Appendix G: Literature review of prognostic resource use and quality of life data

INTRODUCTION

An important component of the guideline development process was an evaluation of the cost-effectiveness of pharmacological and behavioural interventions using an economic model. To build the model, we needed information about common types and patterns of symptoms experienced by people with diagnosed IBS managed in primary care in the UK, and the impact of symptoms on their quality of life and use of health care services.

The purpose of this document was to present a review of the literature on prognosis, health related quality of life and health resource use applicable to UK primary-care patients with diagnosed IBS. This was used to inform the model design and provided data to populate the model.

We considered whether prognosis, health related quality of life or resource use was significantly different by predominant symptom type (e.g. IBS-D, IBS-C, IBS-P, IBS-A) and/or frequency or severity of symptoms.

PROGNOSIS

Methods

A rapid literature review was conducted to identify IBS cohort studies (see end of this appendix for search terms and inclusion criteria). The search terms were chosen to be specific rather than sensitive, so it is possible that some relevant studies may have been missed. To supplement this search, references of included papers were checked for other papers that might be relevant. In addition, the references of selected background reviews[1-12] were also checked.

The initial search yielded 179 papers, of which 8 were selected for inclusion. These fell into two main groups: long-term cohort studies that followed up IBS patients over periods of months and years and assessed stability of diagnosis and symptoms and studies that examined shorter term patterns of symptoms by the use of daily diaries.

Long-term stability of IBS diagnosis and symptoms

The identified studies included a systematic review (El-Serag 2004)[13], which updated an earlier review (Janssen 1998)[14]. The El-Serag (2004) review included two of our identified studies[15;16] (Owens 1995, Svendsen 1985), as well as 12 other studies (Blewett 1996, Chaudhary 1962, Fowlie 1992, Harvey 1987, Hawkins 1971, Hillman 1984, Holmes 1982, Keefer 2002, Lembo 1996, Prior 1989, Stevens 1997, Waller 1997) [17-28], most of which did not meet our inclusion criteria. We also identified one recent study (Adeniji 2004) that was not included in El-Serag (2004)[29].

Characteristics of the 14 studies included in the El-Serag (2004) review and the recently-reported study by Adeniji (2004) are summarised in Table 1. All of the studies were based on cohorts of patients recruited from outpatient clinics, and so might not be representative of patients in primary care. Four studies used the Rome definitions of IBS, and one Manning. The older studies used a variety of definitions of IBS, mostly based on a combination of abdominal pain with altered bowel movements, although three might have excluded patients without pain[18;21;28]. The length of follow-up ranged from 2 months to up to 32 years. The percentage of the original cohort with follow-up data available also varied widely, from 38% to 100%.

The primary outcomes of these studies are summarised in Table 2. As might be expected, given the differing populations and durations of follow-up, changes to and resolution of symptoms varied. Four studies reported whether symptoms were worse, unchanged or improved over the follow-up period (Waller 1997, Hillman 1984, Fowlie 1992, Adeniji 2004). In these studies, between 48% and 65% of patients reported improvement, 30% to 50% no change, and 2% to 14% said their symptoms were worse. The seven studies that reported resolution of symptoms gave widely differing estimates: from 7% to 48%.

Table 1. Characteristics of long-term cohort studies

First author	*Year*	*Country*	*Setting*	*n*	*Age*	*% female*	*Definition of IBS*	*Prior duration of symptoms (years)*	*Follow-up (years)*	*% follow-up*
Chaudhary	1962	UK	Clinic	130	20-60	66%	Other	Up to 10+	Up to 3+	97%
Waller	1969	UK	Clinic	74	Most<40	41%	Other	Up to 10+	1-3	68%
Hawkins	1971	UK	Clinic	163	13-76	61%	Other	Not reported	2-20	92%
Holmes	1982	UK	Clinic	91	22-86	49%	Other	Not reported	6	85%
Hillman	1984	NZ	Clinic	30	16-60	100%	Other	Not reported	2-3	47%
Svendsen	1985	DK	Clinic	112	18+	76%	Other	2	5-7	80%
Harvey	1987	UK	Clinic	104	16-81	56%	Manning	0.5-2	5	93%
Prior	1989	UK	Clinic	41	18-68	100%	Other	Not reported	1	90%
Blewett	1996	UK	Clinic	70	18-65	66%	Other	4/5	0.5-1+	87%
Fowlie	1992	UK	Clinic	75	Mean 39	36%	Other	4	5	73%
Owens	1995	US	Clinic	112	20-64	68%	Rome I	0-1+	1-32	78%
Lembo	1996	US	Clinic	20	18-60	50%	Rome I	>5	1+	100%
Stevens	1997	US	Clinic	25	22-73	68%	Other	15.5	0.2	100%
Keefer	2002	US	Clinic	13	Mean 50	62%	Rome I	14.7	1	77%
Adjeni	2004	US	Clinic	196	20-75	81%	Rome I	Not reported	10-13	38%

Table 2. Primary outcomes of long-term cohort studies

First author	*Follow-up (years)*	*Number with complete follow-up*	*Reported change in symptoms over follow-up*			
			Worsened	No change	Improved	No symptoms
Chaudhary	Up to 3+	126				47 (37%)
Waller	1-3	50	1 (2%)	25 (50%)	22 (48%)	6 (12%)
Hawkins	2-20	150				63 (39%)
Holmes	6	77				29 (38%)
Hillman	2-3	14	2 (14%)	5 (36%)	7 (50%)	1 (7%)
Svendsen	5-7	90			46 (51%)	
Harvey	5	97	17 (18%)			
Prior	1	37				11 (32%)
Blewett	0.5-1+	62				
Fowlie	5	43	2 (5%)	13 (30%)	28 (65%)	
Owens	1-32	87				
Lembo	1+	20				
Stevens	0.2	25				12 (48%)
Keefer	1	10				
Adjeni	10-13	75	8 (11%)	28 (37%)	39 (52%)	6 (8%)

Short-term patterns of IBS symptoms

A systematic review by Guilera (2005)[30] assessed evidence about 1) the distribution of bowel habit subtypes (IBS-C, IBS-D, IBS-A and IBS-N) according to the setting and diagnostic criteria and 2) temporal patterns of IBS symptoms based on daily diaries. The first objective was not relevant for the economic modelling, so it is not discussed further here.

The Guilera (2005) review identified five prospective cohort studies with daily diary data on IBS symptoms (Stevens 1997, Heaton 1991, Hahn 1998, Ragnarsson 1998, Mearin 2003)[27;31-34]. Our literature search identified another publication related to the Mearin study (2004)[35] and two more recently-published studies (Drossman 2005, Mearin 2006)[36;37]. The study characteristics are summarised in Table 3.

The studies all used different methods to report their results, so it is difficult to summarise their findings quantitatively. Guilera (2005) concluded that the studies showed that for most patients symptoms are periodic, with clusters of days with symptoms interspersed with symptom free periods.

- Heaton (1991)[31] evaluated the timing of stools over one month, comparing the mean interval (in hours) reported for hospital outpatients, non-consulters and a non-IBS control group.
- Stevens (1997)[27] estimated that 20% of their specialist clinic sample experienced severe symptoms with non-IBS days and that 80% had severe symptoms with no non-IBS days. They estimated that mean episode duration was 3 days (with a range from 2 to 8 days).
- Hahn (1998)[32] estimated a mean frequency of one episode per week, with a duration of 4-5 days for pain/discomfort bloating and 1-2 days for altered bowel function.
- Ragnarsson (1998)[33]reported that over a six-week diary period, 6% of patients reported no pain, 14 % less than 10 episodes of pain, 65% 10-20 episodes, and 14% reported pain every day.

These four studies were all relatively small, relatively brief (with the exception of Hahn, less than three months) and used older diagnostic criteria (Rome I, Manning or other). Three more recent studies (Mearin 2003, Mearin 2004, Drossman 2005, Mearin 2006)[34-37] were potentially more useful, and their results are discussed in more detail below.

The Mearin studies in particular used large samples of IBS patients from the Spanish primary care system, selected according to Rome II criteria. These patients did not receive any specific IBS treatment, but were managed according to their clinician's usual practice.

The Drossman (2005) study[36] was also large, based on Rome II criteria, with a long follow-up. However, patients were recruited from specialty clinics in the US and Canada, and were participating in a treatment trial. The patients were randomised to receive desipramine, placebo, CBT or an educational intervention. The treatment period lasted for three months, after which patients were observed for a further year. Drossman (2005) noted that they failed to find any significant treatment effects (details not presented in this paper).

Transitions between IBS subtypes

Mearin et al (2003/4) [34;35] classified patients into nine subtypes by frequency and intensity of symptoms:

- Low-frequency symptoms (LF) (no symptoms at least 50% of time)
- Pain predominance with low intensity (P-IBS LI)
- Pain predominance with high intensity (P-IBS HI)
- Diarrhoea predominance with low intensity (D-IBS LI)
- Diarrhoea predominance with high intensity (D-IBS HI).
- Constipation predominance with low intensity (C-IBS LI)
- Constipation predominance with high intensity (C-IBS HI).
- Alternating predominance with low intensity (A-IBS LI)
- Alternating predominance with high intensity (A-IBS HI).

Concordance of these subtypes for the two diary periods was relatively high - 49% of patients (kappa 0.40) were classified in the same group for both periods, rising to 61% (kappa 0.48) if only symptom type (not intensity of symptoms) was considered. Very few patients switched between C and D subtypes, but a sizable minority of the C (42%) and D (27%) patients in period 1 switched to A in period 2. As the frequencies are reported in full, it was possible to estimate the proportion of patients moving between each of the health states. However, the numbers of patients in some of the subgroups (P-IBS HI and D-IBS HI, in particular) were too low to allow a reliable estimation for each to the possible transitions between health states.

Mearin et al (2006)[37] used similar methods as Mearin 2003/4, but with a larger sample over a longer follow-up period. It was not clear whether some of the same patients were included in both studies. The patterns of transitions between IBS subtypes over time were similar. In the 2006 study, very few people switched between C and D subtypes (1% from C to D and 1% from D to C), more moved in and out of the A subtype (10% from C/D to A and 7.5% from A to C/D), and 7% reported normal bowel habit at 12 months.

Drossman et al (2005) [36] found similar patterns, but rather higher rates, of switching between the subtypes than in the Mearin studies. Of the 190 people with 4 follow-up diaries, only 46 retained baseline subtype throughout the year of follow-up. Switching between C and D was quite rare (29%). More patients switched from D to M and from C to M.

Table 3. Characteristics of short-term cohort studies with daily symptom diaries

First author	*Year*	*Country*	*Setting*	*n*	*Mean age*	*% female*	*IBS criteria*	*Follow-up*	*% follow-up*
Heaton	1991	UK	Clinic, community and non-IBS	80	29	100	Manning	4 wk diary	100
Stevens	1996	US	Clinic	25	43	68	Not stated	8 wk diary	100
Hahn	1998	US/UK/NL	Clinic/ primary care	122	49	78	Rome I	12 wk diary	48
Ragnarsson	1998	Sweden	Primary care	80	36	63	Rome I	6 wk diary	79
Mearin	2003/4	Spain	Primary care	209	47	65	Rome II	2, 4 wk diaries over 3 months	80
Drossman	2005	US/Canada	Clinic	317	39	100	Rome II	5, 2wk diaries over 15 months	51*
Mearin	2006	Spain	Primary care/ clinic	400		76%	Rome II	4, 4 wk diaries over 12 months	77

* Percentage completing 15 month diary

Changes in frequency or severity of symptoms over time

Mearin (2006) also reported data on changes in the frequency and severity of symptoms over time. Patient and doctor reported opinions of IBS severity (on a 7 point ordinal scale) were similar. However, there were no differences in perceived severity by IBS subtype. Both patients and doctors reported that they felt symptoms had improved over the initial 3 months. However, there were no clear trends in perceived IBS severity after that. The frequency and severity of pain/discomfort and bloating from the daily diaries was also similar for the subtypes and showed a similar pattern over time, with initial improvements followed by a levelling off.

It is possible that the initial improvement could reflect a non-specific treatment effect, following the baseline consultation in which the patients were recruited. Although patients were not offered any specific treatments in this study, ‘usual practice’ interventions and advice might have had a beneficial effect. Another possibility is that this time pattern could reflect a ‘regression to the mean’ effect. Patients are likely to have been recruited during a bad phase of their illness; the reason for their initial consultation. If so, one would expect a natural improvement as patients return to their usual pattern of symptoms.

Interestingly, Drossman (2005)[36] observed a similar pattern of symptoms over time as did Mearin, with initial improvements over the three-month treatment period that then levelled off over the year of follow-up. The authors state that treatment was not responsible for these effects (data not presented). This may thus represent a generalised treatment benefit (not related to the specific therapies tested) and/or regression to the mean.

Whilst, the numbers of patients in some of the subgroups of the Mearin (2004) cohort study (P-IBS HI and D-IBS HI, in particular) were too low to allow a reliable estimation for each to the possible transitions between health states, it was possible to aggregate the data presented across the different high frequency subtypes and group patients by symptom severity alone. By doing this we estimated that the probability of moving from a high to low symptom severity state was 45%.

HEALTH RELATED QUALITY OF LIFE

Methods

A literature review was conducted to identify relevant surveys of health-related quality of life for people with IBS (see end of document for search terms and inclusion criteria). The search was tailored to finding measures of quality of life suitable for inclusion in an economic study – ‘utility’ or ‘preference’ based measures. The CRD search filter for quality of life studies was added to the disease search terms for the guideline. As with the prognosis search, references of identified papers and other background papers were also checked.

The initial search yielded 99 papers. These included five papers reporting utility-based measures of quality of life that are suitable for estimation of Quality Adjusted Life Years (QALYs) for use in the economic evaluation (Mearin 2004, Akehurst 2002, Smith 2004, Bushnell 2006a, Bushnell 2006b), [35;38-41]. None of these studies reported a break-down of quality-of-life by IBS subtype or severity. To provide some information on this, papers providing estimates of the relationships between a validated, generic measure of quality-of-life and IBS subtypes or symptom frequency or severity were also selected for inclusion. Eleven such papers were identified.

Table 4. Description of studies reporting utilities for people with IBS

First author	*Year*	*Country*	*Setting*	*Study design*	*Population*	*Follow-up*	*Measures*
Akehurst	2002	UK	6 general practices in Trent (selected to be representative)	Matched case-control study	161 patients with IBS known to GP (Rome I) & 213 matched controls (matching by age, sex & social characteristics)	3 months	Questionnaire (SF36, EQ5D & IBS-QOL) at baseline and three months
Smith (Episode study)	2004	UK	Patients managed in primary care and secondary care consulters recruited from community by advertisement	Cross-sectional survey	486 people with IBS (Rome II) - 168 consulted in primary care only and 318 consulted with secondary care.	None	Presence, frequency and severity of symptoms, consulting behaviour and treatment histories, QoL (EQ5D).
Mearin	2004	Spain	Primary care (30 clinics)	Cohort, prospective	209 IBS patients (Rome II). 168 completed study	3 months	Daily diary of symptoms, resource use (clinic visits, tests, hospital stays, drugs) and time off work for two 28-day periods with 4 week interval. QoL questionnaires (EQ5D, IBSQOL, PWBI) administered at end of follow-up
Bushnell	2006a	UK, Spain, Germany	Various: primary care and hospital clinics	Various: case-control, prospective cohort, and cross-sectional surveys	Data from four IBS studies (n=161, 297, 503, 100) including Akehurst 2002 and three other studies reported in abstract form (Ricci 2003, Badia 2003 and Gruger 2001)	None	Baseline assessments of QoL (EQ5D, SF36, IBS-QOL), subjective clinical and global assessments of IBS
Bushnell	2006b	US	Community (advertisement)	Cross-sectional survey	72 patients with IBS (Rome II)	None	IBS-QOL, EQ5D, WPAI:IBS - by paper questionnaire and electronic data capture methods.

Utility impact of IBS

Characteristics of the five studies[35;38-41] reporting a utility-based measure of quality of life are described in Table 4 above. All of these studies use the EuroQOL (EQ-5D) instrument to assess utility. This is a recommended measure to use in NICE economic evaluations. There is an accepted method for scoring the EuroQoL questionnaire, the 'UK tariff' or index, which attaches values to the various possible health states based on the preferences of a large representative sample of the UK general population. The EQ5D is scored on a scale from 0 to 1, where 1 is the best possible health state and 0 is considered equivalent to death. Standard population norms for the UK, by age and sex, are also available from the 1996 Health Survey for England.

Table 5. Mean EuroQol tariff by age and sex, Health Survey for England 1996

	16-24	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75+*	*Total*
Men	0.91	0.92	0.89	0.85	0.80	0.80	0.76	0.86
Women	0.90	0.90	0.87	0.84	0.78	0.76	0.71	0.84
All adults	0.91	0.91	0.88	0.85	0.79	0.78	0.73	0.85

Akehurst (2002) et al[38] conducted a matched case-control study to estimate the impact of IBS on quality of life, time off work and the use and cost of health services. They recruited 161 patients with known IBS (Rome I criteria) from six primary care practices in the UK. 213 non-IBS controls were also recruited, matched for age, sex and social characteristics from the same practices. At baseline patients were given a questionnaire including three validated instruments, the generic EuroQol and SF36 and the disease specific IBS-QOL. This was repeated at three months. The IBS group had significantly worse quality of life across all dimensions of the SF-36 and the EQ5D (Table 6). There were no significant changes in QoL scores between baseline and three months for the IBS patients. Unlike the Mearin (2004) and Drossman (2005) studies reported above, the patients in the Akehurst (2002) study thus appeared to be stable. Note that the score for the non-IBS patients is rather worse than might be expected from UK population norms for the relevant age groups (Table 6).

Table 6. Mean EuroQol score (UK tariff) at baseline, Akehurst et al 2002

	IBS mean (n=139)	*Non-IBS mean (n=201)*	*Mean difference*	*95% CI*
EQ-5D UK score	0.68	0.81	-0.14	-0.19 to -0.08

Mearin (2004)[35], used the Spanish version of the EQ5D to estimate utility at three-month follow-up for their sample of Spanish primary care patients with IBS. They did not report an overall mean utility, but only results broken down by their nine IBS subtypes (see prognosis section for definition of these subtypes), Table 7. Using this data, however, the mean utility for the cohort after three months is easily calculated as 0.76, which is rather less severe than the mean estimate for IBS patients in the Akehurst (2002) study. Note that some of the groups in the Mearin (2004) study were far too small to yield reliable estimates (IBS-P HI and IBS-D HI in particular, but also possibly LF and IBS-C HI). So, we have also calculated the mean results for people with high and low intensity symptoms ignoring the distinction between IBS subtypes (see the bottom row of 7). The mean difference in utility between high and low intensity symptoms (for patients with high frequency symptoms) was calculated to be 0.0713 (95%CI 0.0092 – 0.1334).

Table 7 Quality of life results (Mearin 2004)

	Low frequency	**High frequency and low intensity**				**High frequency and high intensity**			
		IBS-P	**IBS-D**	**IBS-C**	**IBS-A**	**IBS-P**	**IBS-D**	**IBS-C**	**IBS-A**
N	18	24	15	22	38	2	3	14	32
Mean EQ5D	0.83	0.75	0.82	0.78	0.77	0.60	0.75	0.74	0.69
		0.70				0.78			

Smith (2004)[39] conducted a cross-sectional survey of people with IBS (Rome II criteria), recruited from a national newspaper advertisement. Data on 486 people with confirmed IBS were analysed, 318 of whom reported seeing a secondary care doctor for their IBS. Telephone interviews were conducted with the participants to obtain information about their symptoms and quality of life (EQ5D instrument). This also appears a well-conducted study. The method of recruitment, however, might have introduced a selection bias. The participants might not be representative of primary and secondary care IBS patients in the UK. The EQ5D results are presented in disaggregated form, with frequencies of responses to the five individual questions but an overall utility score is not reported.

The two Bushnell (2006a, 2006b) papers were less informative for our purposes. One paper (Bushnell 2006a)[40] assesses the performance of the EQ5D instrument in patients with IBS. This was a secondary analysis of four data sets, including the Akehurst (2002) study described above. The other four datasets were described briefly, but only appear to have been published in abstract form so far, so full details were not available. These included a follow-up to the Akehurst (2002) study in the UK (referenced to an Abstract by JF Ricci and colleagues), a multicentre cohort study in Spain by Badia, Mearin and Caballero, and a German observation study designed to input to a model to estimate the benefits of tegaserod (Grüger et al). The EQ5D scores from these studies were only reported in graphical form.

The other Bushnell paper (2006b)[41] was a relatively small study, conducted in the US to validate the use of electronic methods to capture data on quality of life from IBS patients.

Quality of life by IBS type or symptoms

In addition to an overall estimate of the utility impact of IBS, we needed evidence on whether there are differences in utility between people with different types of IBS, or for those with differing frequency, duration or severity of symptoms.

The data from Mearin (2004)[35] (Table 7 above) was useful for these purposes. This suggested that the utility impact of IBS is worse for people with pain, constipation or alternating bowel habit as their predominant symptom, than for people with diarrhoea as their predominant symptom. The utility for the group with a low frequency of episodes (less than 50% of days) was similar to the non-IBS group in the Akehurst (2002) study.

We found no other studies reporting differences in utility between IBS subtypes or quantifying the relationship between utility and IBS symptoms. So we broadened our search to include studies that considered such relationships with other non-utility measures of generic health-related quality of life that have been validated (such as the SF-36).

El-Serag (2002) conducted a systematic review of health-related quality of life in people with IBS [42]. This included 12 studies reporting health-related quality of life for people with IBS using a validated generic or disease-specific measure. None of these studies used a utility-based measure. From this El-Serag (2002) concluded that severity of bowel symptoms is correlated with quality of life, although no quantitative evidence for this was presented.

El-Serag (2002) included three studies[43-45] (Creed 2001, Schmulson 1999, Simren 2001) that compared the quality of life impact for IBS subtypes (C, D and A). We identified a further four studies[34;36;46;47] (Mearing 2003, Drossman 2005, Coffin 2004, Wilson 2004). The characteristics of these seven studies are described in Table 8. Although some of these studies observed differences between the subtypes, these were statistically significant for only one study[46] (Coffin 2004).

Analyses of the impact of symptom presence, frequency or severity on measures of quality of life are more complicated. For example, Cain (2006) [48] examined quality of life and symptom diary data for 242 women with a diagnosis of IBS (Rome I) recruited for observational studies from a US HMO list or public advertisement between 1997 and 2004. They found significant correlations between the IBSQOL total score and mean IBS symptom severity. In regression analysis (details not presented), pain and diarrhoea were most strongly related to quality of life. Constipation, gas and bloating were all related to quality of life, but not independently of pain. This implies that, in terms of impact on quality of life there are actually two main factors: pain/gas/bloating/constipation and diarrhoea.

Four RCTs of therapeutic interventions were also identified in the El-Serag (2002) review. These suggested that patients who have a 'therapeutic response' to an intervention have corresponding improvements in health-related quality of life.

Table 8. Characteristics of studies reporting on quality of life by IBS subtype

First author	*Year*	*Country*	*Setting*	*Study design*	*Population*	*Follow-up*	*Measures*
Creed	2001	UK	7 secondary and tertiary clinics in North England	Case series - cross-sectional survey with retrospective case note review	257 patients with severe refractory IBS (Rome I)	12 months	Bowel and psychological symptoms, QoL (SF36), health care resource use and costs, patient costs, time off work and lost wages.
Schmulson	1999	US		Cross-sectional survey	625 IBS patients (Rome I) completed questionnaires. 140 patients with IBS-C and 216 patients with IBS-D	None	Symptoms (BSQ), psychological symptom checklist (SCL-90), and health status (SF-36)
Simren	2001	Sweden	Hospital clinic and primary care patients (recruited via advertisement)	Cross-sectional survey	390 patients with IBS (Rome I) were invited to participate. Of these, 343 completed questionnaires: 209 OP and 134 from primary care.	None	IBS subtype, symptoms (GSRS) and QoL (FIS, HAD, STAI & PGWB) assessed by questionnaire.
Mearin	2003	Spain	Community	Cross-sectional survey	A general population sample of 2000 people. 213 (76%) of potential IBS subjects agreed to participate	None	IBS subtype, symptoms, Qol (SF36), consultation, time off work
Drossman	2005	US and Canada	Clinic	Cohort, prospective	317 women with IBS (Rome II) entering NIH treatment trial	15 months (3 month trial + 12 month follow-up)	Clinical factors, QoL (SIP & QoL sum score?) & health care use at randomisation and at end of 3-month treatment trial. + 2 diaries at baseline, at 3 months & at 3 month intervals for one more year.
Wilson S	2004	UK	Community (8 primary care practice lists)	Cross-sectional survey	398 people meeting Rome II criteria for IBS, identified from 4807 responders.	None	Symptom checklist & QoL questionnaire (SF12), symptom severity & QoL (General Health Questionnaire & IBSQOL).
Coffin	2004	France	Non-hospital GI clinics (n=400)	Cross-sectional survey	858 patients with IBS (Rome II)	None	Symptom questionnaire (presence, frequency and intensity) & QoL (GIQLI)

HEALTH CARE RESOURCE USE AND COSTS

Methods

We conducted another literature review to identify estimates of health care resource use and costs for people with IBS (see end of document for search terms and inclusion criteria). The MEDLINE search used a focussed search strategy, designed to identify full economic evaluations (cost-effectiveness, cost-utility or cost-benefit studies), rather than all costing studies. However, we supplemented this with a broad search of a specialist economic database – the Health Economic Evaluation Database (HEED). And as before, some additional papers were found by checking the references of other publications.

The use of health care resources and costs are likely to differ greatly between countries, due to differences in health care systems, cultural differences in clinical practice and economic factors. For this reason we focussed on UK studies. However, we did include non-UK studies if they reported on associations between IBS type or symptom frequency or severity with health care resource use or costs. We focussed on papers reporting quantities of health care resources used (e.g. the number of consultations over a year) or costs for people with diagnosed IBS. Studies that only evaluated the likelihood of consulting in population based samples were not included.

UK estimates of health care use and costs for IBS

Five papers that reported on the use of health services or health care costs for people with IBS in the UK were identified[38;43;47;49;50] (Akehurst 2002, Creed 2001, Wilson 2004, Hahn 1999, Wells 1997). See Table 9 for details.

Akehurst (2002)[38] recruited patients with IBS known to their GP (Rome I criteria), along with matched non-IBS controls. They collected information on use of primary and secondary NHS services over a 12-month period (6 months before and 6 months after recruitment) by reviewing primary care records. The cost of health services were estimated from national or local sources in 1997/8 prices. See Table 9 for a summary of results.

Table 9. Use of NHS services and costs, Akehurst (2002)

Resource	*IBS (n=161)*	*Control (n=213)*	*Mean difference (95% CI)*
GP surgery visits	4.36	3.05	1.31 (0.82 to 1.81)
GP home visits	0.05	0.01	0.04 (0.00 to 0.08)
GP prescriptions	5.62	3.04	2.58 (1.8 to 3.32)
A&E attendances	0.11	0.07	0.05 (-0.01 to 0.11)
Outpatient visits	1.16	0.83	0.34 (0.02 to 0.67)
Inpatient stays	0.14	0.06	0.08 (0.00 to 0.16)
Costs	£316	£193	£123 (£35 to £221)

Table 10. UK studies on health care use and costs for IBS patients

First author	*Year*	*Country*	*Setting*	*Study design*	*Population*	*Follow-up*	*Measures*
Akehurst	2002	UK	6 general practices in Trent (selected to be representative)	Matched case-control study - cross-sectional survey with retrospective case note review	161 patients with IBS known to GP (Rome I) & 213 matched controls (matching by age, sex & social characteristics)	12 months	Number and cost of GP consultations (home and clinic), drugs, A&E attendances, OP visits and IP stays
Creed	2001	UK	7 secondary and tertiary clinics in North England	Case series - cross-sectional survey with retrospective case note review	257 patients with severe refractory IBS (Rome I)	12 months	IP stays, OP visits, day patient attandance, A&E, GP contacts, domiciliary care services, day rehabilitation centres, alternative therapies, prescription medicines and costs, patient costs, time off work and lost wages.
Wells	1997	UK	Various	Analysis of databases and cross-sectional survey of consultants	UK patients consulting with IBS symptoms (or coded as IBS, ICD 564.1)	None	Number and cost of GP visits, use of medication, OP visits and IP stays per annum
Wilson	2004	UK	Community (8 primary care practice lists)	Cross-sectional survey	398 people meeting Rome II criteria for IBS, identified from 4807 responders. 8646 questionnaires posted.	None	Use of health services in the previous six months including GP, practice nurse and secondary consultations, use of prescribed and OTC medication and alternative therapies.
Hahn	1999	US and UK	Patient organisations	Cross-sectional survey	1000 members of patient organisations (500 US and 500 UK) with reported diagnosis of IBS from physician. 343 UK and 287 responded.	None	QoL (IBSQOL, SF-36), self-reported health resource use (ER visits, outpatient visits), time off work

The study by Creed et al (2001)[43] was based on a population of patients with severe IBS recruited from specialist clinics. As might be expected, their estimated cost of health care over the previous year (mean $1,822) was much higher than in the Akehurst (2002) study.

Wells (1997)[50] used a different approach, estimating the total use of NHS services, and costs, from a variety of sources. They estimated GP visits from the Fourth National Survey of Morbidity in General Practice. The number of prescriptions was taken from the DIN_LINK database (constructed from 100 UK practices). Estimates of outpatient visits and inpatient stays were obtained from a survey of consultants in the North of England. Their estimate of the total cost to the NHS in 1995 was £45.6m, or about £90 per consulting person with IBS. This was relatively close to the Akehurst (2002) estimate of £123 extra for the IBS patients. Wells (1997) also presented estimates of consultations and prescriptions by age and sex.

The study by Wilson et al (2004)[47] was less useful for our purposes. People with IBS (Rome II criteria) were recruited from a stratified random sample of 8 primary care practices in Birmingham. In contrast with the Akehurst (2002) study, this study included people who had consulted their GP about IBS and those who had not. Detailed data on the use of health care is presented, but this is not presented separately for consulters and non-consulters.

Finally, Hahn (1999)[49] conducted a survey of members of patients organisations in the UK and US. The results may thus be subject to selection bias, and may not be representative of people consulting with IBS in primary care.

Health care use and costs by IBS type or symptoms

Mearin (2004)[35] also reported some information about resource use. Patients with a low frequency of IBS episodes were less likely to have consulted a doctor. However, differences between the other subtypes were small.

Creed (2001)[43] found no significant differences in resource use or health care costs between IBS-C and IBS-D subgroups. In multiple regression analysis only psychological symptoms (SCL-90R somatisation score) and abdominal pain (VAS) were found to be significantly associated with health care costs, but these only explained a small proportion of the variance (R2= 9.3%). Two other studies (Drossman 2005, Hahn 1997)[36;51] failed to find any significant relationship between health care use or costs and IBS subtype or symptom frequency or severity. Three other studies (Le Pen 2004, Longstreath 2003, Talley 1995)[52-54] found some evidence of such an association, but this was not consistent either within or between studies.

Summary of findings

- The two most relevant cohort studies (Drossman 2005[36], Mearin 2004[35]) both showed an improvement in symptoms in the first 3 months. This could be interpreted as a non-specific treatment effect, as both cohorts received some form of IBS management. Alternatively it could represent regression to the mean whereby patients consult when their symptoms are particularly severe and there is some improvement as symptoms return to their normal level.

- There was evidence that a patient's predominant symptom may change over medium term intervals (1-3 months) resulting in them switching between IBS subtype classifications.

- Akehurst (2002)[38] provided direct evidence of the utility deficit due to IBS for a UK population of patients with IBS managed in primary care using an appropriate measure for economic evaluations (the EQ5D). The reporting and methodological quality of this study was good.

- Information about differences in quality of life by IBS subtype and intensity were provided in the Mearin (2004) study[35]. Mearin found only small differences in utility between the P, C and A subtypes and there was little supporting evidence from elsewhere to maintain a distinction in utility between the IBS subtypes. The systematic review by El-Serag (2002) concluded that the severity of symptoms is related to the degree of quality of life deficit in people with IBS but not the predominant symptom type.

- The Akehurst (2002) study[38] provided the firmest data about the routine use of health services for our population of interest. It reported that direct health care costs were significantly increased for people with IBS compared to matched controls. There was very little evidence from the studies identified for a difference in cost by IBS subtype or symptom severity.

SEARCH STRATEGIES AND INCLUSION / EXCLUSION CRITERIA

Prognosis

Search strategy: MEDLINE

Ovid Technologies, Inc. Email Service

Database: Ovid MEDLINE(R) <1966 to June Week 4 2006> Search Strategy:

1. ((intestin$ or gastointestin$ or colon$ or bowel$) adj2 (motility or sensitiv$ or functional or irritable or irritat$ or gas$ or spastic$ or unstable or instability or spasm$)).mp. (19602)
2. irritable bowel syndrome.mp. (3854)
3. IBS.mp. (2032)
4. irritable bowel syndrome/ (931)
5. colonic diseases, functional/ (3542)
6. or/1-5 (20125)
7. Cohort Studies/ (67230)
8. cohort.mp. (114360)
9. 7 or 8 (114360)
10. 6 and 9 (203)
11. limit 10 to english language (179)

Inclusion/exclusion criteria

Population	People diagnosed with IBS (Manning/Rome I/Rome II)
Study	Prospective cohort study
Setting	Primary care or outpatient
Treatments	Usual care' only - exclude studies with treatment interventions
Measures	Cost, QoL and/or frequency/severity of symptoms
Follow-up	At least three months

Quality of life

Search strategy: MEDLINE

Database: Ovid MEDLINE(R) <1966 to July Week 2 2006>

Search Strategy:

1. ((intestin$ or gastointestin$ or colon$ or bowel$) adj2 (motility or sensitiv$ or functional or irritable or irritat$ or gas$ or spastic$ or unstable or instability or spasm$)).mp. (19668)
2. flatus.mp. (689)
3. iritable bowel syndrome.mp. (3876)
4. IBS.mp. (2041)
5. ((faecal or fecal) adj2 incontinen$).mp. (5826)
6. dyspepsia/ (5308)
7. exp gastrointestinal motility/ (26481)
8. flatulence/ (777)
9. irritable bowel syndrome/ (949)
10. colonic diseases, functional/ (3545)
11. fecal incontinence/ (5260)
12. or/1-11 (54152)
13. (diarrhoea or diarrhea).mp. (60229)
14. diarrhea/ (28975)
15. Constipat$.mp. (10863)
16. constipation/ (6463)
17. or/13-16 (69274)
18. 12 or 17 (118089)
19. value of life/ (4752)
20. quality adjusted life year/ (2651)
21. quality adjusted life.tw. (1876)
22. (qaly$ or qald$ or qale$ or qtime$).tw. (1489)
23. (euroqol or euro qol or eq5d or eq 5d).tw. (827)
24. (hql or hqol or h qol or hrqol or hr qol).tw. (1919)
25. (hye or hyes).tw. (45)
26. health$ year$ equivalent$.tw. (31)
27. health utilit$.tw. (356)
28. (hui or hui1 or hui2 or hui3).tw. (372)
29. disutiliti$.tw. (12)
30. rosser.tw. (58)
31. quality of wellbeing.tw. (1)
32. quality of well being.tw. (194)
33. qwb.tw. (106)

34. willingness to pay.tw. (709)
35. standard gamble$.tw. (394)
36. time trade off.tw. (340)
37. time tradeoff.tw. (121)
38. tto.tw. (227)
39. or/19-38 (12154)
40. 18 and 39 (104)
41. limit 40 to english language (99)
42. from 41 keep 4-5,32-33,37,43-44,54,58,67-68 (11)
43. from 42 keep 1-11 (11)

Inclusion/exclusion criteria	
Population	People diagnosed with IBS (Manning/Rome I/Rome II), no comorbidities
Study	Cross-sectional surveys
Setting	Primary care or outpatient
Treatments	Usual care' only - exclude follow-up of specific treatments
Measures	Utility - direct choice-based measurement (TTO, SG) or indirect MAUS (EQ5D, QWB, HUI, SF6D, Rosser)
Follow-up	NA

Costs and cost-effectiveness

Search strategy: MEDLINE

Database: Ovid MEDLINE(R) <1966 to July Week 4 2006>

Search Strategy:

1 ((intestin$ or gastointestin$ or colon$ or bowel$) adj2 (motility or sensitiv$ or functional or irritable or irritat$ or gas$ or spastic$ or unstable or instability or spasm$)).mp. (19879)
2 flatus.mp. (701)
3 irritable bowel syndrome.mp. (3927)
4 IBS.mp. (2072)
5 ((faecal or fecal) adj2 incontinen$).mp. (5877)
6 dyspepsia/ (5340)
7 exp gastrointestinal motility/ (26676)
8 flatulence/ (792)
9 irritable bowel syndrome/ (966)
10 colonic diseases, functional/ (3573)
11 fecal incontinence/ (5301)
12 or/1-11 (54620)
13 (diarrhoea or diarrhea).mp. (60717)
14 diarrhea/ (29173)
15 Constipat$.mp. (10978)
16 constipation/ (6527)
17 or/13-16 (69857)
18 12 or 17 (119074)
19 Cost-Benefit Analysis/ (39214)
20 cost effectiveness.ti,ab. (17066)
21 cost benefit.ti,ab. (4676)
22 cost utility.ti,ab. (950)
23 cost per QALY.ti,ab. (246)
24 cost per quality adjusted life year.ti,ab. (284)
25 economic evaluation.ti,ab. (2322)
26 economic appraisal.ti,ab. (152)
27 or/19-26 (48594)
28 letter.pt. (573304)
29 editorial.pt. (195612)
30 historical article.pt. (232222)
31 28 or 29 or 30 (991972)
32 27 not 31 (44140)
33 animal/ (4064036)
34 human/ (9681540)

35	33 not (33 and 34) (3078223)
36	32 not 35 (43454)
37	18 and 36 (406)
38	limit 37 to english language (350)

Inclusion/exclusion criteria

Population	People diagnosed with IBS (Manning/Rome I/Rome II), no comorbidities
Study	Cross-sectional surveys, case-control or cohort
Setting	UK primary care or outpatient
Treatments	Usual care' only - exclude follow-up of specific treatments
Measures	Use of health care resources or costs

References

1. Agrawal A,.Whorwell PJ. Irritable bowel syndrome: diagnosis and management. *BMJ* 2006;**332**:280-3.

2. Camilleri M,.Williams DE. Economic burden of irritable bowel syndrome: proposed strategies to control expenditures. *Pharmacoeconomics* 2000;**17**:331-8.

3. Chang L. Impact of chronic constipation and IBS. *Advanced Studies in Medicine* 2006;**6**:S49-S57.

4. Gilkin RJ. The spectrum of irritable bowel syndrome: A clinical review. *Clinical Therapeutics* 2005;**27**:1696-709.

5. Hahn BA. A review of the Clinical Economics of Irritable Bowel Syndrome. *Annals of Gastroenterology* 2002;**15**:234-9.

6. Harris MS. Irritable bowel syndrome: a cost-effective approach for primary care physicians. *Postgraduate Medicine* 1997;**101**:215-6.

7. Hulisz D. The burden of illness of irritable bowel syndrome: current challenges and hope for the future. *Journal of Managed Care Pharmacy* 2004;**10**:299-309.

8. Inadomi JM, Fennerty MB, Bjorkman D. Systematic review: the economic impact of irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics* 2003;**18**:671-82.

9. Lea R,.Whorwell PJ. Quality of Life in Irritable Bowel Syndrome. *Pharmacoeconomics* 2001;**19**:643-53.

10. Martin R, Barron JJ, Zacker C. Irritable bowel syndrome: toward a cost-effective management approach. *American Journal of Managed Care* 2001;**7**:Suppl-77.

11. Maxion-Bergemann S, thielecke F, Abel F, Bergemann R. Costs of irritable bowel syndrome in the UK and US. *Pharmacoeconomics* 2006;**24**:21-37.

12. Simren M, Brazier J, Coremans G, Dapoigny M, Muller-Lissner SA, Pace F. Quality of life and illness costs in irritable bowel syndrome. *Digestion* 2004;**69**:254-61.

13. El Serag HB, Pilgrim P, Schoenfeld P, El Serag HB, Pilgrim P, Schoenfeld P. Systemic review: Natural history of irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics* 2004;**19**:861-70.

14. Janssen HA, Muris JW, Knotterus JA. The clinical course and prognostic determinants of the irritable bowel syndrome: a literature review. *Scandanavian Journal of Gastroenterology* 1998;**33**:561-7.

15. Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: Long term prognosis and the physician-patient interaction. *Annals of Internal Medicine* 1995;**122**:107-12.

16. Svendsen JH, Munck LK, Andersen JR. Irritable bowel syndrome - prognosis and diagnostic safety: A 5-year follow-up study. *Scandinavian Journal of Gastroenterology* 1985;**20**:415-8.

17. Blewett A, Allison M, Calcraft B, Moore R, Jenkins P, Sullivan G. Psychiatric disorder and outcome in irritable bowel syndrome. *Psychosomatics* 1996;**37**:155-60.

18. Chaudhary NA,.Truelove SC. The irritable bowel syndrome. A study of the clinical features, predisposing causes and prognosis in 130 cases. *Quarterly Journal of Medicine* 1962;**31**:307-22.

19. Fowlie S, Eastwood MA, Ford MJ. Irritable bowel syndrome: the influence of psychological factors on the symptom complex. *Journal of Psychosomatic Research* 1992;**36**:169-73.

20. Harvey RF, Mauad EC, Brown AM. Prognosis in the irritable bowel syndrome: a 5-year prospective study. *Lancet* 1987;**1**:963-7.

21. Hawkins CF,.Cockel R. The prognosis and risk of missing malignant disease in patients with unexplained and functional diarrhoea. *Gut* 1971;**12**:208-11.

22. Hillman LC, Stace NH, Pomare EW. Irritable bowel patients and their long-term response to a high fiber diet. *American Journal of Gastroenterology* 1984;**79**:1-7.

23. Holmes KM,.Salter RH. Irritable bowel syndrome - a safe diagnosis? *British Medical Journal (clinical research edition)* 1982;**285**:1533-4.

24. Keefer L,.Blanchard EB. A one year follow-up of relaxation response meditation as a treatment for irritable bowel syndrome. *Behavioural Research Ther* 2002;**40**:541-6.

25. Lembo T, Fullerton S, Diehl D. Symptom duration in patients with irritable bowel syndrome. *American Journal of Gastroenterology* 1996;**91**:905.

26. Prior A,.Whorwell PJ. Gynaecological consultation in patients with the irritable bowel syndrome. *Gut* 1989;**30**:998.

27. Stevens JA, Wan CK, Blanchard EB. The short natural history of irritable bowel syndrome: a time-series analysis. *Behavioural Research Ther* 1997;**35**:319-26.

28. Waller SL,.Misiewicz JJ. Prognosis in the irritable-bowel syndrome. A prospective study. *American Journal of Gastroenterology* 1997;**81**:529-31.

29. Adeniji OA, Barnett CB, Di Palma JA, Adeniji OA, Barnett CB, Di Palma JA. Durability of the diagnosis of irritable bowel syndrome based on clinical criteria. *Digestive Diseases & Sciences* 2004;**49**:572-4.

30. Guilera M, Balboa A, Mearin F, Guilera M, Balboa A, Mearin F. Bowel habit subtypes and temporal patterns in irritable bowel syndrome: systematic review. *American Journal of Gastroenterology* 2005;**100**:1174-84.

31. Heaton KW, Ghosh S, Braddon FEM. How bad are the symptoms and bowel dysfunction of patients with the irritable bowel syndrome? A prospective, controlled study with emphasis on stool form. *Gut* 1991;**32**:79.

32. Hahn BA, Watson M, Yan S. Irritable bowel syndrome symptom patterns. Frequency, duration and severity. *Dig Dis Sci* 1998;**43**:2715-8.

33. Ragnarsson G,.Bodemar G. Pain is temporallly related to eating but not to defecation in the irritable bowel syndrome. Patients' description of diarrhea, constipation and symptom variation during a prospective 6-week study. *European Journal of Gastroenterology & Hepatology* 1998;**10**:415-21.

34. Mearin F, Balboa A, Badia X, Baro E, Caldwell E, Cucala M *et al*. Irritable bowel syndrome subtypes according to bowel habit: revisiting the alternating subtype. *European Journal of Gastroenterology & Hepatology* 2003;**15**:165-72.

35. Mearin F, Baro E, Roset M, Badia X, Zarate N, Perez I *et al*. Clinical patterns over time in irritable bowel syndrome: symptom instability and severity variability. *American Journal of Gastroenterology* 2004;**99**:113-21.

36. Drossman DA, Morris CB, Hu Y, Toner BB, Diamant N, Leserman J *et al*. A prospective assessment of bowel habit in irritable bowel syndrome in women: defining an alternator. *Gastroenterology* 2005;**128**:580-9.

37. Mearin F, Badia X, Balboa A, Benavent J, Caballero AM, Dominguez-Munoz E *et al*. Predictive factors of irritable bowel syndrome improvement: 1-year prospective evaluation in 400 patients. *Alimentary Pharmacology & Therapeutics* 2006;**23**:815-26.

38. Akehurst RL, Brazier JE, Mathers N, O'Keefe C, Kaltenthaler E, Morgan A *et al*. Health-related quality of life and cost impact of irritable bowel syndrome in a UK primary care setting. *Pharmacoeconomics* 2002;**20**:455-62.

39. Smith GD, Steinke DT, Kinnear M, Penny KI, Pathmanathan N, Penman ID *et al*. A comparison of irritable bowel syndrome patients managed in primary and secondary care: the Episode IBS study.[see comment]. *British Journal of General Practice* 2004;**54**:503-7.

40. Bushnell DM, Martin ML, Ricci JF, Bracco A, Bushnell DM, Martin ML *et al*. Performance of the EQ-5D in patients with irritable bowel syndrome. *Value in Health* 2006;**9**:90-7.

41. Bushnell DM, Reilly MC, Galani C, Martin ML, Ricci JF, Patrick DL *et al*. Validation of electronic data capture of the Irritable Bowel Syndrome--Quality of Life Measure, the Work Productivity and Activity Impairment Questionnaire for Irritable Bowel Syndrome and the EuroQol. *Value in Health* 2006;**9**:98-105.

42. El Serag HB, Olden K, Bjorkman D, El Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. *Alimentary Pharmacology & Therapeutics* 2002;**16**:1171-85.

43. Creed F, Ratcliffe J, Fernandez L, Tomenson B, Palmer S, Rigby C *et al*. Health-related quality of life and health care costs in severe, refractory Irritable bowel syndrome. *Annals of Internal Medicine* 2001;**134**:860-8.

44. Schmulson M, Lee OY, Chang L, Naliboff B, Mayer EA. Symptom differences in moderate to severe IBS patients based on predominat bowel habit. *American Journal of Gastroenterology* 1999;**94**:2929-35.

45. Simren M, Abrahamsson H, Svedlund J, Bjornsson ES, Simren M, Abrahamsson H *et al*. Quality of life in patients with irritable bowel syndrome seen in referral centers versus primary care: the impact of gender and predominant bowel pattern. *Scandinavian Journal of Gastroenterology* 2001;**36**:545-52.

46. Coffin B, Dapoigny M, Cloarec D, Comet D, Dyard F, Coffin B *et al*. Relationship between severity of symptoms and quality of life in 858 patients with irritable bowel syndrome.[see comment]. *Gastroenterologie Clinique et Biologique* 2004;**28**:11-5.

47. Wilson S, Roberts L, Roalfe A, Bridge P, Singh S. Prevalence of irritable bowel syndrome: a community study. *British Journal of General Practice* 2004;**54**:495-502.

48. Cain KC, Headstrom P, Jarrett ME, Motzer SA, Park H, Burr RL *et al*. Abdominal pain impacts quality of life in women with irritable bowel syndrome. *American Journal of Gastroenterology* 2006;**101**:124-32.

49. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. *Digestion* 1999;**60**:77-81.

50. Wells NE, Hahn BA, Whorwell PJ, Wells NE, Hahn BA, Whorwell PJ. Clinical economics review: irritable bowel syndrome. [Review] [55 refs]. *Alimentary Pharmacology & Therapeutics* 1997;**11**:1019-30.

51. Hahn BA, Kirchendoerfer LJ, Fullerton S, Mayer E. Patient perceived severity of irritable bowel syndrome in relation to symptoms, health resource utilisation and quality of life. *Alimentary Pharmacology & Therapeutics* 1997;**11**:553-9.

52. Le Pen C, Ruszniewski P, Gaudin AF, Amouretti M, Bommelaer G, Frexinos J *et al*. The burden cost of French patinets suffering from irritable bowel syndrome. *Scandanavian Journal of Gastroenterology* 2004;**39**:336-43.

53. Longstreth GF, Wilson A, Knight K, Wong J, Chiou CF, Barghout V *et al*. Irritable bowel syndrome, health care use and costs: a US managed care perspective. *American Journal of Gastroenterology* 2003;**98**:600-7.

54. Talley NJ, Gabriel SE, Harmsen WS. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology* 1995;**109**:833-4.

55. Harewood GC,.Harewood GC. Economic comparison of current endoscopic practices: Barrett's surveillance vs. ulcerative colitis surveillance vs. biopsy for sprue vs. biopsy for microscopic colitis. *Digestive Diseases & Sciences* 2004;**49**:1808-14.