LONGITUDINAL OUTCOMES OF GASTROINTESTINAL SYMPTOMS IN CANADA (LOGIC): KEY FACTORS FOR AN EFFECTIVE PATIENT RETENTION IN OBSERVATIONAL STUDIES

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ABSTRACT

Background
Longitudinal Outcomes of GastroIntestinal symptoms in Canada (LOGIC) is an ongoing study on irritable bowel syndrome (IBS) treatment patterns and health outcomes in routine Canadian clinical practice. Advancements in understanding IBS, a chronic multifaceted GI disorder, may be possible through methodical observational studies. The objective of this paper is to describe site recruitment techniques and extensive subject follow-up methodology used to facilitate a high return rate of questionnaires from this population-based study of subjects with IBS.

Methods
Invitation letters along with protocol synopses and preliminary site assessment questionnaires were faxed to potential sites across Canada. There were 1,556 subjects enrolled in this study from general practitioner sites (GP) and specialist sites (SP) in Canada. Subjects were compensated for the return of questionnaires reporting symptoms, quality of life, productivity, healthcare and resource utilization at baseline, Month 1, 3, 6, 9, and 12. Upon the return of questionnaires, subjects received thank you cards which included a reminder of the next questionnaire's due date. If subject questionnaires were not received within 2 weeks after the due date, the subjects received a reminder letter in the mail.

Results
The methodology in the LOGIC study allowed for a high patient questionnaire return rate (89%) through extensive subject reminders and follow-up. Subject participation throughout the study was not found to be linked to study site size or type (GP or SP).

Conclusion
Questionnaire based observational studies may benefit from focusing resources on increasing questionnaire return rates to effectively maintain data reliability and also reduce non-response bias.

Keywords: *IBS; recruitment; observational studies; patient retention; Canada*

Irritable bowel syndrome (IBS) is a chronic and episodic gastrointestinal (GI) and sensory disorder. Multiple symptoms are associated with IBS and they often significantly influence a patient's quality of life by affecting sleep, employment, intimacy, leisure, travel, diet and psychological wellbeing.[1] IBS symptoms include abdominal pain or discomfort, bloating and altered bowel habits that vary in frequency of recurrence and severity. The clinical patterns of such symptoms are often the basis of IBS diagnosis rather than unbiased physical findings, as there are no physical diagnostic objectives for IBS.[2] This disorder is not caused by structural problems in GI organs or organic disease; but, is rather a product of multiple biological and

psychosocial factors[3-5] and some findings suggest that IBS may be associated with a systemic neural disorder.[2]

Only a minority of people with irritable bowel syndrome request medical care[6]; however, it remains one of the most common disorders encountered in general medical practice, representing a leading cause of gastroenterology and primary care consultations.[7-10] In Canada, the prevalence of IBS is 12.1% (as diagnosed per Rome II criteria).[11] IBS symptom severity varies from patient to patient and while most symptoms are manageable by a general practitioner[12], nearly 25% of patients have more severe symptoms with significant lifestyle impairment requiring management by a specialist in gastroenterology.[12] Additionally, 5% of patients have such severe and incapacitating symptoms that they require referral to a center with multi-specialty capability.[12]

In addition to individual patient discomfort, the costs related to IBS are substantial. In Canada, the total direct costs related to IBS for 1999 were estimated to be over $300 million with $1 billion in wages lost.[2] In the United States, the total costs associated with the functional bowel disorder include $10 billion in direct medical costs and $20 billion in indirect costs, such as absenteeism and lost work productivity.[13,14]

IBS management may include pharmacological and non-pharmacological therapies with variable patient responses.[3] Unfortunately, IBS medications (laxatives, analgesics, antidepressants, smooth muscle relaxants, and antispasmodics) usually target only one of its multiple symptoms and often aggravate other symptoms leading to use of additional concomitant medications. Tegaserod (Zelnorm®, Novartis Pharmaceuticals, Canada) was approved in March 2002, and is the only single therapeutic approach to treat the multiple symptoms of IBS in Canada. Tegaserod has been shown to be effective for global symptom relief in clinical trials designed to treat the multiple symptoms of IBS with constipation.[12]

Longitudinal Outcomes of GastroIntestinal symptoms in Canada (LOGIC) is an ongoing prospective, observational, population-based, single cohort study designed to evaluate treatment patterns and health outcomes of subjects with GI symptoms in routine clinical practice in Canada. Population-based studies provide critical information for disorders like IBS but, the trend of fewer patients participating in and completing clinical trials could hinder the success of such studies.[15] Both direct recruitment strategies such as radio, television and newspaper advertising and indirect strategies such as intermediary contacts in clinics and hospitals are often employed to overcome patient recruitment challenges.[16] Fundamentally, all clinical trials need ample planning and well-executed methods for recruiting study sites and patients. Without the recruitment and continued participation of adequate numbers of qualified patients and sites, study objectives could not be met.

The methodology in the LOGIC study was an integral part of its potential success. Site and patient recruitment, retention, participation and in particular, the return of patient questionnaires were successful. This overall success is an indication of solid recruitment methods, patient retention strategies and data collection systems that may be practical in future observational studies. The objective of this paper is to describe site recruitment techniques and extensive subject follow-up methodology used to facilitate a high return rate of questionnaires from this population-based study of subjects with IBS.

METHODS

The LOGIC study aimed to recruit 200 general practitioner and specialist sites and 2,000 subjects from 5 provinces across Canada chosen based on market size and accessibility to provincial databases. Subjects who signed an informed consent and met the inclusion criteria were to be followed for one year from the time of enrolment and those who discontinued prematurely were not to be replaced. Approval was received from the IRB Services (www.irbservices.com) in Canada to conduct this study.

Site Recruitment

Invitation letters along with protocol synopses and preliminary site assessment questionnaires were faxed to potential sites across Canada. Sites were asked to complete the preliminary site assessment questionnaire and fax it back to the coordinating center. If after one week a site had not responded, a follow-up phone call was made to remind them to fax back the preliminary questionnaire. Based

on the preliminary questionnaire answers, potential sites were rated on commitment, availability of sufficient expertise, adequate resources to recruit subjects, experience with clinical research and Internet access. Selected sites were subsequently administered site assessment questionnaires by telephone interview to further assess their participation suitability. Sites that failed any stage of the selection process were informed by mail while those who were successful in all stages received a confirmation letter and the study protocol. A flow scheme of the site recruitment process is shown in Figure 1.

Patient Enrolment

At the selected sites, subjects were enrolled into the study after the investigator or study coordinator explained the study to the subject and they provided written informed consent. They were required to be 18 years of age or older with symptoms of abdominal pain/discomfort (associated with altered bowel habits) and one or more of the following symptoms: bloating, constipation, or alternating between constipation and diarrhoea. The subjects should have had these symptoms for at least 3 months or more, not necessarily consecutively, during the preceding 12 months. The study included patients being treated with a variety of therapies for abdominal pain and discomfort, including Tegaserod.

Data Capture

Data capture consisted of both electronically documented data and paper-based questionnaires. Physicians used web-based electronic forms to report clinical data at baseline, end of study and at unscheduled visits. Enrolled subjects submitted paper-based questionnaires at specified time periods by mail. An overview of the data collection and reminder timeline is shown in Figure 2.

Physicians – Electronic Data Capture (EDC)

Electronic forms were designed to capture the physician-reported clinical data. The electronic forms were accessible on a secure, password-protected study website to enable data entry and online reporting. All participating physicians received a password for the study website and received one-on-one interactive web-based training. Initial, baseline clinical data were collected from physicians at the time of the subject's enrolment. There were no scheduled follow-up visits with physicians except at the end of the study (Month 12), or earlier, if the subject discontinued prior to completing the study. However, if the subject saw the physician at any time during the study period the physician was required to document the reason for the unscheduled visit as well as the current treatment for the symptoms and any adverse events in the electronic clinical report forms (eCRFs). All electronic forms contained built-in automatic data edit checks to reduce omissions and errors at the point of entry. Entered data was reviewed, validated, and incorporated in real time into the central database, upon which, queries were generated if inconsistencies were detected during review.

FIG. 1 Flow of Site Recruitment

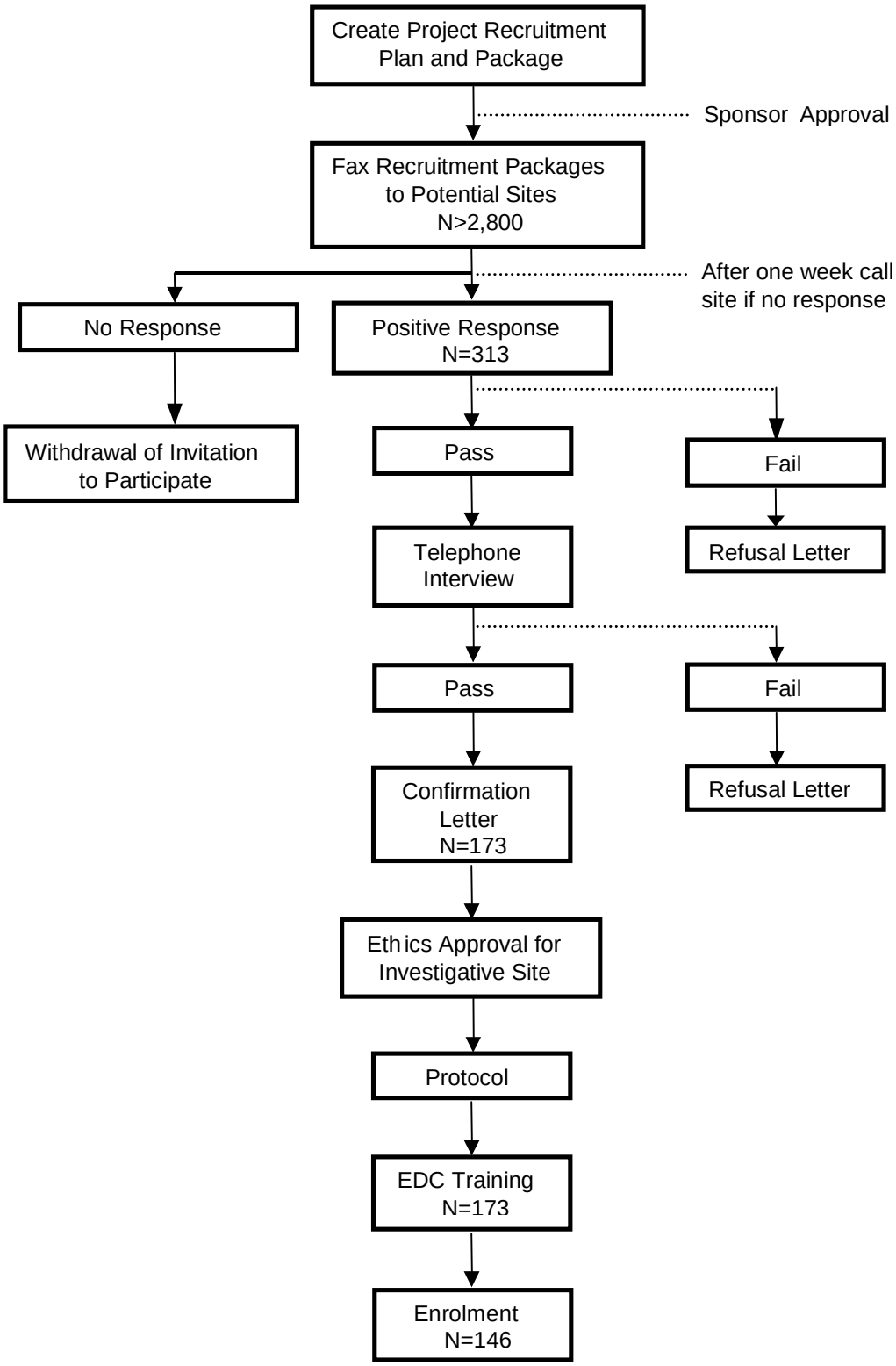
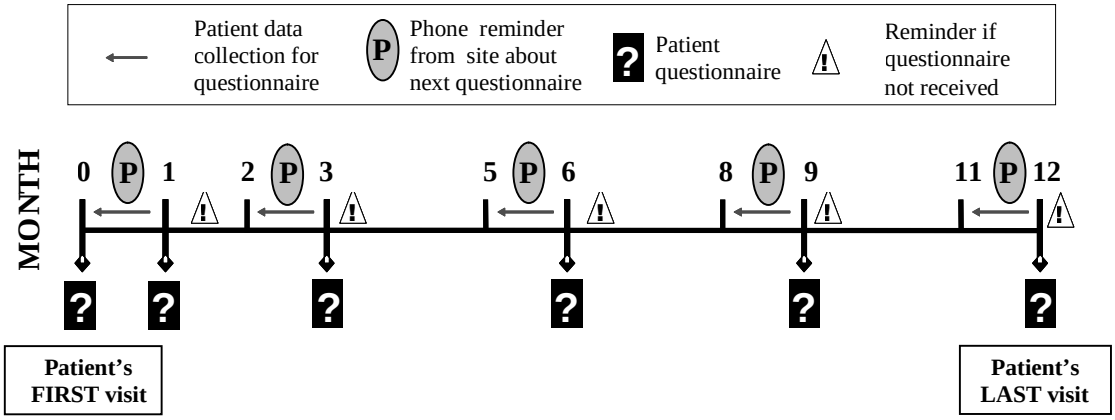


FIG. 2 Data Collection



Subjects – Paper-based Forms

At enrolment, subjects received paper-based forms to report their symptoms, quality of life, productivity, and healthcare resource utilization. The following questionnaires were used for assessment: IBS Subject Symptoms ('Symptoms')[17], Healthcare Resource Utilization ('Healthcare'), Work Productivity and Activity Impairment Questionnaire, Digestive Health ('WPAI')[18], IBS Quality of Life Questionnaire ('IBS-QOL')[19] and EQ-5D Questionnaire ('EQ-5D').[20] Table 1 illustrates the questionnaires that were included in the patient booklets for each scheduled reporting period. Site personnel also gave subjects reporting instructions and business reply envelopes. They were asked to report outcomes at Months 1, 3, 6, 9, and 12 and at any unscheduled visits. The physicians were required to contact the subject prior to the due date of each scheduled subject questionnaire. If subject questionnaires were not received within 2 weeks after the due date, the subjects received a reminder in the mail from the contract research organization (CRO) to submit the questionnaire. Because it was a pre-specified analysis end point, a second reminder letter was sent to subjects for their Month 6 questionnaire if this data was not received within a month of the due date. Reminder calls were also made by the CRO to the physicians to have them contact these patients again.

TABLE 1 List of Questionnaires

	Visit 1/ Baseline	Month 1	Month 3	Month 6	Month 9	Month 12
Questionnaire Type	Symptoms*					
	Healthcare*	Healthcare	Healthcare	Healthcare	Healthcare	Healthcare
	WPAI*	WPAI	WPAI	WPAI	WPAI	WPAI
	IBS-QOL*	IBS-QOL	IBS-QOL	IBS-QOL	IBS-QOL	IBS-QOL
	EQ-5D*	EQ-5D	EQ-5D	EQ-5D	EQ-5D	EQ-5D

*Symptoms = IBS Subject Symptoms; Healthcare = Healthcare Resource Utilization; WPAI = Work Productivity and Activity Impairment Questionnaire; IBS-QOL = IBS quality of Life Questionnaire; EQ-5D = EQ-5D Questionnaire

FIG. 3 Sample of Thank You Card Text

Jane Doe
Address

February 20, 2005

Dear Ms. Doe:

Thank you! Your **month 3** *(6 or 9)* **questionnaire** for the LOGIC Study arrived at Syreon this week. Please note that your **month 6** *(or 9 or 12)* **questionnaire** is due on May 15th, 2005.

We appreciate your cooperation in sending the questionnaires on time because it helps us further the research required to better understand the effect of your gastrointestinal symptoms on your life. Your commitment to this study is very important to its success.

Thank you again for your time and participation,
The LOGIC Study Team

Motivating Subjects

Subjects were compensated for the time they spent completing the questionnaires. They received $20 for each of the Month 1, 3, 6, 9, and 12 questionnaire booklets completed, paid by cheque at Months 6 and 12. Compensation was not withheld if questionnaires were missing some information. Subjects were also sent quarterly newsletters including updates on study site and subject recruitment and general information on the disease. Thank you cards were provided to subjects upon receipt of their questionnaires for Months 3, 6 and 9 which included a reminder for their next questionnaire due date (see Figure 3).

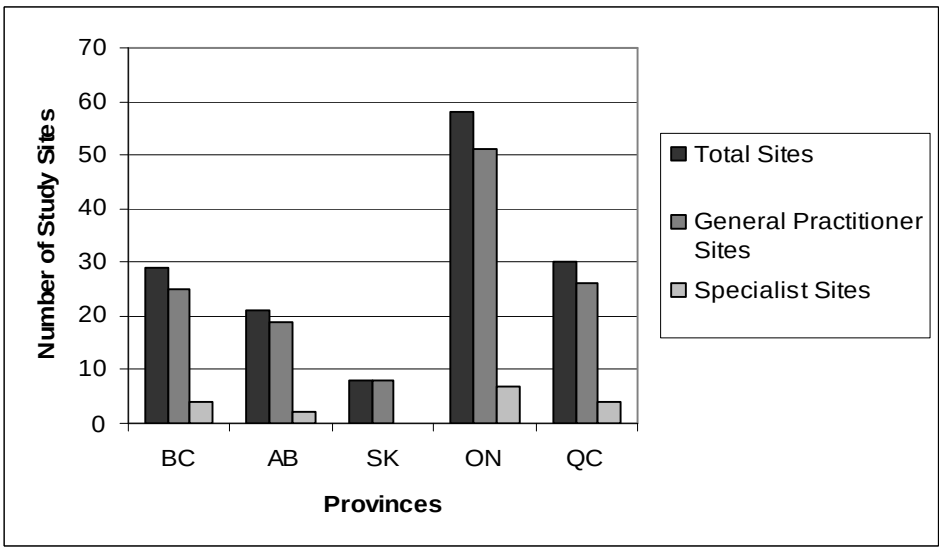
Motivating Physicians and Sites

Physicians were compensated for each subject they enrolled into the study. They received $200 for clinical data and subject questionnaires completed at baseline. They also received $50 at Months 1, 3, 6, 9 and 12 once subject questionnaires were completed and received. Compensation was not withheld if questionnaires were missing some information. Physicians were also sent the same quarterly newsletters sent to subjects.

RESULTS

Between March and September 2004, over 2,800 physicians were invited to participate in the LOGIC study. Invitees were selected by the sponsor and included physicians who prescribe Tegaserod. A total of 313 sites gave a positive response to the invitation to participate and were recruited (1 to 10 ratio). This site to physician recruitment ratio is consistent with large population studies. Of the recruited sites, 173 became participating sites after receiving a confirmation letter of passing the suitability interview. All 173 participating sites received EDC training and of these, 146 enrolled subjects. The 140 sites that chose not to actively participate once they had been recruited did so due to reasons such as time constraints or those subjects whom they approached did not wish to participate in the study. Of the sites that enrolled subjects (146) a total of 17 (11.6%) were specialist sites while all others were general physician sites (GP sites). An illustration of the study site distribution across provinces, including the number of total sites, general practitioner sites and specialist sites, is shown in Figure 4.

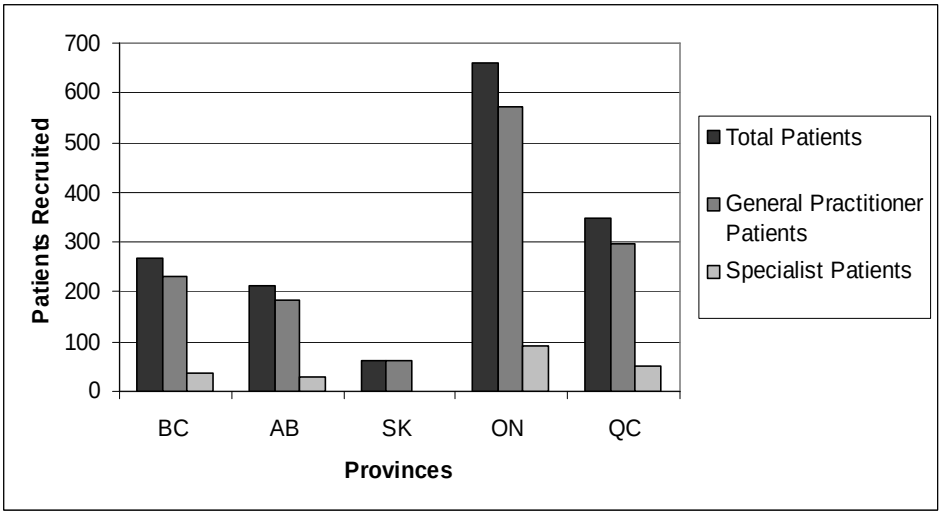
FIG. 4 Study Site Recruitment Distribution across Canada



BC = British Columbia; AB = Alberta; SK = Saskatchewan; ON = Ontario; QC = Quebec

From the first subject enrolment on May 6, 2004 to the end of enrolment on March 31, 2005, 1,556 patients were recruited to participate in the study. There were a proportional number of patients per number of sites recruited in each province with site recruitment ranging from 1 to 30 patients. A distribution of total patients, patients from general practitioner sites and patients from specialist sites is shown in Figure 5. There was no over recruitment from any of the pre-specified study provinces. Provinces were chosen based on market size and accessibility to provincial databases. It had been planned to access the provincial databases for economic modelling purposes but this was never carried out. Patient recruitment to provincial population ratios (based on 2001 census) was similar across provinces (BC 6.83; AB 7.19, SK 6.43, ON 5.8, QC 4.83).

FIG. 5 Patient Recruitment Distribution across Canada



BC = British Columbia; AB = Alberta; SK = Saskatchewan; ON = Ontario; QC = Quebec

The percentages of returned subject questionnaires for each scheduled reporting period are shown in Table 2. Of the expected questionnaires, 97.9% were returned at baseline, 86.5% at Month 6, and 86.3% at Month 12. The expected number of questionnaires decreased at each interval accounting for those subjects who discontinued early. The questionnaire return rate of the total potential questionnaires, not accounting for patients who discontinued the study early, was 97.9% at baseline, 83.0% at Month 6, and 74.8% at Month 12. The total return rate of the expected questionnaires over the duration of the study was 89.0% and the total return rate of the potential questionnaires was 85.2%.

TABLE 2 Expected and potential subject questionnaires returned for each scheduled reporting period

Reporting Period	Returned/Expected* n/N (%)	Returned/Potential† n/N (%)
Baseline	1,524/1,556 (97.9)	1,524/1,556 (97.9)
Month 1	1,422/1,543 (92.2)	1,422/1,556 (91.4)
Month 3	1,342/1,509 (88.9)	1,342/1,556 (86.2)
Month 6	1,291/1,492 (86.5)	1,291/1,556 (83.0)
Month 9	1,212/1,487 (81.5)	1,212/1,556 (77.9)
Month 12	1,164/1,349 (86.3)	1,164/1,556 (74.8)
Study Total	7,955/8,936 (89.0)	7,955/9,336 (85.2)

*Questionnaires of subjects who discontinued early were NOT included in percentage calculations.
†Questionnaires of subjects who discontinued early were included in percentage calculations.

The percentages of potential returned subject questionnaires by site size (number of patients enrolled) and by the type of site (general practitioner (GP) or specialist (SP)) are shown in Table 3. GP Month 12 subject questionnaire return rates were comparable for small (76.4%), medium (77.7%) and large (73.5%) sites. SP Month 12 subject questionnaire return rates were also comparable for small (82.5%), medium (88.5%) and large (88.2%) sites. GP overall questionnaire return rates were comparable for small (86.7%), medium (86.6%) and large (86.6%) sites and also for small (89.8%), medium (96.1%) and large (94.7%) SP sites. There was an overall trend of higher subject questionnaire return rates from SP sites compared to GP sites. Specialist sites had slightly lower subject study discontinuation rates (GP: 85.8%; SP: 90%).

TABLE 3 Potential subject questionnaires returned by site size and type of physician site (month 12 vs. all scheduled questionnaires)

	Smaller Sites* n/N (%)			Medium Sites† n/N (%)			Larger Sites‡ n/N (%)		
	GP§	SP§	Total	GP§	SP§	Total	GP§	SP§	Total
Month 12	389 /509 (76.4)	33 /40 (82.5)	422 /549 (76.9)	234 /301 (77.7)	54 /61 (88.5)	288 /362 (79.6)	393 /535 (73.5)	97 /110 (88.2)	490 /645 (76.0)
All	2,250 /2940 (86.7)	212 /236 (89.8)	2,762 /3176 (87.0)	1,533 /1771 (86.6)	348 /362 (96.1)	1,881 /2133 (88.2)	2,672 /3,084 (86.6)	613 /647 (94.7)	3,285 /3,731 (88.0)

Smaller sites were considered as those that enrolled 1-10 subjects; † Medium sites were considered as those that enrolled 11-20 subjects; ‡ Larger sites were considered as those that enrolled 21-30 subjects; § GP = general practitioner; SP = specialist Note: Questionnaires of subjects who discontinued early were included in percentage calculations. Baseline, Month 1, Month 3, Month 6, Month 9 and Month 12 questionnaires were included in the calculation for 'all' potential subject questionnaires return rate.

DISCUSSION

IBS is a common disorder with high prevalence in Canada and in other countries worldwide. Despite being a widespread disorder, there have been few observational studies conducted to follow patients suffering from IBS-associated symptoms and therapeutic treatment outcomes long term. Thus far, most treatment trials have been conducted on those patients who are referred to specialists even though only a minority of people with IBS seek medical care and those who do are mostly managed by primary physicians.[6] Existing treatments target only one of the multiple symptoms of IBS and possibly exacerbate others, and therefore have limited therapeutic value. However, in Canada, Tegaserod is an approved therapeutic approach taken because it may alleviate several of the various symptoms of IBS with constipation.[12] There are still unanswered questions about the impact of Tegaserod and other treatments in routine clinical practice, economic cost of this disorder, and long-term economic and quality of life data in Canada. This study aimed to answer such questions.

Population based studies, like LOGIC, can potentially provide significant information for disorders like IBS; but, the success of such studies requires a unique study design that considers logistical and statistical challenges. Multi-site research designs have the benefit of increasing sample size and attaining a more representative sample in a shorter time[21] but, also entail added considerations than those necessary with a single site. Recruitment methodology may affect important characteristics of an IBS study group[6] due to differences in characteristics of IBS patients recruited from different sources, particularly in disease symptom number, severity, presence of affective disorders, drug therapy history and tendency to seek care.[8] The process and selection of contracting the right investigators may also directly affect the success or failure of patient recruitment throughout a clinical research study.[15] Additionally, although self completed postal questionnaires are a simple and economical method of data collection and have a higher response rate than other methods of data collection, especially with sensitive medical research questions[22], they are subject to non-response bias.[23] Methodology is thus extremely important in multi-site, questionnaire based, observational studies for successful recruitment, maximized patient response rates and minimal bias.

The LOGIC study methodology included a detailed, pre-planned site and investigator recruitment strategy that laid a strong foundation for subsequent patient recruitment and study success. It is often a challenge in observational post-marketing research to recruit sites, maintain physician participation and have them recruit patients. Unremarkably, the LOGIC study, despite organization and planning, had a high attrition rate amongst physicians, and even some who underwent site training did not recruit patients. This is conceivable due to complication of the local ethic submission process filed by the physicians, possible change of interests or some sites and physicians being too busy to participate in the study as they had hoped. In order to reduce the issue of time constraints on physicians choosing to participate in the LOGIC study, an innovative information system was developed. Physician use of the online electronic data capture for reporting reduced the time commitment of physicians. Additionally, this system allowed real-time patient information, which was beneficial for patient follow ups and facilitated communication between the clinical research organization, the sponsor, and the investigators. Electronic data capture also reduces queries as it contains automatic data edit checks and the data cannot be lost as with mailed or faxed reports. The drawback with the system is that it limits the study to sites with Internet access.

A significant key to the success of the LOGIC study was the methods employed to ensure patient retention and a high rate of return of questionnaires. To increase patient motivation and participation they were remunerated at Month 6 and Month 12 for the time spent filling in preceding questionnaires. In addition, for each returned questionnaire, patients were sent a thank you card confirming it had been received by the CRO and also highlighted the importance of their participation on furthering IBS research. Thank you cards also acted as a reminder of the next questionnaire due date. In cases where patient questionnaires were not received on time there were extensive follow up efforts. In some cases, patients were sent a first reminder letter and a

second reminder letter accompanied by a phone call from the site if their questionnaire was still not returned. A combination of patient compensation, reminders and the establishment of a strong sense of participation resulted in 89.0% of all expected subject questionnaires to be returned. Of the total expected returned questionnaires an estimated 36.4% were returned after the due date and therefore the late return may be attributed to the follow up efforts. Second follow up letters and site phone calls to patients who had not returned their questionnaire at Month 6 were found to increase expected questionnaire return rates by an estimated 22.1%.

There were some key characteristics that differed between the sites that participated in the LOGIC study. Across the 5 provinces there were both GP and SP sites. Site sizes also varied, with some sites recruiting higher numbers of patients. The number of patients recruited by a site and the percent of those patients completing the study were comparable for small (87.0%), medium (88.0%) and large (88.0%) sites. The provincial return rates were also comparable. When dropouts were accounted for, there was slightly higher questionnaire return rate of SP sites compared to GP sites. As follow up methods were the same for all sites, this suggests that perhaps patients from specialist sites are more dedicated to return questionnaires even though they may have more severe symptoms.

Fewer patients were recruited for the LOGIC study than originally planned. Recruitment was stopped early due to time and budget constraints; however, the sponsor felt that the number of subjects enrolled was sufficient to answer questions. Also, higher than expected questionnaire return rate and correspondingly reduced patient attrition rate compensated for any lost statistical power of the smaller sample size. Studies, which focus on recruitment of a larger number of patients, may potentially sacrifice questionnaire return rates because of the unfeasibility of following up adequately with so many patients. Questionnaire based observational studies may benefit from focusing resources on increasing questionnaire return rates to effectively maintain data reliability and also reduce non-response bias.

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