UNIVERSITY OF CALGARY

MEDICAL MANAGEMENT OF INFLAMMATORY BOWEL DISEASE; PATTERNS OF INFLIXIMAB USE AMONGST CANADIAN GASTROENTEROLOGISTS.

by

JENNIFER L. JONES

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Abstract

Background: The last decade has been characterized by an increase in the number of biological agents available to treat inflammatory bowel disease (IBD). Infliximab was approved by Health Canada for the treatment of Crohn's disease (CD) in 2001 and for ulcerative colitis (UC) in 2006. However, little is known of physician's perceptions and practices in using infliximab. **Objectives:** To describe how Canadian gastroenterologists' use and perceptions of Infliximab to treat refractory inflammatory bowel disease (IBD) and to identify factors which may influence a gastroenterologist's decision to initiate Infliximab therapy. **Methods:** A postal questionnaire was distributed to all practicing clinicians captured in the 2007 membership of the Canadian Association of Gastroenterology (CAG). Each physician was contacted up to a maximum of three times. **Results:** 336/466 responded (72%). Two hundred and ninety-two (63 percent) of respondents had completed questionnaires in full. 80 percent indicated that IBD patients comprised less than 30% of their clinical practice. Most prescribed Infliximab at an initial dose of 5 mg per kilogram (97%), prescribed loading doses at 0, 2 and 6 weeks (88%), pre-medicated with corticosteroids (74%), administered maintenance infusions at 8 week intervals (89%), co-administered immunosuppressive agents (81%) and continued Infliximab "indefinitely", as long as effective and well tolerated (76%). Most (> 70 percent) gastroenterologists identified lack of insurance coverage and provincial funding criteria as important barriers to prescribing Infliximab. **Conclusions:** Most Canadian gastroenterologists exhibit similar practice patterns with respect to the use of Infliximab for induction and maintenance therapy of IBD. Common barriers were identified with respect to the initiation of Infliximab therapy.

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List of Abbreviations

Symbol	Definition
IBD	Inflammatory Bowel Disease
TNF-∝	Tumor Necrosis Factor Alpha
CD	Crohn's disease
TDM	Tailored Design Methodology
RA	Rheumatoid Arthritis
CME	Continuing medical education
IBD	Inflammatory bowel disease
CAG	Canadian Association of Gastroenterology
RCPSC	Royal College of Physicians and Surgeons of Canada
ATI	Antibody to Infliximab
IS	Immunosuppression
RCT	Randomized controlled trials

Epigraph

There are in fact two things, science and opinion; the former begets knowledge, the latter ignorance.

Hippocrates, Law

Chapter One: INTRODUCTION

1.1 Inflammatory Bowel disease

Inflammatory Bowel Disease (IBD), including Crohn's disease and Ulcerative Colitis, is a chronic inflammatory disease of the gastrointestinal tract for which there is no cure. IBD is thought to arise as a result of an aberrant immune response to bacterial luminal antigens (1-5). IBD may follow different clinical courses over time including severe intermittent, mild intermittent and less commonly, a chronic continuous course (6). Symptoms include chronic diarrhea, abdominal pain, gastrointestinal bleeding and weight loss. Poorly controlled disease can result in the development of significant complications including intra-abdominal abscesses, intestinal perforation, fistulae, bowel obstruction, and repeated bowel resections resulting in short gut syndrome and malnutrition. The cumulative rate for resective surgery in this patient population has been reported to be as high as 80 percent after 15 years of disease (6). Post-resection clinical recurrence rates following intestinal resection are approximately 30 percent at five years, 44 percent at 10 years and 50% at 15 years (7-9).

1.2 Cost and Societal Burden

Although the management of IBD has increasingly shifted to the outpatient setting, there are still significant costs and resource utilization associated with hospitalization. Estimates of the cost associated with the in-patient care of an individual with IBD exceed 37,000 dollars annually (10). Additional observations from both cohort studies and clinical trials

reveal that IBD is associated with high rates of unemployment and impaired quality of life. Bernstein et al. recently published the largest population-based survey utilizing data from Statistics Canada Person Oriented Information Database describing hospitalization and readmission rates for Canadian IBD patients (11). Over the seven-year period of the study, 73,615 individuals with a diagnosis of IBD were admitted to hospital. The total number of in-patients per year with a primary diagnosis of IBD was 8,700. Between 18 to 20 percent of these patients required re-hospitalization within one year.

1.3 Diagnosis and Treatment

The diagnosis of IBD relies on a combination of clinical symptoms, as well as radiologic, endoscopic and histologic evidence. Through research efforts we now have a more in-depth understanding of the immunopathogenesis of this disease. The recognition that earlier and more aggressive control of inflammatory disease leads to fewer complications, decreased morbidity and improved quality of life, has resulted in an explosion in research related to the development of novel therapeutic agents (12, 13). Before the era of biologic therapy and the use of immunosuppressant agents, clinicians relied heavily on corticosteroids for symptom relief in IBD. Corticosteroids function through potent anti-inflammatory and immunosuppressant mechanisms. Although corticosteroids are effective for short-term relief of symptoms they have been shown to be ineffective when used over a prolonged period (14). Corticosteroids are also associated with a high incidence of steroid-related side-effects (14). Natural history studies of IBD have demonstrated high rates of steroid dependence and steroid refractoriness resulting in the

need for surgical intervention even after just one course of corticosteroid treatment (14, 15).

Medications shown to be efficacious in well-designed clinical trials have lead to a rapid expansion in the therapeutic armamentarium of gastroenterologists. Immunosuppressant medications with proven efficacy for the treatment of Crohn's disease include 6-thioguanine antimetabolites (including azathioprine and 6-mercaptopurine) and methotrexate (16-19). A newer class of medications referred to as "Biologic agents" has been shown to be effective at inducing and maintaining clinical remission. These medications are engineered to target the immune system in a very specific way. One example of a biologic agent is a drug called Infliximab. Infliximab specifically destroys a pro-inflammatory cytokine called tumor necrosis factor (TNF-α), which is up regulated in Crohn's disease. Infliximab has been shown to be efficacious in the induction and maintenance of remission in Crohn's disease in a number of placebo-controlled randomized trials (20-22). This expansion of therapeutic options has been accompanied by the need for increased knowledge related to therapeutic dosing, medication-related side effects, adverse events, and appropriate usage and, particularly in Canada, cost-effectiveness. The need for rapid and effective dissemination of evidence-based practice guidelines is paramount, particularly in such a rapidly progressing discipline.

1.4 Evaluation of Physicians' Medical Management of IBD

A number of sets of clinical and consensus guidelines pertaining to the medical management of IBD have been developed by opinion leaders in the field of gastroenterology (23, 24). Very few studies have been performed to evaluate the therapeutic algorithm employed by gastroenterologists in the management of IBD. Multiple observational survey studies whereby self-report questionnaires have been administered have been conducted to ascertain the practice patterns of gastroenterologists in the use of immunosuppressant agents (25, 26, 27). Overall the results of these studies have demonstrated varied practice patterns in the use of such therapies for the management of IBD. In many of these studies low response rates raise questions with respect to the precision of results. A few studies have been performed in an attempt to determine the patterns and prevalence of medication use by Canadian gastroenterologists (28-30). One study examined the frequency of use and standards of care for the use of 6-thioguanine antimetabolites in the treatment of IBD (28). The second study by Chande and colleagues evaluated the use of methotrexate in CD (31). Both studies suggested that the rates of use of these agents were low (31). Response rates in both studies were just over 50 percent. To date no studies have been carried out which provide an understanding of how Canadian gastroenterologists prescribe Infliximab or an understanding of factors that may influence the decision to use Infliximab therapy. Infliximab was the first biologic approved for use by Health Canada. A second biologic agent, adalimumab, was recently been approved by health Canada in 2006. However, given the longer duration and more

wide spread of use of Infliximab by Canadian gastroenterologists, Infliximab was selected as the biologic of interest.

1.5 Physician Prescribing Behaviour

As in other medical fields, the uptake and implementation of new clinical practice paradigms often lags behind the acquisition of new, high quality evidence to support practice change. Similar issues apply to the medical management of IBD. In order to better understand and explore factors with the potential to influence Canadian gastroenterologist's practice patterns, it is important to first understand what factors influence physician prescribing behaviour as well as the theoretical constructs of knowledge acquisition and uptake by physicians. Improved understanding of such factors will allow application of more effective and efficient dissemination of clinical information and practice-changing algorithms in order to improve the quality and consistency of care provided to patients with IBD.

1.5.1 Theories Pertaining To Knowledge Transfer and Uptake by Physicians

A significant body of research has been dedicated to evaluating the most effective means of information dissemination and physician education. There are multiple theories pertaining to the facilitation of change which, if well understood, could lead to more effective and efficient means of knowledge transfer (32). Traditional models of physician

behaviour emphasize goals including patient outcomes, physician income, prestige and leisure with education, information and financial incentives cited as the key mechanisms to induce behavioural change. The social influence theory proposes that physician behaviour is guided by habit and custom, by assumptions about beliefs and values held by peers, and by prevailing practices and social norms that define appropriate behaviour (33). Some of the most successful strategies for guideline implementation have focused on norm transfer as well as information transfer. Such strategies include training and apprenticeship, academic detailing, consultation, peer discussion and socialization programs. Educational theories emphasize that change is driven by the desire to learn and to be professionally competent. Others believe that through participation in small, interactive, educational sessions, health care givers will take ownership of the final product (32). Although several other theories pertaining to the facilitation of change exist, few have been well studied in physicians (32). Numerous systematic reviews pertaining to interventions designed to promote implementation and uptake of clinically relevant research findings and clinical practice guidelines have been published (34-37). Systematic reviews of interventions designed to alter physician behaviour have consistently shown educational outreach visits, reminders, multifaceted interventions and interactive educational meetings to be the most effective (36-39).

1.5.2 Influences on Physician Prescribing Behaviour

A physician's decision to prescribe a medication can be influenced by a variety of factors including concerns relating to cost-effectiveness, adverse events, early experience with a new drug, social influences on decision making, and mode of exposure to pharmaceutical information (40-49).

There have also been observed associations between certain physician characteristics and prescribing behaviour including gender, location of medical training, number of patients seen and size of medical practice. A study linking two provincial databases looking at all general practitioners prescribing large numbers of prescriptions for elderly beneficiaries of the New Brunswick prescription drug plan, evaluated the association of a number of non-pharmacologic factors on prescribing for the elderly. Higher prescribers were more likely to be male, to have been trained in Canada and be qualified by the College of Family Physicians of Canada (CFPC) (45). They also had a larger patient volume and billed on average 30 percent more during the study period than practitioners with lower patients volumes (45).

In the absence of studies describing patterns of use of Infliximab amongst Canadian gastroenterologists, observations from the rheumatology literature can serve to provide us with some insight pertaining to these issues. Investigators from the University of Pennsylvania recently evaluated the impact of Medicare coverage on physicians' prescribing patterns of Infliximab and etanercept for rheumatoid arthritis (RA) (47). In a

multivariate analysis, type of insurance plan and demographic factors were strong predictors of differential prescribing of etanercept compared with Infliximab whereas disease characteristics were not. Another survey of US rheumatologists evaluating prescribing patterns and perceived barriers to the prescribing of Infliximab demonstrated that costs to patients and insurance coverage were perceived as major barriers to prescribing these agents (50). A review of the rheumatology literature has also shown that access to biological therapies may differ according to geographic location (51). This in turn could have an impact on the decision or ability to initiate such therapy. In Canada access to Infliximab is different in each province. Firstly, Infliximab was approved as an indication for use in Crohn's disease during different years in each province. Infliximab was approved by Health Canada as an induction agent for refractory Crohn's disease in July 2001. However, the only province that approved Infliximab for this indication in 2001 was Saskatchewan (52). Newfoundland and Prince Edward Island did not grant approval for this indication until 2005. Although Infliximab was approved by Health Canada in July of 2001, it is at the discretion of provincial formularies to determine whether or not to reimburse patients for the use of this drug. Reimbursement criteria differ significantly between provinces (52). Such inter-provincial differences might influence the rates and patterns of Infliximab use as a result of limited or difficult access to the drug.

In addition to physician and drug-related factors, patient-related factors could potentially influence the decision to prescribe Infliximab. The Consortium of Rheumatology Researchers of North America (CORRONA) Registry consists of over nine thousand

patients with RA. Using this data, it was demonstrated that a greater proportion of patients with younger onset RA were receiving Infliximab than those with older onset RA, despite identical disease duration, severity and activity (53).

In summary, the results of previously administered, surveys have demonstrated significant practice variation and inconsistency in the use of immunosuppressive agents for medical management of IBD. Physician-related, drug-related and patient-related factors influence physician preference when it comes to prescribing a medication. In the case of biological agents, observations from the RA literature suggest that cost, access, insurance coverage and patient age may influence a physician's decision to prescribe these drugs. To date there is no published literature, which explores factors, which may influence a physician's decision to initiate Infliximab, a novel and expensive therapy, in the treatment of IBD. Such information would allow policy makers and governing bodies charged with the continuing medical education of physicians to develop specific and targeted educational strategies pertaining to the medical management of IBD. It would also allow policy makers to further address regional or provincial discrepancies in the use of biologic agents for the management of IBD.

1.5.3 State of the Literature pertaining to Survey Methodology and Evidence-Based Questionnaire Design

Historically, three of the major limitations threatening the internal validity of survey study design include 1) response bias 2) selection bias and 3) questionnaire bias. Low survey

response rates have long been an issue, which has plagued researchers. Estimates of survey response rates amongst physicians have varied greatly in the literature. However, the observation has been made that reported physician response rates to surveys have fallen over the years (54-56). In fact, the response to the American Medical Association's Periodic Survey of Physicians declined from 80 percent in 1966 to 49 percent in 1977 (54). This observation may be related to the phenomenon of "survey fatigue" or could be reflective of variation in practice demands related to patient volume, acuity and wait lists over time. In fact, it is not uncommon to observe survey response rates amongst physicians of 20 to 30 percent (57). To further compound the issue, it has been shown that specialist physicians respond at a somewhat lower rate (54, 58) than generalist physicians. The vast majority of literature suggests that a response rate of approximately 50 percent can be expected when administering self-report questionnaires by standard mail to physicians (59). However, most of these studies have not overtly employed elements of TDM. Low response rates decrease the precision and accuracy of study results, posing a grave threat to the internal validity of the study. Dillman's method of survey study design is based on social exchange theory and advocates the development of survey procedures that create respondent trust and perceptions of increased rewards and reduced costs for being a respondent. This theory takes into account the context of the survey situation and emphasizes the overall reduction of survey error. Social exchange theory asserts that the actions of individuals are motivated by the return these actions are expected to bring from others (60). Three elements are critical for predicting a particular action: reward, cost and trust. Incorporation of Dillman's survey design methodology has been associated with significantly higher survey response rates. Several other evidence-

based methods have been shown to maximize survey response rates (Table 1, appendix 2). Edwards and colleagues published the most comprehensive systematic review of randomized controlled trials of methods to influence response to postal questionnaires in 2002 (58). In this review, two hundred and ninety-two randomized controlled trials of any questionnaire topic in any population, including over 250,000 participants, were reviewed. Two outcomes were used to estimate the effect of each intervention; 1) proportion of completed or partially completed questionnaires returned after the first mailing and 2) the proportion returned after all follow up contacts had been made. The odds of response were more than doubled when a non-conditional, monetary incentive was used (OR 2.02; 95% CI 1.79 to 2.27), when the questionnaire content was of significant interest to participants (OR 2.44; 95% CI 1.99 to 3.01) and when the questionnaire was distributed by recorded delivery (OR 2.21; 95% CI 1.51 to 3.25). A non-conditional incentive is one that is distributed with the questionnaire. The receipt of this incentive is not dependent upon completion of the questionnaire. Other strategies shown to have a significant influence on response rates include the development of short questionnaires, contacting participants before questionnaire distribution, stamped return envelopes, distribution of a second copy to non-respondents, questionnaires originating from Universities made clear through the use of University logos, the use of colored ink and personalization of questionnaires (61). Studies of physicians have yielded physician response rates of approximately 54 percent (62). Methods studied in randomized trials demonstrated to significantly increase response rate in physicians include shorter questionnaire length, use of a modest non-conditional incentive, inclusion of a thank you letter, use of stamped return envelopes and inclusion of reminder letters after the first mail out to non-responders

(63-75). A second form of non-response, item non-response, can also adversely affect the internal validity of a study. Several measures pertaining to questionnaire study design according to the principles of Choi and Pack (76) have been shown to minimize the frequency of item non-response as a result of ambiguous questions, complex questions, forced choice, missing or overlapping intervals, framing, and leading questions. Questionnaires with simple questions designed to read clearly and to flow in a logical order with mutually exclusive, non-overlapping response options are effective in minimizing item non-response (76).

1.6 Study Objectives

There is no existing literature describing prescribing patterns or factors that might serve to influence prescribing patterns of Canadian physicians for medically refractory Inflammatory Bowel Disease. Medically refractory IBD can be defined as IBD that does not improve with conventional corticosteroid and immunomodulator (methotrexate, azathioprine or 6-mercaptopurine) therapy. The specific objectives of this study were as follows:

1) To describe the clinical patterns of Infliximab use in the treatment of medically refractory IBD by Canadian physicians involved in the medical treatment of patients with IBD.

i) Which patients do physicians treat with Infliximab?

ii) What dosage of Infliximab do physicians use?

iii) How often and at what interval is Infliximab given?

iv) Do physicians co-administer other immunosuppressants with Infliximab?

v) Do physicians use corticosteroids as pre-medication with Infliximab?

vi) How long do physicians treat patients with Infliximab?

vii) What do physicians do when patients lose response to Infliximab?

2) Do certain practice-related and demographic factors influence patterns of Infliximab therapy?

a) Proportion of IBD patients in clinical practice

b) Type of practice (academic vs. community)

c) Years in practice

d) Province in which physician practices

3) To evaluate the association between physician utilization of continuing medical education (CME) and patterns of Infliximab use.

i) Is participation in multifaceted, interactive, educational programs associated with a particular pattern of Infliximab use?

4) To identify specific factors which may influence a physician's decision to initiate Infliximab therapy.

i) Do drug cost, patient insurance, time to complete paper work, provincial funding criteria, lack of infusion facility and lack of trained personnel influence the decision to initiate Infliximab therapy?

   a. Does the region in which a physician practices influence the identification of barriers to Infliximab prescribing?

ii) Do Infliximab-related adverse events influence the decision to initiate Infliximab therapy?

iii) Do specific patient characteristics influence the decision to initiate Infliximab?

   a) age

   b) gender

1.7 Study Design

These questions were addressed in the form of a nationally distributed, survey of physicians actively engaged in the management of patients with IBD. Physicians engaged in the medical management of IBD included gastroenterologists, internists and general surgeons. The results of this survey will serve as a tool by which to understand current patterns of Infliximab use as well as factors that might influence the decision to use this drug.

Chapter Two: METHODS

2.1 Justification of Study Design

The goal of this study was to obtain an understanding of practice patterns and influences pertaining to the use of Infliximab by all Canadian physicians involved in the medical management of IBD. A survey study design was selected given its utility in describing the characteristics of large populations, unlike experimental study designs which rely on highly selected samples through pre-specified inclusion and exclusion criteria (77). A self-administered survey made it possible to obtain sufficient data to explore the associations between variables (56, 77). Such flexibility would not have been afforded by other experimental and observational study designs. In prospective, observational cohort studies the sample size is often limited by cost and feasibility. Typically, a limited number of variables are explored due to sample size constraints. This is very important for descriptive and exploratory analysis, the very purpose of this study, where several variables were to be analyzed. Surveys also were flexible allowing many questions to be asked on a given topic (56). In surveys one can develop operational definitions from study observations as opposed to being restricted to an *a priori* conceptual definition as is the case in an experimental study design. This is particularly useful when very little information exists about a particular topic, as was the case for the administration of Infliximab by Canadian physicians. Finally the survey questionnaire allowed the evaluation of differences between subgroups within the sample being surveyed as the

same question is asked of all individuals surveyed (77). The ability to perform such subgroup analyses in other observational and experimental study designs is constrained by sample size and power considerations. Data acquisition through the use of administrative and pharmacy databases often does not allow the researcher to collect information pertaining to how and why a drug is administered. Such information can only be obtained directly from the prescribers themselves. Surveys can also provide a description of patterns or behaviour at a discreet point in time (77). This was a desirable feature since trends in Infliximab prescribing may change over time. One of the greatest strengths of the self-administered survey study was that, when properly executed, sampling error is minimized allowing generalization to the population of interest, in this case physicians involved in the medical management of IBD in Canada (56, 60, 77). A postal questionnaire allowed the researcher to acquire information pertaining to the prescribing behaviours (as well as factors which might influence these behaviours) of Canadian physicians who treat patients with IBD. From this perspective a postal questionnaire, as opposed to in-person interviews, was the logical choice given its ease and efficiency of administration. Studies comparing e-mail and internet surveys to standard mail surveys have suggested that although administration of electronic surveys result in faster responses, the overall response rates are significantly lower than for those distributed by standard mail. Although a practice audit can provide very detailed information pertaining to clinical practice patterns, the complexity of conducting such an audit as well as the difficulty gathering information regarding practitioner opinion make the use of a self-report questionnaire more appropriate (78).

2.2 Survey Implementation and Maximizing Response Rate

A self-report, postal questionnaire was created and implemented according to Dillman's Tailored Design Method (60). This study conformed to all elements of survey design and implementation according to social exchange theory.

Several evidence-based methods have been shown to maximize survey response rates (Table 1, appendix 2). Methods with at least moderate benefit (greater than 25 percent improvement in the odds of response) were selected for survey implementation (table 1).

2.3 Study Population

This was a survey of Canadian gastroenterologists' practice patterns related to the use of a specific biologic therapy (Infliximab) in the management of refractory inflammatory bowel disease. Eligible participants were those who use, have used or plan to use Infliximab for the treatment of patients with Inflammatory Bowel Disease. Three screening questions were included at the beginning of the questionnaire to determine eligibility for the study (Appendix 6). In a recent study by Moayyedi et al., the number of Canadian gastroenterologists was estimated from the Canadian Institute of Health Information (CIHI) database in 2002 by using the following definition: "a specialist who performs at least 100 upper endoscopies and/or colonoscopies each year". According to this definition a gastroenterologist does not necessarily have to be certified in gastroenterology with the Royal College of Physicians and Surgeons of Canada. The

number of gastroenterologists in Canada was estimated at 1.83 per 100,000 persons (73). The current population of Canada is 32,833785 people (73). Application of this estimate to the entire Canadian population yields an estimate of the total number of gastroenterologists of approximately 590. When compared to other countries, Canada appears to have the least inter-provincial variation in the number of gastroenterologists (79).

The sampling frame consisted of all physician members of the Canadian Association of Gastroenterology (CAG) practicing clinical gastroenterology. Many of these members will have subspecialty training in gastroenterology as indicated by subspecialty certification in Gastroenterology with the Royal College of Physicians and Surgeons of Canada (RCPSC). There are 466 such clinician members (79). The province of employment is captured through the mailing addresses for all members. Based on the previously described definition of a gastroenterologist and the current membership of CAG, this sampling frame likely captures most of the gastroenterologists in Canada. CAG was unable to release the contact information for clinicians within this sampling frame to the public due to privacy laws (79). The executive director of CAG agreed to distribute all surveys and survey-related documents by mail for purposes of this study. As our sampling frame was the same as our population of interest the entire clinician membership of CAG was surveyed with particular emphasis placed on maximizing questionnaire response rate. Demographic information on province, years in practice, gender, percentage IBD seen in clinical practice, type and size of practice were also collected.

2.4 Precision Based Estimate of Sample Size

210 completed respondent questionnaires were required to provide an acceptable sampling error (± 5%) and a 95 percent confidence interval for the obtained point estimate(s). This is based on a conservative estimate of expected maximum variation in answers to questions of interest of 50 percent. Stated another way, a response rate of at least 45 percent is required to ensure precision of the results of survey responses. The equation from which this sample size is derived is as follows(60):

$$Ns = \frac{(Np)(p)(1-p)}{(Np-1)(B/C)^2 + (p)(1-p)} \quad (60)$$

Where Ns= completed sample size needed for the desired level of precision

Np=size of population

P = proportion of population expected to choose one of the two response categories

B = acceptable amount of sampling error of the true population value

C = Z statistic associated with the confidence interval, in this case a 95 percent confidence interval.

Based on a population size of 466 and a conservative estimate of the proportion of people responding to each of the categories (for a dichotomous variable) of 50 percent, the equation becomes:

$$Ns = \frac{(466)(0.5)(0.5)}{}$$

$$(466-1)(0.05/1.96)^2 + (0.5)(0.5)$$

Thus Ns = 116/ 0.55 = 210 (60)

The question of interest upon which this estimate is based is derived is a theoretical question with dichotomous response categories. In the actual survey there were multiple questions, many of which have more than two response categories. This equation assumes the following; 1) a simple random sample 2) a large sample approximation and 3) that typical sources of error such as non-response, poor administration methods, and highly biased results are trivial (60).

2.5 Questionnaire Development

The questionnaire had not been administered before. There were no validated questionnaires designed to evaluate gastroenterologist practice patterns relating to Infliximab use. Questions designed to evaluate practice patterns were scenario-based and composed of largely closed-ended questions. Given that factual, non-subjective information was being sought in this study providing categorical response options was deemed most appropriate. Questionnaire design conformed to the recommendations of Choi and Pack as well as Fowler in order to minimize bias (56, 76). The questionnaire was implemented according to the Tailored Design Method advocated by Dillman (60). (appendix 1). The questionnaire was subjected to pilot testing to exclude design flaws and

to ensure comprehensibility and reliability. Initial testing involved dissemination of the survey to a small group of local gastroenterologists who acted as knowledgeable colleagues and analysts for critical review of content and format. This initial review also sought to identify deficiencies in both the cognitive and motivational qualities of the survey. (Motivational qualities refer specifically to whether or not the questionnaire content is of sufficient interest to the respondent). This served to increase the likelihood of survey completion. The questionnaire was then distributed to a small group of individuals who are not content experts as well as local experts in questionnaire design to ensure that obvious flaws in questionnaire design had not been overlooked.

2.6 Questionnaire Content

Questions were designed to examine each of the following as previously stated objectives: 1) clinical patterns of Infliximab use in the treatment of medically refractory IBD 2) drug-related and non-pharmacologic factors which might influence the decision to prescribe Infliximab 3) Association between CME approach and Infliximab prescribing patterns and 4) practice-related and demographic factors which might influence prescribing of Infliximab. The geographic location in which a physician practiced was captured according to province of practice. Given the small number of physicians in some provinces, geographic location was categorized by region within the country making the assumption that certain practice paradigms and provincial funding criteria are similar amongst provinces that are closer to one another geographically.

2.7 Survey Implementation

Standard letter mail was used to contact subjects. A multiple contact approach, as previously described by Scott (1961), Linsky (1975), and Dillman (1991), was utilized to improve response rate (60). All survey methodology utilized the major principles of the social exchange theory as advocated by Dillman and consisted of four waves or mail outs (appendix3) (60). A brief pre-notice letter was mailed to the respondent 4 days prior to the questionnaire to make subjects aware of the study (appendix 4). The first survey was mailed to potential respondents on May 22, 2007. This mailing also included a detailed cover letter indicating why the participant's response was important (appendix3). A non-conditional financial incentive, in the form of a fifteen-dollar gift certificate to Chapters bookstore, was included with this survey to express appreciation for respondent participation. Although previous research has studied monetary incentives, it was felt that the dollar value of the gift certificates would likely achieve the same result. A replacement questionnaire was mailed to non-respondents 3 weeks after the initial questionnaire was sent on June 12, 2007. A final contact was a reminder notice (including a pre-paid, postage-affixed envelope, with a second replacement questionnaire) to non-respondents 3 weeks after the second survey had been sent on July 5, 2007. A separate, color-coded non-responder form with a few key questions as to how non-responders might differ systematically from responders was included with each questionnaire. Recipients who chose not to complete the questionnaire for whatever reason were encouraged to complete

and return the non-responder form (appendix 6). After the final mail out, 12 weeks were allowed for the return of questionnaires. All responses were tracked by CAG administration. The study codes, not the personal identity, corresponding to non-respondents were then revealed to the student investigator (JJ). Additional questionnaires were sent by CAG to non-respondents as previously described. At no time was the CAG administration made aware of individual responses as the envelopes in which the questionnaires were returned were never opened.

2.8 Ethical Considerations and Confidentiality

All respondents were well informed as to the nature of the survey and what the results were to be used for. Details including the name of the organization conducting the research, who was paying for the research, assurance that cooperation was voluntary and that no negative consequences would befall non-participants, and assurances that respondents could skip any questions they did not want to answer were included in all correspondence (appendix 1 and 5).

All questionnaires were assigned a study code in order to track responses, maintain confidentiality and protect participant identity. CAG was paid for the services of mailing out the questionnaires and tracking study codes on behalf of the investigators. CAG administration assisting with the research destroyed all results pertaining to the personal identities of respondents. Access to completed questionnaires was limited to only those investigators directly involved in the project as respondents returned questionnaires

directly to the investigators. Prior to the initiation of the study, the Conjoint Health Research Ethics Board at the University of Calgary approved all components of the protocol.

2.9 Data Collection and Management

The responses from all questionnaires were then entered into an electronic database by the student investigator (JLJ) and a second individual on two separate occasions in order to minimize transcription errors (double data entry). A random sample of 50 percent of the questionnaire responses was also re-checked by the student investigator (JLJ) to ensure that the data in the final database was accurate. Once the data was entered no one could access the database other than the student investigator (JLJ) or thesis supervisor (RH) unless express permission to do so had been obtained from these investigators. The student investigator managed all source records as well as the electronic database. Source copies (or paper records) were stored by the student investigator in a secure area in the gastroenterology research office at the University of Calgary. The electronic database remained on a secure, password-encrypted server at the University of Calgary Health Sciences Center in the gastroenterology clinic and research office.

2.9.1 Missing Data

Responses to all questions were evaluated, including those from partially completed questionnaires. All missing data was coded as missing. "Partial responders" referred to respondents who had only partially completed the questionnaire and thus had item non-response (even when only one item was not responded to). "Non-responders" referred to those who returned the questionnaires without providing responses to any of the questionnaire elements. "Non-responder form respondents" referred to those returned a non-responder form. The proportion and, more importantly, pattern of missing data was described to determine whether the pattern of missing data was random or non-random. For purposes of analysis, missing data from partial non-responders was ignored however, analysis was repeated with and without the data from partial non-responders to ensure that the responses were not systematically different between questionnaires with complete and those with partial responses.

2.9.2 Data Analysis

Data analysis was descriptive. Response rates were calculated by dividing the number of respondents, both partial and complete (numerator), by the total number of participants to whom the survey was distributed (denominator). In this study the denominator was 466. Characteristics of both respondents and non-respondent members of the sample were presented. All variable responses were categorical. Group comparisons of responses to

each questionnaire item were performed using χ^2 analysis or Fisher's exact testing. Means, standard deviations and ranges of responses were presented and 95 percent confidence intervals constructed for all point estimates. The alpha for all statistical testing was set at 5 percent for each questionnaire item. Adjustment for multiple comparisons was not made as data analysis was descriptive. All data analysis was carried out using STATA SE statistical software package (version 9.0).

A wave analysis was performed to evaluate and compare the nature of survey responses in those questionnaires returned after the first and second wave of mail outs to those returned after the third and final wave to determine if the late responders differed systematically from the earlier responders. "Late responders" have been defined as those participants who respond one to two weeks after questionnaire administration during any wave of survey distribution. This definition has been disputed in the literature given observations that the late respondents, as traditionally defined, do not provide a suitable basis for estimating the characteristics of non-respondents, utilizing the elements of self-report data (55, 80-82). For purposes of this study, the characteristics of "potential non-responders" were utilized to evaluate for response bias. Participants that returned the questionnaire beyond the two-week mark after the third survey was distributed were considered "potential non-responders". The wave was indicated by assigning a number code corresponding to each wave in the upper left hand corner of each questionnaire (appendix 1).

Chapter Three: Study Limitations

Concerns existed in relation to survey non-response and it's potential to result in selection bias. Measures were taken to maximize response rates and to characterize the nature of non-respondents as previously outlined in section 2.4.

Chapter Four: Time Line

The pre-notice was mailed on May 22, 2007, 4 days prior to the first wave of survey dissemination on June 12, 2007. Three weeks were allowed between each mail-out. The final wave of surveys was mailed on July 5, 2007. Data acquisition, cleaning and analysis took place in October and November of 2007.

Chapter Five: Funding

The study was supported by an unconditional grant from the Division of Gastroenterology, University of Calgary, Alberta.

Chapter Six: Results

6.1 Characteristics of Respondents

In total 336 responses (overall response rate including completed questionnaires as well as those returning non-responder forms) were obtained (table 1). Two hundred ninety-two (87 percent) of these responses consisted of completed questionnaires and 44 (13 percent) were non-responder forms (table 1). One hundred and ninety (57 percent) respondents were characterized as early responders (questionnaire received within 3 weeks of the first mail out), and 68 (20 percent) as late responders (questionnaire received within 3 weeks of the third mail out). Of those returned questionnaires, only 5 (2 percent) were partially completed (at least 1 questionnaire item not answered).

The demographic and clinical practice profiles of the respondents (full and partial) summarized in Table 2. The majority of respondents were between the ages of 30 and 59 and had been in practice between 10 to 30 years. The proportion of respondents with a university appointment (53 percent) versus a community practice (47 percent) was similar. Sixty-four percent of respondents had a predominantly clinical practice (consisting of greater than 50 percent clinical duties). The majority of respondents' clinical practices included less than 30 percent of patients with inflammatory bowel disease (IBD) (Figure 1).

6.2 Wave Analysis

A wave analysis was performed to determine if the characteristics of the late responders differed significantly from those of the early responders. Overall, the distribution of age, years in clinical practice and practice profiles of the early respondents did not differ significantly from those of the late respondents (figures 2-9). Likewise, the distribution of respondents who had used Infliximab in the past, present or future did not differ between the early and late respondents (figures 2-9). The demographic and practice profile characteristics, including eligibility criteria, of those who returned non-responder forms were compared to those of the responders (figures 10-18).

6.3 Analysis of Gastroenterologists Who Chose Not to Respond

A non-responder form was returned by individuals surveyed who did not view themselves as being eligible for participation in the survey or who did not want to respond to the survey (those who chose not to respond) (figures 10 – 18). The age distribution of those who chose not to respond differed from that of responders. Specifically, a greater proportion of those who chose not to respond were greater than 60 years of age although this did not reach statistical significance (Pearson chi^2 12.47; p=0.051). The practice profile for the majority of those who chose not to respond was identified as academic practice. Practice composition amongst those who chose not to respond differed from responders in that a greater proportion of those who chose not to respond had practices

consisting of less than 30 percent clinical duties (Pearson chi^2 16.30; p=0.002). There were no other significant differences between the practice profiles of responders and those who chose not to respond. A significantly greater proportion of those who chose not to respond had either never used, did not currently use or would not use Infliximab compared to respondents.

6.4 Study Objective Number One. To describe the patterns of Infliximab use in the treatment of medically refractory IBD by Canadian physicians involved in the medical treatments of patients with IBD

6.4.1 Which patients do physicians treat with Infliximab?

Table 3 summarizes the distribution of responses for Infliximab practice pattern and indication. The vast majority of respondents selected medically refractory IBD, fistulizing Crohn's disease and steroid-dependent disease as indications for which they would administer Infliximab. However, only 67 and 58 percent of respondents selected pyoderma gangrenosum and ankylosing spondylitis, respectively, as indications for Infliximab use. Only 23 percent of respondents identified new onset, severe and extensive CD as an indication for Infliximab use.

6.4.2 What dosage of Infliximab do physicians use?

Most of the respondents provided similar responses with respect to patterns of Infliximab use (table 4). 97 percent of respondents identified that they use the 5 mg per kg dose of Infliximab as the initial dose (95%CI 0.95 to 0.99). Approximately 1 percent of respondents identified that they would use 7.5mg/kg, 10 mg/kg or "don't know" as the initial dose of Infliximab therapy.

6.4.3 How often and at what interval is Infliximab given?

Eighty-eight percent of respondents administer Infliximab induction doses as 3 doses administered at weeks 0, 2 and 6 (95%CI 0.85 to 0.92) (table 5). Two point seven percent of respondents indicated that they administer Infliximab at weeks 0 and 2 (95% CI 0.008 to 0.05), 6.1 percent as a single infusion (95% CI 0.34 to 0.89) and 2.7 percent selected "other"(95% CI 0.008 to 0.046).

Close to 90 percent of physicians administer maintenance Infliximab at 8 week intervals (0.89; 95%CI 0.86 to 0.93). 5 percent of gastroenterologists used Infliximab as episodic or "on demand" therapy (0.051;95%CI 0.026 to 0.078). Maintenance infusions at 6 week intervals , 10 week intervals and 12 weeks intervals were all selected less than 1 percent of the time.

6.4.4 Do physicians co-administer other immunosuppressants with Infliximab?

With respect to the co-administration of immunosuppressive therapy, 80 percent of respondents indicated that they do use concomitant immunosuppressant (IS) therapy (0.80; 95%CI 0.75 to 0.84) (table 4). Only 16 percent do not use concomitant IS therapy (0.16; 95%CI 0.12 to 0.20) and only 4 percent did not know whether or not they use IS therapy (0.041; 95%CI 0.02 to 0.06).

6.4.5 Do physicians use corticosteroids as pre-medication with Infliximab?

Responses were more heterogeneous when physicians were asked whether or not they pre-medicate with corticosteroids (table 5). The majority, 75 percent, indicated that they do pre-medicate with corticosteroid (0.75; 95%CI 0.70 to 0.80) while 25 percent indicated that they do not (0.25; 95%CI 0.20 to 0.30).

6.4.6 For how long do physicians treat patients with Infliximab?

Seventy-seven percent (0.77; 95%CI 0.72 to 0.82) of gastroenterologists indicated that they continue Infliximab therapy indefinitely provided the drug was well tolerated and effective for their patient (table 5). The second most common response for duration of Infliximab therapy was 1 year (0.12; 95%CI 0.086 to 0.162). Approximately 1 percent of

respondents selected 3 months or 6 months as preferred duration of Infliximab therapy. Less than 1 percent of gastroenterologists were uncertain with respect to how long they would continue Infliximab therapy.

6.4.7 What do physicians do when patients lose response to Infliximab?

Seventy-six percent (0.76; 95%CI 0.71 to 0.81) of gastroenterologists indicated that they decrease the interval of Infliximab administration when their patients exhibit a pattern of loss of response to Infliximab suggestive of immunogenicity. Eighteen percent (0.18; 95%CI 0.13 to 0.22) indicated that they increase the dose of Infliximab upon loss of response and less than 1 percent of gastroenterologists discontinue Infliximab therapy. Only 5 percent (0.05; 95%CI 0.03 to 0.08) were uncertain about what to do when their patients exhibit loss of response to Infliximab therapy.

6.5 Study objective number two. Do Certain practice-related and demographic factors influence patterns of Infliximab therapy?

6.5.1 Proportion of IBD Patients in Clinical Practice

Various aspects of Infliximab practice pattern were stratified by the proportion of clinical practice comprised of patients with a diagnosis of IBD. Percentage IBD was categorized as follows: 1) < 30 percent 2) ≥ 30 percent but < 50 percent and 3) ≥ 50 percent (table 5a).

There were no statistically significant differences in the distribution of responses to the questions regarding pre-medication, initial Infliximab dose, initiation dose of Infliximab, maintenance dose of Infliximab, concomitant IS use, duration of Infliximab use or strategic approach to loss of response to Infliximab after stratification for percentage clinical practice comprised of IBD.

6.5.2 Academic Versus Community Practice

Stratification by type of clinical practice (i.e., community or academic) yielded a statistically significant difference in response distribution for, concommittant use of IS and duration of Infliximab therapy (table 5b). Differences in the proportion of use of corticosteroid premedication amongst academic versus community gastroenterologists did not reach statistical significance (Pearson's Chi_2 =3.78; p=0.052). A greater proportion of physicians in community practice used concommittant IS than in academic practice (Pearson's Chi2 = 8.789; p=0.012) and a greater proportion of physicians in community practice responded that they would be more likely to continue Infliximab indefinitely than physicians in academic practice (Pearson's chi2=11.297; p=0.046). Stratification by practice description yeilded no significant differences in the distribution of responses with respect to any of the other aspects of Infliximab practice pattern (table 5b).

6.5.3 Percentage Practice Clinical

The percentage of practice composed of clinical duties did not significantly influence the distribution of responses pertaining to Infliximab practice patterns (table 5c).

6.5.4 Number of Years in Practice

Years in clinical practice were categorized as 1) < 5 years 2) 5 to 20 years and 3) > 20 years. Stratification by years in clinical practice yielded no significant differences in the distribution of responses pertaining to Infliximab use (table 5d)

6.5.5 Physician Age

Physician age was categorized as 1) < 30 years of age 2) 30 to 60 years of age 3) > 60 years of age . Analysis of the distribution of responses pertaining to Infliximab use after stratification by physician age group failed to reveal and significant differences (table 5e).

6.5.6 Geographic region in Which Physician Practices

Stratification by “region” revealed that the region of Canada in which physicians practice influenced the distribution of responses to questions pertaining to Infliximab use (table 5f). Region did influence the approach to Infliximab initiation. Specifically, a larger proportion of physicians in the Western Canada administer initial Infliximab dose(s) as a

single infusion only or as two infusions at weeks 0 and 4 (Pearson's chi_2 = 37.85; $p<0.001$). Region was not associated with any of the other aspects of Infliximab practice pattern.

6.6 Study objective number three. To evaluate the association between physician utilization of continuing medical education (CME) and patterns of Infliximab use.

Figure 19 summarizes the proportion of respondents that indicated participation in various CME activities. Most respondents indicated that they participated in CME activities in one or more of the following formats: large groups, expert seminars, review of clinical guidelines, review of medical text books or journals and consultation with peers. A minority of respondents (n=27) indicated that they often participated in apprenticeships or the clinical observation of an "expert" clinician or opinion leader in the field.

6.6.1 Is participation in multifaceted, interactive, educational programs associated with a particular pattern of Infliximab use?

After stratification by type of CME (stratified by respondents who indicated that they participated "often" in a select CME activity) the distribution of responses for both Infliximab indication and practice pattern were analyzed (table 6a). Only apprenticeship emerged as a CME activity that seemed to alter the response distribution of specific

questionnaire items (table 6b). However, it is important to emphasize that only 27 respondents used apprenticeship "often". Stratification by CME activity did not alter the distribution of responses to the questionnaire item relating to Infliximab indication. However, the responses of physicians who indicated that they participated "often" in apprenticeship were then compared to the responses of those who "rarely" or "never" participated in apprenticeship. The distributions of responses of respondents who use pre-medication were different amongst those who use apprenticeship versus those who did not (Pearson chi^2 6.10; p=0.047).

6.7 Study objective number 4. To identify specific factors that may influence a physician's decision to initiate Infliximab therapy

6.7.1 Drug cost

Over 50 percent of respondents identified drug cost as being an important factor to consider when deciding to initiate Infliximab infusions (0.52; 95% CI 0.46 to 0.57) (table 7a). Interestingly, over 30 percent of respondents felt that drug cost was an unimportant factor to consider when deciding to initiate Infliximab therapy (0.32; 95%CI 0.26 to 0.37).

6.7.2 Insurance Coverage

Over 90 percent of respondents felt that medical insurance coverage for individual patients was an important factor to consider when deciding to initiate Infliximab infusions (table

7a). Only 5.4 percent of respondents felt that this was an unimportant issue (0.054; 95% CI 0.28 to 0.81).

6.7.3 *Provincial Funding Criteria*

Seventy-one percent of respondents considered provincial funding criteria as being either important or extremely important when deciding whether or not to initiate Infliximab infusions (0.71; 95% CI 0.65 to 0.76). Only 16 percent of respondents felt that provincial funding criteria were unimportant (0.16; 95% CI 0.12 to 0.20) (table 7a).

6.7.4 Time

Forty-eight percent of respondents felt that time required to complete paper work in order to obtain coverage for Infliximab was an unimportant factor when deciding weather or not to initiate Infliximab therapy (0.48; 95% CI 0.42 to 0.54) (table 7a). Twenty-seven percent of respondents felt that the time required to complete paper work in order to obtain Infliximab coverage was important (0.27; 95% CI 0.22 to 0.33).

6.7.5 Infusion Facilities

Fifty-seven percent of respondents felt that absence of a facility in which to administer Infliximab infusions was either important or extremely important factor when deciding whether or not to initiate Infliximab therapy (0.57; 95%CI 0.52 to 0.63). Only 26 percent (0.27; 95% CI 0.22 to 0.32) of respondents felt that the absence of an infusion facility was

an unimportant factor to consider when deciding whether or not to initiate Infliximab therapy (table 7a).

6.7.6 Personnel

A lack of trained personnel to administer Infliximab infusions was identified as an important factor to consider when deciding to initiate Infliximab infusions (0.59; 95%CI 0.54 to 0.65). Only 25 percent of respondents felt that this was an unimportant factor (0.25; 95% CI 0.20 to 0.30) (table 7a).

6.8 Study objective number 5. Does region in which a physician practices influence the identification of barriers to Infliximab prescribing?

Responses to questions to the previously identified potential barriers to Infliximab use were then stratified by region in which physician works (table 7b). This stratified analyses revealed that the perceived importance of medical insurance coverage, time required to fill out Infliximab-related paper work, provincial funding criteria, and the absence of an Infliximab infusion differed by region. With respect to medical insurance coverage, a greater proportion of physician's working in Western Canada and Central Canada (Ontario) viewed the possession of personal medical insurance as being important. Similarly, the proportion of physicians who indicated that the time required to complete Infliximab-related paper work and provincial funding criteria were important was greater

in Western and central Canada than in Quebec or Eastern Canada. Finally, the proportion of physicians indicating that the lack of trained personnel to infuse Infliximab was a barrier to Infliximab use was highest in Ontario, followed by Western Canada and then Quebec and finally the Maritimes provinces.

6.9 Study objective number 6. Do Infliximab-related adverse events influence the decision to initiate Infliximab therapy?

6.9.1 Risk Perception in the Context of Mild Disease Activity and Burden

The responses to a series of statements related to 3 clinical scenarios intended to convey low, moderate and high risk of IBD-related disease burden (severity and extent) were evaluated. The distribution of responses was quite uniform with respect to the low disease burden scenario as well as the moderate and high disease burden scenarios (table 8). In response to the scenario intended to convey mild disease activity, when asked whether the risk of minor infection outweighs the benefit of treatment, most respondents disagreed (0.71; 95% CI 0.65 to 0.76). However, when asked if the risk of serious infection outweighed the benefit of treatment the responses were distributed much more evenly over the categories of agree (0.39; 95%CI 0.33 to 0.45) and disagree (0.44;95%CI 0.39 to 0.50). Once again, when asked if the risk of lymphoma outweighed the benefit of Infliximab therapy the distribution of responses was fairly uniform over the categories agree (0.31; 95% CI 0.25 to 0.36) and disagree (0.50 ; 95%CI 0.44 to 0.55). Interestingly, when asked if the risk of infusion reactions, one of the more common adverse events

associated with Infliximab use, was greater than the benefit of Infliximab therapy, 62 percent of respondents disagreed (0.62; 95%CI 0.56 to 0.67). Clearly, in the context of mild disease activity, respondents seem to be much more sensitive to and unclear about the risks of serious infection and lymphoma development. These results imply that the disease burden of an individual influences physician risk perception.

6.9.2 Risk Perception in the Context of Moderate Disease Activity and Burden

In the context of a case intended to convey moderate disease severity to the respondent the majority of respondents disagreed with the statement that the risk of mild infection outweighed any potential benefit of Infliximab therapy (0.89; 95%CI 0.85 to 0.93). Similar responses were observed in the distribution of responses to similar questions pertaining to risk of serious infection, lymphoma development and allergic reactions (table 8).

6.9.3 Risk Perception in the Context of Severe Disease Activity and Burden

The scenario intended to convey severe disease activity and extensive disease burden resulted in similar distributions of responses to all questions asked as those in response to the scenario intended to convey moderate disease activity and burden (table 8). As the degree of disease severity increased from mild to moderate or severe, so did the risk tolerance of the respondents.

6.10 Study objective number 7. Do specific patient characteristics influence the decision to initiate Infliximab Therapy?

6.10.1 Gender

Respondents were asked to indicate the degree to which certain patient-related factors might influence their decision to initiate Infliximab therapy (table 9). The consideration of male gender appeared to be unimportant to the vast majority of respondents with 55 percent of respondents indicating that male gender is an unimportant factor (0.55; 95%CI 0.49 to 0.60). Likewise, 49 percent of respondents indicated that female gender was an unimportant factor when considering initiation of Infliximab therapy (0.49; 95%CI 0.43 to 0.55).

6.10.2 Age

Unlike gender, patient age seemed to be a more important patient-related characteristic in the consideration to initiate Infliximab therapy (table 9). The distribution of responses to the question of whether older age was an important patient-related factor when deciding to initiate Infliximab treatment were evenly distributed the “important” (0.34; 95%CI 0.29 to 0.40), “neutral” (0.36; 95%CI 0.30 to 0.41) and “unimportant” (0.30; 95%CI 0.25 to 0.35) categories. Younger age, however, was considered to be an “important” patient-related

factor by 50 percent of respondents (0.50; 95% CI 0.44 to 0.56). Only 25 percent of respondents felt that this was an “unimportant” patient-related factor.

Chapter Seven: Discussion

To our knowledge, this is the first comprehensive study designed specifically to evaluate the patterns of Infliximab use amongst Canadian gastroenterologists. The results of this study are both reassuring and concerning. Overall, the responses to survey items would suggest that the vast majority of Canadian gastroenterologists use Infliximab in a similar fashion. In instances where the distribution of responses was fairly uniform, there exists solid, high-quality data to support and justify these practice patterns. However, increased heterogeneity in response distribution was observed in response to selected questionnaire items.

7.1 Interpretation of observed clinical practice patterns in the context of existing medical literature and previously conducted research

With respect to the questions pertaining to co-administration of IS agents with Infliximab and the use of corticosteroids as a pre-medication prior to Infliximab infusions, 20 percent of respondents indicated that they do not routinely co-administer IS with Infliximab or “did not know” whether or not to co-administer IS agents with Infliximab. Twenty-four percent of respondents indicated that they do not pre-medicate with corticosteroids before

Infliximab infusions. Additionally, at least 24 percent of respondents indicated that they either increase dose, stop Infliximab or do “other” if a patient were to lose response to Infliximab over time. The fact that approximately one quarter of respondents were not in agreement with respect to these issues is meaningful and reflective of the controversies and uncertainty pertaining to Infliximab dose optimization that currently exist in the medical literature (23, 83-85) .

Infliximab is one of the only approved biologic medications in our armamentarium for the treatment of severe, medically refractory Crohn’s disease in Canada. The only other biologic currently approved for use in Canada for the treatment of medically refractory IBD is adalimumab, a 100 percent humanized, monoclonal anti-TNF antibody(86, 87). Although observed response rates in anti-TNF exposed patients receiving induction therapy with adalimumab approximate 50 percent (20, 86, 88, 89), it has been consistently observed across biologic development programs that the response rate obtained with administration of a second anti-TNF agent is never as high as that obtained with administration with the first anti-TNF agent (90, 91). Rates of clinical response have been observed to approach 60 percent with the first biologic agent and 45 to 50 percent after exposure to the second biologic agent (91, 92). For this reason, it is critically important to engage in medical practices that maximize the duration of effectiveness of the first biologic agent that an individual with refractory CD is initially exposed to, provided that they indeed have a meaningful clinical response to the agent.

Observations derived from post-hoc, sub-group analysis of clinical trials of Infliximab have revealed increased rates of infusion reactions, development of antibodies to Infliximab (ATIs) and decreased duration of response amongst those patients receiving Infliximab without concomitant immunosuppressive therapy (20, 22, 93, 94. ATI's are believed to mediate, in part, the phenomenon of immunogenicity, which is defined as the ability of a substance (called an antigen) to provoke an immune response (84). In large part, these observations have led opinion leaders in the field of IBD to recommend concomitant IS therapy with Infliximab therapy (23). Additionally, it has been observed that immunogenicity could be decreased if Infliximab was administered as scheduled therapy as opposed to episodic therapy (95-97). Pharmacokinetic studies of Infliximab have demonstrated that circulating trough concentrations of Infliximab can be maintained at therapeutic concentrations 8 weeks beyond the initial infusion (98). Thus, consensus was reached amongst opinion leaders that Infliximab should be infused at eight-week intervals.

Most recently, the results of two relatively large, prospective, cohort studies have brought into question the additive benefit of concomitant IS therapy in addition to scheduled therapy, leaving in their wake doubt and confusion with respect to best practice (85, 97). In addition to prolongation of Infliximab's effectiveness, this issue has implications with respect to the development of rare, but potentially serious adverse events in patients receiving long-term therapy with both anti-TNF and IS agents. The sequelae of ongoing suppression of both humoral and cell-mediated immune responses could be significant and have been observed to include the development of rare, but potentially fatal opportunistic

infections and malignancies, particularly hematologic malignancies (99-101). Despite the confusion and lack of high quality data to support the use of concomitant IS therapy the majority of respondents indicated that they do use concomitant IS with Infliximab.

The efficacy of pre-medicating with corticosteroids prior to Infliximab infusions was observed in an RCT performed by Farrell and colleagues in 2003 in which patients receiving episodic Infliximab infusions were randomized to receive Infliximab alone or Infliximab after premedication with 200 mg of IV solucortef (102). In this trial, lower concentrations of ATIs were observed amongst individuals randomized to corticosteroid pre-medication compared to those individuals receiving placebo as pre-medication. Given the questionable additive benefit of IS therapy for prevention of immunogenicity in patients receiving scheduled Infliximab therapy, similar questions pertaining to the additive benefit of corticosteroid pre-medication have been raised. Once again, such controversy likely explains the increased heterogeneity of response distribution pertaining to questions relating to concomitant IS therapy and use of corticosteroids as Infliximab pre-medication.

The responses to questions pertaining to strategy implementation upon loss of response in primary Infliximab responders were not uniform. This question is of particular import to the Canadian health care system, a single party payer system. Biologic agents are extremely expensive therapies, and strategy employed upon loss of response to a biologic can lead to significant cost saving or expenditure, depending upon the strategy employed. In general, immunogenic loss of response can be addressed by increasing Infliximab dose

in order to “overwhelm” antibody response or to decrease Infliximab interval in order to intervene with the next infusion before the trough serum Infliximab concentration drops below known therapeutic levels. In the absence of any high quality data to support the superiority of one strategy over another in the treatment of IBD, clinicians have been left to their own devices to decide how best to deal with such a problem. The fact that the majority of respondents indicated that they would decrease Infliximab infusion interval, is likely reflective of the sense of fiscal responsibility felt by physicians working within the Canadian Health Care system. It is likely that Canadian Gastroenterologists also try to decrease the financial burden placed on patients who cannot afford to cover the residual cost of escalating Infliximab doses. However, no data exists with respect to the efficacy or cost-effectiveness of this approach.

7.2 Influences on Prescribing Pattern

Most physician and practice-related factors including IBD case mix, physician age, years in clinical practice and percentage clinical practice did not influence the distribution of responses pertaining to Infliximab use in any meaningful way. However, it was surprising to note that practice description appeared to have an influence on the distribution of responses such that those physicians with a self-described community practice were slightly more likely to pre-medicate with corticosteroids, more likely to use concomitant IS therapy and more likely to use Infliximab indefinitely than those with a self-described academic practice. These observations are contrary to what one might

have expected. However, it is possible that those gastroenterologists in academic practice work in close proximity with opinion leaders in the field of IBD and attend IBD-related educational rounds more frequently. Thus, they may be more likely to have been exposed to discussion and debate relating to the utility of steroid pre-medication and concomitant IS therapy use. Likewise, increasing concerns regarding the long-term effects of prolonged anti-TNF blockade may have been communicated in a timely manner to gastroenterologists working at academic centers who have the benefit of listening to visiting experts.

Drug cost was identified by approximately half of respondents as a concern or a "barrier" to the prescribing of Infliximab. However, the fact that 90 percent of respondents felt that insurance coverage for their patients was an important factor indicates that clinicians are less concerned about the cost of the drug to the health care system as they are about the cost and affordability of the medication to patients themselves. Physician concerns relating to the cost of medication (to the patient and health care system) have been observed consistently in the medical literature (44, 46-48, 103).

It was interesting to note that aside from younger age, neither sex nor older age was considered to be an important patient-related factor when deciding to initiate Infliximab therapy. Generally, older age has been noted to be an important consideration when deciding to initiate a medical therapy or to perform a procedure in medicine in relation to concerns about concomitant disease, medical therapies and medication compliance (104, 105). The precise reasons for the identification of younger patient age by Canadian

gastroenterologists as an important factor to consider when prescribing Infliximab are not known and were not further explored in this survey. One could speculate that the younger the individual, the longer the commitment to remain on Infliximab therapy. Respondents may have been taking into consideration emerging concerns regarding the long-term safety of Infliximab, particularly in view of the recent spike in the number of incident cases of hepatosplenic T-cell lymphoma (HSL) that have been observed over the past few years in young adults (98, 99). However, almost all of the cases of HSL have developed in males, and gender was not identified as an important issue to consider when prescribing Infliximab (98). This is also an interesting finding given that knowledge pertaining to the safety of Infliximab in pregnancy is still quite limited at this time (98, 106). Although gender-related discrepancies have been described in relation to under-prescription of other medical therapies in the past, it is unlikely that observations from this literature could be applied to patients with IBD given the clear differences in patient populations, study period, drug therapy and disease entity being studied (107). Only detailed, future enquiry in relation to gender and age-specific factors and the use of biologic therapy will serve to clarify this issue.

7.3 Barriers to Infliximab use

Gastroenterologists were asked to indicate whether selected factors including drug cost, insurance coverage, time to complete Infliximab-related paper work, provincial funding criteria, the absence of an Infliximab infusion facility or lack of trained personnel experienced in the administration of Infliximab, influenced their decision to initiate

Infliximab therapy. All factors were deemed important by most gastroenterologists except for one; the time involved to complete Infliximab-related paper work. Only 27 percent of respondents felt that this was an important factor. It is possible that this observation occurred as a result of the desire on the part of respondents to provide a "socially desirable response". The vast majority of respondents felt that lack of personal insurance was an important influence on the decision to initiate Infliximab infusions, once again likely reflecting Canadian Gastroenterologists' concerns relating to the out-of-pocket cost of medical therapy to their patients. This is also in keeping with observations of drug cost as an influential factor on the prescription of new medical therapies in the medical literature (47). Not surprisingly 70 percent of gastroenterologists identified provincial funding criteria as an important influence on the decision to initiate Infliximab therapy. The fact that drug insurance coverage and provincial funding criteria were identified most frequently as potential barriers to Infliximab use is likely reflective of the impact of province-specific funding criteria on the ability for an individual to obtain medical insurance for coverage of Infliximab therapy. Given ethical considerations relating to breach of confidentiality through the analysis of questionnaire by province, particularly provinces with a very low numbers of respondents, the responses to the questionnaire were evaluated by "region" and presented as aggregate data. The country was divided into four regions, "Western Canada", "Ontario", "Quebec" and "Atlantic Canada", based on the relative response rate of each province. Stratification by region revealed a statistically significant difference in the distribution of responses pertaining to the importance of Insurance coverage, time to complete Infliximab-related paper work, provincial funding criteria, absence of an Infliximab infusion facility and the lack of trained personnel for

Infliximab administration. A larger percentage of respondents in Western Canada and Ontario felt that personal insurance coverage and provincial funding criteria were important barriers to the prescription of Infliximab. Ontario had the greatest proportion of respondents indicate that the absence of infusion facilities and the lack of trained personnel for the administration of Infliximab were important factors that might influence their decision to initiate Infliximab infusions. These results are not surprising given that, at the time that this survey was conducted, Ontario, Alberta and British Columbia's provincial funding criteria were the amongst the most stringent in the country (52).

7.4 Continuing Medical Education and Its Influence on Infliximab Prescribing Pattern

Of the modes of CME evaluated, only apprenticeship was associated with an apparent difference in the distribution of responses to questions pertaining to Infliximab administration. A small number of respondents (n=27) identified frequent participation in apprenticeship activities as a major mode of CME. However, this small group of 27 respondents did have greater uniformity of response distribution with respect to Infliximab start dose with 100 percent of respondents engaging in apprenticeship identifying 5 mg/kg as the initial dose of Infliximab. Also, a greater proportion of apprenticeship participators identified the indefinite use of Infliximab as long as the drug was well tolerated and effective for their patients compared to those who did not participate in apprenticeship activities. There was greater heterogeneity of response distribution pertaining to the use of steroid pre-medication and co-administration of immunosuppressant therapy amongst

those respondents participating frequently in apprenticeship activities versus those who did not. Formal statistical testing was not performed given the small size of the apprenticeship subgroup and the potential for type I and type II errors. These observations are quite interesting and consistent with previous findings in the medical literature (36, 38, 39, 108). Active and multifaceted educational interventions targeting physicians appear to be the most beneficial for bringing about behavioural change in. In fact, interventions that adhere to social influence strategies which employ interpersonal and persuasion techniques have been observed to be the most effective for information and norm transfer (33). Apprenticeship falls into the category of the "interpersonal social influence setting" in which one or a few targets are focused on and the level of effort is high. The use of opinion leaders, rounds and participatory guideline review, for example, fall into the "persuasion social influence setting"(33). Although persuasion techniques are generally effective for norm transfer and information transfer, the use of opinion leaders, has been shown to vary with respect to its effectiveness for information transfer. This is likely a result of variability of approach and style of individual opinion leaders when conveying information and interacting with other physicians. The results observed from this study are hypothesis-generating and suggest that future research be focused on the study and standardization of educational strategies (interpersonal and persuasion), which are most effective at both information and norm transfer as opposed to mass media influences which are very poor for achieving normative transfer.

7.5 Risk Perception

Scenarios conveying greater disease severity were associated with the perception of less drug-associated risk. Gastroenterologist's perceived risk of therapy was conveyed through their assessment of the risk-benefit ratio of Infliximab therapy in the context each scenario. The most profound difference in the perceived risk-benefit ratio was observed to have occurred between the distributions of responses to questions relating to mild disease burden as compared to the distribution of responses to questions relating to moderate or severe Crohn's disease burden. Lymphoma and serious allergic reactions were identified as adverse events whose risk was perceived to be greater than Infliximab benefit within the context of the scenario intended to convey mild disease severity. This is likely a direct reflection of the degree of the physician's concern relating to these specific adverse events as opposed to the actual known absolute risk of lymphoma or serious infection derived from the medical literature. Both lymphoma and serious infection occur far less frequently than allergic reactions and mild infections (98, 100, 109). These observations demonstrate that Canadian gastroenterologists are generally more comfortable with the prescribing of Infliximab when the perceived risk-benefit ratio is more favourable. Thus, Canadian gastroenterologists appear to reserve Infliximab's use for patients with more severe disease.

7.6 Methodology

The methodology implemented in the design, development and distribution of this survey adhered to the Tailored Design Method (TDM). TDM is based on the social exchange theory. All aspects of the survey were developed in line with the Social Exchange Theory

with the goal of maximizing respondent trust and the perception of increased reward and reduced cost for responding to the questionnaire (60). Additionally, evidence-based methods shown to increase overall response rates by at least 25 percent were implemented (61). The overall response rate obtained in this study is amongst the highest reported in recent literature. This is likely, in part, as a result of the incorporation of TDM design and other evidence-based design elements. It is important to emphasize that no single technique will assure a higher response rate. Close attention to all other aspects of survey design was required in an effort to maximize response rate. Five key elements were utilized in survey implementation including the use of a respondent-friendly questionnaire, multiple contacts including the use of a pre-notice letter, three questionnaire mailings to non-respondents and a thank-you letter, provision of return envelopes with real stamps affixed, personalization of correspondence and the use of a token prepaid incentive. The respondent friendly questionnaire format adheres to all three elements of social exchange theory. The design improves reward by making the questionnaire appear interesting and important. In our survey, the questionnaire was clearly typed-written on lighter paper with an official, colored university logo affixed to the top of the first page. An introductory paragraph emphasizing the importance of the individual's expertise, time and response was included before the questionnaire began and the confidentiality of individual responses was emphasized. The questions were simple, designed to read clearly and to flow in a logical order with, for the most part, mutually exclusive, non-overlapping response options as per the design suggestions of Choi and Pack (76). The questionnaire was then pilot tested for content, readability and flow amongst a small group of local gastroenterologists (n=5 which comprised only 1 percent of the total sample size). All of

this was done to eliminate or at least minimize the numerous types of bias inherent to questionnaire deign including ambiguous question, complex question, forced choice, missing or overlapping interval, framing, leading question, and recall bias. Although the inadvertent introduction of belief versus behaviour bias may have occurred given the use of case-based scenarios as stems for a number of questions, pilot testing of the questionnaire helped serve to minimize the potential for such bias. The multiple contact approach, with emphasis on variability of look and feel for each communication in order to convey a sense of appropriate renewal of effort to communicate with transparent expenditure of considerably more effort and resources, was used. The timing between contacts was designed such that respondents had enough time to respond but not enough time to forget about the previous contact. The mail out of the thank-you and reminder letters was intended to occur while the previous questionnaire was still in the potential respondent's possession. The use of return envelopes with real postage stamps affixed to them has been shown to increase response rates by several percentage points (60, 61). A "real" stamp is felt to represent a good-will gesture. It is likely that this positive effect is related to the fact that it is difficult to throw away anything with a monetary value. Hence, the questionnaire was less likely to be discarded and was therefore present when the carefully timed reminder was sent. The use of a pre-paid token financial incentive has been shown to increase response rates significantly (60, 61). The use of promised incentives changes the terms of exchange from social to economic. The provision of a good-will gesture such as a token of appreciation in advance creates a sense of reciprocal obligation. It is likely that a combination of all of these techniques led to the observed success in maximizing specialist physician response rate to this questionnaire.

In addition to the implementation of features designed to maximize response rate, more than one technique was employed in an attempt to characterize the nature of non-respondents. This was done to determine whether or not the responses to items in returned questionnaires were representative of the responses from the target population, gastroenterologists who manage patients with IBD. The two strategies, the "wave analysis" and the use of the "non-responder" form were analyzed. Interestingly, the distribution of item response amongst early responders (those returning completed questionnaires after the first mail-out) was no different than the distribution of item response amongst late responders (those returning completed questionnaires after the third mail out). However, the distribution of responses to questionnaire items pertaining to physician demographics and practice features did differ between respondents and those who chose to return a non-response form. It has been demonstrated that the degree of bias present in any given survey can be shown to be a function of the proportion of non-respondents in the total sample and the extent to which there is a systematic discrepancy between respondents and non-respondents on variables relevant to the inquiry (80). The comparison of late respondents to early respondents across key demographic and clinically relevant variables or a "wave analysis" makes the assumption that late respondents that participate only after an appreciable follow-up effort can be regarded as "almost non-respondents" and, therefore, similar to those who do not reply at all. The data related to the use of this method have shown that this assumption is not always tenable (110-112). The use of a non-responder form, provided enough non-responders choose to take the time to fill them out and return them, can provide a more accurate characterization of those

individuals choosing not to complete a questionnaire as well as the reasons why they chose not to complete the questionnaire. In this study, the use of the brief non-response form contributed meaningful information about the characteristics of the non-responders to this questionnaire. Those who chose not to respond and to return a non-response form were indeed systematically different from responders with respect to key demographic and practice-related characteristics. Overall, those choosing to return non-response forms saw fewer patients and less IBD, rarely if ever prescribed Infliximab and were slightly older than responders. These results served to provide confidence that the respondents did indeed represent the intended target population. These results suggest that, when administering a self-report questionnaire to Canadian gastroenterologists, the use of a non-responder form may be a more accurate method to characterize the profile of non-respondents in order to ensure that non-response error has been minimized and that the results are externally valid.

Chapter Eight: Summary, Conclusions and Future Research

Through the application of design strategies adherent to the Tailored Design Methodology significant improvements in physician response rate to a mail-out, self-report questionnaire can be achieved. Maximization of responses and, hence, minimization of non-response bias, has ensured that the results of this questionnaire were accurate and reflective of the population of interest. The results of this survey suggest that Canadian gastroenterologists, where high level medical evidence exists, practice similarly with

respect to the use of Infliximab in the management of patients with medically refractory Crohn's disease. Contradiction and uncertainty in the medical literature appears to be mirrored in the clinical practice of Canadian gastroenterologists when it comes to select aspects of managing medically refractory Crohn's disease with Infliximab. The results of this study will assist gastrointestinal educational governing bodies in the development of specific and targeted educational programs that serve to clarify some of the confusion amongst Canadian gastroenterologists pertaining to the use of Infliximab. These results will also help the Canadian clinical research community in the identification of relevant topics pertaining to the medical management of IBD for future research. Geographic, financial and resource-dependent factors appear to influence Canadian gastroenterologists' decisions to initiate Infliximab. Such findings point to the need for research that explores further the factors responsible for such discrepancies in medical care and what can be done to eliminate regional variation in the quality of care provided to patients with severe Crohn's disease. This information will assist provincial policy makers in the decision making process as it pertains to the development of guidelines and criteria pertaining to funding and resource distribution. Despite small numbers, the results of this survey would suggest that CME apprenticeship activities have the potential to meaningfully alter physician practice pattern. Future research pertaining to the development of focused, efficient and effective CME strategies to further educate Canadian gastroenterologists about issues pertaining to the use of biologic therapies for the medical management of medically refractory IBD are necessary in order to standardize medical care for this unique group of patients.

APPENDIX ONE

Wave Code

Medical Management of Inflammatory Bowel Disease

You have been identified by the Canadian Association of Gastroenteology (CAG) as an active member of the association. The CAG has removed your personal identification details prior to allowing us to give you the accompanying survey in order to protect confidentiality. This survey is voluntary. However, by sharing your expertise, experiences and opinions about the role of Infliximab in the management of IBD you will be contributing to our understanding of the issues and concerns related to the use of Infliximab in clinical practice. If for some reason you choose not to respond please let us know by returning the pink non-responder form in the enclosed stamped envelope by mail. Financial support for this study comes from the Division of Gastroenterology, University of Calgary. This survey will take you 7-10 minutes to complete.

SECTION A: DEMOGRAPHICS

A few questions about yourself, which will assist in the interpretation of the results, and help to ascertain your eligibility for this study.

1. To which age group do you belong ? (*Check one).*
   - ☐ Under 30
   - ☐ 30-44
   - ☐ 45-59
   - ☐ 60-74
   - ☐ 75 and over

2. How many years have you been in clinical practice? (*Check one).*
   - ☐ < 5
   - ☐ 5 - 9
   - ☐ 10- 19
   - ☐ 20 - 30
   - ☐ > 30

3. Which of the following best describes your clinical practice? (*Check one).*
   - ☐ Academic practice *(go to question 4)*
   - ☐ Community practice *(go to question 5)*

4.. I have a university appointment. The proportion of my time that is allocated to clinical duties is best described by the following: (*Check one)*
   - ☐ Less than 30 percent
   - ☐ 31 to 50 percent
   - ☐ 50 to 74 percent
   - ☐ 75 to 100 percent

5. What percentage of your clinical practice is comprised of patients with IBD? (*Check one).*
   - ☐ Less than 30 percent
   - ☐ 30 to 49 percent
   - ☐ 50 to 74 percent
   - ☐ 75 to 100 percent

6. How many times have you prescribed infliximab for either induction or maintenance within the past six months? (*Check one).*

- ☐ Less than 5 times
- ☐ 5 to 10 times
- ☐ 11 to 20 times
- ☐ Greater than 20 times

7* a) Have you **previously** used Infliximab as part of the medical management of IBD patients? *(Check one)*

- ☐ Yes
- ☐ No

7* b) Do you **currently** use Infliximab as part of the medical management of IBD patients? *(Check one)*

- ☐ Yes
- ☐ No

7* c) Do you **intend** to use Infliximab as part of the medical management of IBD patients? *(Check one)*

- ☐ Yes *(if yes, go to question 8)*
- ☐ No

***If you answered "No" to all three of 7 a, 7b, 7c, STOP** here. You are not eligible for this study. Please return this questionnaire **AND** the blank pink "non-responder" form in the prepaid envelope provided. If you answered "Yes" to ANY of 7a, 7b, 7c, please continue with this questionnaire.*

SECTION B: GENERAL QUESTIONS PERTAINING TO THE USE OF INFLIXIMAB.

8. For which of the following indications would you prescribe Infliximab? Patients with "medically refractory" disease can be considered to have failed therapy with corticosteroids and immunosuppressant medications. (*Check all that apply).*

- ☐ Medically refractory Ulcerative colitis
- ☐ Medically refractory Crohn's disease
- ☐ Fistulizing Crohn's disease
- ☐ Inflammatory bowel disease complicated by pyoderma gangrenosum
- ☐ Inflammatory bowel disease complicated by ankylosing spondylitis
- ☐ Newly diagnosed Crohn's disease with endoscopic and radiologic evidence of severe upper and lower gastrointestinal mucosal disease
- ☐ Steroid dependent Crohn's disease
- ☐ Other _____
- ☐ Don't know

9. With respect to the administration of corticosteroids as a pre-medication before Infliximab infusions, which of the following statements best describes your clinical practice? (*Check one).*

- ☐ I do not pre-medicate with corticosteroids
- ☐ I do pre-medicate with corticosteroids

SECTION C: SCENARIO-BASED QUESTIONS (*Please respond to Questions 4 a-f, based on Scenario One.*)

Scenario One.

You see a 36 year-old male with severe, steroid refractory Crohn's ileocolitis who has been treated with Azathioprine for 5 months at a dose of 150mg orally daily (patient weighs 70kg). After a thorough evaluation and consideration of all options, you have decided to prescribe Infliximab.

10(a). Which of the following **best** describes the dose of Infliximab that you would use **initially**? (*Check one).*

- ☐ Infliximab 5 mg/kg
- ☐ Infliximab 7.5 mg/kg
- ☐ Infliximab 10 mg/kg
- ☐ Don't know
- ☐ Other _____

10(b). Which of the following best describes **how** you would **initiate** Infliximab therapy? (*Check one).*

- ☐ Single infusion only
- ☐ Two infusions at weeks 0 and 4
- ☐ Three infusions at weeks 0, 2 and 6
- ☐ Other _____

10(c). The patient has responded to your initial dosing of Infliximab. Which of the following **best** describes **how** you would administer Infliximab as **maintenance** therapy? (*Check one).*

- ☐ Infusions at 6 week intervals
- ☐ Infusions 8 week intervals
- ☐ Infusions at 10 week intervals
- ☐ Infusions at 12 weeks intervals
- ☐ Infusions "on demand" when patient exhibits clinical evidence of a disease flare
- ☐ Other _____

10(d). Would you continue therapy with Azathioprine, 6-MP or Methotrexate after initiation of Infliximab? (*Check one).*

- ☐ Yes
- ☐ No
- ☐ Don't know

10(e). How long would you continue Infliximab therapy in this patient provided that he is **responding to and tolerating** the Infliximab well? (*Check one).*

- ☐ Three months
- ☐ Six months
- ☐ One year
- ☐ Indefinitely
- ☐ Other _____

10(f). Assume that this patient has received 4 maintenance infusions at the interval and dose you selected in the first part of this question. He now tells you that his typical Crohn's-related symptoms recur 2 weeks before the time of his next infusion. You surmise that the patient is starting to lose response to Infliximab. What would you do next? (*Check one*)

- ☐ Decrease the interval between infliximab infusions
- ☐ Increase the dose of infliximab
- ☐ Stop the infliximab infusions
- ☐ Other _____

SECTION D: In this section you are presented with a series of scenarios and asked to indicate your agreement with a series of statements related to each scenario.

Scenario two: You are seeing a 25 year-old male with newly diagnosed, colonic Crohn's disease of moderate severity. He was recently started on prednisone with good clinical response. This patient has asked you about initiating Infliximab. (*Respond to the following statements within the context of this scenario)*

		Strongly Agree ▼	Agree ▼	Neither Agree nor Disagree ▼	Disagree ▼	Strongly Disagree ▼
11a	The risks of **minor infection** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐
11b.	The risk of **serious infection** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐
11c.	The risk of **lymphoma** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐
11d.	The risk of **allergic reactions** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐

Scenario three: You see a 31 year-old male with a three year history of ileocolonic Crohn's disease. He underwent a limited terminal ileal resection one year ago. He now has clinical, endoscopic and radiographic evidence of recurrent neo-terminal ileal disease (inflammatory) which has been unresponsive to Azathioprine and Methotrexate. (*Respond to the following statements within the context of this scenario)*

		Strongly Agree ▼	Agree ▼	Neither Agree nor Disagree ▼	Disagree ▼	Strongly Disagree ▼
12a.	The risk of **minor infection** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐
12b.	The risk of **serious infection** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐
12c.	The risk of **lymphoma** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐
12d.	The risk of **allergic reactions** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐

Scenario four: You are following a 35 year-old male with a five year history of ileal Crohn's disease. He has required 3 extensive ileal resections (80cm each) for stricturing complications. He presents with clinical, radiographic and endoscopic evidence of disease recurrence despite ongoing therapy with Azathioprine (2.5 mg/kg) for 1 year. (*Respond to the following statements within the context of this scenario)*

		Strongly Agree ▼	Agree ▼	Neither Agree nor Disagree ▼	Disagree ▼	Strongly Disagree ▼
13a	The risk of **minor infection** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐
13b.	The risk of **serious infection** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐
13c	The risk of **lymphoma** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐
13d	The risk of **allergic reactions** associated with Infliximab use outweighs its potential benefit	☐	☐	☐	☐	☐

SECTION E: THE NEXT SERIES OF QUESTIONS INQUIRE ABOUT FACTORS THAT MAY INFLUENCE YOUR DECISION TO TREAT PATIENTS WITH INFLIXIMAB.

14. Please indicate the degree to which the following patient-related characteristics might influence your decision to initiate Infliximab. (*Check only one response for each characteristic)*

		Extremely Important ▼	Important ▼	Neither Important or unimportant ▼	Unimportant ▼	Extremely unimportant ▼
14a.	Male sex	☐	☐	☐	☐	☐
14b	Female sex	☐	☐	☐	☐	☐
14c	Older age	☐	☐	☐	☐	☐
14d	Younger age	☐	☐	☐	☐	☐

15. Please indicate the degree to which the following concerns might influence your decision to initiate Infliximab therapy. (*Check only one response for each concern)*

		Extremely Important ▼	Important ▼	Neither Important or unimportant ▼	Unimportant ▼	Extremely unimportant ▼
15a.	The cost associated with in-patient administration of infliximab	☐	☐	☐	☐	☐
15b	The cost for the patient as a result of lack of insurance coverage	☐	☐	☐	☐	☐
15c.	The time and effort required to complete infliximab-related paper work	☐	☐	☐	☐	☐
15d.	The provincial criteria for prescribing infliximab	☐	☐	☐	☐	☐
15e.	The absence of a facility in which to administer out-patient infliximab	☐	☐	☐	☐	☐
15f.	The lack of trained personnel to coordinate infusions and assist in the completion of paper work	☐	☐	☐	☐	☐
15g.	Other: _____ _____	☐	☐	☐	☐	☐

SECTION F. THIS ITEM INQUIRES ABOUT CONTINUING PROFESSIONAL EDUCATION RELATED TO MANAGING PATIENTS WITH IBD.

Please indicate how often you participate in or have participated in each type of educational activity. (*Check only one response for each educational activity*)

	Often ▼	Rarely ▼	Never ▼
16a) Interactive small group sessions including rounds, conferences and guest lecturers	☐	☐	☐
16b) Review of Clinical guidelines	☐	☐	☐
16c) Reading textbooks and medical journals	☐	☐	☐
16d) Large group seminars at conferences	☐	☐	☐
16e) Local seminars given by opinion leaders in the field of IBD	☐	☐	☐
16f) Apprenticeship	☐	☐	☐
16g) Consultation with peers	☐	☐	☐
16h) Other:_____	☐	☐	☐

Thank-you for your participation!

Please fold and return in the envelope provided

APPENDIX TWO

Table 1. Evidence-Based Methods for Maximizing Response Rates to Questionnaires

Category	**Intervention**	**No. Trials**	**No. Participants**	**Odds ratio (OR)**	**95% Confidence Interval**
Incentive	Monetary Incentive	49	46 474	2.02	1.79-2.27
Length	Incentive with questionnaire	40	40 669	1.86	1.55-2.24
Appearance	Brown Envelope	2	5311	1.52	0.67 – 3.44
	Colored Ink	1	3540	1.39	1.16-1.67
Delivery	Stamped return Envelope	14	38 259	1.26	1.13 – 1.41
Contact	Pre-contact	28	28 793	1.54	1.24 – 1.92
	Follow up	12	16 740	1.41	1.22 – 1.70
	Follow up including questionnaire	6	6310	1.41	1.02 – 1.94
Content	More interesting	2	2151	2.44	1.99 – 3.01
	User Friendly	1	3540	1.46	1.21 – 1.75
Origin	More senior Investigator/ Well known	4	2584	1.13	0.95 – 1.35
		13	20 428	1.31	1.11 – 1.54

APPENDIX THREE

Flow Sheet Outlining Survey Implementation

	Time				
	- 4 days	Week 0	Week 3	Week 6	Week 9
Phase 1. Pre-notice letter	X				
Phase 2. First Survey with Incentive		X			
Phase 3. Thank you replacement questionnaire & non-responder card			X		
Phase 4. Second replacement questionnaire & non-responder card				X	
Study Completion					X

APPENDIX FOUR

Date: month/day/year

Inside Address: Respondent Address

A few days from now you will receive by mail a request to fill out a brief questionnaire for an important thesis project being conducted by Dr. Jennifer Jones (MSc candidate) at the University of Calgary under the supervision of Dr. Robert Hilsden.

It concerns the practice patterns of Canadian Gastroenterologists in the management of Inflammatory Bowel Disease (IBD) with particular focus on the use of biologic therapy in this patient population. Your answers are completely confidential and will be released only as summaries in which no individual's answers can be identified. Special study codes will be used in place of any personal information, which could identify an individual. This survey is voluntary. However, you would be helping us tremendously by taking a few minutes to share your experiences and opinions about the role of Infliximab in the management of IBD. Research funds from the division of gastroenterology, University of Calgary, are being used to support this study.

I am writing in advance because we have found that many people like to be notified ahead of the time they will be contacted. The results of this study are important as they may influence the content of national clinical guidelines as well as targeted educational programs through better understanding of actual practice patterns and concerns pertaining to the use of these biologic agents in the IBD patient population.

Thank you for your time and consideration. It is only with the generous help and expertise of people like you that our research can be successful.

Sincerely,

Jennifer L. Jones, MD, FRCPC (MSc candidate)
Robert Hilsden, PhD, MD, FRCPC
Remo Panaccione, MD, FRCPC

APPENDIX FIVE

Date: month/day/year

Inside Address: Respondent Address

I am writing to ask your help for a thesis-based study of physician practice patterns pertaining to the use of Infliximab in the management of inflammatory bowel disease (IBD). This study is part of an effort to understand the issues and concerns related to the use of these agents in clinical practice. You have been selected after identification as a member of the Canadian Association of Gastroenterology with clinical expertise in the management of patients with IBD.

Results from the survey may be used to influence the content of nationally developed clinical guidelines as well as for the design and implementation of educational programs and conferences. More importantly, it is hoped that the results of this survey will lead to improvements in the clinical care of this patient population.

Your answers are completely confidential and will be released only as summaries in which no individual's answers can be identified. Special study codes will be used in place of any information which could identify an individual. This survey is voluntary. However, you would be helping us tremendously by taking a few minutes to share your experiences and opinions about the role of Infliximab in the management of IBD. If for some reason you choose not to respond please let us know by returning the pink non-responder card as well as the blank questionnaire in the enclosed stamped envelope by mail. Research funds from the division of gastroenterology, University of Calgary, are being used to support this study.

If you have any questions or comments about this study we would be happy to talk to you. Our number is 1-403-210-8575, or you can write to us at the address on the letterhead.

Thank you very much for helping us with this very important study.

Sincerely,

Jennifer L. Jones, MD, FRCPC (MSc candidate)
Remo Panaccione, MD, FRCPC
Robert Hilsden, PhD, MD, FRCPC

P.S. Enclosed in a small token of appreciation intended as a way of saying thanks for taking the time to complete our questionnaire.

APPENDIX SIX

If you will not be filling out the main questionnaire either because you were not eligible for the study or because of other reasons, please complete and return this brief form in the postage-affixed envelope that has been provided for you. Your answers are extremely important and will assist the researchers in telling if they have obtained a representative sample of study participants.

1. a) Have you **previously** used infliximab as part of the medical management of IBD patients?
   ☐ Yes
   ☐ No
   b) Do you **currently** use infliximab as part of the medical management of IBD patients?
   ☐ Yes
   ☐ No
   c) Do you **intend** to use Infliximab as part of the medical management of IBD patients?
   ☐ Yes
   ☐ No

2. To which age-group do you belong? (*Check one)*.

☐ **Under 30**

☐ **30-44**

☐ **45-59**

☐ **60-74**

☐ **75 and over**

3. How many years have you been in clinical practice? (***Check one).***

☐ **< 5**

☐ **5 - 9**

☐ **10- 19**

☐ **20 - 30**

☐ **> 30**

4. Which of the following best describes your clinical practice? (*Check one).*

☐ Academic practice (*go to question 5*)
☐ Community practice *(go to question 6)*

5. I have a university appointment. The proportion of my time that is allocated to clinical duties is best described by (*Check one)*

☐ **Less than 30 percent**

☐ **31 to 50 percent**

☐ **50 to 74 percent**

☐ **75 to 100 percent**

6. What percentage of your clinical practice is comprised of patients with IBD? (*Check one).*

☐ **Less than 30 percent**

☐ **30 to 49 percent**

☐ **50 to 74 percent**

☐ **75 to 100 percent**

7. How many times have you prescribed infliximab within the past six months? (*Check one).*

☐ **Less than 5 times**

☐ **5 to 10 times**

☐ **11 to 20 times**

☐ **Greater than 20 times**

Once again, many thanks for your consideration and cooperation. It is only through return of this form that we can assess if the people who complete the full questionnaire are

APPENDIX SEVEN

Table 1. Summary of response rates

Response Rate	N (%)	N denominator
Overall (*includes responders and those choosing to return a non-responder form*)	336 (72)	466
Responders (*only those returning completed questionnaires*)	292 (65)	466
Those who chose to return non-response forms	44 (9.4)	466
Fully Completed Questionnaires	287 (98)	292
Early Responders	190 (65)	292
Late Responders	68 (23)	292

Table 2. Respondent Demographics

Demographic and Practice Related Factors	**N (%)**
Age Group (years)	
< 30	9 (3)
30 – 44	124 (37)
45 – 59	147 (44)
60 – 74	51 (15)
≥ 75	1 (0.30)
Years in Clinical Practice	
< 5	63 (19)
5 – 9	40 (12)
10 – 19	106 (32)
20 – 30	84 (25)
> 30	39 (12)
Practice Description	
Academic	177 (53)
Community	155 (47)
Percentage Clinical	
< 30	41 (20)
31 – 50	34 (16)
51 – 74	51 (24)
75 – 100	84 (40)
Percentage IBD	
< 30	192 (58)
31 – 50	105 (32)
51 – 74	27 (8)
75 – 100	8 (2)

Table 3. Summary of Infliximab indication as identified by respondents

	N (%)	Standard Error	Binomial Wald 95% Confidence Interval
Medically refractory UC	264 (91)	0.017	0.874 to 0.941
Medically refractory CD	291 (100)	1.0	-
Fistulizing CD	285 (98)	0.008	0.963 to 0.996
Pyoderma Gangrenosum	196 (67)	0.028	0.619 to 0.728
Ankylosing Spondylitis	168 (58)	0.290	0.521 to 0.634
New, severe CD	66 (23)	0.025	0.178 to 0.275
Steroid dependent CD	249 (86)	0.021	0.815 to 0.896

Table 4. Patterns of Infliximab use amongst responders

	N	Proportion	Standard error	95% Binomial Wald CI
Steroid pre-medication				
Yes	219	0.75	0.025	0.197 to 0.297
No	72	0.24	0.025	0.703 to 0.802
Infliximab dose				
5 mg/ kg	281	0.97	0.010	0.949 to 0.989
7.5 mg/ kg	3	0.01	0.006	0.002 to 0.030
10 mg / kg	3	0.01	0.006	0.002 to 0.030
Induction therapy				
Single dose	18	0.06	0.014	0.034 to 0.090
0 and 4 weeks	8	0.03	0.010	0.009 to 0.046
0, 2 and 6 weeks	257	0.88	0.019	0.846 to 0.92
Maintenance therapy				
6 week interval	5	0.02	0.008	0.002 to 0.032
8 week interval	260	0.89	0.018	0.858 to 0.929
10 week interval	2	0.007	0.005	0.001 to 0.024
12 week interval	2	0.007	0.005	0.001 to 0.024
On demand	15	0.05	0.013	0.026 to 0.771
Immunosuppressant co-administration				
Yes	232	0.80	0.023	0.750 to 0.843
No	47	0.16	0.021	0.119 to 0.204
Infliximab duration				
3 months	3	0.01	0.006	0.002 to 0.033
6 months	4	0.01	0.007	0.004 to 0.038
1 year	36	0.12	0.019	0.086 to 0.162
Indefinitely	223	0.77	0.025	0.004 to 0.815
Infliximab use upon loss of response				
decrease interval	222	0.76	0.025	0.713 to 0.812
increase dose	51	0.18	0.022	0.131 to 0.219
stop Infliximab	2	0.007	0.005	0.001 to 0.025

* In the cells where the responses to not add up to 100 percent, the remainder of responses consisted of either “other” or “I don’t know”.

Table 5a. Influence of percentage case mix consisting of IBD patterns of Infliximab Use

	< 30 % IBD N (%)	**30-50 % IBD N (%)**	**> 50 % IBD N (%)**	**Pearson Chi^2 (p-value)**
Steroid pre-medication				
Yes	117 (53)	79 (36)	23 (10)	1.07 (0.59)
No	40 (56)	22 (31)	10 (14)	
Infliximab dose				
5 mg/ kg	149 (53)	99 (35)	33 (12)	3.52 (0.74)
7.5 mg/ kg	2 (67)	1 (33)	0 (0)	
10 mg / kg	2 (67)	1 (33)	0 (0)	
Induction therapy				
Single dose	10 (56)	7 (39)	1 (6)	5.84 (0.44)
0 and 4 weeks	3 (38)	5 (63)	0 (0)	
0, 2 and 6 weeks	138 (54)	87 (34)	32 (12)	
Maintenance therapy				
6 week interval	4 (80)	1 (20)	0 (0)	6.49 (0.77)
8 week interval	136 (52)	93(36)	31 (12)	
10 week interval	1 (50)	1 (50)	0 (0)	
12 week interval	2 (100)	0 (0)	0 (0)	
On demand	11 (73)	3 (20)	1 (7)	
Immunosuppressant co-administration				
Yes	127 (55)	82 (35)	23 (10)	4.23 (0.38)
No	22 (47)	16 (34)	9 (19)	
Infliximab duration				
3 months	1 (33)	2 (67)	0 (0)	9.26 (0.51)
6 months	2 (50)	13 (36)	1 (25)	
1 year	18 (50)	82 (37)	6 (14)	
Indefinitely	117 (53)	82 (37)	24 (11)	
Infliximab use upon loss of response				
decrease interval	115 (52)	78 (35)	29 (13)	7.19 (0.30)
increase dose	29 (57)	20 (39)	2 (4)	
stop Infliximab	2 (100)	0 (0)	0 (0)	

- In cells where n < 5, Fisher's exact testing was performed. Pearson's chi squared reported where results of Pearson's and Fisher's exact testing the same.

Table 5b. Influence of practice description on patterns of Infliximab Use

	Academic N (%)	Community N (%)	Pearson Chi^2 (p-value)
Steroid pre-medication			
Yes	108 (49)	111 (51)	**3.78 (0.05)**
No	45 (63)	27 (38)	
Infliximab dose			
5 mg/ kg	146 (52)	135 (48)	3.22 (0.36)
7.5 mg/ kg	2 (67)	1 (33)	
10 mg / kg	2 (67)	1 (33)	
Induction therapy			
Single dose	5 (28)	13 (72)	5.85 (0.12)
0 and 4 weeks	5 (63)	3 (38)	
0, 2 and 6 weeks	140 (55)	117 (46)	
Maintenance therapy			
6 week interval	3 (60)	2 (40)	2.19 (0.82)
8 week interval	136 (52)	124 (48)	
10 week interval	1 (50)	1 (50)	
12 week interval	2 (100)	0 (0)	
On demand	7 (47)	8 (53)	
Immunosuppressant co-administration			
Yes	113 (49)	119 (51)	**8.79 (0.01)**
No	34 (72)	13 (28)	
Infliximab duration			
3 months	3(100)	0 (0)	**11.30 (0.046)**
6 months	4 (100)	0 (0)	
1 year	24 (67)	12 (33)	
Indefinitely	110 (49)	113 (51)	
Infliximab use upon loss of response			
decrease interval	123 (55)	99 (45)	4.46 (0.22)
increase dose	20 (39)	31 (61)	
stop Infliximab	1 (50)	1 (50)	

* In cells where n < 5, Fisher's exact testing was performed. Pearson's chi squared reported where results of Pearson's and Fisher's exact testing the same.

Table 5c. Influence of percentage clinical practice on patterns of Infliximab Use

	< 30 % Clinical N (%)	**30-50 % Clinical N (%)**	**> 50 % Clinical N (%)**	**Pearson Chi^2 (p-value)**
Steroid pre-medication				
Yes	19 (15)	23 (18)	87 (67)	1.09 (0.58)
No	8(15)	6 (12)	38 (73)	
Infliximab dose				
5 mg/ kg	25 (14)	29 (17)	120 (69)	5.58 (0.47)
7.5 mg/ kg	1 (50)	0 (0)	1 (50)	
10 mg / kg	1 (50)	0 (0)	1 (50)	
Induction therapy				
Single dose	0 (0)	1 (17)	5 (83)	2.96 (0.81)
0 and 4 weeks	1 (20)	0 (0)	4 (80)	
0, 2 and 6 weeks	26 (16)	27 (16)	113 (68)	
Maintenance therapy				
6 week interval	0 (0)	0 (0)	3 (100)	9.36 (0.50)
8 week interval	26 (16)	25 (15)	112 (69)	
10 week interval	0 (0)	0 (0)	1 (100)	
12 week interval	1 (50)	0 (0)	1 (50)	
On demand	0 (0)	2 (25)	6 (75)	
Immunosuppressant co-administration				
Yes	18 (13)	21 (15)	97 (71)	2.54 (0.64)
No	7 918)	7 (18)	25 (64)	
Infliximab duration				
3 months	0 (0)	0 (0)	3 (100)	4.78 (0.78)
6 months	0 (0)	1 (25)	3 (75)	
1 year	4 (15)	3 (11)	19 (73)	
Indefinitely	22 (16)	21 (16)	91 (68)	
Infliximab use upon loss of response				
decrease interval	25 (17)	22 (15)	97 (67)	9.95 (0.13)
increase dose	2 (8)	3 (12)	20 (80)	
stop Infliximab	0 (0)	1 (100)	0 (0)	

- In cells where n < 5, Fisher's exact testing was performed. Pearson's chi squared reported where results of Pearson's and Fisher's exact testing the same.

Table 5d. Influence of number of years in clinical practice on patterns of Infliximab Use

	< 5 years N (%)	**5 to 20 years N (%)**	**> 20 years N (%)**	**Pearson Chi^2 (p-value)**
Steroid pre-medication				
Yes	19 (15)	23 (18)	87 (67)	1.09 (0.58)
No	8(15)	6 (12)	38 (73)	
Infliximab dose				
5 mg/ kg	25 (14)	29 (17)	120 (69)	5.58 (0.47)
7.5 mg/ kg	1 (50)	0 (0)	1 (50)	
10 mg / kg	1 (50)	0 (0)	1 (50)	
Induction therapy				
Single dose	0 (0)	1 (17)	5 (83)	2.96 (0.81)
0 and 4 weeks	1 (20)	0 (0)	4 (80)	
0, 2 and 6 weeks	26 (16)	27 (16)	113 (68)	
Maintenance therapy				
6 week interval	0 (0)	0 (0)	3 (100)	9.36 (0.50)
8 week interval	26 (16)	25 (15)	112 (69)	
10 week interval	0 (0)	0 (0)	1 (100)	
12 week interval	1 (50)	0 (0)	1 (50)	
On demand	0 (0)	2 (25)	6 (75)	
Immunosuppressant co-administration				
Yes	18 (13)	21 (15)	97 (71)	2.54 (0.64)
No	7 918)	7 (18)	25 (64)	
Infliximab duration				
3 months	0 (0)	0 (0)	3 (100)	4.78 (0.78)
6 months	0 (0)	1 (25)	3 (75)	
1 year	4 (15)	3 (11)	19 (73)	
Indefinitely	22 (16)	21 (16)	91 (68)	
Infliximab use upon loss of response				
decrease interval	25 (17)	22 (15)	97 (67)	9.95 (0.13)
increase dose	2 (8)	3 (12)	20 (80)	
stop Infliximab	0 (0)	1 (100)	0 (0)	

* In cells where n < 5, Fisher's exact testing was performed. Pearson's chi squared reported where results of Pearson's and Fisher's exact testing the same.

Table 5e. Influence of physician age on patterns of Infliximab Use

	Age Group 1 N (%)	Age Group 2 N (%)	Age Group 3 N (%)	Pearson Chi^2 (p-value)
Steroid pre-medication				
Yes	97 (44)	96 (44)	26 (12)	4.28 (0.12)
No	25 (35)	32 (44)	15 (21)	
Infliximab dose				
5 mg/ kg	118 (42)	122 (43)	41 (15)	11.86 (0.07)
7.5 mg/ kg	0 (0)	3 (100)	0 (0)	
10 mg / kg	0 (0)	3 (100)	0 (0)	
Induction therapy				
Single dose	6 (33)	10 (56)	2 (11)	7.86 (0.25)
0 and 4 weeks	1 (12)	5 (62)	2 (25)	
0, 2 and 6 weeks	109 (42)	112 (44)	36 (14)	
Maintenance therapy				
6 week interval	2 (40)	3 (60)	0 (0)	7.20 (0.71)
8 week interval	110 (42)	114 (44)	36 (14)	
10 week interval	0 (0)	1 (50)	1 (50)	
12 week interval	0 (0)	1 (50)	1 (50)	
On demand	6 (40)	7 (47)	2 (13)	
Immunosuppressant co-administration				
Yes	90 (39)	106 (46)	36 (16)	5.20 (0.27)
No	25 (53)	18 (38)	4 (9)	
Infliximab duration				
3 months	2 (67)	1 (33)	0 (0)	7.36 (0.69)
6 months	1 (25)	3 (75)	0 (0)	
1 year	16 (44)	13 (36)	7 (19)	
Indefinitely	89 (40)	102 (46)	32 (14)	
Infliximab use upon loss of response				
decrease interval	94 (42)	98 (44)	30 (13)	5.88 (0.44)
increase dose	17 (33)	25 (49)	9 (18)	
stop Infliximab	2 (100)	0 (0)	0 (0)	

Age group 1 = < 45 years, 2= 45-59 years and 3= > 60 years

* In cells where n < 5, Fisher's exact testing was performed. Pearson's chi squared reported where results of Pearson's and Fisher's exact testing the same.

Table 5f. Influence of region on patterns of Infliximab Use

	Western N (%)	Ontario N (%)	Quebec N (%)	Atlantic N (%)	Pearson Chi^2 (p-value)
Steroid pre-medication					
Yes	72 (33)	87 (40)	38 (17)	21 (10)	6.94 (0.07)
No	20 (28)	24 (33)	23 (32)	5 (7)	
Infliximab dose					
5 mg/ kg	90 (32)	105 (38)	59 (21)	26 (9)	7.35 (0.60)
7.5 mg/ kg	1 (33)	2 (67)	0 (0)	0 (0)	
10 mg / kg	1 (33)	2 (67)	0 (0)	0 (0)	
Induction therapy					
Single dose	15 (83)	1 (6)	1 (6)	1 (6)	**37.85 (<0.001)**
0 and 4 weeks	5 (63)	2 (25)	1 (13)	0 (0)	
0, 2 and 6 weeks	66 (26)	106 (41)	59 (23)	25 (10)	
Maintenance therapy					
6 week interval	2 (40)	2 (40)	1 (20)	0 (0)	11.52 (0.72)
8 week interval	80 (31)	98 (38)	58 (22)	23 (9)	
10 week interval	1 (50)	1 (50)	0 (0)	0 (0)	
12 week interval	0 (0)	2 (100)	0 (0)	0 (0)	
On demand	7 (47)	4 (27)	1 (7)	3 (20)	
Immunosuppressant co-administration					
Yes	76 (33)	91 (39)	41 (18)	23 (10)	10.80 (0.10)
No	14 (30)	17 (36)	14 (30)	2 (4)	
Infliximab duration					
3 months	0 (0)	2 (67)	1 (33)	0 (0)	17.67 (0.28)
6 months	1 (25)	0 (0)	1 (25)	2 (50)	
1 year	13 (36)	11 (31)	11 (31)	1 (3)	
Indefinitely	70 (32)	89 (40)	43 (19)	20 (9)	
Infliximab use upon loss of response					
decrease interval	61 (28)	89 (40)	49 (22)	22 (10)	12.90 (0.17)
increase dose	20 (39)	17 (33)	11 (22)	3 (6)	
stop Infliximab	2 (100)	0 (0)	0 (0)	0 (0)	

* In cells where n < 5, Fisher's exact testing was performed. Pearson's chi squared reported where results of Pearson's and Fisher's exact testing the same.

Table 6a. Influence of CME participation on patterns of Infliximab Use

	Small Groups N=290	**Peer Consultation N=217**	**Large Groups N=215**	**Texts/ Journals N=260**	**Seminars N=198**	**Apprenticeship N=27**
Steroid pre-medication						
Yes	0.76	0.74	0.75	0.76	0.75	**0.59**
No	0.24	0.26	0.25	0.24	0.25	**0.41**
Infliximab dose						
5 mg/ kg	0.97	0.97	0.97	0.97	0.98	**1**
7.5 mg/ kg	0.012	0.009	0.01	0.01	0.005	-
10 *mg / kg*	0.012	0.009	0.01	0.008	0.005	-
Induction therapy						
Single dose	0.06	0.06	0.06	0.07	0.07	0.04
0 and 4 weeks	0.03	0.03	0.03	0.02	0.02	-
0, 2 and 6 weeks	0.88	0.88	0.88	0.88	0.89	0.93
Maintenance therapy						
6 week interval	0.01	0.02	0.015	0.02	0.01	-
8 week interval	0.90	0.88	0.89	0.89	0.90	0.93
10 week interval	0.01	0.009	0.007	0.008	0.01	0.04
12 week interval	0.01	0.009	0.007	0.008	0.005	-
On demand	0.04	0.05	0.05	0.05	0.05	0.04
Immunosuppressant co-administration						
Yes	0.78	0.79	0.78	0.78	0.80	**0.63**
No	0.18	0.16	0.17	0.17	0.15	**0.22**
Infliximab duration						
3 months	0.01	0.009	0.01	0.01	0.01	-
6 months	0.02	0.02	0.02	0.02	0.015	-
1 year	0.15	0.12	0.12	0.13	0.14	0.15
Indefinitely	0.75	0.76	0.76	0.76	0.76	**0.81**
Infliximab use upon loss of response						
decrease interval	0.75	0.76	0.75	0.75	0.74	0.67
increase dose	0.18	0.18	0.18	0.18	0.20	0.15
stop Infliximab	0.005	0.009	0.01	0.007	0.01	0.04

Table 6b. Influence of Apprenticeship (CME) on Infliximab Practice Patterns

	N	Proportion	Standard Error	95 % CI	*X^2 (p-value)
Steroid pre-medication					
Yes	16	0.59	0.096	0.394 to 0.790	**6.10**
No	11	0.41	0.096	0.209 to 0.605	**(0.047)**
Infliximab dose					
5 mg/ kg	27	100	-	-	2.32
7.5 mg/ kg	0	0	-	-	(0.889)
10 mg / kg	0	0	-	-	
Induction therapy					
Single dose	1	0.037	0.037	-0.039 to 0.113	9.90
0 and 4 weeks	0	0	-	-	(0.129)
0, 2 and 6 weeks	25	0.93	0.051	0.820 to 1.03	
Maintenance therapy					
6 week interval	0	0	-	-	
8 week interval	25	0.93	0.051	0.820 to 1.03	13.26
10 week interval	1	0.04	0.037	-0.039 to 0.113	(0.21)
12 week interval	0	0	-	-	
On demand	1	0.04	0.037	-0.039 to 0.113	
Immunosuppressant co-administration					
Yes	17	0.63	0.094	0.435 to 0.824	**10.12**
No	6	0.22	0.082	0.055 to 0.390	**(0.038)**
Infliximab duration					
3 months	0	0	-	-	4.07
6 months	0	0	-	-	(0.944)
1 year	4	0.15	0.070	0.005 to 0.291	
Indefinitely	22	0.81	0.076	0.658 to 0.971	
Infliximab use upon loss of response					
decrease interval	18	0.67	0.069	0.476 to 0.857	10.02
increase dose	4	0.15	0.092	0.005 to 0.291	(0.124)
stop Infliximab	1	0.04	0.069	-0.039 to 0.113	

***Test of proportion by CME participation across "often", "rarely" and "never"**

****** In cells where n < 5, Fisher's exact testing was performed. Pearson's chi squared reported where results of Pearson's and Fisher's exact testing the same.

Table 7a. Barriers to Infliximab Use

	N	Proportion (%)	Standard Error	Binomial Wald 95% Confidence Interval
Drug Cost	150	52	0.03	0.46 to 0.57
Insurance	264	90	0.02	0.87 to 0.94
Time	80	27	0.03	0.22 to 0.33
Provincial Criteria	206	71	0.03	0.65 to 0.75
Absence Infusion Facility	167	57	0.03	0.52 to 0.63
Lack of Trained Personnel	173	59	0.03	0.54 to 0.65

Table 7b. Influence of region on perceived barriers to Infliximab use

	Western N (%)	**Ontario N (%)**	**Quebec N (%)**	**Atlantic N (%)**	**Pearson's Chi^2 (p-value)**
Drug Cost					
Important	47 (31)	60 (40)	31 (21)	12 (8)	4.36 (0.60)
Unimportant	28 (31)	37 (41)	19 (21)	7 (7)	
Insurance					
Important	89 (34)	101 (38)	47 (18)	26 (10)	**19.69 (0.003)**
Unimportant	1 (6)	7 (44)	8 (50)	0 (0)	
Time					
Important	29 (36)	36 (45)	8 (10)	7 (9)	**13.97 (0.03)**
Unimportant	37 (27)	48 (35)	41 (30)	13 (9)	
Provincial Criteria					
Important	75 (36)	70 (34)	47 (23)	14 (7)	**14.47 (0.03)**
Unimportant	8 (17)	25 (54)	6 (13)	7 (15)	
Absence Infusion Facility					
Important	49 (29)	74 (44)	37 (22)	7 (4)	**19.50 (0.003)**
Unimportant	26 (33)	28 (36)	13 (17)	11 (14)	
Lack of Trained Personnel					
Important	49 (28)	74 (43)	40 (23)	10 (6)	**12.50 (0.05)**
Unimportant	25 (34)	27 (37)	12 (16)	9 (12)	

* In cells where $n < 5$, Fisher's exact testing was performed. Pearson's chi squared reported where results of Pearson's and Fisher's exact testing the same.

Table 8. The effect of disease activity on clinician risk perception

Risk of Infliximab Outweighs benefit	Agree	Disagree	Standard error agree/disagree	Binomial Wald 95% Confidence Interval agree/disagree
Mild disease				
Minor infection	0.15	0.71	0.021 / 0.027	0.11 to 0.19 / 0.65 to 0.76
Serious infection	0.39	0.45	0.029 / 0.029	0.33 to 0.45 / 0.39 to 0.50
Lymphoma	0.30	0.50	0.027 / 0.029	0.25 to 0.36 / 0.44 to 0.55
Allergic reactions	0.23	0.62	0.025 / 0.029	0.18 to 0.28 / 0.56 to 0.67
Moderate disease				
Minor infection	0.08	0.89	0.016 / 0.018	0.05 to 0.11 / 0.85 to 0.93
Serious infection	0.08	0.89	0.016 / 0.018	0.05 to 0.11 / 0.85 to 0.93
Lymphoma	0.10	0.84	0.017 / 0.021	0.06 to 0.13 / 0.80 to 0.88
Allergic reactions	0.09	0.87	0.016 / 0.020	0.05 to 0.11 / 0.83 to 0.91
Severe disease				
Minor infection	0.08	0.89	0.016 / 0.018	0.05 to 0.11 / 0.86 to 0.93
Serious infection	0.10	0.86	0.017 / 0.020	0.06 to 0.13 / 0.82 to 0.90
Lymphoma	0.08	0.86	0.016 / 0.020	0.05 to 0.11 / 0.86 to 0.02
Allergic reactions	0.08	0.88	0.016 / 0.019	0.05 to 0.11 / 0.85 to 0.92

Table 9. Influence of patient-related factors on the decision to initiate Infliximab therapy.

	Important N (%)	Unimportant N (%)	Binomial Wald 95% Confidence Interval
Age			
Older age	100 (34)	87 (30)	0.29 to 0.40 / 0.24 to 0.35
Younger	146 (50)	74 (25)	0.44 to 0.56 / 0.20 to 0.30
Gender			
Male	16 (5)	161 (55)	0.03 to 0.08 / 0.49 to 0.61
Female	33 (11)	144 (49)	0.08 to 0.15 / 0.43 to 0.55

APPENDIX EIGHT

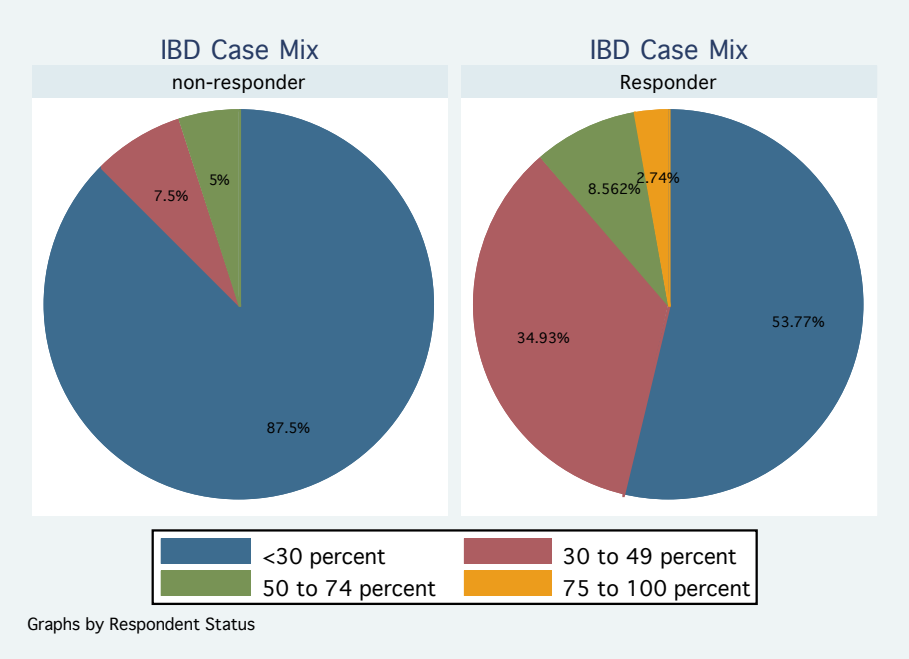

Figure 1. Clinical practice comprised of IBD amongst responders and non-responders.

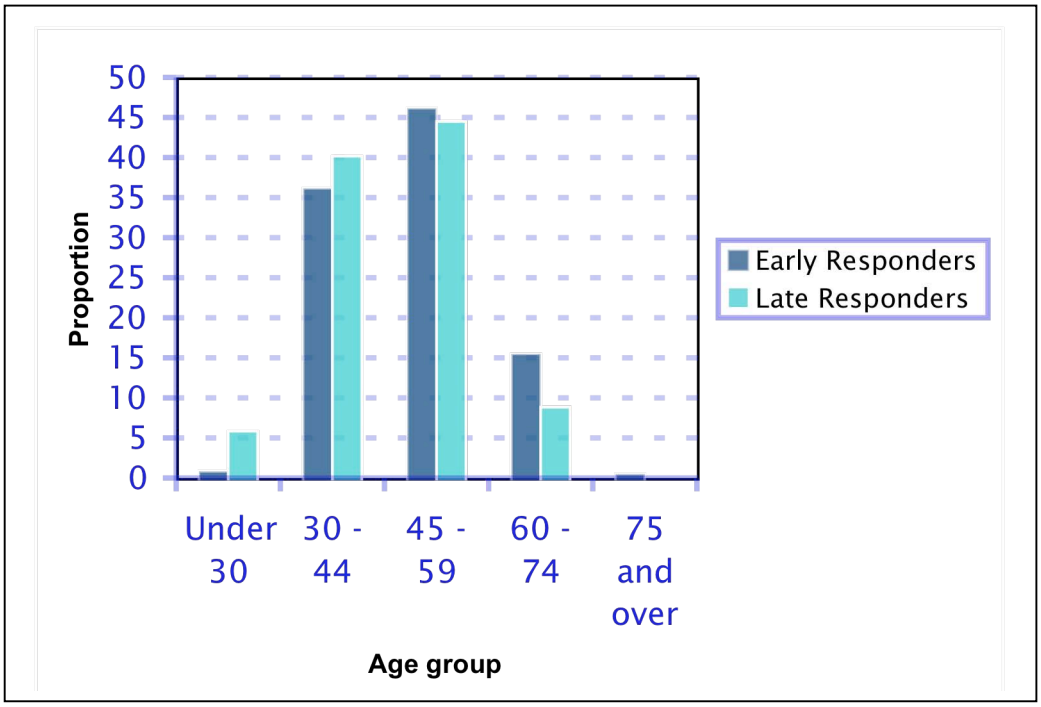

Figure 2. The distribution of age amongst early versus late responders

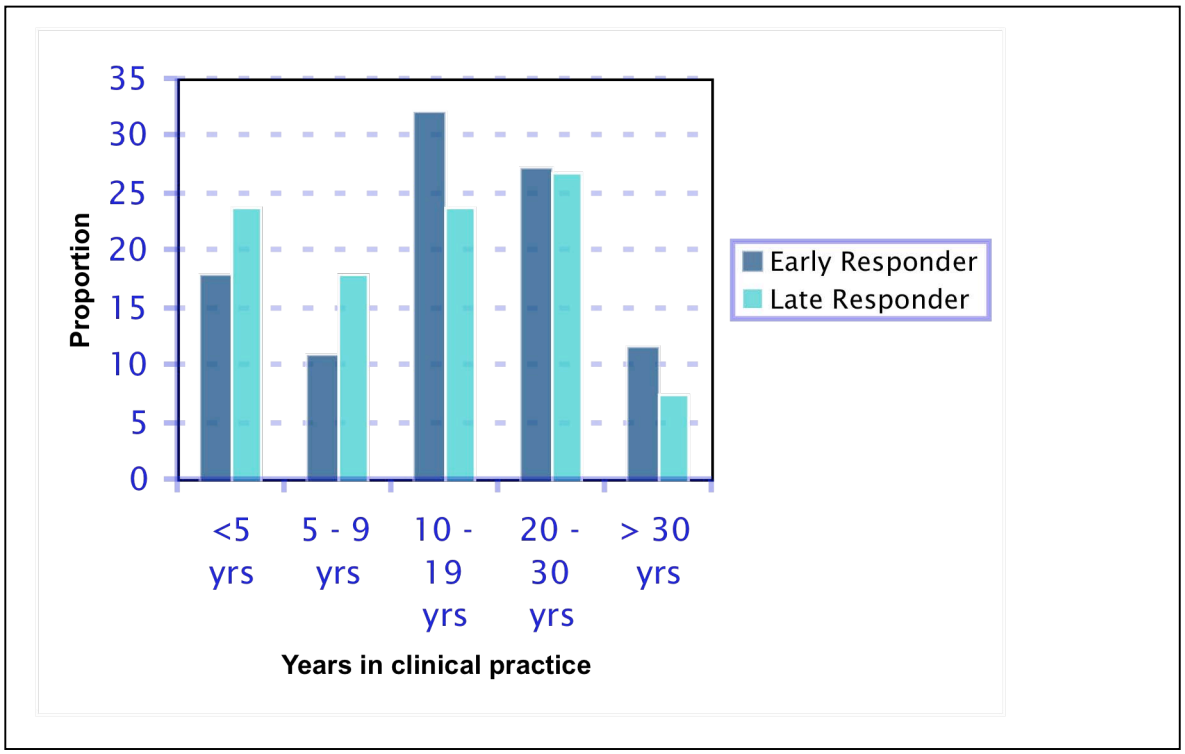

Figure 3. Distribution of years in clinical practice amongst early and late responders.

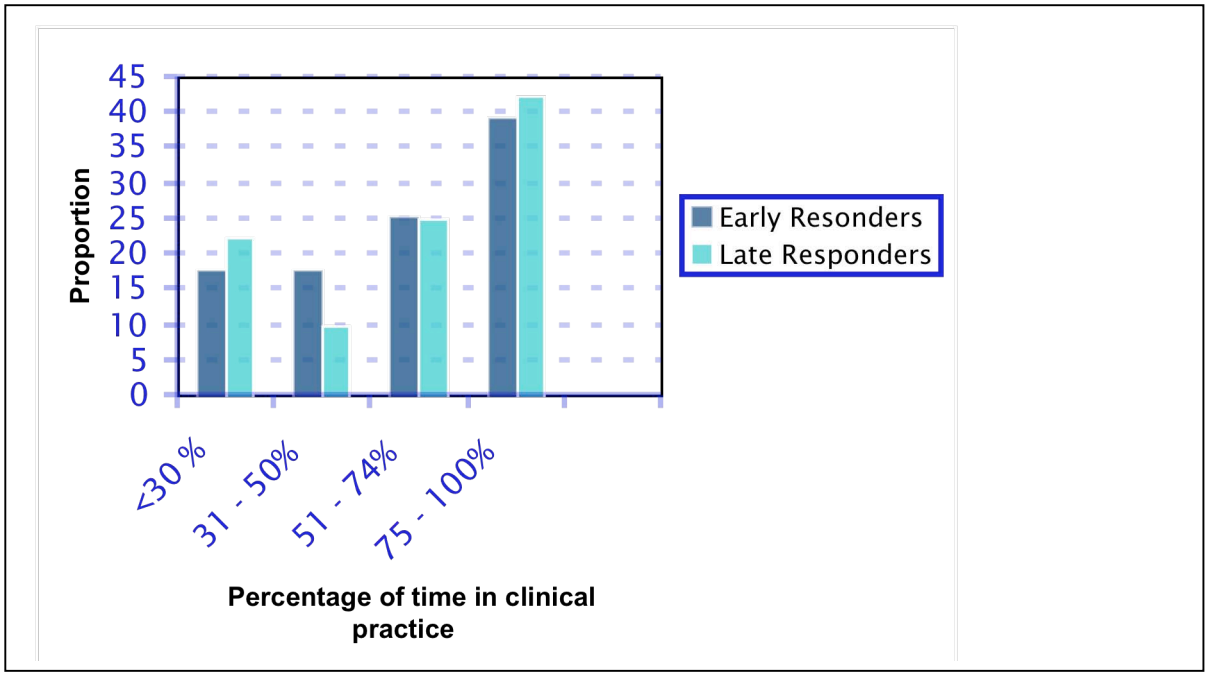

Figure 4. Distribution of proportion of practice that is clinical amongst early and late responders.

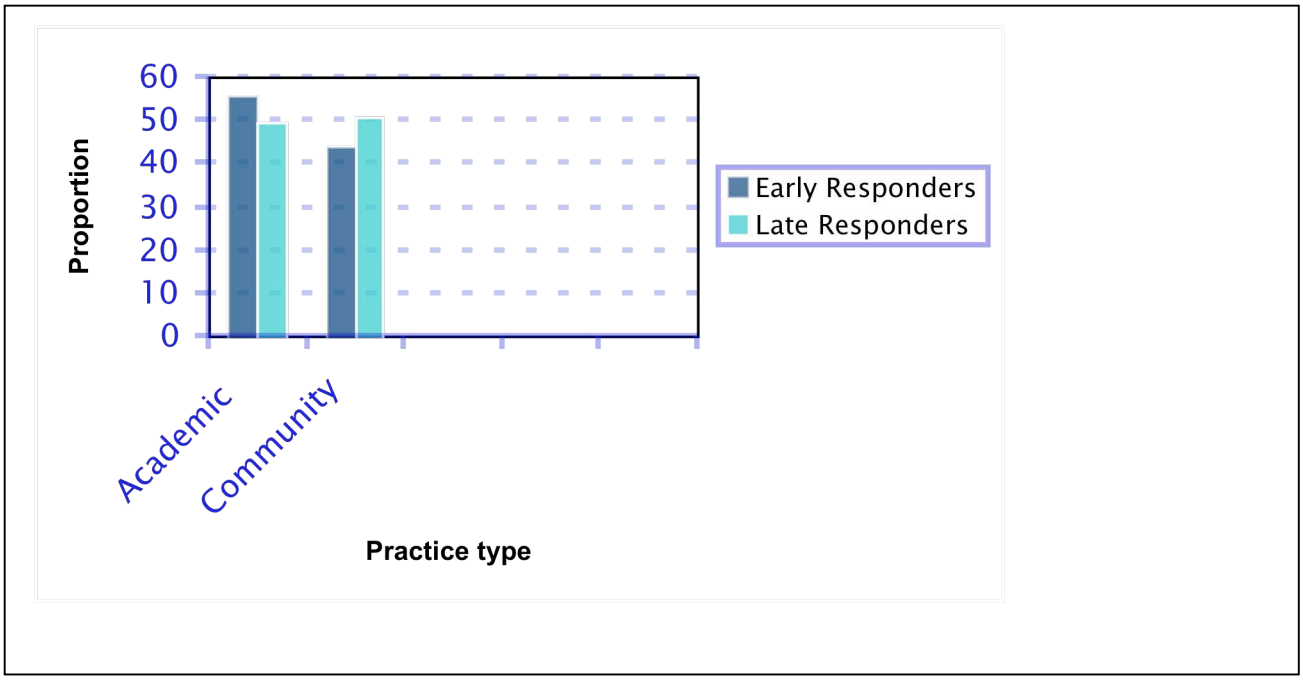

Figure 5. Distribution of practice type amongst early and late responders

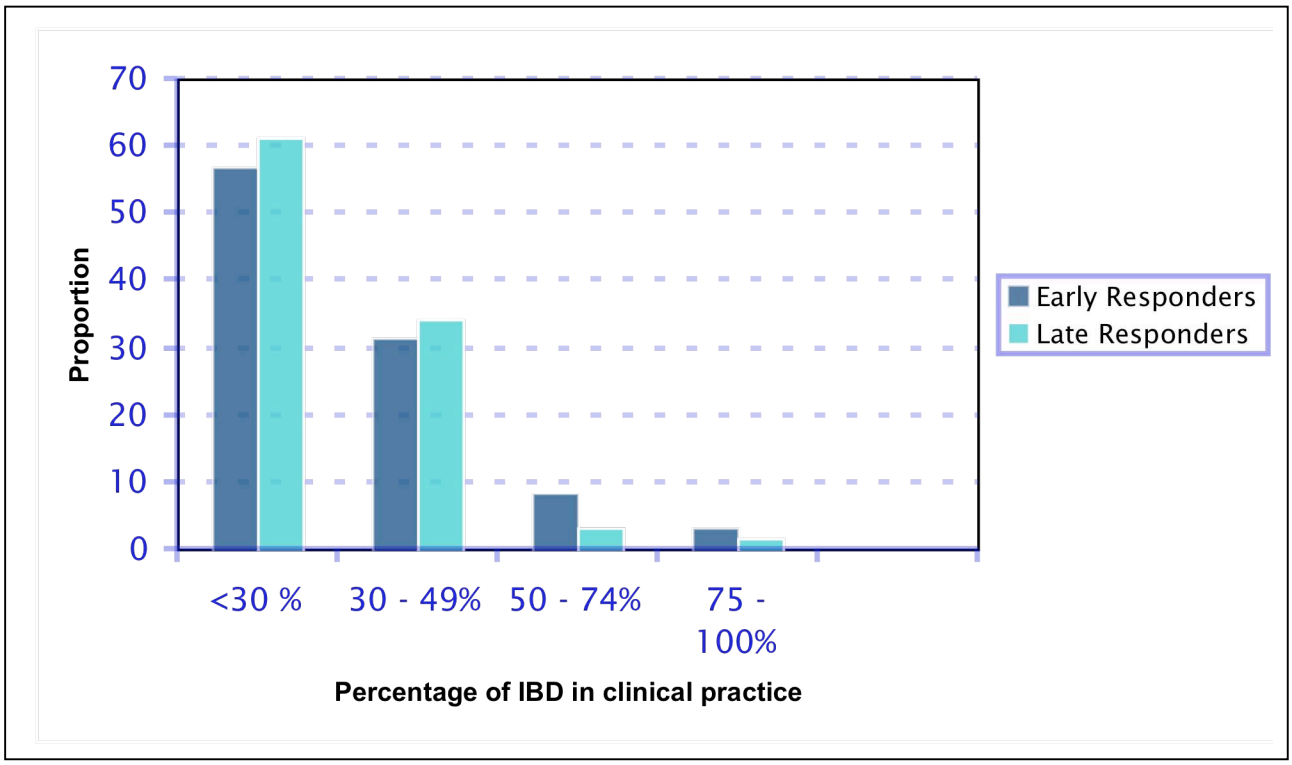

Figure 6. Distribution of proportion of IBD in clinical practice amongst early and late responders.

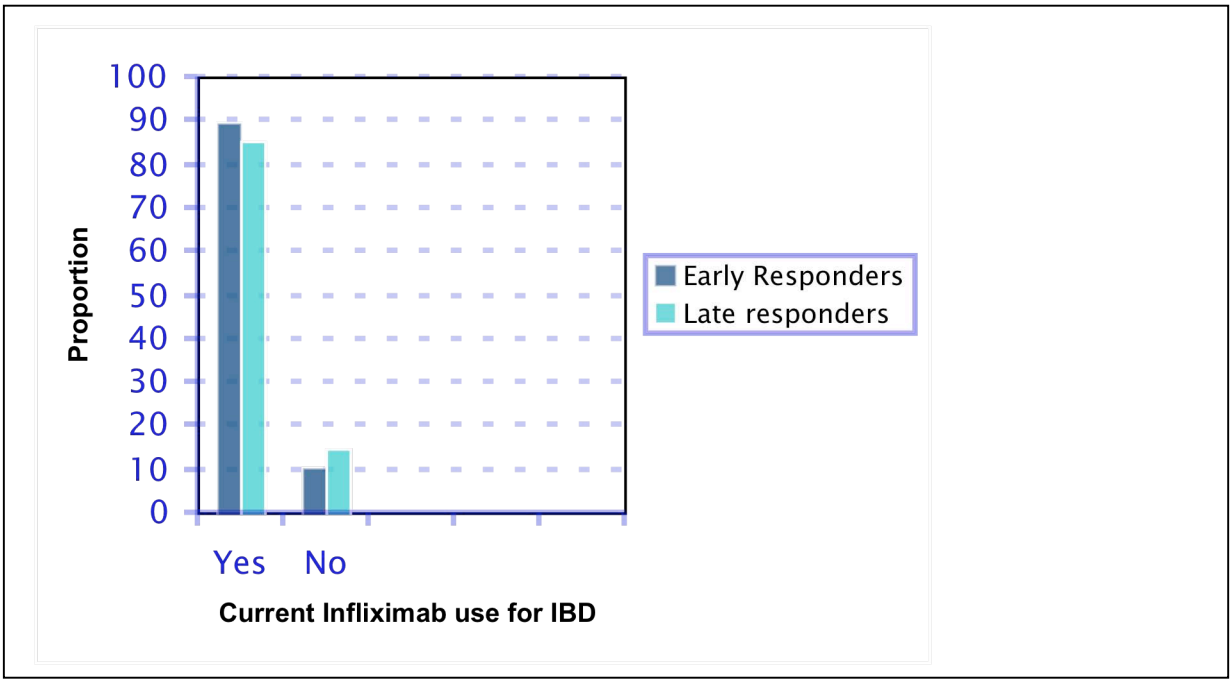

Figure 7. Distribution of current Infliximab use amongst early and late responders.

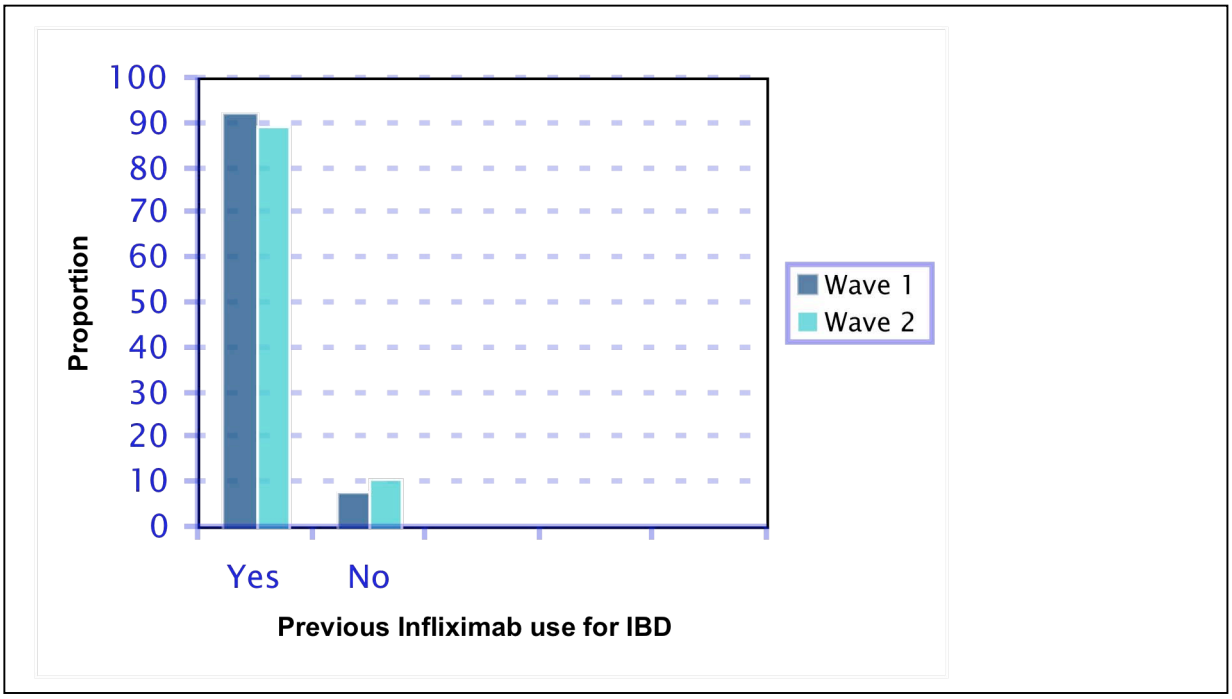

Figure 8. Distribution of previous Infliximab use amongst early and late responders.

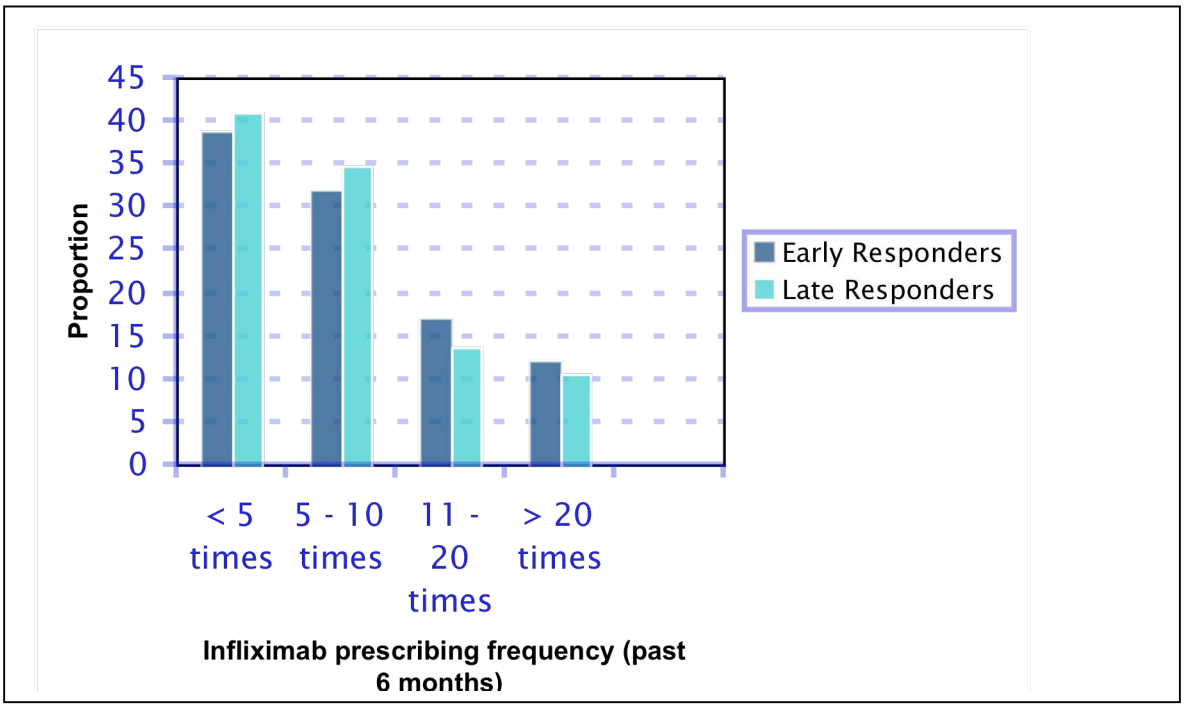

Figure 9. Distribution of Infliximab prescribing frequency amongst early and late responders.

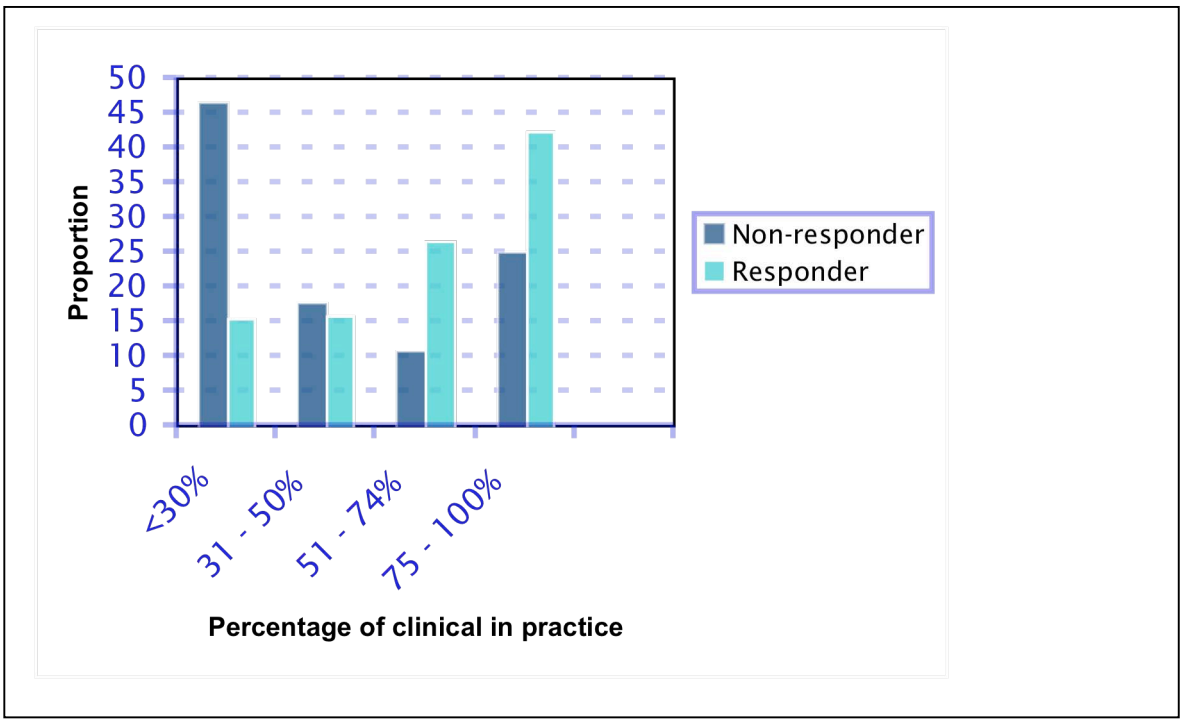

Figure 10. Distribution of proportion of practice that is clinical amongst responders and those who chose to return a non-response form.

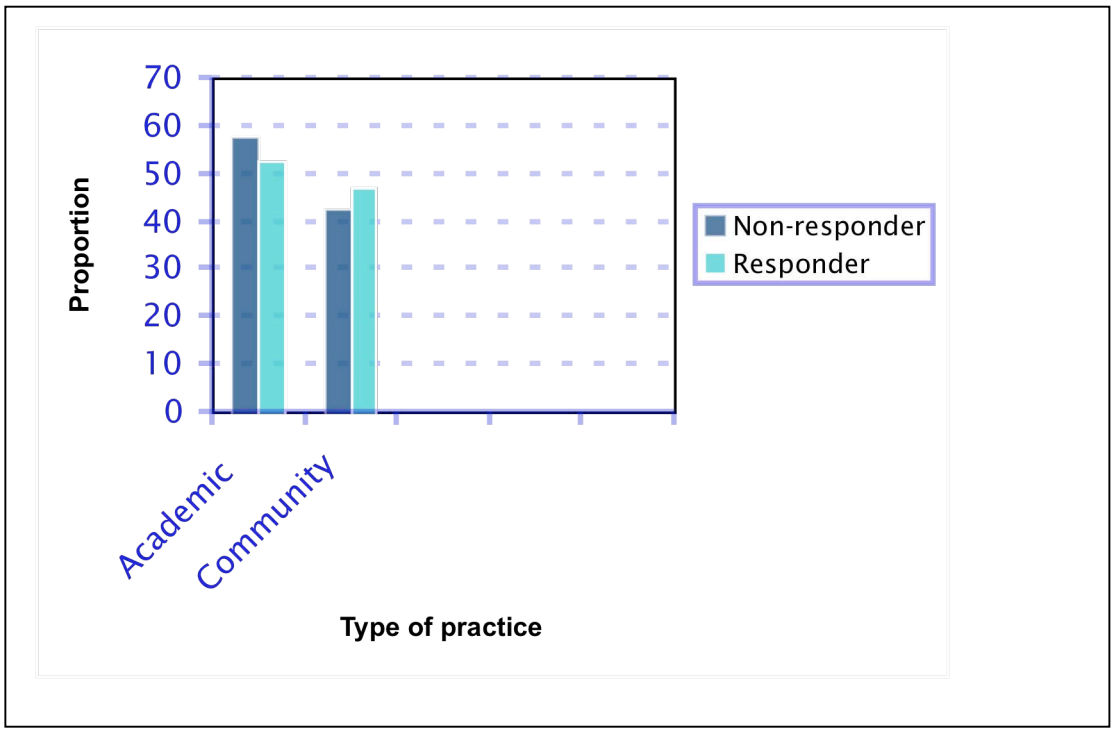

Figure 11. Distribution of practice type amongst responders and those who chose to return a non-responder form.

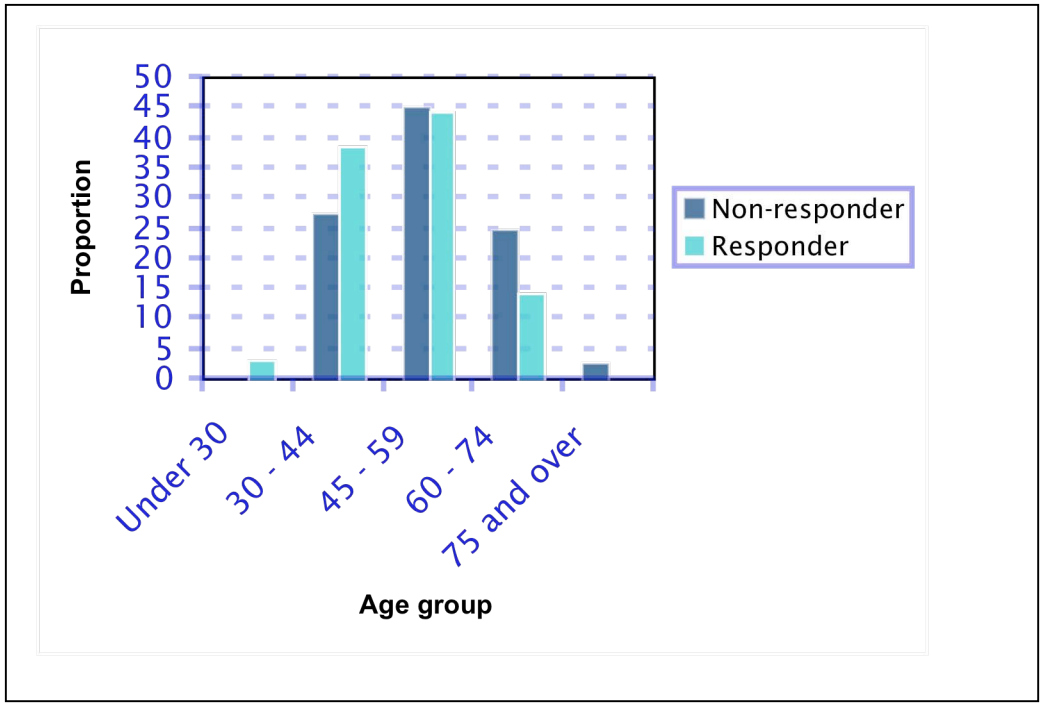

Figure 12. The distribution of age amongst responders and non-responders who chose to return a non-response form.

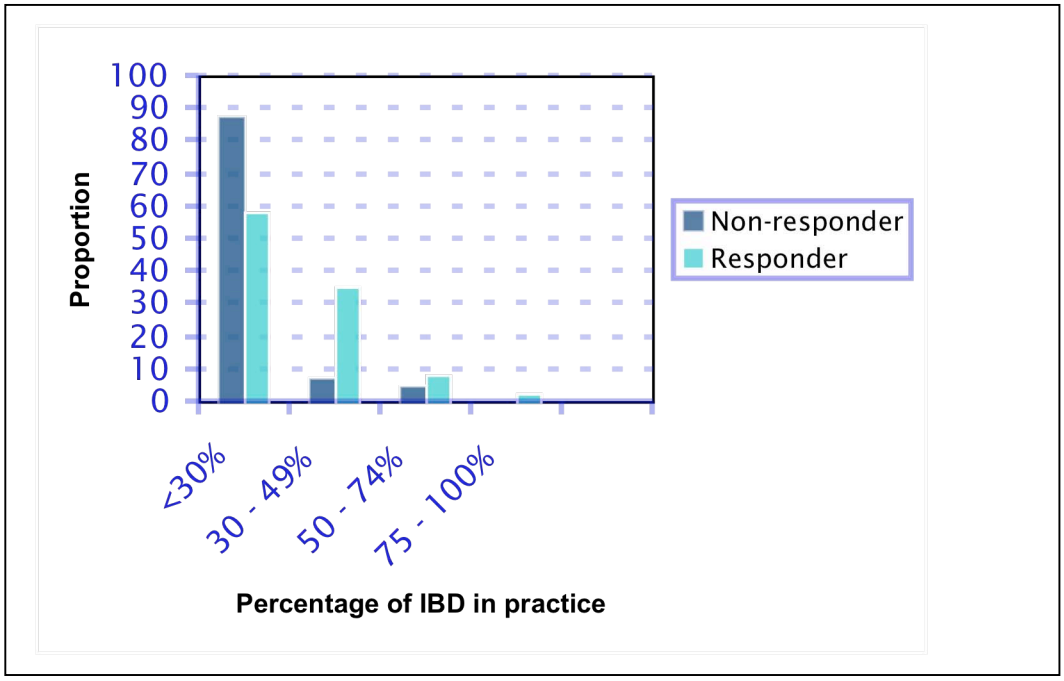

Figure 13. Distribution of proportion of IBD in clinical practice amongst responders and those who chose to return a non-responder form.

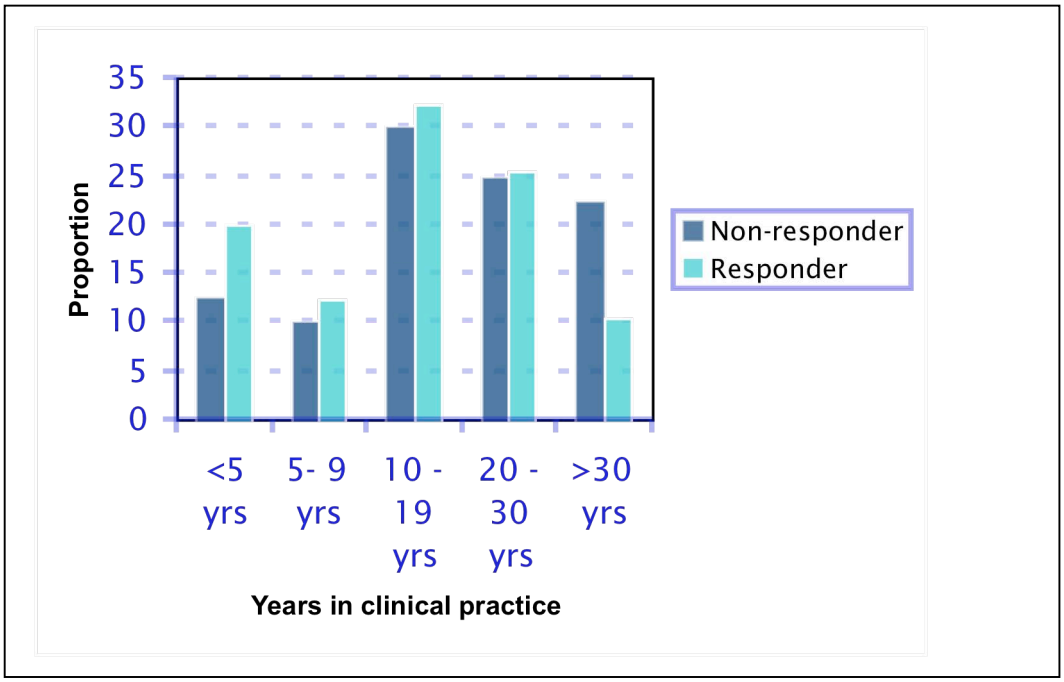

Figure 14. Distribution of years in clinical practice amongst responders and those who chose to return a non-response form.

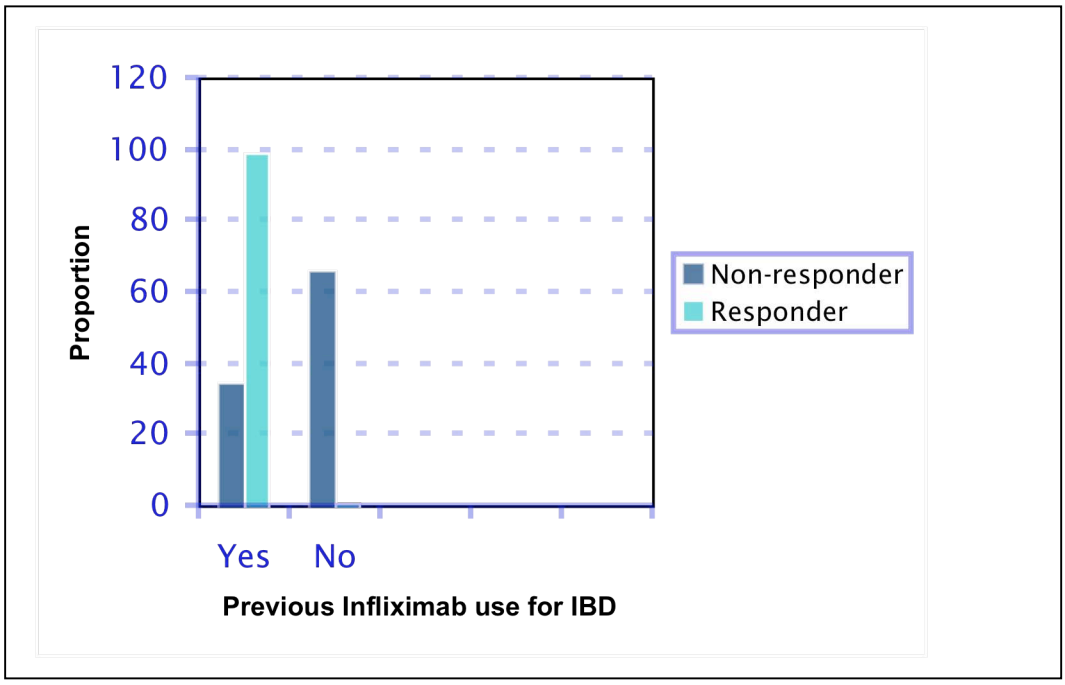

Figure 15. Distribution of previous Infliximab use amongst responders and those who chose to return a non-response form.

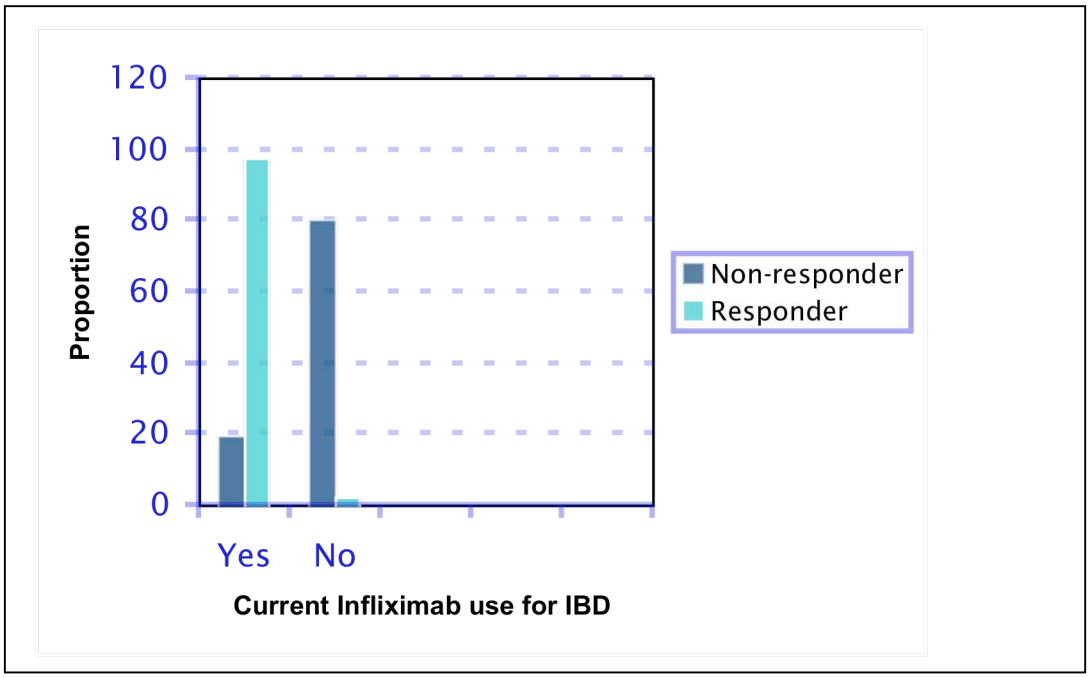

Figure 16. Distribution of current Infliximab use amongst responders and those who chose to return a non-responder form.

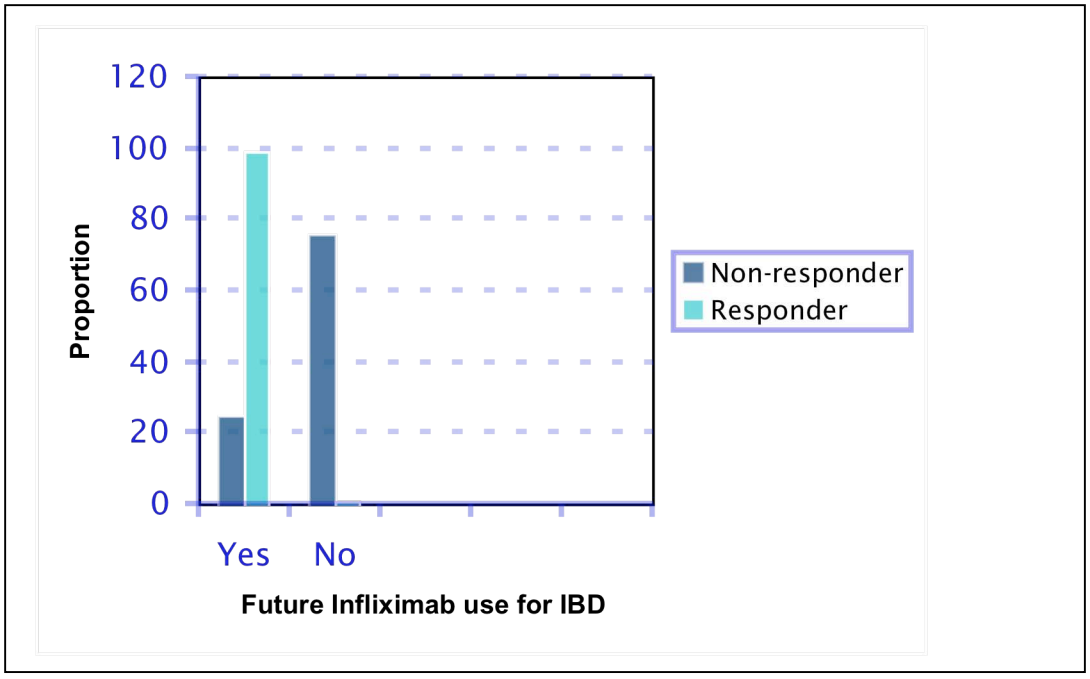

Figure 17. Distribution of future Infliximab use amongst responders and those who chose to return a non-response form.

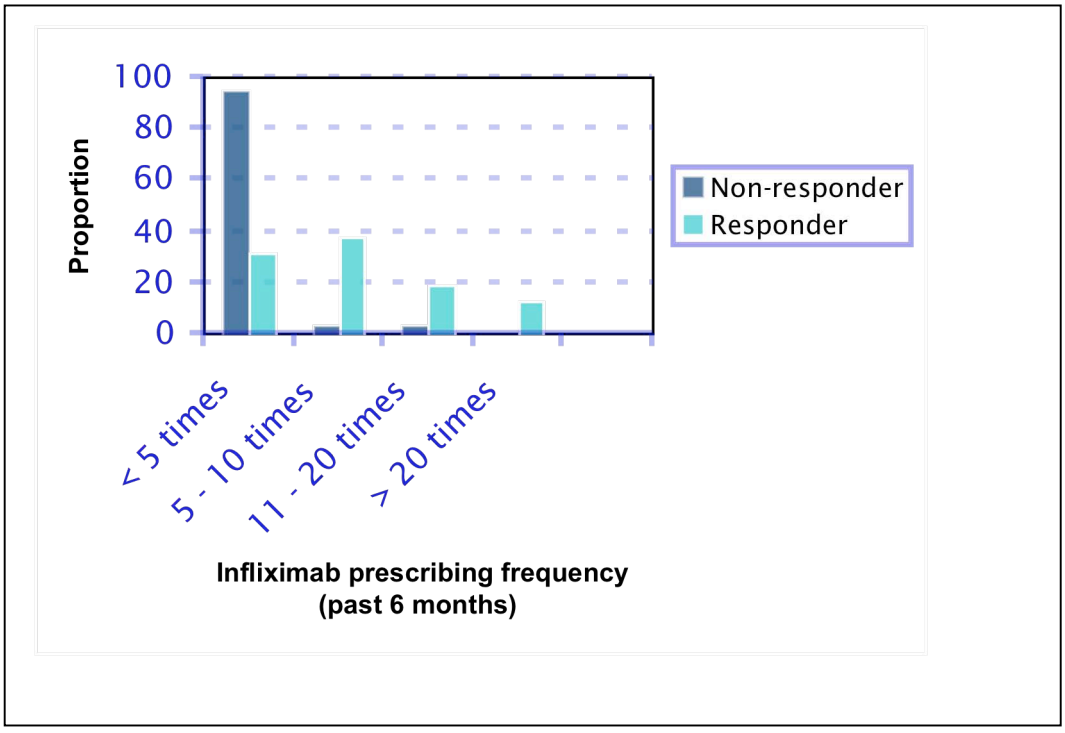

Figure 18. Distribution of Infliximab prescribing frequency amongst responders and those who chose to return a non-responder form.

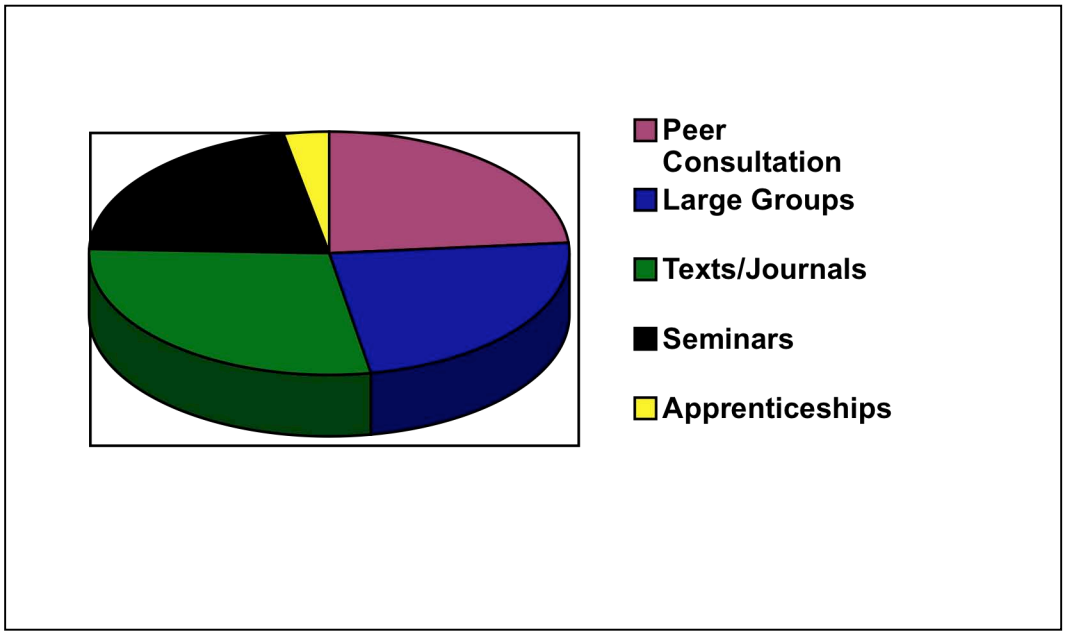

Figure 19. Participation in CME activities amongst survey responders.

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