ASSESSMENT OF DRUG PRESCRIPTION IN THE COMMUNITY: UTILIZATION OF CRITERION-BASED GUIDELINES

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by

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ABSTRACT

Pharmaceuticals are a fundamental component of health care delivery in today's society. Yet the necessity and appropriateness of their prescription is sometimes questionable. We performed two pilot studies to determine the feasibility of: (1) collecting patient specific data from physicians, (2) applying clinical practice guidelines to family physicians' therapeutic decisions and (3) using a trained research team versus an expert panel to measure the appropriateness of these decisions. These studies (a) examined the utilization of drugs for upper gastrointestinal (GI) disorders and (b) antimicrobial agents. In both studies two panels assessed the physicians' diagnostic and treatment decisions. To assess appropriateness of these decisions an expert panel used implicit clinical judgement and a research team applied explicit criterion-based guidelines. Comparisons of the decisions made by these two panels determined that it is feasible for a research team to apply guidelines to patient specific data and make decisions regarding the optimal treatment regime for patients examined.

The first study examined the use of drugs effective in the treatment of upper GI disorders as prescribed by six family physicians. The treatment decisions made by the physicians and subsequently judged by two panels showed that the panels agreed 95% of the time on the optimality of the physicians' decisions. From the high level of agreement we conclude that it is feasible to assess therapeutic decisions through the application of guidelines by a research team versus by an expert panel. However, the decisions made by the expert panel were used to assess the appropriateness of physicians' therapeutic decisions. Of the four drug categories analyzed, the overutilization and underutilization

rates were: proton pump inhibitors 12 and 35%; H_2 receptor antagonists 22 and 14%; antibiotics 3 and 55%; and prokinetics 8 and 0% respectively.

The second study investigated infection-related illnesses and the utilization of antibiotics by four family physicians. Two panels were involved in assessing the necessity for antibiotics and appropriateness of choice, using the *Ontario Anti-infective Guidelines for Community-acquired Infections* (1997). Patient interviews were performed and the congruency between patient and physicians' description of primary symptoms was 90%. Of the 98 patients included in the assessment, 22 were prescribed an antibiotic. When compared to the expert panel's decisions the subsequent application of the guidelines to the physicians' treatment decisions by a research team was highly sensitive and specific regarding the necessity for antibiotics but there was less agreement regarding the appropriateness of the type of antibiotic prescribed.

We conclude from both studies that it is feasible to collect patient specific data from physicians sufficient to assess therapy using a research team versus an expert panel and for the research team to judge prescribing appropriateness by applying explicit criterion-based guidelines. As a result of these pilot studies, two studies were designed to identify inappropriate prescription in the community, and to assess the impact of educational interventions on improving the prescribing practices of family physicians.

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TABLE OF CONTENTS

ABSTRACT ii

ACKNOWLEDGMENTS iv

LIST OF TABLES ix

LIST OF FIGURES xi

CHAPTER I: INTRODUCTION 1

1.1 BACKGROUND 1
1.2 APPROPRIATE PRESCRIBING BEHAVIOR 5
1.3 IMPROVING PHYSICIAN PRESCRIPTION: BACKGROUND 6
1.4 GUIDELINES 10
1.4.1. GUIDELINES AND QUALITY ASSURANCE 10
1.4.2. UTILIZATION OF GUIDELINES TO ASSESS PHYSICIANS' PRACTICE 11
1.5 DRUG UTILIZATION REVIEW 15
1.5.1. UTILIZATION OF EXPLICIT CRITERION-BASED GUIDELINES FOR DUR 17
1.5.2. DEVELOPMENT OF CRITERION-BASED GUIDELINES 18
1.5.3. PERFORMANCE OF DUR 19
1.5.4. FORMS OF DRUG UTILIZATION REVIEWS 21
1.5.4.1. Registry and Patient-Based Review 21
1.6 SUMMARY 25

CHAPTER II: UTILIZATION OF DRUGS FOR UPPER GI DISORDERS 27

2.1 DRUGS FOR UPPER GI DISORDERS: LITERATURE REVIEW 27
2.1.1. UTILIZATION OF UPPER GI DRUGS 27
2.1.2. EPIDEMIOLOGY OF GI DISORDERS 28

CHAPTER III: UTILIZATION REVIEW OF DRUGS FOR UPPER GI DISORDERS - A PILOT STUDY 30

3.1 RATIONALE 30
3.2 METHOD 30
3.2.1. DATA COLLECTION BY A RESEARCH NURSE 32
3.2.2. APPLICATION OF GUIDELINES 32
3.2.3. ETHICS 35
3.2.4. STATISTICAL ANALYSIS 35
3.3 RESULTS 36
3.3.1. PHYSICIAN AND PATIENT CHARACTERISTICS 36
3.3.2. DRUG UTILIZATION REVIEW USING THE EXPERT PANEL 39
3.3.2.1. Diagnosis 39
3.3.2.2. Treatment 40

TABLE OF CONTENTS (CONT'D)

3.3.3. FEASIBILITY OF USING EXPLICIT CRITERION-BASED GUIDELINES IN A DUR 44
3.3.3.1. Diagnosis 44
3.3.3.2. Treatment 45
3.3.4. DRUG TREATMENT BY DIAGNOSES 48
3.3.5. UTILIZATION OF DRUGS EFFECTIVE IN THE TREATMENT OF UPPER GI DISORDERS 49
3.4 CONCLUSIONS 52

CHAPTER IV: ANTIBIOTIC UTILIZATION 53

4.1 ANTIBIOTICS: LITERATURE REVIEW 53
4.2 INTERVENTIONS TO REDUCE ANTIBIOTIC UTILIZATION 56
4.3 SUMMARY 59

CHAPTER V: UTILIZATION REVIEW OF ANTIBIOTIC PRESCRIPTION IN THE COMMUNITY - A PILOT STUDY 60

5.1 RATIONALE 60
5.2 METHOD 63
5.2.1. SUBJECT SELECTION 63
5.2.2. DATA COLLECTION 64
5.2.3. ETHICS 65
5.2.4. EXPERT PANEL REVIEW 66
5.2.5. APPLICATION OF GUIDELINES BY THE RESEARCH TEAM 67
5.2.6. STATISTICAL ANALYSIS 67
5.3 RESULTS 68
5.3.1. PHYSICIAN AND PATIENT CHARACTERISTICS 68
5.3.2. FAMILY PHYSICIANS' ASSESSMENT 70
5.3.3. PATIENT TELEPHONE INTERVIEWS 72
5.3.4. RESEARCH TEAM VS. EXPERT PANEL DECISIONS 75
5.3.5. ASSESSMENT OF TREATMENT DECISIONS BY A RESEARCH TEAM APPLYING GUIDELINES 78
5.3.6. DRUG UTILIZATION SCORES BY PHYSICIANS 81
5.5 CONCLUSIONS 82

CHAPTER VI: DISCUSSION 84

6.1 LIMITATIONS OF PILOT STUDIES 84
6.1.1. DATA COLLECTION 84
6.1.2. APPLICATION OF GUIDELINES BY A RESEARCH TEAM TO ASSESS APPROPRIATENESS 85
6.1.2.1. Utilization of Upper GI Guidelines 85
6.1.2.1. Utilization of Antibiotic Guidelines 86
6.1.3. STUDY POPULATION 87

TABLE OF CONTENTS (CONT'D)

6.2 PROPOSED COMMUNITY STUDIES 88
6.2.1. LIMITATIONS OF THE PROPOSED COMMUNITY STUDIES AND PILOT STUDIES 89
6.3 STRENGTHS AND WEAKNESSES 94

CHAPTER VII: SUMMARY AND CONCLUSIONS 95

APPENDIX A: Consent Form: Upper GI Pilot Study

APPENDIX B: Abstraction Form: Upper GI Pilot Study

APPENDIX C: Criteria For Diagnosis and Treatment of Upper GI Disorders

APPENDIX D: Description of Drugs Used For Upper GI Disorders

APPENDIX E: Protocol for Community-based Upper GI Study

APPENDIX F: Consent Form: Antibiotic Pilot Study

APPENDIX G: Abstraction Form: Antibiotic Pilot Study

APPENDIX H: Abstraction Form: Physician Interview

APPENDIX I: Letter to Patient from Family Physician

APPENDIX J: Abstraction Form: Patient Telephone Interview

APPENDIX K: Criteria for Diagnosis of Infection-related Disease

APPENDIX L: Protocol for Community-based Antibiotic Utilization Study

LIST OF TABLES

1.1 Information Required to Perform DUR 20

3.1 Criteria for Diagnosis of Upper GI Disorders 33

3.2 MCP Billing Codes 37

3.3 Physician Characteristics 38

3.4 Patient Baseline Characteristics 38

3.5 Comparison of Diagnoses Made by Family Physician and Expert Panel 39

3.6 Comparison of Diagnoses Made by Family Physician and Expert Panel When GERD and Nonulcer Dyspepsia are Considered Overlap Disorders 40

3.7 Comparison of Treatment Prescribed by Family Physician and Expert Panel 41

3.8 Comparison of Treatment Decisions Made by the Family Physician and Expert Panel Using a Weighted Kappa Statistic 42

3.9 Treatment Prescribed by Expert Panel and 6 Family Physicians 43

3.10 Appropriate Prescription Rates and Diagnoses of Each Physician 44

3.11 Comparison of Diagnoses Made by Expert Panel and Research Team 45

3.12 Comparison of Diagnoses Made by Expert Panel and Research Team When GERD and Nonulcer Dyspepsia are Considered Overlap Disorders 45

3.13 Comparison of Treatment Decisions Made by the Expert Panel and the Research Team 46

3.14 Comparison of Treatment Prescribed by the Expert Panel and the Research Team Using a Weighted Kappa Statistic 47

3.15 Comparison of Treatment Decisions Made by the Research Nurse and the Expert Panel 47

3.16 Demographic Data and Drugs Prescribed by Family Physicians for Each For Each Upper GI Disorder 49

3.17 Overutilization and Underutilization Rates for Each Drug Group 50

LIST OF TABLES (cont'd)

3.18 Overutilzation and Underutilization Rates of Proton Pump Inhibitors for Each Physician 50

3.19 Data on Patients Who Should Have Received Drugs for Upper GI Disorders but Did Not Receive Them 51

3.20 Data for Inappropriate Prescriptions 51

5.1 Physician Characteristics 68

5.2 Patient Characteristics 69

5.3 Comparison of Rates of Infection and Prescription for Each Physician 70

5.4 Rate of Diagnosis and Antibiotics Prescribed for Each Type of Infection 71

5.5 Reasons for Nonparticipation in Telephone Interviews 72

5.6 Data Obtained Through Telephone Interviews 73

5.7 Signs and Symptoms as Recorded by the Familly Physician and Patient in 7 Cases There was no Agreement Between the 2 Sources 74

5.8 Comparison of Decisions Made by the Research Team and the Expert Panel 75

5.9 Patient Cases Where the Panels Differed in Therapeutic Decisions re Necessity for Antibiotic 76

5.10 Appropriateness of Antibiotic Prescriptions Deemed Necessary 76

5.11 Comparison of Decisions Made By the Expert Panel and the Research Team Approach in the 4 Cases re Appropriateness of Choice of Antibiotic 77

5.12 Comparison of Decisions Made by the Research Team and the Family Physicians 78

LIST OF TABLES (cont'd)

5.13 Appropriateness of the Choice of Antibiotic Prescribed by the Family Physicians 79

5.14 Panels' Therapeutic Decisions Concerning the Choice of Antibiotic Prescribed by the Family Physician 79

5.15 Comparison of Oral and Topical Antibiotics Prescribed by the Physicians as Determined by the Research Team 80

5.16 Utilization and Appropriateness Scores for Each Family Physician 81

LIST OF FIGURES

1.1 Application of Criterion-based Guidelines 14

3.1 Guidelines for the Treatment of GERD, Dyspepsia and Peptic Ulcer Disease 34

CHAPTER I

Introduction

1.1 BACKGROUND

The health care system is one of the most integral and important components of society today. This system is changing in order to accommodate the fluctuating economic status of this country. Canadians value the impressive level of health care that has been provided to them over the years and regard the universality and accessibility of the Canadian health care service as a major advantage of living in Canada.

Canada has the second most expensive health care system in the world. In 1996, health expenditures represented approximately nine percent of Canada's gross domestic product (GDP) which is second only to the almost 14 percent of GDP spent in the United States.[1] On a provincial level, in 1996, Newfoundland and Labrador spent twenty-four percent of the provincial budget on health care.[2] Because of these large expenditures and budgetary deficits, various attempts have been made by all Canadian government to reduce expenditures in health care, while striving to maintain and enhance the quality of health services that are available to Canadians.

The government of Newfoundland and Labrador in 1996 allocated $53 million towards payment for pharmaceuticals by individuals drug subsidization in 1996.[2] However, in Canada, and other countries, a substantial proportion of the prescribing of pharmaceuticals is not consistent with criteria for appropriate, safe and effective health

care.[3] Drug therapeutics is a rapidly changing area of medical care and it may be a factor that contributes to this inappropriate prescribing by physicians.

Various methods have been developed to measure the extent of inappropriate prescribing by physicians and to improve these prescribing patterns. Drug utilization review is a means of determining the incidence of inappropriate prescribing within a community. As the pressure to control health care costs is increasing, this method is becoming more prevalent throughout the country. The widespread use of drug utilization review is attributable to the flexible and ubiquitous nature of this process, which is used to assess unnecessary care among physicians, pharmacists and patients.[4]

One method that has been utilized to curtail the unsatisfactory prescription of pharmaceuticals is the development and implementation of clinical practice guidelines. Attempts have been made to change physicians' prescribing behavior through the utilization of certain guidelines and moderate successes have occurred.[5 6] The feasibility of using such guidelines should be determined before they are implemented as part of an educational intervention, to enhance the probability of their success in changing prescribing patterns.

Provincial governments have made attempts to modify the utilization of pharmaceuticals within the country largely through the implementation of prescription drug formularies or a restrictive list on the type and price of drugs paid for. The financial pressure of prescription drug plans on both private and public purses is not only a Canadian problem but also a global phenomenon. It is seen now that cost containment

strategies like the formularies are minimally effective in restricting the rise of expenditures. Governments are now turning to utilization intervention to maximize the effectiveness of pharmaceuticals while minimizing dollars expended. If utilization measures are adopted, physicians will need to agree to this interventionist approach or face economic pressures that will impede their ability to prescribe what they think should be prescribed.

Most provincial governments in Canada pay a proportion of their residents' drug costs. Residents of Ontario, for example, who are: (1) 65 years of age or older, (2) in special care homes or (3) under 65 years of age and eligible to receive general welfare assistance, family benefits, extended health care benefits, or home care benefits are covered by the Ontario Drug Benefit Plan for prescription drugs. However, in Ontario in 1992 total expenditures for the province's Drug Benefit Plan would exceed one billion dollars. It is seen that various factors contribute to financial stress including the increase of the elderly population, newer and more costly drugs and extended patent protection for products, which limits generic substitution.[7]

A modification of provincial drug plans in Canada is inevitable due to the presence of financial pressures. Stakeholders in the health care system, however, should not lose sight of the fact that prescription drugs are central to modern medical therapy. The benefit and well being of the patient should be a critical component in considering change to provincial drug plans by ensuring that therapeutically safe and effective drugs are used appropriately.

This chapter describes and discusses (1) how drug utilization can be assessed; (2) the advantages and disadvantages of implementing different programs to improve inappropriate prescribing patterns; (3) the feasibility of using criterion-based guidelines to determine the optimal choice of therapy; and finally (4) the effectiveness of various forms of interventions.

Chapters III and VI discuss two pilot studies which were performed to determine the feasibility of (1) performing drug utilization review in the community, and (2) comparing prescribing patterns to clinical practice guidelines. Community-based general practitioners were chosen as the study population in both studies since in Canada it is this group of physicians who write the vast majority of the 230 million prescriptions given out annually.[8] In addition most studies, which have evaluated prescribing patterns of physicians have used hospital-based physicians who prescribe under very different circumstances. The drugs chosen for our investigation are upper gastrointestinal drugs and antibiotics. These drugs have proven efficacy when used appropriately.

The purpose of these pilot studies was to determine whether it was feasible for a research team to apply criterion-based guidelines to patient data and assess the appropriateness of physicians' prescribing patterns. These pilot studies aimed to guide the development of large-scale studies that could identify the extent of and reasons for inappropriate prescribing in the community and the impact that interventions would have on improving physicians' inappropriate therapeutic decisions. The protocols for the intervention studies will be discussed in appendices E and L.

1.2 APPROPRIATE PRESCRIBING BEHAVIOR

Eddy et al. (1988)[9] stated that the appropriateness of a particular practice is ascertained through two steps. Firstly, a combination of the available empirical evidence and clinical judgment must be evaluated to assess health outcomes based upon the effect of the practice. Secondly, a comparison of the practice's favorable and harmful effects must be made to determine if the benefit surpasses the harm.

Lavis et al. (1996)[10] viewed the concept of appropriateness as two distinct theories: (1) appropriateness of a service and (2) appropriateness of the setting in which care is provided. The appropriateness of a service is whether a particular patient is expected to benefit from a service based upon symptoms, physical findings and results of diagnostic tests. The second theory is associated with cost-effectiveness, whereby this appropriateness is determined by whether the services needed by a patient, based on their clinical attributes, correspond to the setting in which the service was delivered. The term 'setting' refers to a proxy measure of the resources utilized to provide care.

The measurement of appropriate provision of a service and of the setting in which it is provided, involves the review of a patient's medical record to obtain a complete clinical history. This information is compared with explicit criterion-based guidelines to determine the severity of the illness and the resources required to provide optimal therapeutic care. The criteria used for determining the appropriateness of a service are primarily specific to a diagnosis or procedure. It is the theory of appropriateness of a service that was measured in the pilot studies that are discussed in Chapters III and V.

1.3 IMPROVING PHYSICIAN PRESCRIPTION: BACKGROUND

Guidelines and interventions to improve prescribing behavior are closely linked to one another. The acceptability of criteria is relative to the success of the intervention, such that if an intervention is associated with penalties of any type (e.g., restriction of prescribing) guidelines must be sound for the intervention to succeed. Furthermore, the optimal utilization of any guidelines will require ongoing, critical reexamination or follow up interventions.[11]

In 1994, the *Effective health care* series published a comprehensive survey of international experience with the use of clinical guidelines. The authors reviewed ninety-one clinical trials and they concluded that the introduction of clinical guidelines can indeed change clinical practice and affect patient outcome. Furthermore, how these guidelines are developed, implemented and monitored influences the likelihood of adherence by physicians.[12]

The increasing sophistication and cost of prescription therapy has necessitated the development and implementation of interventions that are aimed at improving the prescribing behavior of physicians. However, there is no systematic approach to determine which interventions are effective, ineffective, and which may even be hurtful.[13] By educating physicians in the community on the recommended treatment regime outlined in the guidelines, it is possible to see a significant improvement in the appropriate prescription of drugs. A meta-analysis of studies, which evaluated the effectiveness of clinical guidelines, demonstrated that all but 4 of the 59 studies that were

included demonstrated a significant improvement relative to patterns of care prior to the introduction of the guidelines. Thus, it can be concluded that clinical practice can be enhanced through physicians' adherence to explicit criterion-based guidelines.[5]

The form of intervention that has proven to be most effective in enhancing physicians' prescribing behavior, is one involving face-to-face visits with a pharmacist or physician. Through these meetings the physician becomes involved in an interactive educational exchange. In the following studies it was shown that interventions involving only printed materials, either given or mailed to the participating physicians, had little or no impact on the prescribing behavior of participating physicians.

Avorn et al. (1983)[14] and Schaffner et al. (1983)[15] investigated these different forms of intervention. The physicians who were included in these studies were selected based on Medicaid prescribing data. Avorn et al. used a 'face-to-face' and 'print only' interventions in their study of antibiotic prescribing behavior. The latter form induced no significant improvement, as opposed to the face-to-face intervention, which was proven to be effective by reducing the prescription of contraindicated drugs by 14% as compared to a control group ($P = 0.0001$).[14] Schaffner et al. included three forms of intervention - mailed brochures, visits to doctors by a trained pharmacist, 'drug educator', and also visits to doctors by a trained 'physician counselor'. This study showed that an improvement in the appropriateness of physicians' prescribing behavior was associated with visits by a peer physician, which may be attributable to the messenger appearing to be more important than the message.[15] This form of intervention produced strong

attributable reduction in the number of prescriptions written per doctor (AR = 54%; P = 0.0001).

The interventions used in the proceeding studies involved a sequence of phases that addressed different forms of educational methods. The intervention utilized in the De Santis et al. (1994)[16] study was initiated with mailed brochures, followed by a visit from a project pharmacist who assumed the role of an 'academic detailer'. Finally, additional mailings were sent to the physicians in the intervention group reiterating the brochure messages. Although the results demonstrated the intervention group as having an improvement in the percentage of prescriptions consistent with the recommended guidelines there was also a comparable improvement seen in the prescribing patterns of the control group, 60.5% to 87.7% and 52.9% to 71.7% respectively. This demonstrates how adherence to various recommendations may be directly related to who is performing the academic detailing.

In contrast, the interventions used in the Gutierrez et al. (1994)[17] and Ekedahl et al. (1995)[18] studies did not include personal visits by an 'academic detailer' to the participating physicians. The Ekedahl et al. study involved problem oriented group meetings followed by a general group meeting that addressed certain objectives. Although, the results of this study demonstrated a positive change in the prescribing attitudes of participating physicians the reliability of the study could not be determined.[18] Similarly, Gutierrez et al. began their intervention with a training workshop, which was followed by peer review group meetings. Assessments were performed during the

intervention and throughout the follow up period, however, the reliability of these results could not be determined.[17]

Other DUR interventions include an intervention that is executed when the physician writes the prescription, or an intervention that occurs at the point of dispensing by the pharmacist. The former is the futuristic approach where the physician writes prescriptions on a computer terminal. Through the use of computer systems, clinical and prescriptions data will be readily available and enable the physician, pharmacist and decision software to be linked to the same information loop. This intervention will allow the prescriber to be aware of drug-drug interactions, drug-disease interactions and whether or not they are prescribing appropriately. An intervention that is carried out at the point of dispensing is the form of DUR that exists today. This involves the pharmacist screening the medication profile of the patient. By doing this they may be able to detect any drug-drug or drug-disease interactions that may be apparent and therapeutic duplication or potential fraud and abuse.[13] As this is a modernistic form of DUR there is little literature available that is aimed at assessing the effectiveness of this method of DUR in detecting such interactions.

1.4 GUIDELINES

The core elements of drug utilization review include evidence and criterion-based guidelines; accurate patient specific data; and reproducible application of guidelines.

1.4.1. Guidelines and Quality Assurance

The Canadian Healthcare Association (CHA) has adopted a definition for clinical practice guidelines (CPGs) from the Institute of Medicine in the United States. It stated that CPGs are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances".[19] It is assumed that through the implementation of these guidelines the overall quality of health care will be enhanced.

Quality assurance confers a plausible guarantee that the optimal standard in the quality of health care is provided and it is through this process that problems in a physician's practice are detected and corrective measures are instituted. Therapeutics is an area where certain standards need to be met. The regular use of clinical practice guidelines is similar to quality assurance programs in their goal to minimize clinical uncertainty, reduce inappropriate variation in physician practice patterns; while at the same time encouraging experimentation, and relying on sound measurement.[20]

In drug utilization studies, therapeutic guidelines provide a set of standards against which physicians' prescribing patterns can be compared.[16] It is recognized that criterion-based guidelines are usually based upon two or three variables or a sole diagnosis, and that the application of these guidelines is affected by acceptable deviations. However,

certain databases may not contain the variables that are necessary for the decision-making process in determining drug prescription appropriateness. The more patient specific the data necessary to apply optimal therapy criteria, the less likely that these data will be available from government drug plans or other previously mentioned registry-based sources. This will vary from drug to drug, such that a review of a government database will identify elderly patients who shouldn't be taking certain drugs,[21] whereas this database would be inadequate to determine the appropriateness of antibiotic utilization. In the latter instance it could be argued that physicians' records may not contain enough information to determine appropriateness and that patients need to be interviewed to accurately determine which symptoms were present.

1.4.2. Utilization of Guidelines to Assess Physicians' Practice

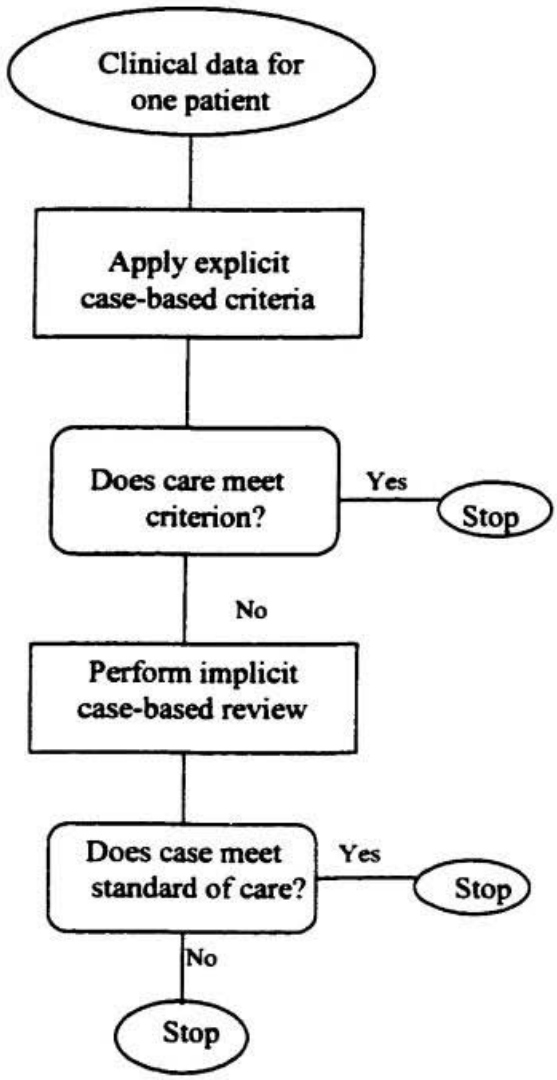
Yu et al. (1991)[22] assessed the antibiotic prescribing habits of physicians. A consensus panel consisting of a chief medical resident, an infectious disease physician, and a clinical pharmacist developed a clinical grade of appropriateness that served as a "gold standard". This panel evaluated the appropriateness of an antibiotic selection for 78 consecutive patients and classified 34.6% as inappropriate. The information that was assessed consisted of a physician interview, patient's medical chart and past medical history, and any subsequent hospital course. This study theorized that clinical guidelines could be utilized to assess physicians' clinical decisions, however, it was not documented in the article whether or not the reliability of the guidelines themselves was assessed.

In 1995, Donnelly et al.[12] conducted a pilot study where clinical guidelines were used to determine the appropriateness of patient placement. Subject selection and data collection methods used by Donnelly et al. differ from the pilot studies discussed in Chapter III and VI of this thesis, yet all studies are similar in their application of criteria to assess the appropriateness of clinical decisions. A multidisciplinary consensus group defined criteria for admission to Intensive and High Dependency Care Units, as published guidelines were not available. Appropriateness of admissions was determined by measuring actual performance against the criteria set for admissions. These correlations demonstrated that the rate of inappropriate placement in Intensive Care Unit was low (0-10%) whereas the rate in the High Dependency Care Unit was as high as 82%. Donnelly et al. (1995) concluded that it is feasible to assess the appropriateness of patient placement through the use of professionally derived guidelines; demonstrated that it was feasible to generate the data necessary to assess the appropriateness of clinical decisions.[12]

Figure 1.1 summarizes the approach taken by an expert panel when applying the guidelines.[23] This process for ascertaining whether the patient's physician made the optimal therapeutic decision is a very lengthy process. It is difficult to assemble the experts in a panel and time consuming to assess the treatment for every patient. The two pilot studies reported in this thesis assessed the utilization of drugs for upper gastrointestinal diseases and antibiotics. They involved 6 physicians (84 patients) in the former study and 4 physicians (99 patients) in the latter one. The protocols for the larger

scale studies derived from the pilot studies involve the recruitment of approximately 80 physicians and over 1200 patient charts. Based on a study that was performed using an expert panel review [24], it was hypothesized that to use an expert panel for a DUR of 1000 patients could take 50 hours, which is a large amount of time for busy physicians and pharmacists. Therefore it would be very difficult to assemble an expert panel to assess over 1200 patient cases as proposed. Consequently, this study can be completed much more efficiently if the researcher can apply guidelines without the use of expert clinical judgment can apply guidelines. By hypothesizing this it was necessary to determine the feasibility of a research team using explicit criterion-based guidelines to assess a family physician's therapeutic decisions.

Figure 1.1: Application of Criterion-Based Guidelines



1.5 DRUG UTILIZATION REVIEW

Drug utilization review is defined as an adaptable process in which predetermined criteria are used to assess the quality and cost-effectiveness of (1) drug prescription by physicians; (2) drug utilization by patients; and (3) drug dispensing by pharmacists.[25 26] Current information, case-based criteria and clinical practice guidelines are consolidated to establish explicit criterion-based guidelines, which are then used to measure the quality of therapeutic decisions made by physicians. This assessment is best achieved through a process known as drug utilization review.

Drug utilization review (DUR) is a form of assessment in use for more than 20 years. Throughout this time considerable research and commercial endeavors have contributed to the formation of an extensive knowledge base which can be applied to question the appropriateness of drug utilization. During the late 1960's and early 1970's, DUR appeared to focus primarily on drug interactions and overuse of regulated drugs. Subsequently, DUR has been expanded due to the recognition of other potential problems with drugs, such as incorrect dose or duration of prescription, and drug-induced diseases (e.g., antibiotic resistance).[27]

A relatively broad definition of DUR has existed since its evolution. This definition includes analysis of various aspects of prescription and dispensing patterns among both physicians and pharmacists, and implementing programs to monitor and control improper patterns in particular settings. These DUR programs incorporate "knowledge, understanding, judgments, skills, constraints, and ethics" into the review so that the

optimum prescription and use of medications is assured while at the same time improving the quality of drug therapy and controlling pharmaceutical costs.[25 27] Although this broad concept has had good results, some problems have also been created. Favorably, it has created a broad arena for the development of many innovative approaches to improving drug use. However, this outcome generated an expectation that a "gold standard" of appropriate drug utilization exists. Even if a "gold standard" did exist, it is not clear that it could be met despite optimal information, education, and behavior of prescribing physicians, pharmacists, and patients. This is likely because we do not live in a static environment and the dynamic and highly competitive international pharmaceutical market creates a major challenge to achieving the optimal utilization of drugs.[11] Therefore, it has been suggested by Barber (1995) to define what physicians should be trying to achieve when prescribing rather than trying to define what constitutes good prescribing. In Barber's model it is illustrated that the physician should strive for four objectives to attain good prescribing habits: (1) maximize effectiveness; (2) minimize risks; (3) minimize costs; (4) respect the patient's choices.[28]

Typically, the purpose of drug utilization review is to ensure that only patients who require drugs get them. A lot of emphasis has been placed on reducing inappropriate overutilization of pharmaceuticals, where patients who do not need drugs receive them. However, the underutilization of medication, where patients who need drugs do not receive them, is of equal importance.[29] Not only must the correct choice of medication be administered, but the prescribed dosage and duration of medication must also be

appropriate. This appropriateness of prescription is based on pharmacokinetic considerations, concomitant medications, comorbidities, and other risk factors peculiar to the individual.

Pharmacoeconomics is another form of DUR that has been defined as "the description and analysis of the costs of drug therapy to health care systems and society".[30] Pharmacoeconomic research involves the measurement and comparison of the costs of pharmaceutical products and services. Inherently, this form of analysis explores the impact (both beneficial and nonbeneficial) of alternative drug therapies and other medical interventions to achieve optimal and cost-effective utilization of pharmaceutical drugs.

1.5.1. Utilization of Explicit Criterion-based Guidelines for DUR

The implementation of a DUR program to determine if a physician has made the optimal diagnostic and therapeutic decision involves the application of explicit criterion-based guidelines by a research team, an expert panel and/or a computer system. In addition to the explicit criterion-based guidelines the latter panel may also uses clinical judgment, i.e. implicit criteria, to determine the appropriateness of treatment prescribed by the physician.

It is argued that clinical freedom, innovation and individual case discretion are restricted through the use of clinical guidelines.[31] However, there is evidence that guidelines provide long-term benefits by increasing the level of health care[32] and controlling costs.[33] Unfortunately, successful implementation of guidelines continues to

be a formidable obstacle.[34] An intervention may be implemented to ensure that these guidelines are communicated properly and to the appropriate people.

1.5.2. Development of Criterion-based Guidelines

Criteria are predetermined elements against which the quality and economy of drug use are judged. It is these criteria which represent the ideal to which actual drug use is compared. They must be useful, efficient and relevant to the outcomes that are being measured. Criteria that are clinically and scientifically grounded provide a foundation from which clinical guidelines are developed. Computers use guidelines to screen millions of prescriptions rapidly and therefore, guidelines must be explicit and capable of reduction to simple rules for initial application. The prescribing, dispensing, and patient compliance of a pharmaceutical agent are involved in the assessment of appropriateness, where empirical data and application of criteria may be used to identify "norms" about the appropriate pharmacological use of a prescription drug.[35]

The criteria upon which the guidelines are based may be either implicit, where the criteria are based on an individual's expert judgment, clinical experience, and knowledge of literature, or they may be explicit, where compendia, texts and literature form the basis upon which these criteria are developed. Although implicit criteria involve clinical experience and expert judgment, this approach does not yield results that are as reproducible as those obtained through the utilization of explicit criteria. The explicit criteria approach may be more consistent and reliable in its findings, regardless of who applies the criteria. However, this approach does not include the complete assessment of

an individual patient. Since the utilization of pharmaceuticals is very complex, a convergence of both implicit and explicit criteria could be the optimal strategy.[36] A combination of these criteria would provide the basis for criterion-based guidelines.

In order to develop and maintain credible criterion-based guidelines, it is necessary that they be based on generally acclaimed literature that is scientifically and clinically grounded. Criterion-based guidelines used in clinical practice are considered technically valid if they lead to cost-effective clinical practice, improved patient outcomes and quality of health care.[37] Not only must the criterion-based guidelines be technically valid and reliable, they should be accepted by the appropriate experts, academic, clinical and/or industrial, and the subjects that are being evaluated through that DUR program must also perceive them as valid.[25] Once the reliability and validity of the explicit criterion-based criteria has been proven, both the guidelines and their rationale should be made available to all physicians.

1.5.3. Performance of DUR

Brater et al. formed a panel that determined the information necessary to perform a DUR[38] (Table 1.1).

Table 1.1 : Information Required to Perform DUR

Drug Utilization Review Information	
1. Patient characteristics	Age and birthdate Sex Weight and Height Drug allergies Specific diagnoses and, when relevant, an estimate of disease severity
2. Drug data	Chemical entity Dose (strength and frequency) All medications the patient is taking, including over-the-counter products Longitudinal history of drug intake
3. Health care utilization	Hospitalizations and Emergency room visits Office visits Nursing home use Home health care

The information that is mentioned above allows for various endpoints relating to drug therapy to be assessed. The following endpoints are relative to the objectives of the pilot studies described in Chapters III and V:

1. Noncompliance – patient does not take medication as directed (i.e. dose, duration or frequency).
2. Overutilization – frequency of patients who did not need a class of drugs but received them.
3. Underutilization – frequency with which patients that needed a class of drugs did not receive them.

1.5.4. Forms of Drug Utilization Reviews

There are two types of drug utilization review, registry-based and patient-based, and two manners in which these reviews are performed, retrospectively and prospectively. These forms of DUR differ in the source of information and the manner in which the necessary information about drug use is obtained. There are advantages and disadvantages to each type.

1.5.4.1. Registry and Patient-Based Review

Registry-based

The prescribing behavior of physicians is inadequately measured through self-reporting, which has led researchers to use registry-based prescribing records, that is national, provincial or statewide administrative claims databases, to assess changes in prescribing behavior.[21] Medicaid databases have proven to be very effective and allow for efficient and cost-effective studies to be performed on drug and health care utilization in the United States.[14 15 39 40] However, this information is generally in a crude statistical form for the purposes of paying claims and does not confer details relative to the patient and the conditions for which their individual physicians prescribed medication. Moreover, it is very difficult to obtain information concerning the use of over-the-counter (OTC) preparations by members of the community through registry-based data.

Retrospective registry-based reviews audit both pharmacy and medical claims data. Through this analysis inappropriate patterns and trends pertaining to various prescription drugs and physician prescribing practices are identified[41] and this type of review also

permits the maximum amount of information, for a large number of patients, to be obtained at a minimal cost.[25] However, the information that is obtained in this manner is limited and should not be used to make inferences concerning the general population. Such registry-based databases are not designed for research and in the absence of diagnostic information the results obtained from this secondary data will contain inherent error and bias. An inherent bias may be present in a study population that is involved in a registry-based review. For example, a Medicaid prescription claims database lists prescription drugs used by the poor and this population does not represent the general population.

Prospective patient-based drug utilization reviews use systems that enable the researchers to detect a problem before the pharmacist dispenses the prescription. Although this form of DUR is beneficial in the detection of potentially dangerous drug-drug interactions, therapeutic duplication or abuse, and excessive prescribing behavior, it is agreed that this DUR would not address problems of inappropriate dosage, duration or incorrect prescribing. There is very little literature pertaining to the utilization of these reviews as they require extensive and complicated software programs and, although they may play a useful role in improving prescription drug use, their use is limited.[4]

Patient-based

Patient-based DUR is a tedious and costly method to document changes in physicians' prescribing behavior, which involves a thorough review of each patient's chart. This form of DUR examines the drug therapy that is prescribed to individual patients and then

assesses the appropriateness of prescription by measuring against predefined criterion-based guidelines. The advantage of this retrospective form of review is that, in addition to the patient's chart providing the information that is necessary to accurately assess physicians' prescribing behavior, the review can correlate drug prescription to the age, sex, employment, social status, or disease of patients. Unfortunately, where such records are made available for review it has usually been on a modest scale and the physicians who consent to participate may be specially motivated physicians whose prescribing may not be characteristic of the general population.[42] Furthermore, there are only a limited number of Canadian studies that have assessed this method of DUR. A meta-analysis performed by Einarson et al. involved summarizing the results of 33 articles that utilized criteria for identifying drug therapy appropriateness, which were based on expert opinion, to evaluate drug prescription. The average rate of inappropriate prescribing overall was 43%, which included drug indication, choice of drug, and drug administration (dose, duration or route). However, the greater part of these studies assessed prescribing patterns in a hospital setting as opposed to the prescribing patterns of community based general practitioners.[43]

Despite the fact that these prospective DUR computer systems have existed for over 15 years at the pharmacy level, they are practically nonexistent at the physician practice level. However, as more physicians' offices become equipped with computer systems, the probability of incorporating prospective drug utilization reviews that will influence the physician's decision before the drug is prescribed will increase significantly. The

most successful prospective DUR program acts as a reminder and alerts the physician of any discrepancy when his/her prescribing is compared to optimal practice.[36]

The two pilot studies that are discussed in chapters III and VI implement the retrospective patient-based form of DUR. This involves using pre-determined criteria to critique the utilization of drugs after physicians have prescribed them. This type of drug utilization review generally concentrates on preventing a reoccurrence rather than dealing with an imminent problem. Although it is a very tedious and costly method it has been argued that retrospective patient-based DUR is the most feasible and adaptable approach to obtain accurate patient specific data and, unlike the majority of registry-based DUR, it does not limit the patients being assessed to those who are using administrative claims databases. In order to ensure that optimal results are obtained precise definitions and analyses of what constitutes inappropriate drug use must be applied to the data.

1.6 SUMMARY

The health care delivery system is under intense pressure to control costs. Recent evidence indicates that in Canada and other countries a substantial proportion of prescribing practice is inconsistent with criteria for appropriate health care.[3] It is this waste of limited health care resources that makes it necessary to enhance drug utilization review. Drug utilization may be reviewed through government/private drug plan databases, however, the appropriateness of therapeutic decisions may be best achieved through the application of explicit criterion-based guidelines using patient based DUR. The purpose of both pilot studies reported herein was to test the feasibility of a research team applying criterion-based guidelines to accurately assess the therapeutic decisions made by a family physician, i.e. patient-based DUR. Drugs for upper gastrointestinal diseases and antibiotics were assessed.

A review was performed on literature pertaining to (1) upper gastrointestinal disorders and their optimal treatment; (2) epidemiology of upper GI disorders; (3) utilization of antibiotics; (4) prevalence of antibiotic resistance; and (5) using criteria to assess the rate of prescription and the appropriateness of therapeutic decisions made by family physicians. The articles reviewed in Chapters II and V, in addition to those pertaining to the efficacy of the various classes of drugs, enabled explicit criteria to be developed for these studies.

Throughout these studies the following questions were asked to determine the feasibility of using explicit criterion-based guidelines to assess the appropriateness of general practitioners' prescribing patterns.

CHAPTER II

Utilization of Drugs for Upper GI Disorders

2.1 DRUGS FOR UPPER GI DISORDERS: LITERATURE REVIEW

There is a lack of literature pertaining to physicians' prescription of upper gastrointestinal (UGI) drugs although there is an abundance of literature associated with UGI disorders and the efficacy of various types of treatment. Although upper gastrointestinal disorders are common in today's society, the actual frequency of these disorders is underestimated considering that people often treat their symptoms with over-the-counter medications, rather than report them to their physician.

2.1.1. Utilization of Upper GI Drugs

There are few studies that have used criteria to determine the rate and appropriateness of upper gastrointestinal drug prescription. One study was published in 1990 but is now outdated since newer drugs have been approved for the treatment of gastroesophageal reflux disease, nonulcer dyspepsia and peptic ulcer disease.[44]

According to Raisch et al (1990)[44] the mean rate of histamine (H_2) receptor antagonists and sucralfate for inappropriate indications range from 41.3% to 52.1%. The criteria used in this assessment were representative of the standards of practice within the community at that time. Subsequent to these results other classes of drugs have been approved for the treatment of these disorders, including proton pump inhibitors ± antibiotics and prokinetics. No study has been performed to determine the appropriate utilization of all currently available classes of upper gastrointestinal drugs.

The current treatment of upper gastrointestinal disorders involves six categories of drugs; proton pump inhibitors (PPI), prokinetics (Prok), histamine H_2 receptor antagonists (H2RA), antibiotics (Abs), cytoprotective agents, and antacids. These drugs are efficacious when prescribed for the appropriate upper GI disorder, yet can be futile if used inappropriately. In the current study there were no prescriptions of cytoprotective agents and antacids, so only the first four agents will be referred to in this thesis. (See Appendix D for mechanisms and indications).

During 1995, in Newfoundland, there were no limitations on prescriptions of drugs for upper GI disorders. By 1996 expenditures on proton pump inhibitors had become so high that the Newfoundland provincial government implemented a policy restricting their provision by the provincial formulary in the absence of an explicitly justified request by the doctor. Although this was intended to be a cost saving measure, it may have led to people who needed proton pump inhibitors not being prescribed them. As a result, inappropriate drugs may have been prescribed in their stead, resulting in the underutilization of one class of efficacious drugs and overutilization of other classes.

Recently, clinical practice guidelines were developed for the treatment of upper gastrointestinal disorders: dyspepsia, peptic ulcer disease and gastroesophageal reflux disease. These guidelines were jointly developed by Newfoundland and Labrador's Department of Health, Medical Association and the Newfoundland Pharmaceutical

Association, as well as members of School of Pharmacy and Faculty of Medicine. These guidelines provided a foundation for the criterion-based guidelines that were used in the pilot study that assessed the utilization of upper gastrointestinal drugs. Appendix C gives a more detailed description of the information used to develop these guidelines.

2.1.2. Epidemiology of GI Disorders

A study of the epidemiology of upper GI disorders is encumbered by the lack of physical markers for both gastroesophageal reflux disease and dyspepsia. A measurement of the latter is further impeded by existing discrepancies pertaining to the definition of this functional disorder.

Despite similar difficulties in the diagnosis of peptic ulcer disease, attempts have been made to determine the prevalence and incidence of this disorder. Perforated ulcers cause patients to suffer a singular attack of pain and shock which enables a prompt diagnosis, however, the lack of symptoms associated with uncomplicated and bleeding ulcers obscure their diagnosis.

Langman (1985)[45] referred to the attempts that were made to establish the point prevalence of peptic ulcers. This included an endoscopic survey of 358 normal Finnish subjects, which revealed duodenal ulcers in 1.4%. Drossman et al. (1993)[46] performed a household survey in the United States that found the annual prevalence of peptic ulcer to be 1.6%. However confirmation of the ulcers was unattainable and "silent" ulcers were not detected. Various studies indicated a 10% prevalence of peptic ulcer with a point prevalence of 1-2% in developed countries. According to Thompson (1996) the

incidence of peptic ulcer is approximately 0.1% per annum. In Copenhagen, Denmark the incidence of duodenal ulcer in men was determined to be 0.15% and 0.03% per annum in women. Similarly, in Yorkshire the incidence in men and women were 0.21% and 0.06% per annum respectively.[47]

Upper gastrointestinal functional disorders require a complete epidemiological reassessment. The reassessment is necessary due to the emergence and discovery of the bacterium *Helicobacter pylori*. The ubiquity of this organism is astonishing and most humans are infected with *H. pylori* yet experience no symptoms. Although, Robert Koch's (1843 - 1910) postulates [48] [49] [50] are fulfilled for acute gastritis, they have not established *H. pylori* as a cause of either peptic ulcer or functional dyspepsia. Significant evidence shows that non-NSAID ulcers occur where *H. pylori* is present. A review of 15 studies concluded that 92% of patients with duodenal ulcers are infected with *H. pylori*.[47]

Another source of peptic ulcer disease is NSAID use with a point prevalence of 15-30% in chronic NSAID users. The ideal treatment for these ulcers would be the discontinuation of the offending agent. Yet many patients are unwilling to forego the relief of pain and inflammation provided by NSAIDs.[51] Due to this unwillingness it is necessary for a prescription of proton pump inhibitors, which are more effective than H_2 receptor antagonists in the treatment of NSAID induced ulcers.[52] [53] [54] [55]

CHAPTER III

Utilization Review of Drugs for Upper GI Disorders: Pilot Study

3.1 RATIONALE

Restriction of access to proton pump inhibitors through the Newfoundland and Labrador Drug Program could lead to underutilization of these efficacious agents and overutilization of other less appropriate drugs in patients with upper GI disorders. The pilot study was undertaken to test the feasibility of using criterion-based guidelines, applied by a research team, so that current medical practice for upper GI disorders could be assessed. This pilot study collected patient specific information and compared the diagnosis and treatment provided by the family doctor to that of the decisions made by an expert panel, a research team and a trained research nurse. The criterion-based guidelines used to make a diagnosis were based upon information obtained from the literature and clinical experts, based on symptoms of gastroesophageal reflux disease, non-ulcer dyspepsia and peptic ulcer disease and the mechanisms of the drugs used to treat upper GI disorders (Appendix C & D).

The criterion-based guidelines for optimal treatment of upper gastrointestinal disorders were based primarily on the jointly developed, *Guidelines for Gastrointestinal Conditions: Dyspepsia and Gastroesophageal Reflux Disease*,[56] and the *Canadian Consensus Conference on the Treatment of Gastroesophageal Reflux Disease (1997)*.[57] The former guidelines are supported by an algorithm that was developed by Brun

(1996).[58] The criterion-based guidelines used in this pilot study are those accepted by the Provincial Drug Program and recommended for use in Newfoundland and Labrador.

3.2 METHOD

A patient based retrospective drug utilization review was performed using patient chart and physician interview to obtain history and treatment of upper gastrointestinal disorders, and the application of the criterion-based guidelines for diagnosis and treatment (Appendix C and Fig. 3.1) to these cases by (a) an expert panel, (b) a research team, and (c) a research nurse. The research team consisted of a researcher and a clinical epidemiologist who provided content expertise support[a] to the researcher. The schema used by all 3 assessors is illustrated in Fig. 3.1.

3.2.1. Data Collection

Diagnostic and treatment data were abstracted from the patients' charts, using a standardized instrument (Appendix B). The past medical history of each patient, including concomitant medications and comorbidities, was obtained. Following this data collection each physician was interviewed by a research nurse, which provided additional information and a verification of the data collected from each patient chart.

3.2.2. Application of Guidelines

The data collected from each patient's chart, using the abstraction form (Appendix B), was reviewed by an expert panel that was comprised of a gastroenterologist, pharmacist and epidemiologist. This panel determined the diagnosis and treatment necessary for

[a] content expertise support refers to a physician's clinical knowledge and experience

each patient based on the information obtained from their medical record. The appropriateness of diagnoses and treatment decisions made by the family physician was determined by comparing them to the decisions made by the expert panel. The rate of appropriateness of the treatment prescribed by each doctor was determined by the frequency with which patients who needed a class of drugs and did not get them (underutilization) and by the frequency with which patients who did not need these drugs received them (overutilization).

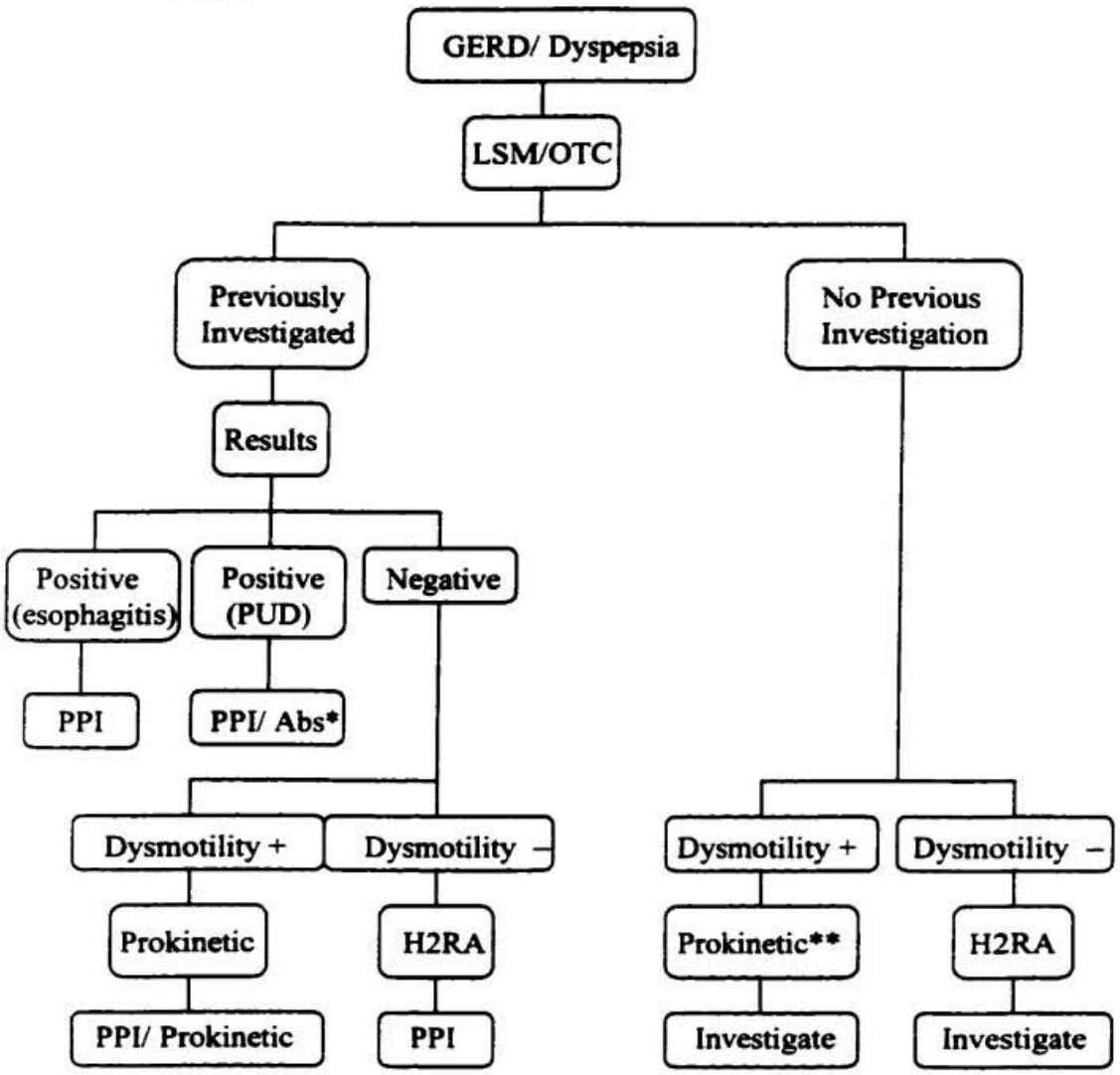
Criterion-based guidelines for diagnosis and treatment were applied to each patient's case by the research team. Decisions made by the researcher were compared to the expert panel's decisions. Areas of disagreement were discussed and criteria were improved to reach a consensus with the expert panel. As this is a pilot study being used to ensure that appropriate and sound guidelines are developed, the guidelines were improved during the process of the study. A research nurse also applied the criteria who had no part in the research project but who was trained in how to apply the criterion-based guidelines. Criteria used for diagnosis are shown in table 3.1 and the guidelines used for treatment decisions are shown in figure 3.1. Criteria providing a further explanation of the guidelines for treatment, as derived from consensus of the expert panel and literature, are shown in Appendix C.

Table 3.1 : Criteria for Diagnosis

Diagnosis	Symptoms
Gastroesophageal Reflux Disease (GERD)	heartburn, acid regurgitation, retrosternal pain, reflux
Dyspepsia (nonulcer)	epigastric pain, upper abdominal pain, nausea, indigestion, dysmotility[†]
GERD/ Dyspepsia	symptoms, past or present, of GERD and dyspepsia
Peptic Ulcer Disease (PUD)	symptoms of dyspepsia with confirmation of gastric/duodenal ulcer (without NSAID use), seen on endoscopy or barium meal, or inflammation of the duodenal bulb (duodenitis)

[†] dysmotility symptoms = gas, bloating, fullness

Figure 3.1 : Guidelines for Treatment of GERD, Dyspepsia and Peptic Ulcer Disease



* = *H. pylori* eradication therapy; Abs = Antibiotics
** = add a PPI if severe heartburn is present

Legend:

LSM/OTC = Lifestyle modifications &/or Over-the-counter medications
+ = symptoms present; — = symptoms not present

3.2.3. Ethics

The Human Investigations Committee of Memorial University of Newfoundland approved this study. Patient consent was not required as no procedure was performed on patients. All physician and patient information was kept confidential. Numerical identifiers, known to the researchers, were used to distinguish the patients and physicians enrolled in the study. Physicians were the focus of this study, and a research nurse made initial contact. Information was obtained from those physicians who signed a consent form (Appendix A) and agreed to participate in the study.

3.2.4. Statistical Analysis

The data obtained from the study population were analyzed with the Statistical Package for Social Sciences (SPSS). Descriptive statistics were used to characterize the physicians and patients. Cross tabulations were performed to compare the decisions of the family physician, expert panel and the guidelines pertaining to the appropriateness of prescription as applied by a research team and a research nurse. Where possible a quadratic weighted kappa score was calculated to allow for a correction for chance determinations of appropriateness. The quadratic weighted kappa statistic was utilized, as it is the statistic of choice for measuring agreement with ordinal data.[59] This form of statistic is derived from the original Kappa statistic with assigned weights based on the magnitudes of observational disagreements.[60]

3.3 RESULTS

The results portion of this chapter, 1. describes the overall characteristics of the physicians and the patients who were involved in the study; 2. illustrates the results obtained when criterion-based guidelines are used to assess the prescribing patterns of upper GI drugs by family practitioners. The latter section of this chapter is divided into four components. The first component demonstrates the feasibility of using explicit criterion-based guidelines to make an accurate diagnosis and treatment decision. This was accomplished by comparing the decisions of the expert panel to that of the research team applying the guidelines, and to that of the research nurse. The second component assessed the family physicians' decisions, using the expert panel's decisions as the acceptable assessment tool. An evaluation of upper gastrointestinal diagnosis and drug prescription rates in the St. John's - Mount Pearl area is shown in the third component. This evaluation is also based upon the judgements made by the expert panel. The last component characterizes the appropriateness of drug prescription for upper gastrointestinal disorders.

3.3.1. Physician and Patient Characteristics

Six family physicians participated in the study, 1094 patients were identified from their billing records during a 6 month period and the 15 most recent patients seen by each physician for upper GI disorders were studied. Children and pregnant women were excluded. Patients with the following Medicare Plan (MCP) billing codes were included:

Table 3.2 : MCP Billing Codes

MCP Billing Codes	
Code	Diagnoses
530	Disease of the esophagus
531	Gastric ulcer
532	Duodenal Ulcer
534	Peptic ulcer, site unspecified
535	Gastrojejunal ulcer
536	Gastritis and Duodenitis
537	Disorders of function of stomach and duodenum
537	Dyspepsia
787	Dysphagia

Patients included in the pilot study presented with the following symptoms/ conditions:

1. upper abdominal pain/ discomfort
2. upper retrosternal pain/ discomfort
3. epigastric pain
4. heartburn
5. gastritis
6. peptic ulcer disease
7. esophagitis
8. problems with the stomach and duodenum
9. dysmotility
10. acid regurgitation/ reflux
11. dysphagia

Of the 90 patients reviewed, 5 did not present with the above upper GI symptoms/ conditions, and one case provided insufficient data, resulting in 84 cases suitable for analysis.

Information about the six physicians who participated in the study is shown in table 3.3. All physicians were in group practice settings that were located throughout the St. John's - Mt. Pearl region. There was a wide range in the number of patients seen with upper GI disorders by each physician within the six month period (range = 34 - 753).

Table 3.3 : Physician Characteristics

	Gender	Year Graduated	# Patients Seen *
Physician 1	Male	1975	60
Physician 2	Male	1957	34
Physician 3	Male	1977	83
Physician 4	Male	1979	474
Physician 5	Male	1991	753
Physician 6	Male	1975	290

* patients seen for upper GI disorders within a 6 month period

Table 3.4 summarizes the characteristics of the 84 patients included in the study.

Table 3.4 : Patient Baseline Characteristics

Patient Baseline Characteristics (N = 84)	
Age	
Mean	47.3 yrs
Range	
18 - 29 yr.	7 (8.3%)
30 - 44 yr.	37 (44.1%)
45 - 59 yr.	19 (22.6%)
60 - 74 yr.	17 (20.2%)
≥ 75 yr.	4 (4.8%)
Sex	
Female	32 (38.1%)
Male	52 (61.9%)
Allergies	
Penicillin	4 (4.8%)

Within a six month period there was a total of 1094 patients with upper GI disorders (mean = 182) seen by the six physicians. Of these 1094 patients 84 were included in the study. The mean age was 47 (range 18 - 83) years and the percentage of female subjects was 38% (N=32).

3.3.2. Feasibility of Using Guidelines Without An Expert Panel

3.3.2.1. Diagnosis

A comparison of the expert panel and research team's diagnoses are shown in Tables 3.5 and 3.6. Diagnosis was based on symptoms, yet dyspeptic and GERD symptoms frequently overlap or vary over time. Furthermore, the treatment for mild to moderate cases of both GERD and nonulcer dyspepsia is similar and it was considered reasonable to combine the two diagnoses into one category, GERD/Dyspepsia (Table 3.6). Cross-tabulations were performed on the data to report the percentage of agreement between the research team and the expert panel and the Kappa statistic was used on the data in table 3.6. A substantial improvement in agreement, 67% (95% CI = 0.56 to 0.77) → 100% (K = 1.00), occurred when nonulcer dyspepsia and GERD were considered overlap disorders (Table 3.6).

Table 3.5 : Comparison of Diagnoses Made by Expert Panel and Research Team

		Research Team				
		Peptic Ulcer Disease	Nonulcer Dyspepsia	GERD	GERD/ Dyspepsia	Insufficient Data
Expert Panel	Peptic Ulcer Disease	14	-	-	-	-
	Nonulcer Dyspepsia	-	23	13	7	-
	GERD	-	2	17	4	-
	GERD/ Dyspepsia	-	-	-	1	-
	Insufficient Data	-	-	-	2	1

Table 3.6 : Comparison of Diagnoses Made by Expert Panel and the Research Team When GERD and Nonulcer Dyspepsia are Considered Overlap Disorders

		Research Team		
		Peptic Ulcer Disease	GERD/ Dyspepsia	Insufficient Data
Expert Panel	Peptic Ulcer Disease	14	-	-
	GERD/ Dyspepsia	-	69	-
	Insufficient Data	-	-	1

3.3.2.2. Treatment

When the guidelines and the expert panel's treatment decisions are compared the agreement is 95% (95% CI = 0.88 to 0.99) as shown in Table 3.7.

It should be remembered that the expert panel and the research team were not independent of each other. As previously mentioned the research team consisted of a researcher who was trained by the gastroenterologist on the expert panel and a clinical

epidemiologist. The data suggests that explicit criteria and guidelines may be applied without an expert panel and that a research team could apply the guidelines provided expert support from a physician is provided. For the data demonstrated in table 3.7 a quadratic weighted kappa statistic was used. The data is grouped in such a way that a direct comparison is made between the prescription of H_2 receptor antagonists and proton pump inhibitors, with all other agents and combinations grouped under the term 'other'. This is due to the similar actions of the H2RA's and PPI's and the indications for their utilization. Whether a research nurse could apply the guidelines without expert support to determine the appropriate treatment is shown in table 3.9.

Table 3.7: Comparison of Treatment Decisions Made by the Expert Panel and the Research Team

		Research Team					
		H2RA	PPI	PPI+ Ab	Prok. Combo	LSM/ OTC	None
Expert Panel	H2RA	54	2	-	1	-	-
	PPI	1	11	-	-	-	-
	PPI+Ab	-	-	11	-	-	-
	Prok. Combo	-	-	-	1	-	-
	LSM/ OTC	-	-	-	-	2	-
	None	-	-	-	-	-	1

Table 3.8 : Comparison of Treatment Decisions Made By the Research Team and the Expert Panel using a Weighted Kappa Statistic

		Research Team		
		H2RA	PPI	Other
Expert Panel	H2RA	54	2	1
	PPI	1	11	-
	Other	-	-	15

The weighted kappa for the above data continues to demonstrate a high level of agreement between the research team and expert panel with respect to their decisions of treatment (K_w = 0.93; 95% CI = 0.72, 1.14)

Table 3.9 : Comparison of Treatment Decisions Made By the Research Nurse and the Expert Panel

		Research Nurse					
		H2RA	PPI	PPI+ Ab	Prok. Combo	LSM/ OTC	None
Expert Panel	H2RA	40	7	1	2	-	7
	PPI	4	8	-	-	-	-
	PPI+Ab	1	-	10	-	-	-
	Prok. Combo	-	-	-	1	-	-
	LSM/ OTC	1	-	-	-	1	-
	None	-	-	-	-	-	1

When the treatment decisions of the expert panel and the research nurse are compared there is 73% agreement. When a weighted kappa statistic was performed on this data (K_w

= 0.50; 95% CI = 0.30 to 0.70), using the same method as described for table 3.8, the level of agreement between the research nurse and expert panel was shown to be much lower than the level of agreement shown between the research team and the expert panel. It was concluded that a research team with content expertise support could apply the guidelines, whereas a research nurse without such support could not do so. It was also decided that in cases where disagreement occurred between the physician's decision and research team's application of the guidelines, such cases should be sent to arbitration by an independent expert panel. Cases where LSM/OTC is cited as the appropriate treatment refer to patients whose charts record the visit in question as the first upper GI complaint that has been made to this family physician. (See figure 3.1)

3.3.3. Drug Utilization Review Using the Expert Panel

3.3.3.1. Diagnosis

Tables 3.10 and 3.11 show the percentage of agreement between the family physicians' diagnosis and that of the expert panel when cross-tabulations were performed on the data. When GERD and nonulcer dyspepsia were combined in table 3.11 the agreement between the expert panel and family physicians increased from 46% (95% CI = 0.36 to 0.58) → 83% (95% CI = 0.74 to 0.91). As previously mentioned these two disorders require similar treatment. Nonetheless 43% of the 14 cases that were diagnosed as peptic ulcer disease by the panel, were labeled dyspepsia/GERD by the family physicians.

Table 3.10 : Comparison of Diagnoses Made by Family Physician and Expert Panel

		Expert Panel				
		Nonulcer Dyspepsia	Peptic Ulcer Disease	GERD	GERD/ Dyspepsia	Other
Family Physician	Nonulcer Dyspepsia	13	4	-	-	-
	Peptic Ulcer Disease	3	8	1	-	-
	GERD	15	2	18	2	1
	GERD/ Dyspepsia	9	-	4	-	1
	Other	3	-	-	-	-

Diagnoses made by either the expert panel or research team were based on the same information that was available to the family physicians. The cases where the family

physicians and the expert panel differ in their diagnosis of PUD, are cases where there was a positive result from an investigation recorded in the patient's chart. This misdiagnosis would be a key factor in the underutilization of *H. pylori* eradication therapy.

Table 3.11 : Comparison of Diagnoses Made by Family Physician and Expert Panel When GERD and Nonulcer Dyspepsia are Considered Overlap Disorders

		Expert Panel		
		Peptic Ulcer Disease	GERD/ Dyspepsia	Other
Family Physician	Peptic Ulcer Disease	8	4	-
	GERD/ Dyspepsia	6	62	1
	Other	-	3	-

3.3.3.2. Treatment

According to the literature and the case-based criteria that were used, the treatment for peptic ulcer disease is unambiguous. This differs from the treatment for gastroesophageal reflux disease and nonulcer dyspepsia, which is dependent on the stage of the disease (i.e. mild, moderate or severe).

The appropriate treatment determined by the expert panel and family physicians are compared in Table 3.12 and demonstrate 73% agreement (95% CI = 0.62 to 0.82). This comparison is described by individual physician in table 3.14 and these data are summarized in table 3.15. The agreement between the expert panel and individual physicians ranged from 60 - 89%. The data from table 3.12 was grouped in such a way to demonstrate the level of agreement of the expert panel and family physicians therapeutic

decisions using a weighted kappa statistic (K_w = 0.50; 95% CI = 0.29 to 0.71). The data is grouped such that a direct comparison is made between the prescription of H_2 receptor antagonists and proton pump inhibitors, with all other agents and combinations grouped under the term 'other', due to the similar actions of the H2RA's and PPI's and the indications for their utilization.

Table 3.12 : Comparison of Treatment Prescribed by Family Physician and Expert Panel

		Expert Panel					
		H2RA	PPI	PPI+Ab	Prok. Combo	None	LSM/ OTC
Family Physician	H2RA	46	1	3	-	-	-
	PPI	4	8	1	-	-	-
	PPI+Ab	2	-	5	-	-	-
	Prok. Combo	3	2	2	1	-	-
	None	2	1	-	-	1	2

Table 3.13 : Comparison of Treatment Prescribed by Family Physician and Expert Panel using a Weighted Kappa Statistic

		Expert Panel		
		H2RA	PPI	PPI+Ab
Family Physician	H2RA	46	1	3
	PPI	4	8	1
	PPI+Ab	2	-	5

Table 3.14 : Treatment Prescribed by Expert Panel and 6 Family Physicians.

		Expert Panel				
		H2RA	PPI	PPI+ Ab	Prok Combo	None
Family Physician 1	H2RA	9	-	2	-	-
	PPI	1	1	-	-	-
	PPI+ Ab	-	-	-	-	-
	Prok Combo	-	-	1	-	-
	None	-	1	-	-	-
Family Physician 2	H2RA	10	-	-	-	-
	PPI	-	-	-	-	-
	PPI+ Ab	-	-	-	-	-
	Prok Combo	3	1	-	-	-
	None	-	-	-	-	-
Family Physician 3	H2RA	4	-	1	-	-
	PPI	2	2	-	-	-
	PPI+ Ab	1	-	3	-	-
	Prok Combo	-	-	1	1	-
	None	-	-	-	-	1
Family Physician 4	H2RA	7	1	-	-	-
	PPI	1	2	1	-	-
	PPI+ Ab	1	-	-	-	-
	Prok Combo	-	-	-	-	-
	None	2		-	-	-
Family Physician 5	H2RA	10	-	-	-	-
	PPI	-	2	-	-	-
	PPI+ Ab	-	-	1	-	-
	Prok Combo	-	-	-	-	-
	None	-	-	-	-	2*
Family Physician 6	H2RA	6	-	-	-	-
	PPI	2	1	-	-	-
	PPI+ Ab	-	-	1	-	-
	Prok Combo	-	1	-	-	-
	None	-	-	-	-	-

* Panel decided that no prescription treatment was needed but LSM/OTC was needed.

Table 3.15 : Appropriate Prescription Rates and Diagnoses of Each Doctor

Doctor	Patients with PUD	Patients with GERD/Dyspepsia	Appropriate Prescriptions
1	4	11	10/15 (67%)
2	-	14	9/14 (64%)
3	6	10	11/16 (69%)
4	1	14	9/15 (60%)
5 *	1	13	13/15 (87%)
6	2	7	8/9 (89%)

* the missing case contained insufficient data for diagnosis

3.3.4. Drug Treatment by Diagnoses

The demographic and clinical data for patients with each diagnosis as made by the panel are shown in table 3.14. Sixty-four percent (N= 9) of patients diagnosed with peptic ulcer disease were prescribed a treatment other than eradication therapy. Thirty six percent (N=5) were prescribed maintenance therapy with H_2 receptor antagonists.

Table 3.16 : Demographic Data and Drugs Prescribed by Family Physicians For Each Upper GI Disorder

	Diagnoses By Expert Panel					
	Peptic Ulcer Disease N = 14		GERD/ Dyspepsia N = 68		None N = 2	
Mean Age	38		56		36	
	N	%	N	%	N	%
Male	8	57	43	63	1	50
H_2 Receptor Antagonist	5	35.7	44	65	1	50
Proton Pump Inhibitor	1	7.1	12	18	-	-
PPI + Antibiotics	5	35.7	2	3	-	-
Prokinetic Combo	2	14.3	6	9	-	-
None	1	7.1	4	6	1	50

3.3.5. Utilization of Drugs Effective in the Treatment of Upper GI Disorders

As mentioned previously the measurement of overutilization and underutilization is based on whether a drug was prescribed when not needed or not prescribed when needed respectively. Table 3.15 shows the overutilization and underutilization rates for each upper GI drug group and these rates are shown for each physician in table 3.16.

Table 3.17 : The Overutilization and Underutilization Rates for Each Drug Group

	Proton Pump Inhibitors	H_2 Receptor Antagonists	Antibiotics	Prokinetics
Patients Who Needed Drug	23	57	11	1
Patients Who Did Not Need Drug	61	27	73	83
Drug Not Prescribed But Needed	8	8	6	0
Drug Prescribed But Not Needed	7	6	2	7
Underutilization Rate	8/23 (35%)	8/57 (14%)	6/11 (55%)	0/1 (0%)
Overutilization Rate	7/61 (12%)	6/27 (22%)	2/73 (3%)	7/83 (8%)

Table 3.18 : Overutilization and Underutilization Rates of Proton Pump Inhibitors for Each Physician

Physician	PPI needed	PPI prescribed	Underutilization Rate of PPI	Overutilization Rate of PPI
1	5	2	4/5 (80%)	1/10 (10%)
2	1	0	1/1 (100%)	0/13 (0%)
3	7	9	2/7 (29%)	3/9 (33%)
4	4	5	1/4 (25%)	2/11 (18%)
5	3	3	0/3 (0%)	0/12 (0%)
6	3	3	0/3 (0%)	0/6 (0%)

The average number of patients seen by each physician who needed a proton pump inhibitor was N = 4 and the underutilization rates for each physician varied considerably. Unfortunately these results, which are based a small sample population, may be somewhat unstable and need to be verified through a larger scale study such as the one described in Appendix E.

Table 3.17 demonstrates the cases where it was determined by the expert panel that certain upper GI drugs were underutilized by the family physician and the diagnoses that were assigned to each case by this panel. All 6 cases where it was determined that antibiotics were underutilized had a positive investigation (i.e. endoscopy) recorded in their chart confirming the presence of peptic ulcer disease.

Table 3.19 : Data on Patients Who Should Have Received Drugs for Upper GI Disorders But Did Not Receive Them.

	Proton Pump Inhibitors N = 8		H_2 Receptor Antagonists N = 8		Antibiotics N = 6	
	N	%	N	%	N	%
Peptic Ulcer Disease	6	75	-	-	6	100
Nonulcer Dyspepsia	2	25	1	12	-	-
Gastroesophageal Reflux Disease	-	-	7	88	-	-

Instances where the prescription of an upper GI drug was deemed inappropriate are shown in table 3.18. It was determined by the expert panel that 5 of the 7 prescriptions for PPIs were inappropriately prescribed for nonulcer dyspepsia.

Table 3.20 : Data for Inappropriate Prescriptions

	Proton Pump Inhibitors N = 7		H_2 Receptor Antagonists N = 6		Antibiotics N = 2		Prokinetics N = 7	
	N	%	N	%	N	%	N	%
Peptic Ulcer Disease	-	-	4	67	-	-	2	29
Gastroesophageal Reflux Disease	2	29	2	33	-	-	3	43
Nonulcer Dyspepsia	5	71	-	-	2	100	1	14
GERD/ Dyspepsia	-	-	-	-	-	-	1	14

3.4 CONCLUSIONS

The pilot study pertaining to the prescription of upper gastrointestinal drugs demonstrated that it is possible to develop explicit criterion-based guidelines for the treatment of upper gastrointestinal disorders. These guidelines enable a research team to determine the appropriate diagnosis and therapy for individual patients. It was also deemed possible to collect sufficient patient specific information from family physicians so that the diagnosis and therapeutic decisions of these physicians can be compared to the explicit criterion-based guidelines that have been developed.

With content expertise support it is feasible for a research team to apply the criterion-based guidelines to assess therapeutic decisions made by the family physicians. This statement is substantiated by the results of this pilot study where the level of agreement between the research team and expert panel was 100% for diagnosis and 95% for treatment decisions. Although there was a high level of agreement, it was concluded that an objective expert panel would be helpful in arbitrating between the physicians' decisions and the research team's conclusions. Originally disagreement occurred in differentiating between gastroesophageal reflux disease and nonulcer dyspepsia, however this was overcome by combining the two diagnoses for mild to moderate cases, where the treatment is similar.

It was also deemed feasible to report the overutilization and underutilization rates for the prescription of various classes of drugs through the use of patient based retrospective drug utilization review and criterion-based guidelines.

CHAPTER IV

Antibiotic Utilization

4.1 ANTIBIOTICS : LITERATURE REVIEW

Antibiotics are arguably one of the most important advances in the history of medicine. Sir Alexander Fleming's discovery of a penicillin-producing mold in 1928[61] opened the door to the development of antibiotics that have greatly reduced the morbidity and mortality that is associated with infections. Unfortunately these 'wonder drugs' have been overutilized and as a result adverse consequences have occurred.[15 17] Aside from antibiotics being expensive and/or potentially toxic, their misuse appears to be endemic which has greatly contributed to the emergence of antibiotic resistance.[62] The modification of pathogenic bacteria to form resistant strains, is now a significant factor in the resurgence of previously conquered life threatening bacterial diseases.

Pathogens such as *Neisseria gonorrhoeae*, *Neisseria meningitis*, and *Streptococcus pneumoniae* were once susceptible to most antibiotics but have now formed a resistance to some forms of therapy,[63 64 65] and subsequently spread rapidly throughout various countries.[66] This is largely a result of the widespread misuse and overuse of antibiotics in addition to other contributing factors. Generally these resistant bacteria have undergone mutations, genetic alterations, enabling them to gain the upper hand in this rapid spread of antibiotic resistance. For example, infections with *Streptococcus pneumoniae* are among the leading causes of illness and death among young children, persons with debilitating medical conditions, and the elderly worldwide.[67]

Patients who are not compliant with the prescription regime are also contributors to the overall problem of antibiotic resistance. Patients who cease taking the antibiotic when their symptoms have lessened are killing the highly susceptible bacteria but failing to destroy all the pathogens. Powerful surviving strains remain which will reproduce and aid in the development of resistant bacterial strains.[68] A study of patients, who visited a university clinic, demonstrated another form of antibiotic misuse. It was apparent that self-treatment by patients was also a common occurrence,[69] including unused antibiotics that are regularly stored in medicine cabinets that are used freely and are also passed on to people who are suffering from similar symptoms.[68] These forms of antibiotic misuse are not only contributing to antibiotic resistance, they can also bring harm to the patient (e.g., unknown drug allergies).

Currently, over 95% of *Staphylococcus aureus* strains are resistant to Penicillin G, with an increasing number of strains developing resistance to other antibiotics such as methicillin (MRSA), oxacillin, nafcillin, and cephalosporins.[65] Due to the large number of infections that are treated within a hospital, the highly resistant bacterial strains tend to be found there. As a result, a significant number of deaths each year are due to nosocomial bacterial infections.[70]

Of recent concern is the emergence of resistance to the antimicrobial vancomycin, VRE (vancomycin resistant enterococci), which has been thought of as the only effective treatment for enterococcal infections.[71] [72] The reemergence of serious infections that were thought to be virtually eliminated (i.e., tuberculosis), intensify the necessity for new antibiotics. Yet, the development of newer antibiotics has been delayed due to the changing economic environment of health care.

Not only has the microorganism-human symbiotic relationship been affected by this inappropriate utilization of antibiotics, but at the more pragmatic level it is very costly and diverts resources that could be channeled into other patient services. There is an increasing need for explicit guidelines pertaining to the treatment of infection related illnesses, if such guidelines will result in a rational approach to antibiotic therapy. Ultimately, these recommendations for optimal empiric treatment should improve overall antibiotic utilization within the community.[73]

Many pharmaceutical companies are now searching for newer and better antimicrobials. Yet, it will be a long time before these recently inspired pharmaceutical companies will be in a position to release these much needed medications.[68 72] Perhaps the most useful recent advance has come in the form of beta-lactamase inhibitors.

4.2 INTERVENTIONS TO REDUCE ANTIBIOTIC UTILIZATION

The utilization of clinical practice guidelines has shown an improvement in physicians' therapeutic decisions concerning bacterial and viral infections.

De Santis et al. (1994)[16] performed a randomized controlled parallel group trial where physicians from matched, geographically separated locations were allocated to control and intervention groups. De Santis measured the quality and appropriateness of antibiotic prescribing according to physicians' compliance with the recommendations in the antibiotic guidelines that they used as their recommended treatment. According to the first phase of the De Santis et al. study, broad spectrum antibiotics, which are discouraged by the guidelines, accounted for 40% of the 796 prescriptions written by all participating physicians. It was shown that after a three month educational intervention, involving mailed brochures and a face-to-face visit by a pharmacist, the study group's adherence to the recommended treatment increased from 60.5% to 87.7% (P <0.05).

A study conducted by Avorn et al. (1983)[14] aimed to reduce excessive utilization of various drugs. 435 physicians participated in the study and wrote an average of 1259 cephalexin prescriptions over a nine month period in 1980. A significant reduction in the inappropriate prescription of cephalexin per physician (intervention=1029 and control=1240) followed a face-to-face intervention.

Two groups of oral antibiotics were assessed in the study conducted by Schaffner et al. (1983).[15] The first group consisted of three contraindicated antibiotics, chloramphenicol, clindamycin and tetracycline, with the latter pertaining to children

under 8 years of age. The second group included an examination of the prescribing of cephalosporins. The intent of the intervention performed in this study was to eliminate the inappropriate utilization of the first group of antibiotics and to reduce, not eliminate, the overall prescription of the second group. During the year prior to the intervention, a group of physicians (N=372) wrote 1,883 prescriptions for 1,087 patients for contraindicated antibiotics and 35,316 prescriptions for 17,636 patients for oral cephalosporins. A reduction was noted in the proportion of physicians prescribing the contraindicated antibiotics (Attributable Reduction=18%; P=0.04), whereas the oral cephalosporin prescribers continued to use these antibiotics after the intervention. Schaffner tested three forms of intervention (1) mailed brochures, (2) visit by a drug educator, and (3) visit by a physician counselor. Although the drug educator and physician counselor demonstrated an attributable reduction, it was the physician counselor form that proved to be most effective.

Gutierrez et al. (1994)[17] performed an educational intervention study aimed at improving treatment of acute diarrhea by family physicians in 2 primary health care units in Mexico City. Throughout the intervention it was recommended that drug prescription be decreased and that the use of oral rehydration therapy be increased. Antibiotics were one of the most common prescriptions (67.7%), with ampicillin the foremost prescribed antibiotic (19.9%). Following the intervention, which involved a workshop and a peer review, the study group demonstrated a significant change, with the frequency of antibiotic prescriptions decreased from 35.4% to 14.3% (P<0.01). In addition to the observed decrease in prescription frequency there was a comparable increase in the

prescription of the recommended oral rehydration therapy for children < 5 years of age, 31.4% to 73.8% (P<0.01).

4.3 SUMMARY

Research suggests that it is feasible to use criteria or guidelines in the assessment of physicians' performance. The criteria must be scientifically and clinically established and the reliability and validity of using these guidelines in a certain setting must be confirmed. The choice of intervention strategy that will be implemented to improve the antibiotic prescribing patterns of physicians, depends on the results of the baseline assessment. This will enable the research team to establish and understand the prominent areas of inappropriate prescribing behavior. The intervention should focus on these areas and aim to enhance the physicians' knowledge and therapeutic decisions. According to Hepler et al. (1982)[74] three criteria should be met when implementing a drug prescribing intervention: 1. theoretical validity, 2. evidence of general efficacy, and 3. evidence of need. An educational, process-orientated intervention that is aimed at the areas in which prescribing behavior is inappropriate should be encouraged.

CHAPTER V

Utilization Review of Antibiotic Prescription in the Community: A Pilot Study

5.1 RATIONALE

Newfoundland has the highest rate of antibiotic prescription in Canada. This is a public health concern due to the potential for (1) development of resistant organisms,[75] [76] (2) unnecessary side effects[76], and (3) increased health care costs.[77] [78] However, even with these life threatening concerns, the rate of bacterial infection in the population, the rate of inappropriate prescriptions of antibiotics, and the reasons for inappropriate utilization are unknown. It is this information that is needed to design an intervention aimed at enhancing the appropriate prescription of antibiotics.

Physician choices of drugs may be less than ideal and it has been shown that antibiotic prescribing patterns are influenced by a variety of factors such as the physicians' approach to health care, differing standards for diagnoses, and variant perceived patient demand.[79] [80] A recent study that was performed in the St. John's area, assessed a group of family physicians' prescription pattern for ciprofloxacin. It was determined, by both an academic and industry panel separately, that between 40% and 60% of ciprofloxacin prescriptions were inappropriate. The reasons for these inappropriate prescriptions included cheaper alternatives available, inadequate coverage of likely pathogens and wrong indications.[24] These results, and the emergence of drug-resistant bacterial strains, indicate there is need for professional and public educational interventions aimed at improving antibiotic utilization.

The effects and patterns of antibiotic utilization are very different in hospitals than in office-based practice. Broad- to medium-spectrum oral antibiotics, e.g., tetracyclines, penicillins, and erythromycin are more commonly prescribed in office practice for respiratory infections.[62] Unfortunately, the incidence of antibiotic resistance is much more highly correlated with the utilization of broad-spectrum antibiotics than narrow-spectrum antibiotics. It has been determined that office-based physicians habitually prescribe antibiotics for viral upper respiratory infections. Seasonal respiratory illnesses such as colds, upper respiratory tract infections (URIs), and bronchitis possess a viral etiology in >90% of cases. Therefore, treatment with antibiotics has minimal clinical benefit.[81 82]

When a patient presents with an infection-related illness, the physician is faced with two decisions: (1) Whether or not the patient needs an antibiotic prescription for their particular illness, and (2) if an antibiotic is deemed necessary, the appropriate type of antibiotic must be prescribed. The focus of the next chapter is to determine whether or not it is feasible to assess these two decisions made by a family physician through the use of explicit case-based criteria.

Kunin et al. (1973)[62] wrote an exposition on how antibiotics were being used. They referred to an unpublished study in which the use of antibiotics was judged according to the assessors' clinical knowledge and relevant literature. Three of the five categories they used to judge the use of antibiotics were applicable to the judgments made in our antibiotic pilot study. They include:

1. Agree with the use of antimicrobial therapy, the program is appropriate.
2. Agree with the use of antimicrobial therapy, but a different (usually less expensive/ or less toxic) antimicrobial is preferred.
3. Disagree with the use of antimicrobial therapy, administration is unjustified.

The actual measurement of appropriateness is not faultless. The lack of an acknowledged standard for measuring appropriateness results in an inability to accurately determine the sensitivity and specificity of a measurement tool.[83] In this pilot antibiotic study, the appropriate utilization rates are calculated by adding those patients who needed and received an appropriate antibiotic to those who didn't need and weren't given an antibiotic, and dividing by the total number of cases.

The criteria for diagnosis and treatment of infection-related diseases were based upon the *Ontario Anti-infective Guidelines for Community-acquired Infections*.[84] These guidelines were developed by an independent panel, consisting of family physicians, specialists and pharmacists, to make it easier for physicians to understand the precise role of the many new anti-infectives that are used in the treatment of infection-related diseases. Existing guidelines, both Canadian and international, were the basis of the initial draft of guidelines. These preliminary guidelines were reviewed at four consensus conferences and feedback from 120 physicians and medical associations across Canada as reviewed at a fifth consensus conference. It is evident that the development of credible guidelines is a perpetual process, thus the second edition of these guidelines was used in this study.

5.2 METHOD

This pilot study is a patient based, retrospective drug utilization review. Using data that was abstracted from charts and physician interviews, an expert panel reviewed each case to determine the optimal diagnostic and treatment decisions for infection related illnesses. Similarly, the research team independently applied explicit criteria for diagnosis (Appendix K) and the Ontario *Anti-infective Guidelines*[84] for treatment to assess each patient case.

5.2.1. Subject Selection

This pilot study involved family physicians that were informed that a research nurse would evaluate all the charts from their patients seen for the previous 2.5 days. A research nurse recorded the total number of patients seen by each physician throughout those days and selected only those patients seen for infection related ailment to be used in the study.

Inclusion Criteria

Physicians:

- office or community based family physicians within the St. John's/ Mt. Pearl region
- must consent to participate in the research study

Patients:

- both adults and children that presented with an infection related illness

Exclusion Criteria

Patients:

- presenting with conjunctivitis, acne or intertrigo since these diagnoses were not included in guidelines

5.2.2. Data Collection

Diagnostic and treatment data, i.e., exact diagnosis, investigation and treatment plan, were extracted from those patients' charts, using a standardized instrument (Appendix G). Once the relevant data had been collected, the research nurse using a standardized questionnaire (Appendix H) interviewed each physician. All enrolled patients were sent letters (Appendix I) asking permission to interview them by phone about their illness. Phone interviews were conducted to ascertain symptom information using another standard questionnaire (Appendix J). To determine whether the patient interviews provided any additional information, each patient's symptoms recorded through these interviews were compared to the symptoms recorded from the patient's chart and physician interview. A panel assessed the diagnosis, necessity for antibiotics, and prescription appropriateness using the criteria developed for the Ontario *Anti-infective Guidelines*. The research team answered the same questions using the same Ontario guidelines.

From the information obtained through the patients' charts and physician interviews, several rates were constructed: (a) number of patients with infection symptoms/ total number of patients -- a measure of the overall burden of infection in GP practice at that time; (b) number of infections requiring antibiotic prescriptions/ number of patients seen -- a measure of rate of diagnosis of bacterial infection; (c) number of patients in which

antibiotic prescription was appropriate/ number of patients with infection symptoms -- a "target" for level of overall prescription and measure of competency of diagnosis of bacterial infection; (d) number of appropriate selections of antibiotic (as per Ontario *Anti-infective Guidelines*)/ number of patients in which antibiotic prescription was needed (as determined by the panel) -- a measure of competency of antibiotic selection.

The diagnosis and treatment decisions of the family physicians were compared to the decisions made by the expert panel. The appropriateness of the treatment prescribed by each family physician was determined by whether antibiotics were needed, in addition to the frequency with which patients who needed an antibiotic were prescribed the correct type of agent. Subsequently a research team, independent of the expert panel, applied the guidelines for diagnosis and treatment of infection-related illnesses that were based upon the Ontario *Anti-infective Guidelines* to each patient case. The decisions made by this research team were compared to those made by the expert panel.

5.2.3. Ethics

The Human Investigations Committee of Memorial University of Newfoundland approved this study. Physicians were the focus of the study, and a research nurse and principal investigators made initial contact. Information was only obtained from those physicians who signed a consent form (Appendix F) and agreed to participate in the study. Although patients were not the primary focus of this study their consent was required in order to obtain information from them through a phone interview. Initial contact concerning this phone interview was made by their family physician and phone interviews were obtained from only those patients who agreed to participate in the study. Information was recorded from the patients who participated and the reasons for

nonparticipation were also recorded. All patient information was kept confidential, with numerical identifiers for both the patients and physicians that were known only to the researchers.

5.2.4 Expert Panel Review

An expert panel that consisted of an infectious disease specialist, pharmacist, epidemiologist, and a family physician reviewed the data collected from patient charts and physicians interviews on the 98 patient cases that were obtained from the four community-based family physicians. Using the Ontario guidelines and their clinical knowledge they determined whether an antibiotic prescription was needed. Furthermore, if the family physician prescribed an antibiotic, the panel determined if the optimal type of antibiotic was prescribed. The reasons for prescription of inappropriate antibiotic include:

1. Lower line recommended (Cheaper alternative or first line agent available) - the first, second and third line agents that are recommended in the Ontario guidelines were carefully chosen according to various factors, i.e., the antibiotic's spectrum of activity, predicted efficacy, sensitivity, and safety. The cost of the antibiotics is of importance, especially when there are agents that have similar efficacy, spectrum of activity, and safety.
2. Inadequate coverage - the antimicrobial agent prescribed does not have an adequate spectrum of activity to treat the infection.

5.2.5. Application of Guidelines by the Research Team

The research team reviewed clinical data on the 98 patients, obtained from patient charts and physician interviews, and applied explicit case-based criteria to determine the appropriateness of treatment. The criteria used to make the diagnosis are shown in Appendix K. The criteria for treatment followed the Ontario *Anti-infective Guidelines for Community-acquired Infections (1997).*[25] The research team was independent of the expert panel.

5.2.6. Statistical Analysis

The data for this study were analyzed with a Statistical Package for Social Sciences (SPSS). Various cross tabulations were performed to compare the decisions made by the family physician or academic panel and the decisions made using the explicit criterion-based guidelines.

Kappa scores were calculated to compare agreement between raters on decisions made using the guidelines, by the expert panel and family physicians. This statistic corrects for chance and allows for nominal scale assessment of the level of agreement between the two evaluators or an evaluator and the family physicians.[59]

The proportion of agreement between the two evaluating panels was studied to determine (1) whether the expert panel review would be necessary in the larger scale study, (2) the feasibility of obtaining sufficient information through the data collection process, and (3) the ability of a research team to apply guidelines to make sound judgments pertaining to drug utilization.

5.3 RESULTS

The results portion of this chapter, 1. describes the overall characteristics of the physicians and the patients who were involved in the study; 2. illustrates the results obtained when criterion-based guidelines are used to assess the prescribing patterns of antibiotics by family physicians.

5.3.1. Physician and Patient Characteristics

Eight family physicians were approached to participate in this pilot study and four agreed. Three of the four participating physicians represented group practice settings, with physician #1 and #3 located in the same practice and physician #4 in a private practice. All four participants completed an interview where each patient case included in the study was reviewed.

Table 5.1 : Physician Characteristics

	Gender	Year Graduated	# Days Reviewed	# Patients Seen
Physician 1	Male	1968	2.5	111
Physician 2	Male	1970	2.5	137
Physician 3	Male	1970	1.5	83
Physician 4	Male	1982	2.5	83

Ten of the original 108 cases with infection had conjunctivitis, acne or intertrigo and were excluded from the study (N = 98). Sufficient data for analysis was provided in the remaining cases. The patient characteristics are summarized in the following table.

Table 5.2 : Patient Characteristics

Patient Characteristics (N = 98)	
Age	
Mean	28.8 yrs
Range ≤ 2 yr.	4 (4.1%)
3 - 14 yr.	28 (28.6%)
15 - 24 yr.	17 (17.3%)
25 - 44 yr.	25 (25.5%)
45 - 64 yr.	18 (18.4%)
≥ 65 yr.	6 (6.1%)
Sex	
Female	45 (45.9%)
Male	53 (54.1%)
Allergies	
Sulfa	5 (5.1%)
Penicillin	2 (2.0%)
Pen/ Keflex/Cipro	1 (1%)
Erythromycin	1 (1%)
Cephalosporins	1 (1%)
System Affected	
Respiratory	82 (83.7%)
Genitourinary	7 (7.1%)
Skin	8 (8.2%)
Other	1 (1.0 %)

This following portion of the result section has five components. The first describes the information that was obtained from the family physicians' assessment of the patient during the visit in question. The second presents the information that was obtained through the patient interviews. The third assesses the congruence of the decisions made by the academic panel and by the research team. Treatment decisions made by the family physicians are compared to the decisions made by the research team who applied the criterion-based guidelines which is demonstrated in the fourth component. These comparisons are used to determine both the need for an antibiotic and the appropriateness

of antibiotic choice. The final component presents the appropriateness of antibiotic utilization for the four participating physicians.

5.3.2. Family Physicians' Assessment

Throughout approximately 2.5 days, the four participating physicians saw 414 patients in total of which 26.1% were classified as having an infection. The mean age for these 108 patients was 28.6 years (range 6 mths - 80 years) and 54.6% (N=59) were female. The rate of diagnosis of bacterial infection (as determined by the family physicians' prescription of antibiotics) was 7.0%: - 29 antibiotic prescriptions for presumed bacterial infection/ 414 patients seen by the physicians.

A comparison is made of the rate of infection and prescription in Table 5.3 for each of the four physicians that participated in the study. The average rate of infection was 26.8% (range 21% - 31%) and the rate of antibiotic prescription ranged from 6% - 8%.

Table 5.3: Comparison of the Rates of Infection and Prescription for each Physician.

	Rate of infection	Rate of prescription overall	Rate of prescription for infection cases
Doctor 1	28/111 25%	9/111 8%	9/28 32%
Doctor 2	29/137 21%	8/137 6%	8/29 28%
Doctor 3	25/83 30%	5/83 6%	5/25 20%
Doctor 4	26/83 31%	7/83 8%	7/26 27%

The percentages of various forms of infection related illnesses that were seen by the physicians are shown in table 5.4. Upper respiratory infection accounted for 76% of all

infection-related illness, skin and soft tissue infection 12%, urinary tract infection 6.5%, other infections 5.5%.

Table 5.4: Rate of Diagnosis and Antibiotics Prescribed for Each Type of Infection

	URI	UTI	Skin	Other
N patients with diagnosis	82	7	13	6
% patients with diagnosis	76%	6.5%	12%	5.5%
N antibiotics prescribed	15	4	7	3
% antibiotics prescribed	18%	57%	54%	50%

5.3.3. Patient Telephone Interviews

The patient telephone interviews were conducted to determine the feasibility of obtaining any additional relevant information pertaining to the patient's visit and the proportion of patients who could be contacted for a telephone interview. We tried to contact 108 patients (including patients with conjunctivitis, intertrigo, or acne). Only 63% (68/108) of the patients could be contacted for phone interviews. The reasons for this low rate of participation are described in table 5.5. See Appendix J for the protocol used during the telephone interviews.

Table 5.5: Reasons for Nonparticipation in Telephone Interviews

Reasons	N = 40
Patient requested not to be called	10
Sensitive nature of illness	4
No phone number available	3
Patient couldn't recall the visit	2
Patient was in hospital	1
Patient couldn't be reached	20

Some data obtained from the 68 patients who participated in the telephone interview are shown in table 5.6.

Table 5.6: Data Obtained Through the Telephone Interview.

Information From Patient	N = 68
Expected an antibiotic	38 (55.9%)
Received an antibiotic	19 (27.9%)
Filled the prescription	18 (26.5%)
Early termination of antibiotic (noncompliance)	3 (4.4%)
Would be disappointed if they weren't prescribed an antibiotic	18 (26.5%)
Would travel > 2 hrs to nearest physician with this illness	35 (51.5%)
On a drug plan	43 (63.2%)*

* 5 patients were unsure if they were on a drug plan or not

Of the 38 patients who expected an antibiotic, 19 did not receive an antibiotic, of which 10 were disappointed that they weren't prescribed an antibiotic. Of 19 patients who received an antibiotic 1 did not fill the prescription and a further 3 were not compliant.

Information on primary symptoms obtained from the physicians and the patients revealed agreement in 90% (61/68). There were 5 other patient cases where more information was obtained from the physician's data, which further supports the assumption that the information obtained from the physician and patient is proportional in 97% of cases (66/68). Table 5.7 describes the cases where either the family physician or the patient provided more information pertaining to the symptoms present at the time of the visit. In the 2 cases where information differed between the informants, the therapeutic decision was the same.

Table 5.7: Signs and Symptoms as Recorded by the Family Physician and Patient in 7 Cases Where There Was Not Agreement Between the 2 Sources.

Case Number	Symptoms Recorded By Family Physician	Symptoms Recorded By Patient
1	ear ache, headache, redness, itching, pain	itching ear, dryness
2	ear ache, red TM, fluid discharge, severe pain	irritable, pulling at ear, decreased appetite
3	ear ache, red TM, sore throat, febrile	poking at ear, pain, fever
4	coryza, rales, sore throat, cough	stuffy head, cough
5	coryza, cough, sore throat, fever, rales, chest congestion	cough, chest congestion
6	sore throat, rales	cough, congestion, sore throat
7	coryza, cough, congestion, rhonchi	sore throat, fatigue, congestion

TM = tympanic membrane

Although this tables refers to disagreement, some of the data recorded from family physicians were observations and clinical terminology that the patients would not able to recall. In view of the low patient interview rate and the high agreement between the doctor and the patient concerning symptoms, it was concluded that patient interview was not necessary for a review of antibiotic utilization. Should data be required concerning patient compliance or expectation, then patient interviews would be necessary.

5.3.4. Research Team vs. Expert Panel Decisions

For each of the 98 patient cases included in the assessment it was determined whether an antibiotic prescription was needed. If an antibiotic was prescribed and needed, it was also decided whether the choice of antibiotic was optimal.

If the expert panel is considered the gold standard, the characteristics of the application of the guidelines by the research team demonstrate a sensitivity of 100% and specificity 96%. This is not surprising since the expert panel used the same criterion-based guidelines as the research team. The comparison of the two panels' decisions is shown in table 5.8. The three occasions where the panel and the researchers differed in therapeutic decision are outlined in table 5.9.

Table 5.8: Comparison of Decisions Made by the Research Team and the Expert Panel

		Expert Panel		
		Antibiotic Needed	Antibiotic Not Needed	Total
Research Team	Antibiotic Needed	20	3	23
	Antibiotic Not Needed	-	75	75
	Total	20	78	98

The above comparison of the therapeutic decisions made by the two panels demonstrates agreement in 97% of decisions regarding the necessity for an antibiotic (95% CI = 0.91 to 0.99). The kappa score was 0.91.

Table 5.9 : Patient Cases Where the Panels Differed in Therapeutic Decisions re Necessity for Antibiotic

Patient Case	Physician Diagnosis	Physician Treatment	Research team	Expert Panel
1	sinusitis	no prescription	antibiotic needed	no antibiotic needed
2*	otitis media	antibiotic prescribed	antibiotic needed	no antibiotic needed
3	folliculitis	antibiotic prescribed	antibiotic needed	no antibiotic needed

* this case was a recheck after a 10 day treatment with an antibiotic which caused an allergic reaction. Symptoms had improved but not disappeared.

Table 5.10 compares the decisions made by the research team and the expert panel concerning the appropriateness of the choice of antibiotic. Using the expert panel as the gold standard, the sensitivity of using a research team to apply the guidelines was 80% and specificity was 100%. i.e., 12 had received appropriate antibiotics according to the research team, of the 15 patients who the expert panel felt had received appropriate antibiotics (80%), and 5 had not received appropriate antibiotics according to both the research team and expert panel (100%).

Table 5.10: Appropriateness of Antibiotic Prescriptions Deemed Necessary

		Expert Panel		
		Antibiotic Appropriate	Antibiotic Not Appropriate	Total
Research Team	Antibiotic Appropriate	12	0	12
	Antibiotic Not Appropriate	3	5	8
	Total	15	5	20

Agreement concerning the appropriateness of choice of antibiotic was 85% (95% CI = 0.62 to 0.97), with a kappa score of 0.67.

Table 5.11 describes the 4 cases where the research team and the expert panel differed in their opinion re the appropriateness of choice of antibiotic prescribed by the family physician. Table 5.10 included only the cases where an antibiotic was deemed necessary by the expert panel, thus showing 3 cases where the panels differed. However, there was a patient case where the research team felt an antibiotic was needed but the inappropriate choice of antibiotic was prescribed, whereas the expert panel deemed an antibiotic unnecessary (see table 5.11).

Table 5.11: Comparison of Decisions Made By the Expert Panel and the Research Team in the 4 Cases re Appropriateness of Choice of Antibiotic

Patient Case	Physician Diagnosis	Research Team	Expert Panel Decision
1	Folliculitis	Inappropriate - inadequate coverage	Not needed
2	Dog Bite	Inappropriate - inadequate coverage	Appropriate
3	Otitis Media	Inappropriate - lower line recommended	Appropriate
4	UTI	Inappropriate - lower line recommended	Appropriate

We concluded that the research team was likely to apply the guidelines more vigorously than the expert panel but that it would be necessary to describe the reasons why antibiotic choices were considered inappropriate. This is because the quality of care should be determined by whether adequate coverage was provided rather than by cost. However there are instances where the cost-effectiveness of the antibiotic prescribed is a factor, such as those cases in this pilot study where an equally effective and less expensive antibiotic is available and recommended.

5.3.5. Assessment of Treatment Decisions by a Research Team Applying Guidelines

Using the guidelines applied by the research team, we assessed the decisions made by the family physician re (a) the necessity for antibiotics (Table 5.12), (b) appropriateness of antibiotic choice and the reasons that the choice was not appropriate (Table 5.13). The decisions made by the research team were used as the standard in lieu of the expert panel due to the published nature of the Ontario guidelines, which required that they were based upon consensus and underwent peer review.

Of the 22 prescriptions of antibiotics that were made by the family physicians there was 100% agreement with the research team pertaining to the necessity of antibiotics. However, the criterion driven approach demonstrated that there was 1 patient where an antibiotic was needed but was not prescribed by the family physician. Thus, the overutilization score was zero and the underutilization score was 4.3% (Table 5.16).

Table 5.12: Comparison of Decisions Made by the Research Team and the Family Physicians

		Family Physician		
		Antibiotic Prescribed	Antibiotic Not Prescribed	Total
Research Team	Antibiotic Needed	22	1	23
	Antibiotic Not Needed	-	75	75
	Total	22	76	98

Although the decision to utilize antibiotics by the family physician was highly appropriate, the choice of antibiotic was less appropriate, as shown in table 5.13. Of 22

decisions to prescribe an antibiotic, 41% were considered to involve inappropriate choice. The nine differences between the actual decision and the research team are outlined in table 5.14.

Table 5.13: Appropriateness of the Choice of Antibiotic Prescribed by the Family Physicians

Research Team	
Antibiotic Appropriate	13
Antibiotic Inappropriate	9
(a) Inadequate Coverage	5
(b) Lower line or cheaper alternative recommended	4

* Three of these 22 prescriptions were for topical agents

Table 5.14: Panels' Therapeutic Decisions Concerning the Choice of Antibiotic Prescribed by the Family Physician

Patient Case	Family Physician Diagnosis	Type of Antibiotic Prescribed	Research Team
1	dog bite	cloxacillin	inadequate coverage
2	UTI	norfloxacin	lower line recommended
3	community acquired pneumonia	amoxicillin trihydrate	inadequate coverage
4	folliculitis	trimethoprim-sulfamethoxazole	inadequate coverage
5	otitis media	amoxicillin-clavulanate	lower line recommended
6	community acquired pneumonia	clarithromycin	lower line recommended
7	impetigo	gentamicin sulfate	inadequate coverage
8	pharyngitis (strep throat)	amoxicillin trihydrate	inadequate coverage
9	UTI	amoxicillin trihydrate	lower line recommended

Although all prescriptions of antibiotics were analyzed, it is the oral antibiotics that are of greater significance. Table 5.15 stratifies the type of antibiotics that were prescribed by oral and topical agents, and demonstrates whether or not the guidelines confirmed that the antibiotic was needed and whether the appropriate antibiotic was prescribed.

Table 5.15: Comparison of Oral and Topical Antibiotics Prescribed by the Physicians as Determined by the Research Team

	Oral Antibiotics	Topical Antibiotics
# Prescribed	18	4
# Needed	18	4
# Inappropriate type of antibiotic prescribed	(N = 7)	(N = 2)
•Alternative recommended	4	-
•Inadequate coverage	3	2

5.3.6. Drug Utilization Scores by Physicians

Table 5.16 stratifies the overutilization, underutilization and appropriateness scores for each of the family physicians.

Table 5.16: Utilization and Appropriateness Scores for Each Family Physician

Family Physician	(a) Overutilization Score	(b) Underutilization Score	(c) Appropriateness Score
1	(0/18) 0%	(1/5) 20%	(19/24) 79%
2	(0/20) 0%	(0/7) 0%	(26/28) 93%
3	(0/20) 0%	(0/4) 0%	(21/24) 88%
4	(0/17) 0%	(0/6) 0%	(21/23) 91%

The scores for the above table were determined by the following frequencies:

(a) = Antibiotic prescribed and not needed/ N where antibiotics not needed

(b) = Antibiotic not prescribed but needed/ N antibiotics needed

(c) = Antibiotic prescribed, needed and choice appropriate + antibiotic not prescribed and not needed / N infection cases

The appropriateness score that was calculated for each physician can be summarized for the total group (N = 98) by including the cases where an antibiotic was not prescribed and not needed (N = 75) with the cases where an antibiotic was prescribed, needed and the choice was appropriate (N = 13). This results in an appropriateness score of 90% (88/ 98).

5.5 CONCLUSIONS

Through the implementation of this pilot study regarding the prescription of antibiotics it was deemed possible to collect sufficient patient specific data from physicians so that the diagnosis and therapeutic decisions can be compared to the Ontario *Anti-infective Guidelines*. From the results of the 68 patient telephone interviews that were conducted it was considered to be unnecessary to interview patients because more clinical information is not provided over and above that provided by the family physician.

It is feasible for the research team to apply the guidelines to make decisions on the necessity of an antibiotic for individual patients, and does not require an expert panel to review all of the patient charts. This statement is supported by the 97% agreement that was demonstrated when the decisions of the research team and expert panel, regarding the necessity of an antibiotic, were cross-tabulated ($K = 0.91$). However, a lower percentage of agreement was demonstrated when the research team and expert panel's decisions pertaining to the appropriateness of choice of antibiotic were compared (85%, $K = 0.67$). This decrease in the rate of agreement suggests that solely the research team should not make decisions regarding the appropriateness of the type of antibiotic prescribed.

It was also found to be possible to report the overutilization and underutilization of antibiotics that are prescribed by family physicians.

CHAPTER VI

Discussion

The main objective of both pilot studies was to evaluate the feasibility of utilizing explicit case-based criteria to assess the diagnosis and therapeutic decisions made by a family physician.

Each study addressed an area of medicine of concern to the Department of Health of the Province of Newfoundland. One concentrated on the utilization of upper gastrointestinal drugs, and the other on antibiotic prescription. This section will discuss the methodological considerations and the various limitations associated with each pilot study, and then we will discuss the larger studies where some possible solutions will be addressed.

6.1 LIMITATIONS OF PILOT STUDIES

6.1.1. Data Collection

A medical history is completed for every patient who visits a physician. However, the amount of information documented in each chart varies among physicians. Therefore, one methodological issue concerned the feasibility of retrospective data collection to determine the patient's individual needs. The data collection process used in both studies is lengthy. Each patient chart must be reviewed thoroughly to ensure that a complete medical history is obtained. This comprehensive patient profile is essential for the expert and research panels to apply the guidelines and accurately determine the optimal therapeutic decision.

Although the degree of information recorded by each physician in the patients' chart could vary, there were few instances in which the panel was unable to make a decision because of inadequate information. This may have resulted from the use of a standardized data abstraction form and a physician interview subsequent to chart abstraction, whereby the interview substantiated the information compiled from the patients' charts and in some cases, provided additional information. Only 1 case was rejected in the upper GI study due to inadequate data and none in the antibiotic study.

6.1.2. Application of Guidelines by a Research Team to Assess Appropriateness

6.1.2.1. Utilization of Upper GI Guidelines

The Newfoundland guidelines for the treatment of upper gastrointestinal disorders, together with a multidisciplinary expert panel and an extensive literature review, were involved in the development of optimal diagnosis and treatment guidelines (Appendix C). The decisions made by the expert panel were compared to those of a research team applying the guidelines, which demonstrated a substantial disagreement between the two methods concerning original diagnosis, particularly for nonulcer dyspepsia and GERD. This resulted from (a) the vague and nonspecific nature of the symptoms (b) the similarity of the symptoms that characterize both gastroesophageal reflux disease and nonulcer dyspepsia, and (c) differences in the way that past and current symptoms were integrated to make a diagnosis. Frequently patients with symptoms of GERD had symptoms of nonulcer dyspepsia in the past, and vice versa. When the two disorders were considered an overlap condition, GERD/Dyspepsia, diagnostic agreement increased to 100%.

A 95% agreement between the researcher and the panels' therapeutic decisions enabled an inference that decisions concerning the optimum treatment regime could reasonably be based primarily on symptoms, signs and medical history rather than a specific diagnosis. It has been shown that there is a high proportion of patients with ill-defined symptoms, which in turn makes it difficult to treat a patient based on an accurate diagnosis.[8] Beers et al. (1997)[40] demonstrated that it is feasible to evaluate the utilization of medication with criterion-based guidelines in the absence of specific diagnoses. It has been necessary to use this approach with guidelines in instances where relative inaccuracies exist in certain medical records, i.e., nursing home records.

6.1.2.1. Utilization of Antibiotic Guidelines

The criteria used to assess the family physicians' therapeutic decisions were based on the *Ontario Anti-infective Guidelines for Community-acquired Infections* (1997).[84] These guidelines were consensus driven, evidence based and published. However, there were instances where the expert panel's clinical knowledge caused them to veer from the recommended line of treatment. Comparisons of the expert panel and decisions made by the research team using the guidelines demonstrated strong agreement concerning decisions on whether a prescription for an antibiotic was necessary. This agreement diminished when decisions on the appropriate choice of antibiotic were assessed. Analysis of each case in which disagreement occurred between the two methods suggested that adherence to the guidelines was preferable. It was concluded that it is feasible for a research team to determine the necessity for an antibiotic through the use of guidelines that are applied to information obtained through extensive data procedures,

which included patient information extracted from the chart by a nurse, physician interviews and patient interviews.

6.1.3. Study Population

In the antibiotic study, four of the eight physicians who were approached refused to participate in the study. The physicians who agreed to participate have well established practices and it could be assumed that they are confident in their prescribing behavior. The low rate of antibiotic prescription and the optimal therapeutic decisions that were made by these physicians would support this hypothesis.

A larger and more diverse group of physicians is required to ensure that the data collected is representative of what happens in the community. It is hoped that if 80% of all physicians in the St. John's - Mt. Pearl region participate in the larger study both appropriate and inappropriate prescribers will be represented in the study population.

6.2 PROPOSED COMMUNITY STUDIES

Two studies were designed to assess drug utilization in the community. The protocols for these larger scale studies were based upon the pilot studies that were discussed in this thesis. (See Appendix E & L)

The objective of the upper gastrointestinal (UGI) study is to assess the utilization of UGI drugs within the community and to determine the effectiveness of an educational intervention on the improvement of the appropriate prescription of these drugs by family physicians, i.e. reducing underutilization of proton pump inhibitor. This study will be a randomized controlled study involving retrospective patient chart review by a research nurse. Subjects will be randomized to intervention or control groups and followed to document outcome. Through the use of accepted criterion-based guidelines, the appropriateness of prescription will be measured in both groups to ascertain if the intervention was effective.

The second study's objective is to determine the rate of antibiotic prescription in the treatment of upper respiratory, urinary tract and skin and soft tissue infections within the community and whether it is possible to reduce the rate of overutilization of antibiotic prescription through the implementation of an educational intervention. This will be a pre/post intervention trial where the prescription behavior of family physicians will be assessed. A retrospective review of patient charts by a research nurse will provide the information needed to determine whether the antibiotic prescription was necessary and whether the appropriate antibiotic was prescribed.

6.2.1. Limitations of the Proposed Community Studies and Pilot Studies

Certain areas within the protocols and pilot studies present limitations that need to be addressed.

1. Method of recruitment. A physician's consent is required before any charts can be reviewed. This introduces the Hawthorne effect, whereby the knowledge that their behavior is being monitored in a study may alter the prescribing behavior of the participating physicians.[16] Furthermore, subjects who volunteer to participate in a study are not randomly selected and represent a distinct group whose generalizability to the total population of physicians is significantly reduced. It is this volunteer nature of the study subjects which creates an inherent bias. The physicians who do not agree to participate in the study may be the very physicians who are prescribing inappropriately.

   With the use of the provincial database (MCP) the Hawthorne effect will be monitored by measuring the rate of antibiotic prescription/ number of patients seen before and after the study. If prescription rates decrease during the baseline study it would support the Hawthorne effect. However, it would also demonstrate that prescribing behavior can be influenced by the process of drug utilization review.

2. Retrospective review of medical records. Misclassification bias may occur if pertinent findings and information from the clinical history and examination are absent from the patient's record or are recorded improperly.[85 86] For example, previous investigations and past medical history are necessary to determine whether the dyspeptic symptoms experienced by a patient are ulcer or nonulcer in nature. Similarly, in many cases there is a fine line between whether an infection is bacterial or viral when relying only on

the patient's symptoms and clinical history to make diagnostic and therapeutic decisions.[87] Both cases substantiate the importance of a consistent and thorough medical history for each patient.

3. Physician interview. As physicians verify and/or provide additional information concerning their therapeutic decisions this could bias results in favor of their decisions. Although it is thought that the interviewers' knowledge of the research hypothesis may cause such a bias, it is unlikely since the majority of data is obtained from the patients' records.[85]

   In some instances in the upper GI study the physician was required to recall a visit that occurred some months prior to the interview. This increases the distinct possibility of either recall error or bias occurring,[88] yet it is assumed that the information obtained from the patient's chart will alleviate some of this bias. Unlike the upper GI study, the physician interviews for the anti-infective study took place no later than three days following the visit in question, limiting the issue of recall bias.

4. Concurrent events which may influence the results of the study (cointervention). According to Guo et al. cointervention includes pharmaceutical companies' promotional detailing, patients' demands, noncompliance, federal or states policies, clinical pharmacists' consultations, third-party payer reimbursement policy, cost of medications, or academic conferences, meetings, lectures and seminars.[27] A particular event which occurred in the middle of data collection for the upper GI study was the restriction of proton pump inhibitors by the provincial drug formulary. Physicians were required to fill out and submit forms to warrant a prescription for proton pump

inhibitors. This newly implemented restriction may have altered the physicians' prescribing practices.

5. Randomization. In lieu of randomizing the physicians individually, the concept of randomly allocating the subjects by physician practices was considered. If we used an appropriateness score per practice as the primary outcome measure 56 practices would need to be enrolled, but this would not be feasible within the geographic area of the proposed study (St. John's-Mt. Pearl region). It was thought that this method would eliminate some of the contamination that is attributable to the exchange of information between the control and intervention subjects within the same practice.[89] However, this would not exclude the communication of information among physicians throughout St. John's and Mt. Pearl, some of whom may be in the intervention group.

   It is anticipated that the presence of a control and intervention group will reduce the effect that cointervention will have on the results. This cointervention may be a result of information from pharmaceutical representatives, peer physicians and available literature. If the subjects are truly randomized to the two groups, it is assumed that any changes that are not a direct result of the intervention will be demonstrated in the control group.

6. Generalizability. Clearly the pilot studies do not reflect what is happening in the community, as only a few select physicians participated. This will be alleviated in the community based study because it is hoped that the family physicians who are randomly allocated to the control and intervention groups will provide two groups that are similar in characteristics. However, only those physicians who agree to participate in the study will be enrolled in the randomization process which may cause the

generalizability of the results to be questionable. To generalize the results to the rest of Canada, one must assume that when compared to Newfoundland, physicians' education, health care delivery and patients are similar in the other provinces.

7. Seasonality. It is recognized that respiratory infections have a higher incidence rate during the winter months.[90 91 92] This pilot study on antibiotic utilization took place during the last week of May and first week of June, at which time the rate of infection is probably lower. It is possible that during the winter months the physicians are overwhelmed with patients and may not have sufficient time to completely assess the patient. This may result in a prescription of an antibiotic as an indication that the consultation is over.[8]
8. Sample Size. Initially, the sample size calculation for the upper GI study did not take into account the problem of assuming independence of the individual treatment decisions made by each physician. To achieve this sample size each physician will enroll 18 patients into the study of which it would be assumed that 5 patients need proton pump inhibitors. Thus, similar patients may be entered into the study and may not be considered independent of each other.

   To overcome this problem of independence it was decided to use an arbitrarily appointed score for each physician. Thus, the physicians themselves are used as the basis of the calculation (or the unit of randomization) rather than the patient visits. However, it is not clear how many patient visits would be necessary to provide a valid score for each physician. Furthermore, the pilot study does not really provide a reasonable estimate of the range of scores per physician, or the likely average score for

physicians in the community. It is shown that both ways of estimating the sample size have their limitations.

Although it is common practice to use a two-sided hypothesis, a one-sided hypothesis was used in the design of this study. The primary outcome of the study was to determine the positive effect that an intervention had on the intervention group. This positive outcome was shown by an increase in the physicians' adherence to recommended guidelines and criteria. A negative outcome would be classified as no observed change in the prescribing patterns of the intervention group, as it is assumed that the intervention will not have a negative effect on the prescribing practice of the participating physicians.

9. Blinding. Due to the necessity for a physicians' consent to participate in these studies it is not possible to completely blind the subjects. Although the participating physicians will not be aware of what the study specifically entails, they will know that their patients' charts are being reviewed and this may alter their prescribing patterns (Hawthorne effect). Retrospective data collection from patients' charts, rather than self-reporting by physicians, is used in an attempt to eliminate as much bias from the physician as possible.[40] If physicians know they are in the control group they may acquire new information and thus confound the beneficial impact of the educational intervention.

6.3 STRENGTHS AND WEAKNESSES

The strength of these intervention studies is that they allow the physicians to learn more about their prescription patterns and will give them the opportunity to improve the level of care that they give to their patients. Continuing medical education (CME) is an essential aspect of clinical medicine and through this study the physicians who are in the intervention group will receive CME pertaining to diagnostic and treatment guidelines for upper GI disorders and infection-related illnesses. The pre- post design of the antibiotic study is a result of the Department of Health of Newfoundland and Labrador requirement that all physicians be given the opportunity to receive the same information rather than just a select group. If this intervention is effective in enhancing optimal prescribing patterns, it will improve the level of health care that is provided to the patients of the physicians in the community. The actual length of time that the physicians will sustain the effect of the intervention and prescribe optimally is unknown. A follow up period, six months after the third phase, would give a good indication of the sustainability of the intervention's effectiveness in the physicians of the study group.

The main weakness is the requirement for a physician's consent to participate in the study such that necessary information can be obtained. Some physicians may feel threatened that their practice of medicine is being monitored. As previously mentioned a change in their prescribing pattern may also occur due to the knowledge that they are being assessed. It is necessary for measures to be taken, i.e. control group or external validation, to ensure that this bias is accounted for in the results.

CHAPTER VII

Summary and Conclusions

Drug utilization review is an appropriate means of determining the appropriateness of prescription by physicians within a community. DUR may be patient-based or registry based depending upon the information required to answer the research questions. The design of the DUR that is used may be either retrospective or prospective, with the former having been proven the most feasible and cost-effective method for current use. The utilization of guidelines to assess physicians' prescribing behavior was discussed, including the development of guidelines, their involvement in quality assurance, the implementation of these guidelines to assess physicians' practice, and how these criterion-based guidelines are used in performing a DUR.

Both guidelines and interventions are used to improve the appropriateness of prescription by physicians. The measurement of appropriateness has been discussed and the most effective form of intervention has been established as being a face-to-face intervention that is conducted by a peer physician. Clinical practice guidelines developed by physicians from clinical and scientific knowledge in conjunction with clinical trial data are more likely to be accepted by physicians in general. This is under the presumption that each guideline has been tested against actual patient cases prior to their implementation, which would not be possible with registry-based DUR.

The utilization review of drugs effective in the treatment of upper gastrointestinal disorders determined that it was possible to collect patient specific data from physicians and it was feasible for a researcher with content expertise support to apply the guidelines

to these data. It is possible to report the over/underutilization and appropriateness rates from this form of retrospective patient-based DUR.

A large scale study is needed to assess the effectiveness of an educational intervention in improving the appropriateness of prescription of drugs for upper GI disorders and the issues arising from the design of this study were addressed.

Antibiotics are of extreme importance but their misuse contributes to the global problem of antibiotic resistance. Various studies have been performed to reduce antibiotic overutilization through an educational intervention.

A retrospective patient-based DUR of antibiotic utilization determined that it was possible to collect patient specific data from physicians and it was feasible for a research team with content expertise support to apply the guidelines to these data. It was deemed unnecessary to interview the patients as no additional clinical information was provided through this process. It was determined through this retrospective DUR that it is possible to report the overutilization and appropriateness rates using this method of evaluation.

A larger scale study is necessary to accurately assess the extent of antibiotic misuse within the community. The form of intervention that is to be used in this study will be determined subsequent to the baseline assessment.

The utilization of various drugs has been less than ideal due to inefficiencies in physicians' prescribing practices. Further research is necessary to determine the actual extent of these inefficiencies and whether an educational intervention will have a favorable effect on improving inappropriate prescribing practices. This thesis investigated the feasibility of using criteria and guidelines to assess the remedial effectiveness of drug utilization in the community. It was established that a researcher

could collect the necessary information and utilize predetermined criteria and guidelines to determine the optimal treatment regime.

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Appendix A

Faculty of Medicine
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Consent To Participate In Bio-Medical Research

Title: The Effectiveness of an Educational Intervention on The Improvement of Physicians' Inappropriate Prescription of Upper GI Drugs

Investigators: Dr. F. Bursey
Dr. P. Parfrey

Sponsor: Astra Pharma Inc.

You have been asked to participate in a research study. Participation in this study is entirely voluntary. You may decide not to participate or may withdraw from the study at any time.
Confidentiality of information concerning participants will be maintained by the investigator. The investigator will be available during the study at all times should you have any problems or questions about the study.

The Purpose of the Study.

Clinical practice guidelines have been developed to improve the diagnosis and treatment of upper gastrointestinal disorders. The use of an intervention designed to increase the use of clinical practice guidelines by primary care physicians may improve the quality of patient care.

A pilot study has been completed and has proven the feasibility of this intervention study.

This study will demonstrate the frequency of each diagnosis as well as the frequency and type of treatment prescribed for each condition. The study will determine the effectiveness of an educational intervention on the improvement of physicians' inappropriate prescription of upper GI drugs.

Description of Procedures and Tests

You will be asked to review a list of your patients who have been seen recently for upper GI disorders. These patients will be identified through the use of your computerized billing codes. These codes will identify patients with gastroesophageal reflux disease,

esophagitis, peptic ulcer disease, gastritis, and functional disorders including nonulcer dyspepsia.

A research nurse will interview you using a uniform abstraction instrument. Data on all patients will be obtained from the charts and from the interview.

Duration of Subject Participation

You will be asked to designate a period of time from your practice to review all cases of upper GI disorders identified by your computerized billing list. You will be asked to review each patient's record while being interviewed by a research nurse who will complete a questionnaire. The time will vary depending on the number of cases identified.

Benefits Which the Subject May Receive

Physicians will receive an honorarium of $20.00 for each case reviewed.

Liability Statement

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities.

Other Relevant Information

Your identity and the identity of your patients will remain confidential. Unless required by laws or other regulatory agencies only Dr. Ford Bursey and his research assistants will have access to the data identifying subjects by name.

I, _____, the undersigned, agree to my

participation in the research study described.

(Signature of Participant) (Date)

(Signature of Witness) (Date)

To be signed by investigator

To the best of my ability I have fully explained to the subject the nature of this research study. I have invited questions and provided answers. I believe that the subject fully understands the implications and voluntary nature of the study.

(Signature of Investigator) (Date)

Phone Number

Appendix B

PILOT STUDY QUESTIONNAIRE:

AN EDUCATIONAL INTERVENTION TO IMPROVE THE PRESCRIPTION OF UPPER GI DRUGS

Questionnaire for Doctor Interview

DATE OF INTERVIEW:

PATIENT INFORMATION

PREVIOUS UPPER GI DIAGNOSIS ? (SPECIFY) YES ☐ NO ☐

Patient Number	Sex:	1. Male 2. Female	Date of Birth: / / DD/MM/YY

Date of Previous Diagnosis (DD/MM/YY)	Description of Previous Diagnosis	Treatment (**make note of any lifestyle changes recommended**)
/ /		
/ /		
/ /		
/ /		
/ /		
/ /		
/ /		
/ /		
/ /		
/ /		
/ /		
/ /		

PREVIOUS INVESTIGATIONS:

Type of Investigation	Date of Investigation (DD/MM/YY)	Results
1 Endoscopy	/ /	
2	/ /	
1 Upper GI Series	/ /	
2	/ /	
3	/ /	
4	/ /	
Ultrasound of the Gall Bladder	/ /	
Gall Bladder Series	/ /	
Barium Enema	/ /	
EKG, Stress test, etc...	/ /	
Other (specify)	/ /	

HAS THE PATIENT HAD PREVIOUS UPPER GI SURGERY ? YES ☐ NO ☐

CONCOMITANT MEDICATIONS:

Drug (Generic Name)	Start Date (DD/MM/YY)	Dosage	Frequency	Ongoing (Y/N)
	/ /			
	/ /			
	/ /			
	/ /			
	/ /			
	/ /			
	/ /			
	/ /			

Is the patient compliant ? Yes ☐ No ☐

Is the patient on any other form of treatment ? Yes ☐ No ☐

HISTORY OF PRESENT ILLNESS

Signs And Symptoms (Circle all those applicable):

1. Retrosternal pain	10. Epigastric pain
2. Bloating	11. Belching
3. Dysphagia	12. Odynophagia
4. Substernal pain	13. Early Satiety
5. Heart Burn / Dyspepsia	14. Sensation of a lump in throat
6. Coughing	15. Chest pain
7. Bleeding	16. Stomach burning
8. Nausea	17. Other (specify)
9. Waterbrash	

CURRENT DIAGNOSIS: DATE:

TREATMENT:

Non-Pharmaceutical Action Taken (Circle all those applicable):

1. Elevate head at night	4. Avoid acidic foods	7. Weight loss
2. Avoid chocolate	5. Stop smoking	8. Avoid alcohol
3. Avoid caffeine	6. Discontinue NSAID	9. Other

Pharmaceutical Action Taken:

Drug (Generic Name)	Start Date DD/MM/YY	Dosage	Frequency	Duration (weeks)	Indication
	/ /				
	/ /				
	/ /				

FOLLOW UP INVESTIGATIONS:

Type of Investigation	Date of Investigation DD/MM/YY
Endoscopy	/ /
Upper GI Series	/ /
Ultrasound of the Gall Bladder	/ /
Helicobacter pylori antibodies test	/ /
Referred to Specialist (specify)	/ /
Other (Specify)	/ /

ACCOMPANYING OR UNDERLYING DISEASE OR CONDITION WHICH MIGHT HAVE INFLUENCED CHOICE OF TREATMENT (CIRCLE THOSE APPLICABLE):

1. Ability to pay

2. Underlying Disease (specify duration and severity)

3. Allergies (specify)

4. Other (specify)

Appendix C

Criteria for Diagnosis and Treatment of Upper GI Disorders

The vast majority of all upper gastrointestinal symptoms are classified under three diagnoses; 1. gastroesophageal reflux disease (GERD); 2. nonulcer dyspepsia (NUD); and 3. peptic ulcer disease (PUD).

Gastroesophageal reflux disease varies in severity. This spectrum of severity encompasses very mild GERD, no apparent inflammation, to very severe, involving stricture formation and ulceration.[93] [94] The cardinal symptoms of this condition are heartburn, classic burning sensation in the low retrosternal area that usually radiates up to the neck, and acid regurgitation, the perception of retrograde flow of gastric contents into the pharnyx. Other symptoms include nonspecific chest pain, dysphagia, water brash, and respiratory symptoms.[95]

Nonulcer dyspepsia (NUD) is a recurrent pain or discomfort in the upper abdomen. The symptoms of nonulcer dyspepsia include (1) immediate postprandial pain, (2) postprandial fullness, bloating or distension, (3) early satiety, (4) postprandial nausea and vomiting, and (5) belching, gas or flatulence.[95] GERD and NUD can co-exist as part of a more diffuse disorder of gastrointestinal motility.[96] [97]

The manifestations of peptic ulcer disease and nonulcer dyspepsia are comparable. In fact, it was suggested by Spiro in 1974 that ulcer and nonulcer dyspepsia are the same disease and that the ulcer is incidental and transient.[98] [99] [100] Since then it has been established that the etiology of these two disorders are different. Unlike nonulcer

dyspepsia, peptic ulcer disease is associated with the presence of acid and *Helicobacter pylori* or NSAID use.[101] Peptic ulcer disease usually presents as chronic, intermittent epigastric pain. It is necessary to perform an investigative technique, endoscopy or radiography, to accurately diagnose the presence of an ulceration.[102 103 104]

Criteria for Treatment:

Effective treatment and accurate diagnosis of upper gastrointestinal problems requires the physician to obtain a thorough medical history of the patient. A patient history should include an explicit description of the symptom, such as its occurrence, location, periodicity, and associated factors, any past gastrointestinal disorders or surgery, and any systemic illnesses which may affect the stomach.[105] Any alarm symptoms, including anemia, weight loss and severe abdominal pain, may indicate an organic disease or a more serious gastrointestinal disorder that would require immediate treatment and careful investigation.[93] A rational approach must be developed which will allow them to determine the cause of these symptoms. If, they are caused by peptic ulcer or malignancy, immediate treatment is necessary. Although gastroesophageal reflux disease and nonulcer dyspepsia are not as critical, the patient's quality of life will be impeded and significant morbidity may occur if these disorders are treated inadequately or not at all.

The treatments recommended for gastroesophageal reflux and non-ulcer dyspepsia are similar. Initial treatment involves life style modifications ± OTC therapy.[53] An inadequate response justifies a prescription of H_2 receptor antagonists, or prokinetics if the gas-bloat syndrome is present. The guidelines used in this study require that the

patient be referred to a gastroenterologist if symptoms persist. If an investigation establishes a diagnosis of esophagitis, treatment with proton pump inhibitors has proven to be clinically superior to H_2 receptor antagonists.[54 106 107 108]

Once it has been ascertained through an upper GI investigation, e.g. endoscopy or UGI series, that peptic ulcer disease is present the treatment is unequivocal as previously mentioned. Recently it has been shown that over 90% of nonmalignant ulcers, not induced by NSAIDs, are associated with *H.* pylori.[109 110 111 112] Due to this high prevalence of *Helicobacter pylori* infection of ulcer patients, eradication therapy is the recommended treatment.[108 113 114 115] Although there has been some discussion on the use of antibiotic based therapy for the treatment of NSAID induced ulcerations it has not been proven to be move effective than treatment with a proton pump inhibitor, i.e. omeprazole.[112 113]

Guidelines for Treatment:

1. First line treatment should be lifestyle modifications and/or over-the-counter medications (LSM/OTC).
2. Any patient over the age of 40 presenting with symptoms of an upper GI disorder should be referred for an investigation, if no investigation has been performed in the past 5 years. They should be treated with the most recently effective maintenance therapy is prescribed (short term treatment) and patient is referred for an investigation
3. If symptoms/investigations show that GERD is mild to moderate, H2RAs or prokinetics are equally effective and could be prescribed if LSM and OTC therapy were ineffective. However the cheapest drug is the most cost effective choice.

4. If alarm symptoms are present (i.e. anemia, weight loss, aspiration, dysphagia) the patient should be either referred for an endoscopy immediately, or if an investigation has previously been done, then the most effective treatment should be prescribed.

Criteria for Treatment with Proton Pump Inhibitors

- Peptic ulcer disease = PPI + antibiotics (*Helicobacter pylori* eradication therapy)
- NSAID induced ulceration = discontinue NSAIDs, if possible, and treat with a PPI.
- If eradication therapy has been prescribed previously and the patient returns within 2-3 weeks with recurrent dyspeptic symptoms, a PPI should be prescribed and a further investigation performed
- If symptoms/investigations show that GERD is severe then a PPI should be prescribed

Criteria for Treatment with PPI's (cont'd)

- Barrett's esophagitis and severe esophagitis are permanent conditions, therefore any documentation of these conditions requires that the patient be treated with a PPI
- GERD complicated with stricture
- Ulcerative esophagitis warrants long term treatment
- If the patient is nonresponsive (persistent symptoms for 1 month or recurrent symptoms for over 2-3 months) to H2RAs, then a prescription of PPI is deemed appropriate.

Appendix D

Description of Drugs Effective in the Treatment of Upper GI Disorders

Proton pump inhibitors are the newest drugs used in upper GI diseases. A commonly used proton pump inhibitor (PPI) is Omeprazole, which is a substituted benzimidazole. This compound is a weak base that becomes protonated in the acidic environment of the parietal cell, and it is this active form which binds irreversibly to the H^+,K^+-ATPase (proton pump) enzyme. This inhibitory complex blocks the final step of gastric acid secretion , thus preventing basal and stimulated acid secretion.[117]

Histamine H_2 receptor antagonists (H2RAs) are competitive antagonists for the histamine H_2 receptor located on the basolateral membrane of the parietal cell.[94 118] By binding to the H_2 receptor, these compounds prevent histamine from stimulating gastric acid secretion. However, the parietal cell is also stimulated by acetylcholine and the hormone gastrin. This makes it possible for the parietal cell to be stimulated despite the presence of an H_2 receptor antagonist, i.e. meal stimulated gastric secretion. An illustration of the mechanisms of action of proton pump inhibitors and H_2 receptor antagonists is shown after the remainder of upper GI drugs are discussed.

Prokinetic agents are compounds which enhance contractile force and accelerate motility throughout the length of the gastrointestinal tract.[119 120] The most commonly prescribed prokinetic agent is cisapride, a third-generation prokinetic agent. Unlike the first and second generation prokinetics, cisapride is devoid of any central depressant or antidopaminergic effects. The rationale for this form of therapy is to alleviate defects in

the gastrointestinal neuromuscular activity by stimulating acetylcholine release, which is mediated by specific enteric nerves. This agent results in increased motility and clearing peristalsis, and increases lower esophageal sphincter pressure.

Antibiotics are essential elements in therapy used to eradicate *Helicobacter pylori*. It has been determined that if an ulceration is not related to NSAID use, then *H. pylori* infection is a significant causative factor for peptic ulcer disease.[104] To date triple therapy is the most effective form of eradication therapy of which there are two styles:

- Classical = bismuth containing compound + 2 antibiotics
- Newer = proton pump inhibitor + 2 antibiotics

The more frequently prescribed newer form of eradication therapy involves a shorter treatment regime (1 week vs. 2 weeks), which increases patient compliance, and there are less side effects.[112]

Appendix E

Improving Prescription of Upper GI Drugs: Study Design

Research Question

Is it possible to improve the appropriateness of prescription of drugs for upper GI disorders, primarily by reducing the underutilization of proton pump inhibitors, through the implementation of an educational intervention?

Research Design

A randomized controlled intervention study involving community based family physicians. The presence of the control group will allow any effect that cointervention (e.g. emergence of new guidelines/ policies during the trial) had on the results to be assessed. The design of the study involves two phases:

Phase I: expose the study group to the intervention(s), which is aimed at enhancing the appropriateness of drug prescription by the physicians

Phase II: measurement of the physicians' prescription patterns after the intervention has been completed.

Intervention

The continuing medical educational module, on the long-term management of peptic ulcer disease, gastroesophageal reflux disease and nonulcer dyspepsia, will be the basis of the intervention. The articles selected through the literature review demonstrated that the most appropriate and effective form of educational intervention involved one-on-one/ face-to-face visits by either a pharmacist or physician.[32 37 121]

The educational intervention to be implemented in this study will involve:

(a) a visit to each physician's office by a pharmacist to provide detailing on the appropriate treatment of gastroesophageal reflux disease, peptic ulcer disease and nonulcer dyspepsia and,

(b) a group educational dinner lecture will be given by a gastroenterologist.

The content of both the visit by the pharmacist and the dinner lecture will follow diagnostic and treatment guidelines and education material that is approved by the Canadian Association of Gastroenterology.

Primary Outcome: Underutilization of Proton Pump Inhibitors

The underutilization rate of proton pump inhibitors refers to patients who need a PPI but are not prescribed one. This outcome measurement has been chosen partly due to the current restriction by the provincial drug program limiting the prescription of proton pump inhibitors, which may lead to underutilization in subgroups of patients who may benefit from these drugs, e.g. patients with peptic ulcer disease and severe GERD.

Secondary Outcome: Under/Overutilization Rates of all Upper GI Drugs

Under and overutilization rates of all classes of upper GI drugs including H_2 receptor antagonists, prokinetics, cytoprotective agents, antibiotics, and antacids.

Sample size

There are two manners in which the sample size can be calculated and issues arose for both. These issues were discussed in chapter VI.

Sample Size #1

One method would be to categorize physicians as having acceptable underutilization rates or not. This avoids the problem of assuming independence of decisions for like cases by individual physicians when each physician contributes more than one therapeutic decision to the results. Such an assumption would be unlikely to be true because physicians are more likely than not to make similarly correct or incorrect decisions about patients with the same types of problems. In any case it is the physician who is the unit of randomization and not the prescription, so one cannot just calculate the group average underutilization rate for PPI's ignoring how many case are contributed per physician. An arbitrary cut point of <20% underutilization could be defined as acceptable. The pilot study suggests that the proportion of physicians with an underutilization rate of <20% should be approximately 33% before the intervention. If the intervention is successful it is hoped that the proportion of physicians with an underutilization rate of <20% will increase to 55% in the intervention group, but will remain at 33% in the control group.

- $\alpha = 0.05$
- $\beta = 0.2$
- Two independent groups - Proportions

- one-tailed hypothesis will be used since we are determining if an intervention had a positive effect on the study subjects, whereas if its implementation was unsuccessful the costly nature of the intervention would prohibit its future use.
- The calculation of sample size is based upon the results of the pilot study, with the underutilization rate as the basis of the arbitrarily assigned score.

$$n/\text{group} = 2[(Z_\alpha + Z_\beta) / (2\sin^{-1}\sqrt{\pi_1} - 2\sin^{-1}\sqrt{\pi_2})]^2$$

$$n/\text{group} = 2[(1.65 + 0.84) / (2\sin^{-1}\sqrt{0.33} - 2\sin^{-1}\sqrt{0.55})]^2$$

n/group = 61 physicians are required for both the intervention and control groups.

- Using this sample size formula for two independent groups (proportions), 61 physicians will be needed in each study group. An issue arising with this approach is how many cases should each physician treat to provide a reliable reflection of his/her prescribing practice. From the pilot study it was shown that of the 15 patient charts per physician included in the study, there were on average 4 patients who needed a PPI (27%). If an individual physician were found to prescribe PPI's to say 4 of 5 who needed them, the confidence interval around the observed inappropriateness rate of 20% would be very broad. Thus one could not use these results to accurately classify that individual physician. However, misclassification into acceptable of unacceptable underutilization groups should be unbiased and therefore results for the group should be interpretable. If 122 physicians were available for the study, a total of 2196 patient charts would have to be reviewed by the research team to ensure that about 5 patients needing PPI's were seen by each physician. However, there are only 110

physicians located in the St. John's/Mount Pearl region and it may not be feasible to obtain consent from all of them.

Sample Size #2

An alternative method that would also get around the independence of decisions made by doctors, could be based on a comparison of the mean percent inappropriate underutilization of PPI's across physicians in each group. For this method the proportion underutilized would be first determined for each physician and then the group mean and standard deviation for this measure would be calculated. This approach depends upon the assumption that the underutilization rates are normally distributed within each group.

- $\alpha = 0.05$
- $\beta = 0.2$
- Two independent groups - Means
- one-tailed hypothesis will be used since we are determining if the intervention had a positive effect on the study subjects, whereas if its implementation was unsuccessful the costly nature of the intervention would prohibit its future use.
- In the pilot study, the mean underutilization rate of proton pump inhibitors by the physicians studied was 39%. However, within an observed range of 0 - 100%, the rates per physician were not normally distributed about the mean. However, the sample size in the pilot was small. If one assumes that a larger study would also observe a range of underutilization rates of 0-100%, and that the rates would be normally distributed within this range, then one could reasonably infer that the range

would encompass 3 standard deviations on either side of the mean. This would imply a standard deviation of about one sixth of 100%, or about 17%. If, as suggested by the pilot data, the underutilization rate will be approximately 39% in the control group, and one wishes to be able to show a fall to 29% in the intervention group.

$n/group = 2[(Z_\alpha + Z_\beta) \sigma/\Delta]^2$

$n/group = 2[(1.65 + 0.84) 17/10]^2$

$n/group = 36$

As with method #1 above this approach also requires that one observe the percent inappropriate underutilization of PPI's per physician. Yet again one is faced with the problem of determining how many cases need to be reviewed per physician to determine that rate. In this case one would need to examine many more than 5 cases needing a PPI as otherwise the proportion underutilized would be constrained to lie at 0, 20, 40, 60, 80, or 100% only. This would make it impossible to determine whether there was a normal distribution of underutilization rates within a group. Therefore one might wish to examine enough charts to find 10 cases per physician where PPI's were indicated.

With 110 physicians in the region it should be feasible to enroll 80 of them in the study. On average each physician would need to provide 10 cases where a PPI was indicated. The pilot study suggests that this would require review of an average of 38 charts per physician for a total of 3,040 charts.

Randomization

This study will be a randomized control trial, which is the standard approach to evaluating the effectiveness of an intervention. Physicians, who have agreed to participate, will be randomly allocated to a control or intervention group based upon numbers in sealed envelopes. An individual who is independent of this study will confidentially assign an envelope to each subject. Although some contamination may occur within the control group as a result of discussions between physicians who work within the same practice, it was determined that to randomize physicians by groups was not feasible. The number of practices that would have to be randomized to ensure statistically significant results exceeds the number of practices that are available for randomization within the St. John's - Mt. Pearl area. This number of available practices will also decrease when account is taken of the number of physicians who will not consent to participate in the study, causing a further reduction in the feasibility of carrying out such a randomization.

Method

After receiving the consent from the physicians (N=80) to participate in the study the research team conducting the study will randomly allocate the physicians into the control and intervention groups. The intervention group (N = 40) will receive a phone call from the investigator to request their participation in the continuing education sessions and also to request that they not discuss what is covered at these sessions with their peers due to the nature of the study. Subsequently a pharmacist will visit each physician in the

intervention group for a one-on-one information session on the appropriate treatment of upper GI disorders.

Six months after the educational intervention is completed, a research nurse will visit the practices of all 80 physicians, and review the MCP billing codes of the patients seen within the previous 6 months to identify those seen for upper gastrointestinal disorders. Of those patients the most recent 17 cases will be identified for patient specific data abstraction which will result in a total of 1360 cases which will be included in the data analysis. Predefined diagnostic and treatment data will be abstracted from the patients' charts using a standardized questionnaire (Appendix B). Subsequent to this data collection, each physician will be interviewed by the research nurse to obtain further information about the patient which could not be determined from the chart. In order to determine the effects of the educational intervention and eliminate as many confounders as possible, the data collection for both the control and intervention groups are to be done throughout the same time period. This is based on the assumption that all doctors will receive the same amount of background education from the pharmaceutical companies and that seasonal variation in prescribing practices occurs and must also be controlled for. To check whether the results obtained have been affected by external confounders, information will be obtained from the International Medical Systems (IMS) Canada data source which will show the overall prescribing patterns throughout the period in which data collection was done. This external validation will determine whether seasonality or

any restrictions in the drug formulary had an adverse effect on the prescribing patterns of physicians at that time.

Due to the large number of patient charts it would be unreasonable to assume that an expert panel comprised of a gastroenterologist, epidemiologist and pharmacist would be able to review all 1360 cases within a limited amount of time, therefore this data will be reviewed by the research team. Following predefined criteria each patient will be assigned a diagnosis and treatment and through comparison with guidelines the appropriateness of the physicians' prescribing practice will be assessed. In order to ensure that the assessment of these cases was consistent and correct every one in 10 of the cases where it was determined that PPIs were underutilized and any cases where a difference between the research team and the prescribing physician exists will be reviewed by an expert panel.

Statistical Analysis

All data will be analyzed with SPSS, a statistical computer program. The frequency of prescription for each drug group will be calculated and the percentage of inappropriate prescriptions for each physician will be calculated first, followed by description of the distribution of these rates by group. The inappropriate prescription frequencies will demonstrate both inappropriate overutilization (those who received the drug and didn't need it) and inappropriate underutilization (those who needed the drug and didn't receive it) for each drug group. Confidence intervals will be calculated for the difference in

proportions between the control and intervention groups. A t-test for independent groups will be used to compare the mean underutilization rate of PPI's between groups.

The hypothesis (H_A) for this study is that an educational intervention will increase the physicians' adherence to recommended guidelines, thus leading to a difference in the rate of inappropriate prescribing by physicians in the control (C) and intervention (I) groups.

$H_0 : C \geq I$

$H_A : C < I$

The involvement of two assessment teams (research nurse and research panel) requires the assessment of interrater reliability with the use of kappa scores. This statistic allows for nominal scale assessment of the level of agreement among the two evaluators. Excellent agreement beyond chance is considered to exist when kappa is greater than 0.75, while values between 0.40 and 0.75 represent fair to moderate agreement.[122]

Effectiveness of the Intervention

In a parallel group randomized trial changes from baseline seen within the control group are assumed to result from chance, regression to the mean, contamination, or external factors other than the intervention (e.g. drug company detailing, changes in governmental reimbursement policy). Unfortunately, if the changes in the intervention group are equal to those seen in the control group the null hypothesis can not be rejected and it could be difficult to differentiate an ineffective intervention from contamination of the control group, or the effect of strong external factors. However, to help identify these problems, data will be obtained from an external source (e.g. IMS) to determine the

overall prescription rate of upper GI drugs within the region before and after the intervention.

Ethics

The family physicians will be asked to sign a consent form (Appendix A) to show that they agree to participate in this study and that they consent to have information obtained from their patients' charts and a physician interview to be used in the analysis. The consent form will explain the measures which will be taken to ensure that the confidentiality regarding the physicians and their patients will be maintained. Although information pertaining to patients will be used in this study, the consent of each patient will not be obtained because any information capable of identifying a patient will not be collected.

Appendix F

FACULTY OF MEDICINE
MEMORIAL UNIVERSITY OF NEWFOUNDLAND
ST. JOHN'S, NEWFOUNDLAND A1B 3V6

Consent to Participate in Bio-Medical Research

TITLE: **Pilot Study: Antibiotic Use in the Community (Phase I)**

INVESTIGATORS: Dr. J. Hutchinson, Dr. P.S. Parfrey

SPONSORS: Provincial Dept. of Health
Abbott Laboratories Ltd.
Bayer Inc.
Glaxo Canada Inc.
Pfizer Inc.

You have been asked to participate in a research study. Participation in this study is entirely voluntary. You may decide not to participate or may withdraw from the study at any time. Confidentiality of information concerning participants will be maintained by the investigator. The investigator will be available during the study at all times should you have any problems or questions about the study.

Purpose of study:

This study will describe the current medical management of infection related illness. Baseline data will be collected on patients with infection related illness so that population rates can be calculated for a) the burden of infection in the community b) bacterial infection requiring antibiotics c) reasons for antibiotic prescriptions

Description of procedures:

Under your supervision a research nurse will come to your office to review all cases seen in your practice on the two previous days. You will decide the day of the week that is best for you but you will not know which week. Data will be extracted from the charts of patients who were seen for infection related illness. You will be interviewed by the research nurse so that more data can be collected on these cases (20 in all). Your interview will last approximately 5 minutes for each case reviewed.

Those patients with infection related illness will receive a letter from you explaining that you are participating in a research study. The letter will also explain that a research nurse/assistant will contact them by telephone to ask for their participation. They will be advised that they may decide to participate or not participate without affecting their normal treatment. If they are willing, they will be asked questions about their illness using a standardized extraction form. Their interview will last 5 minutes.

Duration of subjects participation:

The study will be conducted from May 1997 to June 1997. You will be asked to designate a period of time from your practice to review 20 cases of infection related illness occurring in your practice during the previous two days. The time of the interview will be 1 hour to 1 1/2 hrs.

Foreseeable risks, discomforts, or inconveniences:

Each case reviewed will take approximately 5 - 10 minutes of your time.

Liability Disclaimer Statement:

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities.

I,_____, the undersigned, agree to my participation in the research study described.

Any questions have been answered and I understand what is involved in the study. I realise that participation is voluntary and that there is no guarantee that I will benefit from my involvement. I acknowledge that a copy of this form has been given to me.

_____

(Signature of Participant) (Date)

(Witness Signature) (Date)

To be signed by investigator:

To the best of my ability I have fully explained to the subject the nature of this research study. I have invited questions and provided answers. I believe that the subject fully understands the implications and voluntary nature of the study.

(Signature of Investigator) (Date)

Phone Number _____

If Appropriate:

(Signature of Minor Participant)

(Age __)
Relationship to Participant Named Above _____

Appendix G

Use of Antibiotics in the Community
Demographic Data

Case Number _____

Date Pt. Visited _____/_____/_____ Doctor # _____ Patient #_____
Y M D

Date of Birth _____/_____/_____ Gender 1. ___Male 2. ___Female
Y M D

First Name _____ Last Name_____

MCP _____

Address _____ Telephone (H) _____

_____ Telephone (W)_____

_____

Postal Code _____ Family Physician_____

(This form will be filed separately from questionnaire and interview data. Only the case number will be used to identify the patients on the questionnaire and interview data forms.)

Clinical Data

Case Number _____

Date Pt. Visit _____ (YMD) **Doctor #** _____ **Patient #** _____

Age: ____yrs____mos **Sex:** 1. Male. 2. Female **New Patient** 1. Yes 2. No

Presenting Complaint _____ **Code** _____

Relevant Past Medical History

Pregnancy.	1. Yes 2. No	
Diabetes....	1. Yes 2. No	
COPD ...	1. Yes 2. No	
Renal Insufficiency	1. Yes 2. No	
CHF ..	1. Yes 2. No	
Antibiotic Allergy	1. Yes 2. No	Specify _____
Smoker	1. Yes 2. No	# Pack Years _____
Prior Occurrences	1. Yes 2. No	When _____
Culture Taken	1. Yes 2. No	Result _____
Other ..	1. Yes 2. No	Specify _____

_____

_____

Usual Tx _____

Response _____

Other Comments _____

_____

_____

HPI (as per chart)

_____

_____

_____

_____

_____

Current Medications

Current / Recent Antibiotic Treatment 1. Yes 2. No

Start Date	Current Drugs	Dose	Duration	Stop Date	Compliance

RESPIRATORY DIAGNOSIS	CLASSIFICATION	SYMPTOMS
UPPER 1. rhinits 2. sinusitis 3. otitis (type) 4. laryngitis 5. pharyngitis 6. other _____ LOWER 7. AECOPD 8. bronchitis 9. bronchiectasis 10. pneumonia (community acquired, nsg home) 11. cystic fibrosis 12. whooping cough 13. other _____	SEVERITY 1. mild 2. moderate 3. severe ACUITY 1. acute 2. chronic 3. acute on chronic PROBABLE MICRO ORGANISM(S) 1. virus 2. bacteria 3. other _____	2. chills 4. congestion (where, amount) _____ 5. cough(how long, productive) _____ 8. discharge/drainage (where, type, amount) _____ 9. dyspnea (describe) _____ _____ 11. fever 12. hemoptysis 17. nodes enlarged 20. pain (where, type, severity) _____ _____ 21. rales/crackles 23. rhonchi/wheeze 24. rigor 26. sputum (colour, amount)

GENITOURINARY DIAGNOSIS	CLASSIFICATION	SYMPTOMS
1. UTI 2. cystitis 3. prostatitis 4. pyelonephritis 5. orchitis 6. epididymitis 7. epididymoorchitis 8. PID 9. urethritis 10. cervicitis 11. other _____	SEVERITY 1. mild 2. moderate 3. severe ACUITY 1. acute 2. chronic 3. acute on chronic PROBABLE MICRO ORGANISM(S) 1. virus 2. bacteria 3. other _____	2. chills 8. discharge (where,colour, amount) _____ 10. dysuria (describe) _____ _____ 11. fever 17. nodes enlarged (where)_____ 20. pain (where, type, severity)_____ _____ 24. rigor 28. urgency/frequency other_____

SKIN /SOFT TISSUE DIAGNOSIS	CLASSIFICATION	SYMPTOMS
1. abscess 2. bite 3. cellulitis 4. chicken pox 5. diabetic foot 6. decubitous ulcer 7. facial erysipelas 8. herpes (genital) 9. herpes (simplex) 10. impetigo 11. shingles other _____ LOCATION_____	SEVERITY 1. mild 2. moderate 3. severe ACUITY 1. acute 2. chronic 3. acute on chronic PROBABLE MO 1. virus 2. bacteria 3. other_____	8. drainage (where, type,amount)_____ _____ 11. fever 14. lesion (where, type) _____ 20. pain (where, type,severity) _____ _____ 22. redness 27. swelling other_____

OTHER DIAGNOSIS	CLASSIFICATION	SYMPTOMS
1. bone joint infection 2. gastro-enteritis 3. meningitis 4. intra abdominal infection 5. other _____	SEVERITY 1. mild 2. moderate 3. severe ACUITY 1. acute 2. chronic 3. acute on chronic PROBABLE MO(S) 1. virus 2. bacteria 3. other_____	8. drainage (where, type, amount) _____ _____ 11. fever (temperature)_____ 17. nodes enlarged (where) _____ 20. pain (where, type, severity) _____ _____ 22. redness 25. seizure 27. swelling other_____

Culture

Sample Collected 1.Yes 2. No Date _____ Type _____

Results _____

Treatment

A) Antibiotic prescribed 1. Yes 2. No

Start Date	Prescription	Dose	Duration	Stop Date	Indication

Appendix H Questionnaire for Physician Interview

Factors influencing Antibiotic Prescription Decision:

1. Medical Indication

Uncertain				Very Clear
..... 1	2	3	4	5

2. Patient/Parent Expectation or demand

No influence				Strong Influence
..... 1	2	3	4	5

3. Time Constraint

No influence				Strong Influence
..... 1	2	3	4	5

4. Sense that patient would attend another physician if they did not receive an antibiotic prescription

No influence				Strong Influence
..... 1	2	3	4	5

B) Over the Counter Treatment 1. Yes 2. No (specify)

_____

C) Referral 1. Yes 2. No (specify)

_____

D) Advised 1. Yes 2. No (specify)

_____

_____

_____

Additional comments:

_____

_____

_____

_____

_____

Appendix I

Letter to Patient

Date

Dear _____:

Our clinic is participating in a study which is being conducted by Dr. J. Hutchinson, a specialist in infectious diseases, at the Health Sciences Centre.

We are interested in learning more about the rate of infection in the community and the reasons for antibiotic prescriptions. In order to do this Dr. Hutchinson has asked all family physicians in the St. John's area to identify patients treated for infection related illnesses such as chest infections, urinary tract infections, skin infection, etc. I am asking you to participate because you had a recent visit to my clinic for an infection related illness. Your participation is entirely voluntary. You may participate or not participate without affecting your normal treatment.

A research nurse will contact you by telephone. If you are willing to participate you will be asked some questions about the symptoms you had at the time of your clinic visit and if they have improved. You will also be asked some questions about what antibiotic treatment you expected, if any, and if there were other factors that influenced your decision to visit the doctor that day.

If you do not wish to be contacted by the research nurse please complete the enclosed pre-addressed stamped card and return it in the mail.

We hope that with your participation we can answer questions and learn more about the rate of infection in the community and the reasons for antibiotic prescriptions.

Yours truly,

Family Doctor

Revised May 8, 1997

Appendix J

Patient Telephone Interview

CN _____

Date _____/_____/_____ **Physician Number** _____
Y M D

Patient Number _____

Why did you go to the doctor? _____

What were your **symptoms**? (Use symptom list to record symptom number and name, give description when appropriate)

A)_____
How long did you have it before clinic visit? _____Days
How long did you have it after clinic visit? _____Days

B)_____
How long did you have it before clinic visit? _____Days
How long did you have it after clinic visit? _____Days

C)_____
How long did you have it before clinic visit? _____Days
How long did you have it after clinic visit? _____Days

D)_____
How long did you have it before clinic visit? _____Days
How long did you have it after clinic visit? _____Days

Do you still have symptoms? 1. Yes 2. No
Describe_____
_____

If you were more than 2 hours journey from the nearest physician, would you have visited the doctor with this illness? 1. Yes 2. No

Before your visit did you feel that your illness would be helped by an antibiotic? 1. Yes 2. No

Would you have been disappointed if you had not received an prescription for and antibiotic?. 1. Yes 2. No

Would you have sought the opinion of another physician if you had not been given a prescription for an antibiotic? 1. Yes 2. No

Did you ask for a prescription for an antibiotic? 1. Yes 2. No

Did you suggest the type of antibiotic that you felt was best for you? 1. Yes 2. No

Did fear of missing work/school influence your decision to visit the doctor? 1. Yes 2. No

Were you required by work/school (e.g. absentee note) to visit the doctor for this illness? .. 1. Yes 2. No

Prescription

Do you have a drug plan 1. Yes 2. No
Did you expect a prescription? 1. Yes 2. No
Did you receive a prescription? 1. Yes 2. No
Was your prescription filled? 1. Yes 2. No 3. Not Applicable
Did you take it as prescribed? 1. Yes 2. No 3. Not Applicable
(If no, describe.)

_____
_____

Did you have side effects from drug? 1. Yes 2. No
Describe_____
_____

Follow-up

..

Have you sought further treatment for the same problem ? 1. Yes 2. No
Describe visits, treatments and investigations.

_____
_____

Have you been hospitalized since your clinic visit? 1. Yes 2. No
Describe. .._____

Appendix K

Criteria for Infectious Disease Classification

Respiratory Infections

Bacterial Pharyngitis: [Approximately 80 - 90% of the time pharyngitis is not bacterial in adults and children.]

Children: 1. Fever > 39.5 °C

2. Pharyngeal exudate

3. Tender submandibular lymph nodes

4. Palatine stippling

If 3 criteria are present there is an 83% positive predictive value for streptococcal throat infection, and this increases to 88% if 4 criteria are present.

Adult: 1. Absence of cough

2. History of fever over 38°C (101°F)

3. Tonsillar exudate

4. Swollen, tender anterior nodes

If only one criteria is present then neither a throat swab nor antibiotics are indicated; 2 - 3 criteria present a throat swab is required and antibiotics started only if culture is positive; and if all 4 criteria present penicillin may be started immediately based on clinical grounds.

Acute Otitis Externa: Symptoms include pain, itching, and a sensation of fullness in the ear. Exudate, erythema, and edema may be seen in the canal.

Acute Otitis Media: Inflamed ear drum with fluid and one of the following: pain, fever, irritability

Acute Sinusitis:

Adults : 1. Maxillary toothache

2. Poor response to nasal decongestants

3. Colored nasal discharge by history or examination

4. Abnormal transillumination

Other symptoms include fever, malaise, cough, and headache or facial pain exacerbated by bending forward.

Children: 1. Nasal discharge (may be thin or thick and clear mucoid or purulent)

2. Daytime cough and may worsen at night

The child may not appear very ill and with low grade fever.

Sinusitis may also appear as an unusually sever URI with severe symptoms (high fever, purulent nasal discharge.)

[Persistent symptoms - last more than 10 days and less than 30 days and have not begun to improve. The 10 day mark differentiates simple viral infection from sinusitis and the 30 day mark separates acute from subacute and chronic sinusitis.]

Acute Bronchitis: 1. Productive cough with purulent sputum and wheeze

2. Nonproductive cough or colorless sputum for > 5 days

80% of all cases of acute bronchitis are viral, however it is difficult to distinguish between viral and bacterial pathogens since both result in purulent sputum.

Acute bronchitis in children is generally always viral.

Acute Exacerbations of Chronic Bronchitis: 1. Increased cough and purulent sputum
2. Pathogenic bacteria on sputum culture

50% of AECB are non-bacterial. Chronic bronchitis is defined clinically as excessive cough, productive of sputum on most days, for at least 3 months a year during at least two consecutive years

Pneumonia: 1. Chills, fever, cough with pleuritic chest pain, purulent sputum, rales, and/or pulmonary consolidation
2. Respiratory symptoms with new infiltrates on chest x-ray

Severe Pneumonia: 1. Respiratory failure (Pa O_2 <60 mmHg-with exception of patients with COPD who may be hypoxemic without pneumonia)
2. Respiratory rate more than 30 per minute
3. Sepsis with evidence of end organ dysfunction
4. Extrapulmonary septic complication
5. Cavitation or involvement of more than one lobe on chest radiograph

Viruses are responsible for pneumonia in the majority of children under 5 years of age

Whooping Cough: 1. Cough with inspiratory whoop
2. Cough > 7 days, paroxysmal in nature
3. Cough ending in apnea, vomiting or gagging for which there is no other known cause

Genitourinary Tract Infections

Uncomplicated Acute Cystitis: Urinary frequency, dysuria, lower abdominal-suprapubic pain in females, normal genito-urinary tract

Complicated UTI:
1. Symptoms of cystitis with high fever and chills
2. Includes obstruction, chronic catheter, spinal cord injury, etc.
3. Symptoms of UTI, known genito-urinary pathology
4. Symptoms of UTI in males

Recurrent Cystitis:
1. Recurrence of symptoms within 1 month of treatment
2. Three or more episodes per year

Asymptomatic UTI:
1. Pregnancy
2. Pre-operative genito-urinary procedures

Acute Prostatitis:
1. Fever, acute perineal pain/ discomfort/ ± dysuria or frequency
2. Tender prostate

Chronic Prostatitis:
1. Relapsing UTI in men
2. Chronic bacteruria with same organism

Chronic cases are less likely to be true bacterial prostatitis.

Epididymitis: Inflammation of the epididymis manifested by acute onset of unilateral testicular pain and swelling, often with tenderness of the vas deferens with erythema and edema of the overlying skin. This does not usually occur in prepubertal boys.

Note that when epididymis is accompanied by urethritis, it is presumed to be a sexually transmitted infection

Pelvic Inflammatory Disease: 1. Lower abdominal pain, vaginal discharge ± dysuria, fever, chills, nausea, vomiting

2. Cervical tenderness, adnexal tenderness

Cervicitis: mucopurulent or purulent cervical discharge, stapid chlamydia screen

Urethritis: dysuria, frequency, purulent urethral discharge, rule out GU. increase with punnis [MCP as defined by: (1) absence of vaginal itch, vaginal candidiasis, genital or rectal gonorrhea, (2) increase in punnis; (3) at least four of the following: history of vaginal discharge, purulent or mucopurulent secretions emanting from the cervical os, endocervical piability.]

Skin and Soft Tissue Infections

Impetigo: Focal erythema that progresses to pluritic vesicles, erosions, and honey-colored crusts. Lesions usually form on the face and spread locally.

Folliculitis: Usually associated with an infected hair follicle. Infectious folliculitis usually presents as bigger pustules (2-3mm), and there is more inflammation as manifested by a red halo and tenderness. The lesions may be clustered rather than scattered.

Cellulitis: A superficial, spreading, warm , erythematous inflammation of the skin.

Appendix L

Improving Antibiotic Prescription: Study Design

Research Questions

What is the rate of antibiotic utilization within the St. John's - Mt. Pearl region? Is it possible to improve the utilization of antibiotics, by reducing their overutilization, through the implementation of an educational intervention aimed at improving physicians' prescribing patterns?

Research Design

A pre/post intervention trial is planned involving family physicians who will receive an educational intervention that focuses on the appropriate prescription of antibiotics in the treatment of upper respiratory, urinary tract and skin and soft tissue infections. The participating physicians will be assessed 6 months prior, at baseline, and 6 months after the intervention has been implemented. The baseline assessment will determine the overall rate of antibiotic prescription within the St. John's - Mt. Pearl region. Although the pre/post design will make it difficult to differentiate the impact of an intervention from concomitant change which may occur in the health care delivery sector, an external validation of the data will be done which is discussed in the method section of this protocol. Other confounders which may affect the results (e.g. seasonality) were discussed in Chapter VI.

Primary Outcome

The appropriate utilization rate of antibiotics (patients who needed an antibiotic and received the optimal choice + patients who did not need an antibiotic and did not receive one, divided by the total number of patients seen by the physicians with infection) and whether this rate is increased after the implementation of an educational intervention which focuses on the optimal utilization of antibiotics.

Secondary Outcome

The underutilization and overutilization of antibiotics will be determined and whether the educational intervention was effective in reducing these rates. The overutilization of antibiotics is of specific importance because of the potential impact in promoting selection of antibiotic resistant organisms in the community, together with unnecessary drug-induced adverse events and costs.

Sample Size

The results obtained in the pilot study may not be reflective of the prescribing patterns of the general population of family physicians in the St. John's - Mt. Pearl region. The number of antibiotic prescriptions that are filled each year in Newfoundland per physician is much higher as determined by International Medical Systems (IMS) Canada database than the rate seen in the pilot study. Since it is not possible to calculate a sample size from these pilot study results it will be necessary to rely on results reported in a similar intervention study that was aimed at improving antibiotic prescription.

As a partner of this study and due to the importance of this study, the Newfoundland and Labrador Department of Health would like to enroll as many family physicians as possible from the St. John's - Mt. Pearl area to ensure that the maximum community impact is made through this study. As a result it is hoped that 80% of family physicians in this area will agree to participate (N = 88). To determine whether such a group would be large enough to detect relevant changes in appropriateness of antibiotic prescription one can use the experience of other investigators as a guide.

A study that was performed in Australia by De Santis et al (1994)[37] is very similar to the study I have proposed. Their pre/post educational intervention study centered on general practitioners and recommendations that were made in *Antibiotic Guidelines*. Their measurement of appropriateness of prescription was based on the physician's adherence to the guidelines and how the educational intervention improved their prescription of appropriate antibiotics for tonsillitis. Prior to the initiation of the educational intervention, prescriptions consistent with the guidelines were given to 52.9% and 60.5% of the control and intervention groups respectively. Using the average of these two rates, 56.7%, an approximation of the necessary sample size can be made based upon the appropriateness of antibiotic prescription made by family physicians.

- $\alpha = 0.05$
- $\beta = 0.2$
- Two related groups - Proportions

- one-tailed hypothesis will be used since we are determining if the intervention had a positive effect on the study subjects, whereas if its implementation was unsuccessful the costly nature of the intervention would prohibit its future use.
- Due to the inadequate results that were obtained in the pilot study the rate of appropriate antibiotic prescription as determined by De Santis et al. is used to calculate the sample size. It is assumed that prior to the intervention the appropriateness rate will be approximately 57%, however we wish to be able to statistically detect an increase to 85% following the intervention.

n prescriptions pre/post = $[(Z_\alpha \sqrt{\pi_0 (1 - \pi_0)} + Z_\beta \sqrt{\pi_1 (1 - \pi_1)} / (\pi_1 - \pi_0)]^2$

n prescriptions pre/post = $[(1.65 \sqrt{0.57 (0.43)} + 0.84 \sqrt{0.85 (0.15)} / (0.85 - 0.57)]^2$

n prescriptions pre/post = 16

This number (N = 16) would represent the minimum number of antibiotic prescriptions that would need to be observed to obtain results which were statistically significant. Thus a planned study involving 88 physicians should have ample power to detect a change of this magnitude in appropriateness of antibiotic prescription. From another comparison of the previously mentioned drug formulary data and the International Medical Systems (IMS) Canada database, it was determined that approximately 25% of visits to a family physician result in a prescription for an antibiotic. Therefore only a few charts per physician would have to be reviewed to determine the impact of the intervention.

Method

The consent of 88 physicians to participate in the study will be obtained. The protocol for this study is comprised of three phases:

Phase I: baseline assessment of antibiotic prescriptions by family physicians

Phase II: physicians participate in an educational intervention that is aimed at improving their adherence to guidelines for anti-infectives

Phase III: remeasurement of antibiotic utilization and physicians' conformity to the guidelines

All family physicians (N = 110) in the St. John's - Mt. Pearl region (population 127,455) will be invited to participate in the study during a visit to their office by the principal investigator. A baseline assessment of antibiotic utilization will occur between September 1997 - February 1998. This will involve a research nurse who will visit each physician's office at a randomly selected time, and review the charts of patients seen within the previous 2 days. Patients that were seen for infection related illnesses, such as upper respiratory, urinary tract or skin and soft tissue infections, will be identified and the total number of infection related cases will be recorded. However, relevant clinical data will only be extracted from a maximum of 15 consecutive charts using a revised standardized questionnaire (Appendix H). A thorough patient history will be recorded which will include all presenting complaints, results of previous investigations, co-morbid illnesses, allergies, concomitant medications, and treatment prescribed. Subsequently, each physician will be interviewed by a research nurse or research

assistant, once information pertaining to each patient has been collected. This interview will allow for the researcher to obtain any additional clinical information that was not recorded in the patient's medical record.

Following the baseline assessment an educational intervention will be implemented which will involve face-to-face visits from a physician or pharmacist. The focus of this intervention will be determined after the baseline assessment has been completed and the areas of concern regarding antibiotic utilization are determined.

Overall antibiotic utilization by quantity and type will be obtained from the pharmacies within the St. John's - Mt. Pearl region. These data will be collected for the 6 months prior to the commencement of Phase I and also during Phase II of this study, which will demonstrate any shifts in prescribing behavior which occurred at either of these times, allowing an external validation of the data collected. This external validation process will allow the assessors to be able to determine if the changes in prescribing behavior are a result of external confounders, or are a direct result of the educational intervention that was implemented throughout the study.

It was determined through the pilot study that it is feasible for a research team to use case-based criteria to assign a diagnosis and apply guidelines to determine the optimal treatment for each patient. To ensure that this assessment is consistent and objective, the expert panel will review one in 10 of cases where it was determined that antibiotics were overutilized.

Intervention

The articles that were selected through the literature review assessed the effectiveness of various forms of intervention. The most appropriate and effective one was determined to be the intervention that involved one-on-one or face-to-face visits by either a physician or pharmacist.[32 37 121] Doctor specific data from phase I of the study together with feedback from the physicians will form the basis for the focus of the intervention which will be used in Phase II of the study. The Department of Health want to reduce inappropriate antibiotic utilization immediately and are less concerned about vigorously testing various interventions.

Statistical Analysis

All data will be analyzed with SPSS, a statistical computer program. Various frequencies will be calculated which will allow the determination of :

(a) overutilization rate of antibiotic prescription per total visits and per specific diagnoses - a measure of overall antibiotic utilization, with underutilization of antibiotics being the secondary variable;

(b) level of overall adherence to recommendations in the Ontario Anti-infective guidelines.

The hypothesis (H_A) of this study is that after the physicians have participated in the intervention, the overutilization rate of antibiotic prescription will decrease in comparison to the overutilization rate of antibiotic prescription that was measured before the intervention was implemented. The null hypothesis (H_0) would be that the

overutilization rate of antibiotic prescription either remains the same or increases after the intervention has been completed.

A = overutilization rate of antibiotic prescription after the intervention

B = overutilization rate of antibiotic prescription before the intervention

$$H_A = B > A$$

$$H_O = B \leq A$$

A McNemar's Chi-squared test will be used to compare the proportion of antibiotic prescriptions that are appropriate before and after the intervention. The remaining clinical assessments, the reasons for antibiotic prescription and baseline characteristics of physicians and patients will be summarized through the use of descriptive statistics.

Ethics

Since the subjects of this study are family physicians they will be asked to sign a consent form (Appendix F) verifying that they (1) agree to participate in this study, (2) approve of the acquisition of information from their patients' charts and (3) consent to a physician interview, whereby all information will be used in data analysis. This consent form explains to the physician the measures that will be taken to ensure their confidentiality, their patients whose charts will be reviewed and any relevant information that will be used in the analysis. Any information capable of identifying the patient will not be revealed at any time to anyone other than the researchers who have collected the information. Although the rates of diagnosis and prescription will be assessed, the identity of participating physicians will be unknown to the researchers.