (3-4) reflects the interventions for the TOM and OMA study.
### Table 3-4  Summary of the interventions in the TOM and in the OMA study

<table>
<thead>
<tr>
<th>TOM</th>
<th>OMA</th>
</tr>
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<tbody>
<tr>
<td>- The intake</td>
<td>- The intake</td>
</tr>
<tr>
<td>- Regular drug use evaluation</td>
<td>- Regular drug use evaluation</td>
</tr>
<tr>
<td>- Pharmacist-patient contact when drugs are collected in the pharmacy</td>
<td>- Pharmacist-patient contact when drugs are collected in the pharmacy</td>
</tr>
<tr>
<td>- Half yearly consultations and evaluations with the patient</td>
<td>- Half yearly consultations and evaluations with the patient</td>
</tr>
<tr>
<td>- Improving knowledge of and adherence to medication</td>
<td>- Improving knowledge of and adherence to medication</td>
</tr>
<tr>
<td>- Installing and coaching of self-management in co-operation with the GP</td>
<td>- House visits if patient is unable to come to the pharmacy</td>
</tr>
<tr>
<td>- Regular inhaler instruction</td>
<td>- Attempt to decrease the use of benzodiazepines</td>
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</tbody>
</table>

The results of both studies are described in chapters 4, 5 and 6 of this dissertation.

### 3.9 References to Chapter 3


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